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DIENST GENEESKUNDIGE VERZORGING**
Comité voor de evaluatie van de
medische praktijk inzake geneesmiddelen

The management of menopause

Literature review: full report

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1 Abbreviations

CEE: conjugated equine estrogen
CHD: coronary heart disease
CI: confidence interval
CMH: Chinese medicinal herbs
CO: crossover RCT
CVA: cerebrovascular accident
CVD: cardiovascular disease
DB: double blind
E1: estrone
E2: estradiol
E3: estriol
EPT: estrogen-progestagen therapy
ET: estrogen therapy
GSM: genitourinary symptoms of menopause (lack of lubrication, discomfort, and pain during sexual activity)
HR: hazard ratio
HRT: hormone replacement therapy
ITT: intention-to-treat analysis
MA: meta-analysis
MBS: most bothersome symptom
MCID: minimal clinically important difference
MD: mean difference
MI: myocardial infarction
MPA: Medroxyprogesterone acetate
n: number of patients
N: number of studies
NA: not applicable
NETA: Norethisterone acetate
NR: not reported
NS: not statistically significant
NT: no statistical test
OL: open label
PG: parallel group
PO: primary outcome
QoL: Quality of life
SB: single blind
SD: standard deviation
SMD: standardized mean difference
SR: systematic review
SS: statistically significant
T2DM: type 2 diabetes mellitus
TD: transdermal
VMS: vasomotor symptoms
VTE: venous thromboembolism

2 Methodology

2.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference “**The management of menopause**” which will take place on the 30th of May 2024.

2.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

1. Beschrijving klinisch beeld en diagnose
 - a. Hoe wordt ‘menopauze’ gedefinieerd?
 - b. Hoe wordt de diagnose gesteld?
 - c. Welke zijn mogelijke klinische uitingen van de menopauze (verschillende klachtenpatronen?) en wat is het epidemiologisch patroon ervan?
 - d. Heeft een differentiatie tussen menopauze en menopauzale klachten belang? Wat is het verschil in duur tussen de menopauze en de menopauzale klachten?
 - e. Hoe wordt de menopauze best opgevolgd?
1. Description du tableau clinique et diagnostic
 - a. Comment définit-on la "ménopause" ?
 - b. Comment le diagnostic est-il posé ?
 - c. Quelles sont les manifestations cliniques possibles de la ménopause (différents types de symptômes ?) et quel est son profil épidémiologique ?
 - d. La différenciation entre la ménopause et les symptômes de la ménopause est-elle importante ? Quelle est la différence de durée entre la ménopause et les symptômes de la ménopause ?
 - e. Quelle est la meilleure façon de suivre la ménopause ?
2. Farmacologische behandelingen
 - a. Welke zijn de verschillende farmacologische behandelingsmogelijkheden?
 - b. Welke beschikbare toedieningsvormen kunnen gebruikt worden (voor- en nadelen)?
 - c. Welke zijn hun ongewenste effecten?
 - d. Wat zijn indicaties voor het opstarten van HST, bij vrouwen met en zonder klachten?
 - e. Wanneer en hoe kan er overgegaan worden van hormonale contraceptie naar HST?
 - f. Wanneer en hoe kan/moet er gestopt worden met HST?
2. Traitements pharmacologiques
 - a. Quelles sont les différents schémas de traitement pharmacologique ?
 - b. Quelles sont les formes d'administration disponibles (avantages et inconvénients) ?
 - c. Quels sont leurs effets indésirables ?
 - d. Quelles sont les indications pour commencer un THM, chez les femmes avec ou sans symptômes ?
 - e. Quand et comment passer d'une contraception hormonale à un THM ?
 - f. Quand et comment peut-on/doit-on arrêter le THM ?

3. Wat is de invloed van HST op het bewegingsstelsel (osteoporose, spieraandoeningen, artralgie, ...)?
 - a. Bij vrouwen mét en vrouwen zonder klachten
 - b. Bij vrouwen mét en vrouwen zonder risico-factoren
3. Comment le THM affecte-t-il le système locomoteur (ostéoporose, troubles musculaires, arthralgie, ...) ?
 - a. Chez les femmes présentant ou non des symptômes
 - b. Chez les femmes présentant ou non des facteurs de risque
4. Wat is de invloed van HST op neurologische en psychologische aandoeningen/symptomen (zoals Alzheimer, depressie, brain fog, ...)?
 - a. Bij vrouwen mét en vrouwen zonder klachten
 - b. Bij vrouwen mét en vrouwen zonder risico-factoren
4. Comment le THM affecte-t-il les maladies/symptômes neurologiques et psychologiques (tels que la maladie d'Alzheimer, la dépression, le brouillard cérébral, etc.)
 - a. Chez les femmes présentant ou non des symptômes
 - b. Chez les femmes présentant ou non des facteurs de risque
5. Wat is de invloed van HST op cardiovasculaire aandoeningen (ischemische hart- en vaatziekten, veneuze trombo-embolie, ...)?
 - a. Bij vrouwen mét en vrouwen zonder klachten
 - b. Bij vrouwen mét en vrouwen zonder risico-factoren
5. Comment le THM affecte-t-il les maladies cardiovasculaires (cardiopathie ischémique, thromboembolie veineuse, ...) ?
 - a. Chez les femmes présentant ou non des symptômes
 - b. Chez les femmes présentant ou non des facteurs de risque
6. Wat is de invloed van HST op het risico op kanker?
 - a. Bij vrouwen mét en vrouwen zonder klachten
 - b. Bij vrouwen mét en vrouwen zonder risico-factoren
6. Comment le THM affecte-t-il le risque de cancer ?
 - a. Chez les femmes présentant ou non des symptômes
 - b. Chez les femmes présentant ou non des facteurs de risque
7. Welke zijn de risicopopulaties voor HST?
 - a. Hoe ermee omgaan?
 - b. Wat zijn de relatieve en absolute contra-indicaties voor HST in dergelijke populaties?
7. Quelles sont les populations à risques pour le THM ?
 - a. Comment y faire face ?
 - b. Quelles sont les contre-indications relatives et absolues au THM dans ces populations ?
8. Welke zijn bestaande niet-hormonale behandelingen in het kader van de menopauze?
 - a. Wat is hun wetenschappelijk aangetoond/bewezen effect?
 - b. Wat zijn hun ongewenste effecten en risico's?
8. Quels sont les traitements non hormonaux existants dans le cadre de la ménopause ?

- a. Quel est leur effet scientifiquement démontré/prouvé ?
- b. Quels sont leurs effets indésirables et leurs risques ?

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
 - See 2.3.1 for guideline inclusion criteria.
- To perform a literature review:
 - To search and report relevant **RCTs or systematic reviews/meta-analyses of RCTs**, and for certain questions, **observational studies**, to provide an answer to certain research questions.
 - See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.
 - To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
- See section “10 Additional safety information from other sources”.

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found. However, given that the jury questions were changed multiple times after the start of the analysis, some discrepancies may exist between the jury questions and the information provided in this document.

Question 1 – General (diagnosis, definition, etc.)
This question will be answered by an expert-speaker.
Question 2 – pharmacological treatments
• The task of literature group for this question is limited to the treatment of postmenopausal symptoms. • The literature group will discuss the selected guidelines. Recommendations can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs for the treatment of menopausal symptoms with hormone therapy. The results of the literature search can be found in chapter 6 and details in appendix 11. • Additional sources (see 2.3.2) will also be consulted for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 3 – Osteoporosis
• The literature group will discuss the selected guidelines. This discussion can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 8 (fractures) and appendix 13. • The literature group will provide additional information from additional sources (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10.

• An expert speaker will provide comments and additional information.
Question 4 – Neurological and psychological outcomes
• The literature group will discuss the selected guidelines. This discussion can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 6 (depressive symptoms) and chapter 8 (cognition and dementia) and appendix 13 and appendix 16. • The literature group will provide additional information from additional sources (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 5 – Cardiovascular disease
• The literature group will discuss the selected guidelines. This discussion can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 8 (primary prevention), chapter 9 (secondary prevention), chapter 14 (non-oral HT vs oral HT for VTE) and in appendix 13, appendix 16 and appendix 14. • The literature group will provide additional information from additional sources (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 6 – Cancer
• The literature group will discuss the selected guidelines. This discussion can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 8 and in appendix 13 and appendix 15. • The literature group will provide additional information from additional sources (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.
Question 7 – Populations at risk
This question will be answered by an expert-speaker.
Question 8 – Non-pharmacological treatments
• The literature group will discuss the selected guidelines. This discussion can be found in chapter 5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs for black cohosh only. The results of the literature search can be found in chapter 7 and appendix 12. • The literature group will provide additional information from additional sources (see 2.3.2) for safety outcomes. The results of additional sources can be found in chapter 10. • An expert speaker will provide comments and additional information.

2.3.1 Guidelines

Guidelines will be selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2017 onwards are to be selected. Exceptions can be made when only older guidelines regarding a certain topic are available.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain “Rigour of development”. More information can be found on <http://www.agreetrust.org/>.¹

This table gives an overview of the items assessed in this domain according to the Agree II score.¹

No.	Description of the item
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table: Items assessed by the domain "Rigour of development" in Agree II score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable. In the chapter about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,... or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

2.3.2 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies. To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If some of the included studies in a meta-analysis do not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with a small sample size, or studies with drugs that are not on the Belgian market), this meta-analysis may be included in our review if judged to be sufficiently relevant. In this case, the discrepancies with our inclusion criteria will be discussed clearly.

RCT's

- Research question matches research question for this literature review
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Post hoc (subgroup) analyses are excluded.

Observational studies

- prospective or retrospective cohort studies with a control arm
- minimum sample size of 1000
- observational studies will only be searched for long-term outcomes (at least one-year follow-up) and if no suitable RCTs were found for the outcome of interest

Other sources for safety, contra-indications, specific subgroups, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
 - *Gecommentarieerd geneesmiddelenrepertorium/ Répertoire Commenté des Médicaments*
 - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 40th edition

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.3 Specific search criteria

2.3.3.1 Treatment of menopausal symptoms

Population	menopausal women with symptoms • Vasomotor symptoms • Genitourinary symptoms • sexual problems • depressive symptoms Exclusion: • Patients with active cancer, cancer in medical history or known BRCA mutation carriers. • Trials consisting of only or mainly patients with other serious comorbidity such as HIV, hepatitis, rheumatological disease etc.	
Intervention	• estrogens only • oestroprogestagens • estrogen + bazedoxifene • tibolone • Intravaginal prasterone (DHEA, dehydro-epiandrosterone) • levonorgestrel containing IUD • cimicifuga racemosa Exclusion: • Compounded bioidentical hormone therapy (individualized preparations by pharmacist)	Exclusion of studies comparing different doses of estrogen or different doses of progesterone. RCT's for levonorgestrel containing IUD were only searched after the search date of the source document Grant 2015.
Comparison	• Placebo • Each other	
Outcome	Outcomes included: Efficacy of treatment • QoL • Change in menopausal symptom scores • Vasomotor symptoms • Vulvovaginal atrophy symptoms • sexual problems/ dyspareunia • mood/ depression / burnout Safety • Total adverse events • Serious adverse events • Cardiovascular adverse events • Other hard endpoints	
Study design	RCTs Minimum 40 participants per treatment arm Minimum treatment duration of 12 weeks	

2.3.3.2 Long-term risks and benefits of hormonal replacement therapy for menopause

Population	- menopausal women - menopausal women with cardiovascular disease history Exclusion: - Patients with active cancer, cancer in medical history or known BRCA mutation carriers. - Trials consisting of only or mainly patients with other serious comorbidity such as HIV, hepatitis, rheumatological disease etc.	
Intervention	- oestroprogestagens - estrogens only - tibolone - levonorgestrel containing IUD	For tibolone, we only searched for breast cancer, endometrial cancer, venous thromboembolic events, and mortality.
Comparison	- Placebo - Tibolone versus other hormone therapy	
Outcome	(risk of) (can be either positive or negative) Outcomes included: - Mortality (all cause; cardiovascular; cancer) - Fractures - Muscle mass/strength - Dementia (+ Alzheimer disease +mild cognitive impairment) - Cardiovascular events (AMI, CVA, VTE, cardiovascular mortality) - Diabetes - Cancer diagnosis (breast, endometrium, other) - Other hard endpoints (safety)	Hard endpoints only For the outcome muscle mass/strength (not a hard endpoint), RCT's were searched from 2014.
Study design	RCTs (minimum 40 participants/treatment arm) Minimum duration follow-up: 1 year For the primary prevention of chronic conditions, we allowed the inclusion of large observational cohort studies (n>1000) for outcomes where there was no evidence available from RCTs.	

	For the comparison non-oral hormone therapy versus oral hormone therapy, we exceptionally allowed the inclusion of large case-control studies besides large cohort studies. For the evaluation of levonorgestrel containing IUD, RCTs and large cohort studies (n>1000) were allowed.	

2.4 Search strategy

2.4.1 Principles of the literature search

Relevant RCTs, meta-analyses and systematic reviews were searched in a stepwise approach.

As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, systematic reviews for included guidelines) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.

In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews that were published after the search date (03/07/2023) of our selected systematic reviews.

Guidelines were searched on the website of CEBAM Digital Library for Health (www.cdlh.be). These contain links to the national and most frequently consulted international guidelines. Guideline search engines, like G-I-N, TRIP-database and Dynamed were also searched.

Due to the postponement of the consensus conference that was originally planned for December 2023, an additional literature search was performed. Studies published after the original search date of July 3th 2023 were included up until December 1st 2023.

A search was also performed for new guidelines. No new guidelines were identified.

2.4.2 Source documents

The following systematic reviews were selected as source documents and starting points to find relevant publications for our literature review:

Topic	Source document
Hormone therapy for the treatment of menopausal symptoms	Grant 2015(1)
Hormone therapy for primary prevention of chronic disease	Gartlehner 2022(2)
Hormone therapy for secondary prevention of cardiovascular disease	Boardman 2015(3)

Black cohosh (<i>Cimicifuga</i> spp.) for menopausal symptoms	Leach 2012(4)

For all these research questions, a search string was developed to search Medline via PubMed from the research date of the selected source document up until 1st July 2023.

2.4.3 Search strategy details

The full search strategies can be found in the appendix chapter 17.

2.5 Selection procedure

A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was retrieved to decide on inclusion or exclusion. Unclear eligibility for inclusion was resolved through discussion with a second researcher. In - and exclusion criteria of the different types of studies are found in “2.4.3. Specific search criteria” with relevant populations, interventions, endpoints and study criteria. The selection of the studied drugs and supplements was based on discussions with experts of the organisation committee. The list of articles excluded after reading of the full text can be found in chapter 18.

2.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use ‘levels of evidence’, a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence. The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies. The GRADE system assesses the following items:

Study design	+ 4	RCT
	+ 2	Observational
	+ 1	Expert opinion
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data
Publication bias	- 1	High probability of publication bias
	Evidence of association	+ 1 Strong evidence of association (RR of >2 or <0.5)

For observational studies		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization:** If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, ...) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding:** Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.

A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good “consistency” means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as “NA” (not applicable).

Consistency is judged by the literature group based on the total of available studies, whilst taking into account:

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤ 0.5 to ≥ 1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: <http://www.gradeworkinggroup.org>

2.7 Synopsis of the study results

The complete report contains:

- (Comprehensive) summary of selected guidelines.
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).

The synopsis report contains:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions of this report have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

3 Critical reflections of the literature group

3.1 Guidelines

We searched for guidelines published in the last 5 years about hormone therapy in postmenopausal women. It is important to note that we only selected guidelines that report levels of evidence in their recommendations and that are based on a good systematic search and review of the literature. Only general guidelines about menopause were selected; guidelines on specific topics like osteoporosis and cancer were not selected.

The focus of this report is on the primary care setting. Patients with severe comorbidity, patients with cancer in their history or patients with an increased risk of breast cancer were not included in the questions to the jury. However, statements and recommendations found in the included guidelines were mentioned in the summary of the guidelines for the interested reader.

The organizing committee did not request from the literature group to specifically focus on recommendations about the different hormone treatments, initiation, duration and follow-up of the treatment or on short-term side effects. However, we did include this information in the report for context.

3.2 Literature study

3.2.1 Treatment of menopausal symptoms

3.2.1.1 Population

A first difficulty is in defining the population to be studied: women who are peri- or postmenopausal as well as having symptoms attributable to menopausal transition.

This period can span many years, and different studies use various definitions and inclusion and exclusion criteria to select their populations. Trial populations differ by age, menopausal status (perimenopausal, early postmenopausal, late postmenopausal), uterine status etc. The systematic review we used as a source material(1) pooled all these studies.

Menopausal symptoms are also not always easily defined. They include the typical complaints such as vasomotor symptoms (hot flushes) and symptoms related to vulvovaginal atrophy. These symptoms have been fairly well studied, and HRT seems to have clear efficacy for treating these symptoms. Quality of life has also been fairly well studied and HRT seems to improve it. Guidelines agree that HRT can be recommended to women with vasomotor or vulvovaginal atrophy symptoms that impact their quality of life.

However, the effect of HRT on other, more complex symptoms also linked to menopause are less clear. These symptoms, which include low mood, sleep problems, "brain fog", problems in sexual function, burnout, and others are possibly multifactorial, in which hormonal, psychological, social and societal factors may play a role. Although some trials show improvement in these symptoms with HRT, they are less well- studied and the effect of HRT also seems more limited or even absent. The risk-benefit ratio is less clear.

3.2.1.2 Interventions

Our task was to investigate the efficacy of HRT. Hormone therapies vary by preparation, type, and administration route.

Many of the studies are quite old, and some of the formulations used in the studies are not or no longer on the Belgian market. It is not clear to what extent different formulations of estrogen (and progestogens if associated) differ from each other in terms of efficacy and safety.

The AHRQ systematic review(1) pooled all different estrogens (+/progestogens). It is possible that efficacy and/or safety may actually differ between different forms.

To our knowledge, there are very few head-to-head RCTs of different estrogen formulations. The few studies directly comparing different administration routes (transdermal versus oral) showed no difference in terms of efficacy.

Many supplements and supplement formulations exist, not all of these are available in Belgium. A systematic review of supplements was not feasible for this report. We limited our literature search to black cohosh, given that this is the only registered supplement in Belgium for menopausal symptoms. Recommendations regarding the use of other supplements can be found in the summary of the guidelines.

3.2.1.3 Outcomes

For feasibility reasons, a limited number of outcomes to be reported was chosen (see 2.3.3). For some outcomes, we found no trials that evaluated them.

Symptom scales are used for most outcomes in studies of menopausal symptoms. In the meta-analyses we reported, different scales were pooled, so results had to be expressed in SMD.

An SMD value of 0.2 is considered small, 0.5 moderate and 0.8 large. However, this is a very crude way of expressing the size of an effect and makes it difficult to evaluate the true clinical relevance of the results.

Short-term undesirable effects were not reported from the studies but are described in chapter 10.

Long-term risks are described in chapter 8. However, these risks are calculated mainly from studies in postmenopausal women in whom menopausal symptoms were not the main reason for starting HRT. It cannot be ruled out that the long-term risks are different in women who take HRT for longer periods because of menopausal symptoms.

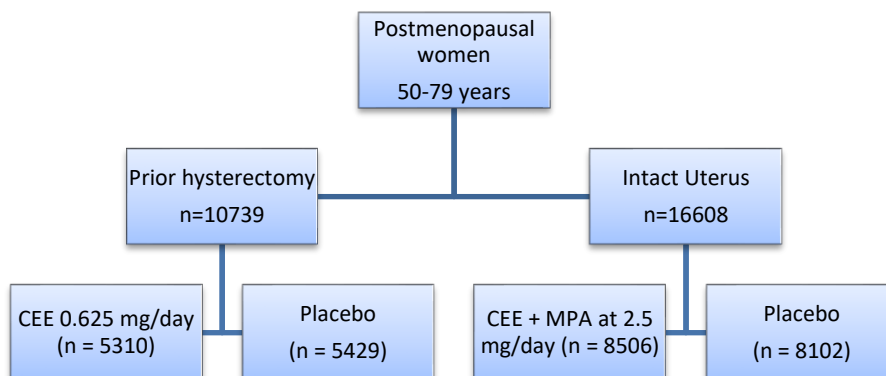
3.2.2 Primary prevention of chronic conditions

We selected the systematic review and meta-analysis of Gartlehner 2022(5), which is used by the US Preventive Services Task Force for their recommendations, to evaluate the benefits and harms of hormone therapy for the primary prevention of chronic conditions.

The AHRQ report from Gartlehner 2022 searched for RCT's. For outcomes with no evidence, large cohort studies were included. Almost no data was found for hormone regimens that are used today in menopausal women in Belgium. Almost all of the evidence is based on the much-debated Women's Health initiative (WHI) studies that evaluated CEE and MPA in women (mean age of 63 years) about 10 years older than the average age women experience menopause. Due to the lack of RCTs with contemporary hormonal preparations, we included the results of the WHI studies in this report.

3.2.2.1 The WHI hormone therapy trials

The WHI consisted of two randomized trials conducted in the USA.



When evaluating this trial (study design, outcomes, etc.), one must consider the time period this study was initiated since nowadays other research questions (see for example the timing hypothesis further in text) need to be answered than those raised in the WHI trial. The WHI trial was performed in a time when hormone therapy was widely used in the USA in menopausal women (not only for menopausal symptoms). Then, based on observational data, it was believed that hormone therapy had beneficial cardiovascular effects. However, the WHI trial concluded that hormone therapy should not be initiated for primary prevention of coronary heart disease (CHD). Given the results of the WHI study, it is sometimes referred to as an example of the need to confirm results based on observational data with randomised controlled trials.

The primary efficacy and safety outcomes in the WHI trial were coronary heart disease (CHD) and invasive breast cancer, respectively. The CEE + MPA treatment was **stopped early** in July 2002 following 5.6 years (median) of intervention on the basis of an observed elevation in breast cancer incidence and health risks that exceeded health benefits, while the CEE treatment was also **stopped early** in February 2004 following 7.2 years (median) of intervention, partly on the basis of an elevation in stroke risk of a magnitude similar to that observed for CEE + MPA. Postintervention follow-up is ongoing for 20 years.

Participant **attrition rates** in the WHI estrogen plus progestin trial and the WHI estrogen only trial was low, respectively 3.5% and 5.2%. After the trial interventions were stopped and treatment assignments were unmasked, fewer than 4% of participants reported personal postintervention use of systemic menopausal hormones.

3.2.2.2 Limitations Gartlehner 2022

Gartlehner 2022(5) discusses several limitations of their review. For some outcomes, such as ovarian cancer, cervical cancer and endometrial cancer in the WHI estrogen plus progestin trial, there were **low event rates** limiting the confidence of the results. These results need to be interpreted cautiously. For ovarian cancer for example many epidemiological studies found a higher risk of ovarian cancer in women who used hormone therapy, in contrast to the WHI estrogen plus progestin study.

Some outcomes that relied on **self-reporting** (e.g., diabetes and urinary incontinence) might be affected by potential biases or limited by disparate adherence rates (e.g., cognitive function) (WHIMS: 61.4% vs. 32.3% for placebo vs. estrogen plus progestin, respectively). Trials often used

different measures for ascertaining outcomes, which limited comparisons across trials. For cognitive function for example, WHIMS was the only trial to use a thorough adjudication process for probable dementia and mild cognitive impairment, whereas other trials used batteries of cognitive tests.

Most trials had high **attrition** or **low adherence** to medications; this was true even for the WHI, in which 40 to 50 percent of participants discontinued their medications during the trial. Nevertheless, secondary analyses of the WHI limited to adherent women were generally similar to intention-to-treat results but with accentuated findings.

The authors point out that **the average age** of women in the included studies ranged from 50 to 79 years, which is older than the average age of women experiencing menopause (51 years). For example, in the WHI, the average age of women was 64 years; approximately 30 percent of women in the WHI were ages 50 to 59 years at the time of enrollment, and 12.5 percent were ages 50 to 54, an age range when most women are likely to consider hormone therapy for the treatment of menopausal symptoms.

The majority of findings came from the WHI, which tested only **one dose, formulation, and route of administration** of hormone therapy in each trial. The PEPI trial was the only study that directly compared different formulations of estrogen and progestin combinations. **To date, however, the evidence regarding the effect of different formulations, doses, and modes of delivery of hormone therapy on benefits and risks is insufficient to draw firm conclusions.**

3.2.2.3 The timing hypothesis

Gartlehner 2022 also performed analyses to evaluate differences in treatment effects based on subgroups (age, race, or oophorectomy status) and differences in treatment effects based on timing of the intervention (the “timing hypothesis”). The timing hypothesis theorizes that estrogen therapy has a more favorable effect in younger women **closer to the onset of menopause** than in older women, especially in terms of effects on heart disease. The purported health benefits of early hormone therapy have been extended to lower mortality, reduced risk of dementia, and better cognition. Most of these claims are based on observational studies; post hoc subgroup analyses of the WHI also reported benefits of an early commencement of hormone therapy, although most differences did not reach statistical significance. The timing hypothesis was not a research question for this literature report. We refer to Gartlehner 2022 for more details.

3.2.2.4 The effect of dose and mode of delivery of hormone therapy

With the exception of the included meta-analysis from Rovinski 2018 (see further) comparing non-oral hormone therapy with oral hormone therapy for the risk of VTE, no studies were included in this report evaluating the effect of the mode of delivery of hormone therapy. In our search for the treatment of menopausal symptoms, studies comparing different doses of estrogen or different doses of progesterone were excluded.

One of the experts of the organizing committee pointed out that several observational studies suggest that lower doses of estrogen are associated with lower risks of stroke and that lower risks (DVT, breast cancer, etc.) are observed with some progestins. Given that Gartlehner 2022 was an important source for this report, we mention here information and conclusions on this topic that they provided in their publication.

Gartlehner 2022 states that to date, the evidence regarding the effect of dose and mode of delivery of hormone therapy on benefits and risks is still **insufficient** to draw firm conclusions(5)). In treatment studies, progestins and natural progesterones differ in their metabolic action and risk of adverse effects on blood lipids, breast tenderness, and headaches. **The risk-benefit profile of each type of progestin and progesterone for use in hormone therapy is currently still unclear.** In the systematic review of Gartlehner 2022, the PEPI trial was the only eligible study that used different types (regular synthetic and micronized progestins) and regimens of progestins (continuous and sequential progestin regimens) within the same study. Results reported no differences in benefits and harms between different types and regimens. The sample size of the PEPI trial (n=875) was too small to detect potential differences in outcomes that are of interest for the prevention of chronic conditions. All the other studies included in the review from Gartlehner 2022 used continuous progestin regimens.

While observational studies suggest transdermal estrogen has a lower risk of **venous thromboembolism (VTE)** compared with oral estrogen, there were no eligible trials of transdermal estrogen identified by Gartlehner 2022. However, we included a systematic review and meta-analysis by Rovinski 2018 in this report that evaluated observational data (they also found no eligible RCTs) showing a lower VTE risk with **non-oral hormone therapy** compared to oral hormone treatment. No separate analysis was performed for patches or gels. The moderate heterogeneity ($I^2=58\%$) in the meta-analysis is, according to the authors, possibly due to differences in progestin type and dose in the group that received oral hormone treatment. Furthermore, this review found no difference in VTE risk between non-oral forms of estrogen only or estrogen plus progestin and controls. The authors of the review only included studies with postmenopausal women who did not have diseases that could increase the VTE risk.

3.2.3 Secondary prevention of chronic conditions: cardiovascular disease

The Cochrane review from Boardman 2015(3) assessed the effects of hormone therapy for the prevention of **cardiovascular disease** in post-menopausal women. The authors searched for RCTs comparing **oral hormone therapy** with placebo/control for a follow-up duration of $\geq$ six months. The review includes analyses for primary prevention, secondary prevention and both. In this report, we only included information about secondary prevention from Boardman 2015. The primary prevention of cardiovascular disease and other outcomes was already discussed based on the AHRQ review from Gartlehner 2022.

Based on meta-analyses, there was a higher risk for **venous thromboembolism** for oral hormonal therapy compared to placebo but **no difference for other outcomes** like mortality, stroke, and pulmonary thromboembolism in postmenopausal women with established cardiovascular disease. The majority of the studies were done with conjugated equine estrogen (CEE). Boardman 2015 did not stratify between estrogen-only and combination hormone therapy, which is a limitation of the review.

Boardman 2015 also evaluated the timing hypothesis. The results of the subgroup analysis (starting treatment either <10 or ≥ 10 years after menopause) provided some supportive evidence for the timing hypothesis. This was the case for the outcomes of death from all causes and coronary heart

disease but not for the outcomes stroke and venous thromboembolism. Studies for both primary and secondary prevention of cardiovascular disease were included in this subgroup analysis. The timing hypothesis was not a research question for this literature report. We refer to Boardman 2015 for more details.

3.2.4 Limitations literature search

Because of the limited time in which we perform this literature search and the multitude of clinical questions, we are forced to use a stepped approach when searching for literature. We search one or more source documents, which are systematic of which the search questions match ours as closely as possible, and in a second step perform a search in Pubmed to find the articles published after the search date of the source document.

A limitation of this strategy is that the source documents may occasionally use a search strategy, or inclusion/exclusion criteria that are (slightly) different from ours. As a result, some articles (published before the start date of our search) that are relevant to our search query may not have been found; or some outcomes may not have been reported for a specific intervention or comparison of interventions.

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 1.

Abbreviation	Guideline
AWMF 2020(6)	AWMF-Registernummer 015-062; Leitlinienklasse S3 Stand; Peri- und Postmenopause –Diagnostik und Interventionen ; januari 2020
FR 2021(7)	F. Trémollières , N. Chabbert-Buffet et al., Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines (Short version); Gynécologie Obstétrique Fertilité & Sénologie 49 (2021) 305–317. Long version includes in a special issue: - Non-hormonal alternatives for the management of menopausal hot flushes. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - How to diagnose menopause? Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Nutritional advices for postmenopausal woman. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Differential diagnosis of vasomotor symptoms. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Effects of physical activity and decreased sedentary behaviours in menopausal women. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Benefit–risk balance of hormone replacement therapy: Cancers and mortality. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - The HRT follow-up consultation. What to do in case of breast pain. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - The HRT follow-up consultation. What to do in case of breast tumour (clinical or radiological) and microcalcifications. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Management of side effects under hormonal replacement therapy in menopausal women: Abnormal uterine bleeding. Postmenopausal women

	management: CNGOF and GEMVi clinical practice guidelines - Menopause hormone treatment. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Menopause and risk of thromboembolic events. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Menopause, menopause hormone therapy and osteoporosis. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Genitourinary menopause syndrome. Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines - Menopause hormone therapy and cognition. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines - Menopausal hormone therapy an cardiovascular risk. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines Management of vulvovaginal atrophy: Physical therapies. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines
NHG 2022(8)	NHG-Standaard De overgang (M73) versie 3.0, june 2022
NICE Upd 2019(9)	- Menopause: diagnosis and management. Clinical Guideline NG23. September 2015/update december 2019
USPSTF 2022(2)	US Preventive Services Task Force, Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons, JAMA November 1, 2022 Volume 328, Number 17

Table 1: Selected guidelines and their abbreviations as used in this report.

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table 2 to 10.

AWMF 2020		
Grades of recommendation: Starke Evidenzstärke→Grad A oder Grad B Empfehlung Mäßige Evidenzstärke→Grad A oder Grad B oder Grad 0 Empfehlung Schwache Evidenzstärke→Grad B oder Grad 0 Empfehlung	A	Starke Empfehlung mit hoher Verbindlichkeit: Soll / Soll nicht
	B	Einfache Empfehlung mit mittlerer Verbindlichkeit: Sollte / Sollte nicht
	0	Offene Empfehlung mit geringer Verbindlichkeit: Kann / Kann nicht
Levels of evidence According to Oxford evidence assessment system	1a	Systematic reviews (with homogeneity) of RCT
	1b	Individual RCT (with narrow Confidence Interval !)
	1c	All or none§
	2a	Systematic reviews (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
	2c	"Outcomes" Research; Ecological studies
	3a	Systematic reviews (with homogeneity) of case- control studies
	3b	Individual Case-Control Study
	4	Case-series (and poor quality cohort and case- control studies§§)
	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Table 2: Grades of recommendation and Level of evidence of the AWMF 2020 guideline.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders. Some patients died before the Rx became available, but none now die on it.

Table 3: Grades of recommendation and Level of evidence of the FR 2021 guideline.

FR 2021				
Degree of agreement and judgement The formulation of the guidelines varies according to the results obtained at the end of the rating process for consensus obtention.	“It is recommended...”	Proposal judged appropriate	Grades of recommendation	A: Based on established scientific evidence (NP1)
	It is recommended to not...”	Proposal judged inappropriate		B: Based on scientific presumption (NP2)
				C: Based on low level of evidence (NP3 or NP4)
				Expert opinion: in the absence of (conclusive) studies, the recommendations resulted from an agreement between experts of the working group and after consultation with the reading group.
				“The current state of knowledge does not allow a conclusion to be reached about...”.
	“given the current state of knowledge and absence of consensus, it cannot be recommended...”	Proposal judged uncertain (lack of consensus)		
Levels of evidence	Level 1 (NP1)	• High-power randomized comparative studies • Meta-analysis of randomized comparative studies • Decision analysis based on well-conducted studies		
	Level 2 (NP2)	• Low-power randomized comparative studies • Well-conducted non-randomized comparative studies • Cohort studies		
	Level 3 (NP3)	• Case-control studies		
	Level 4 (NP4)	• Comparative studies with major biases • Retrospective studies • Case series		

NHG 2022		
Grades of recommendation GRADE maakt een onderverdeling in sterke en voorwaardelijke (zwakke) aanbevelingen. Het NHG brengt dit tot uitdrukking door de formulering van de aanbeveling	STERK VOOR Voorkeursformulering: We bevelen [interventie] aan.	De voordelen zijn groter dan de nadelen voor bijna alle patiënten. Alle of nagenoeg alle geïnformeerde patiënten zullen waarschijnlijk deze optie kiezen.
	STERK TEGEN Voorkeursformulering: We bevelen [interventie] niet aan.	De nadelen zijn groter dan de voordelen voor bijna alle patiënten. Alle of nagenoeg alle geïnformeerde patiënten zullen waarschijnlijk deze optie kiezen.
	ZWAK VOOR Voorkeursformulering: Overweeg [interventie], bespreek de voor- en nadelen.	De voordelen zijn groter dan de nadelen voor een meerderheid van de patiënten, maar niet voor iedereen. De meerderheid van geïnformeerde patiënten zal waarschijnlijk deze optie kiezen.
	ZWAK TEGEN Voorkeursformulering: Wees terughoudend met [interventie], bespreek de voor- en nadelen.	De nadelen zijn groter dan de voordelen voor bijna alle patiënten. Alle of nagenoeg alle geïnformeerde patiënten zullen waarschijnlijk deze optie kiezen.
Levels of evidence Het beoordelen en graderen van het bewijs heeft plaatsgevonden met de GRADE-methode.	Hoog	Het werkelijke effect ligt dicht in de buurt van de schatting van het effect.
	Redelijk	Het werkelijke effect ligt waarschijnlijk dicht bij de schatting van het effect, maar er is een mogelijkheid dat het hier substantieel van afwijkt.
	Laag	Het werkelijke effect kan substantieel verschillend zijn van de schatting van het effect. Zeer laag We zijn onzeker over het werkelijke effect.

Table 4: Grades of recommendation and Level of evidence of the NHG 2022 guideline.

NICE upd 2019		
Grades of recommendation	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term “offer”, “refer”, “advise” or similar...	Strong recommendations: there is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Weak recommendations: reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute levels of evidence to each particular recommendation. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect.	

Table 5: Grades of recommendation and Level of evidence of the NICE upd 2019 guideline.

USPSTF 2022		
Grades of recommendation	A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial. For practice: Offer or provide this service.
	B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. For practice: Offer or provide this service.
	C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. For practice: Offer or provide this service for selected patients depending on individual circumstances.
	D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. For practice: Discourage the use of this service.
	I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. For practice: If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.
Levels of evidence	Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
	Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
	Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

Table 6: Grades of recommendation and Level of evidence of the USPSTF 2022 guideline.

4.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 11. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
AWMF 2020	7	5	7	7	7	7	7	5	52	92,9
FR 2021	5	4	5	6	7	6	3	1	37	66,2
NHG 2022	7	5	6	5	7	7	5	5	47	83,9
NICE upd 2019	7	7	6	5	7	7	6	7	52	92,9
USPSTF 2022	7	7	6	6	7	5	5	5	48	85,7

Table 7: AGREE score of selected guidelines on item “Rigour of development”, see methodology for a description of the items.

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AWMF 2020	
Population	• Alle peri- und postmenopasualen Frauen Including: • nach Mammakarzinom • nach Genitalkarzinom • nach kolorektalen und anderen Karzinomen
Interventions	• Placebo • HRT • Vaginale ET • Cimicifuga racemosa; syn. Actaea racemosa (Cimicifuga) • Phytoöstrogene • Ginseng • Johanniskraut (Hypericum perforatum) • Akupunktur • Tiefenentspannung • Sport • Chinesische Kräuter (Chinese herbal medicine, CHM) • Tibolon • Bioidentische HRT (BHT) • Dehydroepiandrosteron (DHEA) • Psychopharmaka • Kognitive Verhaltenstherapie (CBT)
Outcomes	• Sicherheit • Vasomotorische Symptome • Sexuellen Funktion • Urogenitale atrophie • Harninkontinenz • Rezidivierenden Harnwegsinfekten • Koronare Herzkrankheit • Zerebrovaskuläre Erkrankungen • Venöser Thrombosen und Lungenembolien (VTE) • Osteoporose-assoziierte Frakturen • Kognition • Demenzen • Mammakarzinomrisiko • Mammakarzinom Rezidivrisiko/Gesamtüberleben • Endometriumkarzinomrisiko • Ovarialkarzinomrisiko • Genitalkarzinom Rezidivrisiko/Gesamtüberleben • Risiko kolorektaler Karzinome

	• kolorektalen und anderen Karzinomen Rezidivrisiko/Gesamtüberleben • Gallenwegserkrankungen

Table 8: Included population, intervention and main outcomes of the AWMF 2020 guideline.

FR 2021	
Population	• Femmes ménopausées • Femmes en période de périménopause ou ménopausées se plaignant de BVM, avec ou sans antécédent personnel de cancer du sein. • Femmes ménopausées atteintes de SGUM, avec ou sans antécédent de cancer du sein, traitées ou non par hormonothérapie. • Femmes ne prenant pas de THM et non déjà prises en charge pour une ostéoporose primitive ou secondaire • Femmes traitées pour la prévention de l'ostéoporose post-ménopausique • Femmes ménopausées avec SUA sous THM. • Femmes en période de ménopause se plaignant d'un SDM diffus ou focal, prenant un THM ; <u>exclusion</u> : SDM lors de la prise en charge du cancer du sein ou séquellaire d'une prise en charge chirurgicale Exclusion: Ces recommandations ne concernent pas le champ de l'insuffisance ovarienne prématurée
Interventions	• Placebo • THM • Inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) (paroxétine, citalopram, scitalopram, fluoxétine, sertraline) • Inhibiteurs de la recapture de la noradrénaline et de la sérotonine (IRNS) (venlafaxine, desvenlafaxine) • Gabapentine • Prégabaline • Clonidine • Oxybutynine • Homéopathie • Produits naturels (phytoestrogènes, oméga 3, huiles essentielles, vitamine E, extraits de pollens, bêta-alanine) • Approches non pharmacologiques [acupuncture, hypnose, autres (yoga, exercice physique, relaxation, thérapie en pleine conscience), aromathérapie, perte de poids volontaire...]

Outcomes	• Fréquence et/ou la sévérité et/ou le score (fréquence x sévérité) des BVM • Symptômes vulvovaginaux • Symptômes sexuels • Symptômes urinaires • DMO, DXA , FRAX, • Marqueur clinique de perte de densité osseuse, • Marqueur biologique de perte de densité osseuse • Risque de cancers gynécologiques et extra-gynécologiques • Risque de maladie cardiovasculaire et/ou thromboembolie. • Cognition • Démence • Mortalité • Abnormal uterine bleeding • Fréquence, et/ou la sévérité et/ou le score (fréquence x sévérité) du SDM

Table 9: Included population, intervention and main outcomes of the FR 2021 guideline.

NHG 2021	
Population	• Vrouwen met opvliegers en/of nachtelijke zweetaanvallen • Vrouwen met opvliegers en/of nachtelijke zweetaanvallen en anticonceptiebehoefte
Interventions	• Placebo • Gewichtsreductie • Lichaamsbeweging • Zilverkaars • fyto-oestrogenen • Stressreducerende psychologische interventies, waaronder: ○ cognitieve gedragstherapie (CGT) ○ op mindfulness gebaseerde therapie • Hormoontherapie met oestrogeen (alle toedieningsvormen), al dan niet gecombineerd met progestageen (alle typen) Voor ernstige bijwerkingen is hierbij onderscheid gemaakt naar: ○ oestrogeen monotherapie ○ oestrogeen gecombineerd met continu toegevoegd progestageen (alle typen) ○ oestrogeen gecombineerd met sequentieel toegevoegd progestageen (alle typen) Voor vrouwen met een uterus: ○ oestrogeen gecombineerd met progesteron ○ oestrogeen gecombineerd met dydrogesteron ○ oestrogeen gecombineerd met medroxyprogesteron ○ oestrogeen gecombineerd met norethisteron ○ oestrogeen gecombineerd met drospirenon ○ oestrogeen gecombineerd met lynestrenol

	• Hormoonspiraal plus oestrogeen • Tibolon • Transdermaal oestrogeen • Vaginaal oestrogeen • Clonidine • Antidepressiva (SSRI's, SNRI's) • Gabapentine
Outcomes	• Hinder/ernst van opvliegers en/of nachtelijke zweetaanvallen • Kwaliteit van leven • Stemming • Aantal opvliegers en/of nachtelijke zweetaanvallen • Seksuele klachten - spier- en gewrichtsklachten • Bijwerkingen: - voor zilverkaars : onder andere leverfunctiestoornissen, interacties met medicatie - voor fyto-oestrogenen, hormoontherapie en transdermaal oestrogeen: ernstige: borstkanker; endometriumhyperplasie of -carcinoom; coronaire hartziekten (hartinfarct, acute hartdood); beroerte; veneuze trombo-embolie (diepe veneuze trombose, longembolie); andere: onder andere onregelmatig vaginaal bloedverlies • Voor stressreducerende psychologische interventies ook slaap

Table 10: Included population, intervention and main outcomes of the NHG 2022 guideline.

NICE upd 2019	
Population	• Menopausal women (covering the perimenopause and postmenopause) • Women with premature ovarian insufficiency (irrespective of cause) Exclusion: • Women who are pregnant • Women who are breastfeeding • Men • Transgender women.
Interventions	• Hormonal pharmaceutical treatments: - oestrogen combined with progestogen (oral) - oestrogen combined with progestogen (transdermal) - oestrogen (oral) - oestrogen (transdermal) - oestrogen (depot) - progestogen alone - testosterone - tibolone - bio-identical hormones licensed for use in the UK

	- tissue-selective oestrogen complexes - selective oestrogen-receptor modulators • Non-hormonal pharmaceutical treatments: - selective serotonin reuptake inhibitors - serotonin–noradrenaline reuptake inhibitors - gabapentin - clonidine • Non-pharmaceutical treatments: - phytoestrogens - herbal preparations (including black cohosh and red clover) - acupuncture - lifestyle advice • Psychological therapy: - cognitive behavioural therapy Exclusion • Systemic oestrogen-based hormonal treatment in women who have an increased risk of, or are undergoing treatment for, breast cancer • Treatments of chronic diseases that are common in postmenopausal women, such as osteoporosis and CVD
Outcomes	• Menopause-related symptoms, including: - symptomatic relief (specifically vasomotor, musculoskeletal and psychological symptoms, and altered sexual function), - preventing long-term sequelae of the menopause (especially osteoporosis and cardiovascular disease [CVD]) • Risks and benefits of treatments Exclusion: • Premenopausal prevention of symptoms usually associated with the menopause (specifically vasomotor, musculoskeletal, urogenital and psychological symptoms, and altered sexual function) • Induction of puberty in children and young people

Table 11: Included population, intervention and main outcomes of the NICE upd 2019 guideline.

USPSTF 2022	
Population	Asymptomatic postmenopausal persons who are considering hormone therapy for the primary prevention of chronic medical conditions. Exclusion: • Persons who are considering hormone therapy for the management of perimenopausal symptoms, such as hot flashes or vaginal dryness. • Persons who have had premature menopause (primary ovarian insufficiency) or surgical menopause.
Interventions	Oral or transdermal hormone therapy: • combined estrogen and progestin (persons with an intact uterus) • estrogen alone (persons who have had a hysterectomy) taken at or after the time of menopause. We limited our evaluation to medications that have been approved by the FDA for this purpose and that are available for use in the United States Exclusion: local formulations of hormone therapy
Outcomes	• Coronary Heart Disease • Breast Cancer • Fractures • Diabetes • Colorectal Cancer • Thromboembolic Events • Stroke • Dementia • Gallbladder Disease • Urinary Incontinence • All-Cause Mortality

Table 12: Included population, intervention and main outcomes of the USPSTF 2022 guideline.

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

AWMF 2020	
Development group	Die fachliche, inhaltliche Angemessenheit einer Leitlinie wird durch die Leitliniengruppe erzeugt, die sinnvollerweise erfahrene Anwendende (z.B. Ärzt*innen, Pflegekräfte, Physiotherapeut*innen, Psycholog*innen, Angehörige weiterer Berufsgruppen) und Patienten*innen bzw. Bürger*innen repräsentiert. Es gibt keine Mindestanzahl an zu beteiligenden Fachgesellschaften / Organisationen. Die Auswahl der Mitglieder sollte professionelle und wissenschaftliche Expertise im Themenbereich der Leitlinie repräsentieren sowie die Perspektive der Betroffenen. Herausgeber: - Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) - Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) - Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG)
Target audience	Ärzte, die peri- und postmenopausale Frauen über die physiologischen Veränderungen sowie Störungen und deren Behandlungsmöglichkeiten beraten und behandeln: • Gynäkologen in der Niederlassung • Gynäkologen mit Klinikanzstellung • Ärzte, die peri- und postmenopausale Frauen beraten bzw. deren Beschwerden und Erkrankungen behandeln, wie z. B. Allgemeinärzte, Internisten, Psychiater, Neurologen, u. a.

Table 13: Members of the development group and target audience of the AWMF 2020 guideline.

FR 2021	
Development group	Comité d'organisation désigné par le Collège National des Gynécologues et Obstétriciens Français (CNGOF) et le Groupe d'Etude sur la Ménopause et le Vieillissement hormonal (GEMVi) : Nathalie Chabbert-Buffet, Geneviève Plu-Bureau, Florence Trémollières, Patrice Lopes, Olivier Graesslin et Xavier Fritel

	Un groupe de travail a été constitué associant des soignants d'origine géographique et d'écoles de pensée diverses
Target audience	Praticiens concernés pour la prise en charge des femmes ménopausées sous tous ses aspects, tant en termes d'hygiène de vie que de prise en charge thérapeutique (symptômes vasomoteurs, syndrome génito-urinaire de la ménopause, prévention de l'ostéoporose)

Table 14: Members of the development group and target audience of the FR 2021 guideline.

NHG 2022	
Development group	Het streven is naar een evenwichtige samenstelling, omdat dit het draagvlak van de richtlijn ten goede komt. Uitgangspunten zijn: • De werkgroep bestaat uit 8-10 personen. • Minstens de helft van de werkgroepleden is – bij voorkeur praktiserend – huisarts, met én zonder specifieke expertise op het betreffende gebied. • Werkgroepleden nemen bij voorkeur niet vaker dan 2 keer deel aan een werkgroep over hetzelfde onderwerp. • Als er een expertgroep van huisartsen bestaat over het onderwerp, wordt deze gevraagd 1 of 2 leden af te vaardigen. Een wetenschappelijk medewerker en senior wetenschappelijk medewerker van het NHG-cluster Richtlijnontwikkeling begeleiden de werkgroep. Een van hen treedt meestal op als voorzitter van de vergaderingen. Een epidemioloog schrijft de wetenschappelijke onderbouwing van de aanbevelingen. Er is ook een adviseur farmacotherapie bij betrokken. De standaard is ontwikkeld in samenwerking met de Nederlandse Vereniging voor Obstetrie en Gynaecologie.
Target audience	Huisartsen

Table 15: Members of the development group and target audience of the NHG 2022 guideline.

NICE upd 2019	
Development group	A multidisciplinary Guideline Development Group comprising healthcare professionals and researchers as well as lay members developed this guideline (see the list of group members and acknowledgements). NICE funds the NCC-WCH and thus supported the development of this guideline. The Guideline Development Group was convened by the NCC-WCH and chaired by Professor Mary Ann Lumsden in accordance with guidance from NICE.

Target audience	• Healthcare professionals who care for women in menopause. • Women in menopause, and their families and carers

Table 16: Members of the development group and target audience of the NICE upd 2019 guideline.

USPSTF 2022	
Development group	• It comprises a multidisciplinary and balanced group of experts in primary care and clinical preventive services, including methodological experts and clinicians. There are currently 16 members on the Task Force. Members are nationally recognized experts in prevention, evidence-based medicine, and primary care who are also skilled in the critical evaluation of research and the implementation of evidence-based recommendations in clinical practice. Members' fields of practice include behavioral health, family medicine, geriatrics, internal medicine, pediatrics, obstetrics and gynecology, and nursing. Currently the Task Force is led by a Chair and two Vice-Chairs. • The USPSTF seeks the input of disease specialists as expert consultants and reviewers and engages patient advocacy groups and consumer organizations for their opinions and input at various stages of the evidence review • The USPSTF solicits patient, consumer, and public involvement during the draft research plan, draft evidence review, and draft recommendation stages.
Target audience	• Patients • Clinicians

Table 17: Members of the development group and target audience of the USPSTF 2022 guideline.

5 Information and recommendations from guidelines

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in bold.

Supplemental information are shown in plain text.

Comments from the bibliography group are written in italic.

Although NICE uses the GRADE methodology it does not explicitly categorize recommendations in strong and weak recommendations. The strengths of the recommendations are expressed in the wording of the recommendations. Similarly while the FR guideline assessed the quality of evidence when formulating its recommendations.

Overview of the selected guidelines

A total of 5 guidelines were selected, all focusing on menopause. More specific guidelines focusing on osteoporosis, breast cancer or any other topics that may include population and or intervention broader than those concerning menopause were not considered for this review.

All the guidelines except USPSTF 2022 concern menopausal symptoms in peri and/or postmenopausal women. These 4 guidelines (AWMF 2020, FR 2021 NHG 2022 and NICE upd 2019) also discussed the effect of HRT on cardiovascular and cancer risks. AWMF 2020, FR 2021 and NICE upd 2019 also focused on the musculoskeletal effects of HRT and the effects on neurological/psychological symptoms. The American USPSTF 2022 guideline is more specific and only focused on prevention of chronic conditions in menopausal women without symptoms.

The organizing committee did not request from the literature group to focus on recommendations about the different HRT, initiation, duration and follow-up of the treatment or on short term side effects. However, we did include this information in the report for context.

5.1 Different hormonal therapies, dosages and schema of administration

Schema of administration

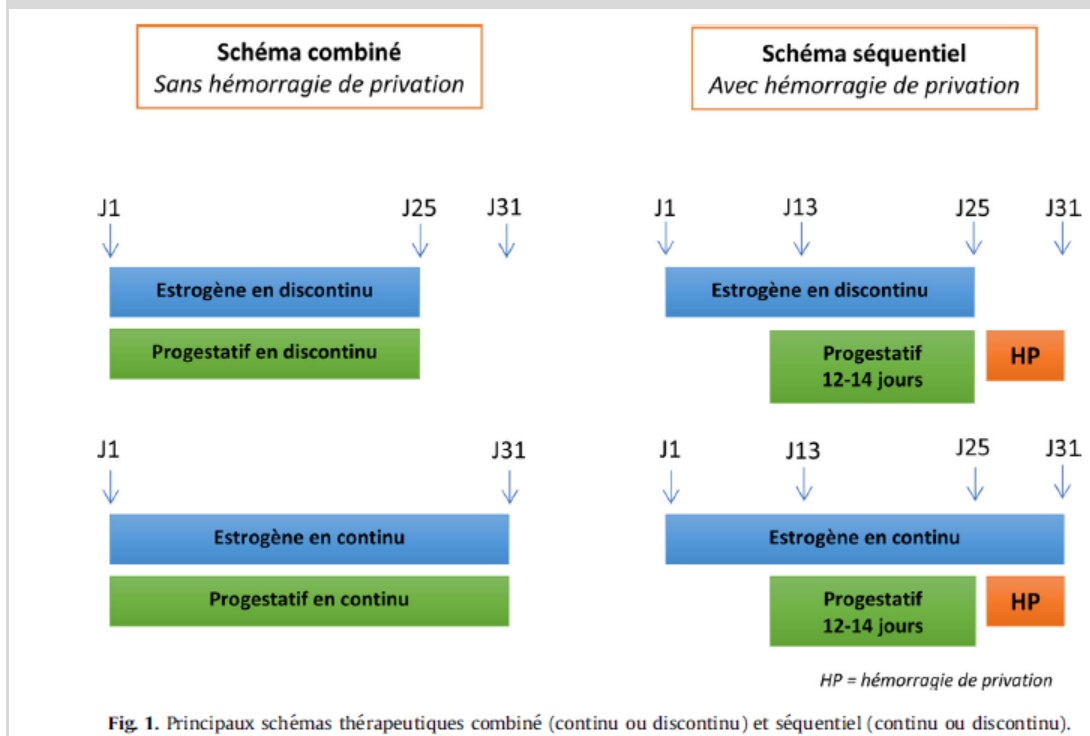
AWMF 2020, FR 2021, NHG 2022 and NICE upd 2019 all recommend to give women with uterus combination therapy, to reduce the risk of endometrial carcinoma and to give women without uterus estrogen monotherapy. (strong recommendation)

In addition, in women without uterus but with endometriosis, NHG 2022 recommends to give combination therapy regardless of menopausal status and prefers continuous administration of progestogen.

In women with uterus:

According to NHG 2022 continuous administration of progestogen is preferred in postmenopausal women.

In perimenopausal women, continuous administration causes frequent and prolonged bleeding. NHG 2022 states that in this group sequential administration (14 days per month) is the most obvious option. This causes monthly withdrawal bleeding.



FR 2021 proposes 4 different schema and fails to recommend any particular regimen as being associated with the most favorable benefit-risk balance. The recommended duration of progestogens intake in sequential HRT should be at least 12 days per month or at best a combined regimen.

FR 2021 adds that a continuous combined regimen is to be preferred in the event of flushing during the discontinuation period, symptoms linked to hormonal variations (migraines) or difficulties in complying with a sequential regimen (expert opinion). They also state that the most commonly used regimen is the combined one, because of its superiority in terms of endometrial risk (NP1).

AWMF 2020 also proposes two regimens (cyclical or continuous) for progestogen in a combined HRT, with a minimum duration of use of 10 - 14 days as shorter application times, can lead to endometrial hyperplasia or carcinoma. Regarding the risk of endometrial cancer, they formally mention that:

- A reduction in the risk of endometrial cancer was observed with continuous combined HRT with CEE and MPA with an average duration of use of 5.6 years (level of evidence 2, consensus strength ++).
- Continuous combined HRT with <5 years of use can be considered safe, sequential-combined HRT may increase the risk of developing endometrial cancer (level of evidence 2, consensus strength +++).
- Sequential combined HRT with a duration of use of less than 5 years and using a synthetic progestogen can be considered safe (level of evidence 3, consensus strength +++).

- Sequential-combined HRT may increase the risk of developing endometrial cancer. The effect depends on the duration, type and dose of progestogen use (level of evidence 3, consensus strength ++).

In women without uterus

FR 2021 formally mentions that in the case of hysterectomy, there is no benefit to combining progesterone or a progestin with estradiol for the risk of breast cancer (Grade A).

Pharmacological treatment options

(see also chapter 5.8 on cardiovascular risks and 5.9 on cancer risks)

AWMF 2020 specifies that good evidence for the benefit-risk ratio is only available for therapy with conjugated estrogens (CEE) plus medroxyprogesterone acetate and that large RCT comparing different hormone preparations and forms of application are lacking.

According to AWMF 2020, 17 β -estradiol and CEE appeared equally effective for hot flushes reduction. However according to FR 2021 the metabolic impact and venous thromboembolic risk of oral 17 β estradiol and estradiol valerate are lower than with CEE.

FR 2021 recommends to prefer of 17beta-estradiol or estradiol valerate in combination with progesterone or dydrogesterone (Grade B). In hysterectomized women, FR 2021 recommends the use of estradiol or estradiol valerate alone, without associated progesterone or progestin (Grade B).

According to FR 2021, HRT can be initiated at a minimal dose and must subsequently be adapted to the patient's profile, tolerance and efficacy. Standard estrogen doses are:

- 2 mg/d for oral 17-beta estradiol
- 50 μ g/d for 17-beta estradiol transdermally
- 1.5 mg/d for 17-beta estradiol percutaneously.

There is a dose-dependent effect of estrogens on most tissues with the breast, endometrium and bone tissue being the most ET-dependent. The efficacy of HRT on climacteric symptoms is also dose-dependent.

FR 2021 recommends to add:

- For a sequential regimen: a dose of 200 mg of natural progesterone or 20 mg of dydrogesterone per day for at least 12 days (grade B).
- For a combined regimen FR 2021 proposes the minimum dose of natural progesterone of 100 mg or 10 mg of dydrogesterone per day (to be adapted to the dose of estradiol and endometrial tolerance) (grade B).

Regarding the selection of the progestogen, FR 2021 recommends that ET be combined with progesterone or dydrogesterone in non-hysterectomized women to limit the increased risk of breast cancer attributable to HRT (grade B).

According to NHG 2022, the effect of hormone therapy on vasomotor symptoms is slightly more pronounced at the dose of 1 mg oral estradiol per day (or equivalent), but even at the lower dose of 0.5 mg oral estradiol per day, the effect may still be clinically relevant. Dydrogesterone is preferred because it has the lowest risk of serious side effects. Progesterone is second choice. (Low recommendation, low level of evidence)

For postmenopausal women with a uterus or women without uterus but with endometriosis, NHG 2022 advises:

- If oral preparation (+ continuous progestogen):
 - estradiol 1 mg + dydrogesteron 5 mg: 1dd 1 tablet (first choice)

- estradiol tablet 1 dd 1 mg + progesterone tablet 100 mg 1 dd 2 for the night (second choice)
- option: low dose combination preparation with estradiol 0.5 mg + dydrogesterone 2.5 mg: 1 dd 1 tablet

- If transdermal estradiol (continuous progestogen)

- estradiol patch 50 microg/24 h, 2× per week replaced + dydrogesterone tablet 1 dd 10 mg (first choice)

- estradiol patch 50 microg/24 h, 2× per week replaced + progesterone tablet 100 mg 1 dd 2 for the night (second choice)

- option: low dose: estradiol patch 25 microg/24 (1/2 patch, off label) 2× per week replaced + dydrogesterone tablet 1 dd 10 mg

For women without uterus and without endometriosis, NHG 2022 advises oral estradiol oral tablet 1 dd 1 mg or transdermal estradiol, 50 microg/24h patch, 2× per week replaced.

For perimenopausal women without contraception need, NHG 2022 advises sequential progestogen oral or transdermal estradiol + for 14 days dydrogesterone 10 mg daily (first choice) or progesterone tablet 100 mg 1 dd 2 before night (second choice)

Administration forms

FR 2021 recommends that the cutaneous route of administration of estradiol should be preferred, as there is no increased venous risk associated with this route of administration (Grade B). AWMF 2020 agree that transdermal forms of estradiol are preferable given the more favorable benefit-risk ratio (no excess venous risk) (not formulated as formal recommendation).

NHG 2022 rather recommends to discuss the respective advantages and disadvantages of oral and transdermal administration of estradiol, and decide together with the woman (Low level of evidence).

In case of transdermal administration, estradiol patches are the preferred option.

Tibolone

AWMF 2020 and NHG 2022 mention that HRT is significantly more effective than tibolone against vasomotor symptoms but unregulated bleeding occurs more frequently with HRT than with tibolone.

Neither FR 2021 (Grade B) nor NHG 2022 (strong against) recommend tibolone as a first-line treatment (less favorable cardiovascular benefit-risk balance than for conventional HRT-FR 2021 or less well studied-NHG 2022).

Hormonal IUD

NHG 2022 recommends to consider hormonal IUD with 52 mg levonorgestrel in case of simultaneous symptoms of heavy menstrual bleeding (in perimenopausal women) (Low recommendation, low level of evidence) or in perimenopausal women with contraceptive desire. In this case it has to be combined with transdermal or oral estradiol.

A second option for these women is oral contraception (combination preparation). Take contraindications into account and weigh up the risk of VTE, breast cancer and cardiovascular disease, which is higher because of age. Discuss the general advice to stop hormonal contraception at the age of 52 years. If vasomotor symptoms persist, the policy for postmenopausal women applies (unless there is still a cycle).

5.1.1 AWMF 2020

Eine ET soll nur bei hysterektomierten Frauen durchgeführt werden. Eine kombinierte EPT bei nicht hysterektomierten Frauen soll eine mindestens 10-, besser 14-tägige Gestagenanwendung pro Behandlungsmonat enthalten. (Evidenzgrad LLA, Empfehlungsgrad A, Konsensusstärke ++)

For non-hysterectomised women, oestrogen-progestogen therapy (EPT) with adequate progestogen content may be considered, and for hysterectomised women, ET. (Evidence level 1a, recommendation level A, consensus strength ++)

Die Gestagengabe in einer EPT kann zyklisch oder kontinuierlich erfolgen. Auf eine mindestanwendungsdauer eines potenten Gestagens von 10 – 12 tagen pro behandlungsmonat ist zu achten. Kürzere anwendungszeiten, Progesteron-oder Dydrogesterongaben können zu endometriumhyperplasien oder –karzinomen führen.

Generell sollten transdermale applikationsformen bevorzugt werden, da sie möglicherweise ein günstigeres nutzen-risiko-verhältnis haben.

Andererseits liegt eine gute evidenz für das nutzen-risiko-verhältnis nur für die therapie mit konjugierten Östrogenen plus Medroxyprogesteronacetat vor.

Es fehlen große randomisierte boppelblindstudien, die verschiedene hormonpräparate und applikationsformen vergleichen.

Table below presents the efficacy of different interventions on vasomotor symptoms and safety according to AWMF 2020.

Tabelle 10: Wirksamkeit und Risiken verschiedener Interventionen bei Hitzewallungen

	Nutzen nachgewiesen	Nutzen möglich	Nutzen unwahrscheinlich
Geringes Risiko für Schaden bzw. Therapieabbruch	Abwarten bzw. Placebo, CBT (Achtsamkeit, kognitive und Verhaltenstherapie)	Cimicifuga 5 – 6.5 mg/d (herbal preparation), Isoflavone 30-80mg/d, inkl. Phytoöstrogen-reiche Ernährung, Rotklee, S-Equol, Genistein 30-60 mg/d, Rheum rhapontikum Akupunktur, Johanniskraut 300 mg/d	Sport (3 - 6 Monate) Tiefenentspannung (4 - 12 Wochen), Vitamin E
Mittleres Risiko für Schaden bzw. Therapieabbruch	Östrogene, Tibolon	SSRI, SNRI, Gabapentin, Clonidin	DHEA (Dehydroepian-drosteron) Raloxifen
Risiko für Schaden nicht ausreichend untersucht			Chinesische Kräuter im Rahmen der TCM, Melatonin

17β-estradiol

Unter BHT verstehen die Autoren 17β-Östradiol.

BHT reduzierte die Häufigkeit von hitzewallungen unabhängig von der dosis und Applikationsform effektiver als Placebo.

Auch niedrige Dosierungen waren wirksam. Höhere Dosierungen könnten die wirksamkeit erhöhen, waren aber mit einer höheren nebenwirkungsrate verbunden.

BHT und CEE (konjugierte equine Östrogene) schienen gleich wirksam zu sein.

Tibolon

Tibolon ist wirksamer gegen vasomotorische Beschwerden als Placebo, die HRT ist signifikant wirksamer. Unter HRT treten häufiger unregelmäßige Blutungen auf als unter Tibolon.

Tibolon reduziert klimakterische Beschwerden und vermindert den Endometriumaufbau. Auch wurde eine Verbesserung der Knochendichte beobachtet, so dass Tibolon für die Behandlung der postmenopausalen Osteoporose zugelassen ist. In einer Beobachtungsstudie war das Brustkrebsrisiko bei Tibolon-Anwendung größer als nach alleiniger Östrogengabe, aber geringer als nach Östrogen-Gestagen-Kombinationen (Beral et al., 2003). In der gleichen Studie wurde ein erhöhtes Risiko für Endometriumkarzinom durch Tibolon beobachtet (Beral et al., 2005). Die Verordnungen von Tibolon sind seit vielen Jahren kontinuierlich rückläufig (Strowitzki 2017).

Schema of administration (see also chapter on cancer risks)

Combined EPT in non-hysterectomised women should include at least 10, preferably 14 days of progestogen use per month of treatment.

Bei einer kontinuierlich kombinierten HRT mit konjugierten equinen Östrogenen und Medroxyprogesteronacetat als Gestagen mit durchschnittlich 5,6 Jahren Anwendungsdauer wurde eine Reduktion des Endometriumkarzinomrisikos beobachtet. (Evidenzgrad 2, Konsensusstärke ++)
Eine kontinuierlich-kombinierte HRT mit <5 Jahren Anwendungsdauer kann hinsichtlich des Endometriumkarzinomrisikos als sicher angesehen werden. (Evidenzgrad 2, Konsensusstärke +++)
Die sequentiell-kombinierte HRT kann das Risiko der Entstehung eines Endometriumkarzinoms erhöhen. Der Effekt ist von der Dauer, Art und Dosis der Gestagenanwendung abhängig. (Evidenzgrad 3, Konsensusstärke ++)

Die sequentiell-kombinierte HRT mit einer Anwendungsdauer unter 5 Jahren und unter Verwendung eines synthetischen Gestagens kann hinsichtlich des Endometriumkarzinomrisikos als sicher angesehen werden. (Evidenzgrad 3, Konsensusstärke +++)

Die EPT wird entweder sequentiell oder kontinuierlich kombiniert durchgeführt. Eine sequentielle EPT mit einer mindestens 10-tägigen Anwendung eines Gestagens pro Behandlungsmonat erhöhte das Endometriumkarzinomrisiko bei Anwendungszeiten von bis zu ca. 5 Jahren nicht. Eine längerfristige sequentielle EPT kann das Endometriumkarzinomrisiko erhöhen. Die Reduktion der Anwendungsdauer des Gestagens von unter 10 Tagen pro Monat erhöht das Endometriumkarzinomrisiko ebenfalls (RR 3,0-4,4).

Bei Einnahme eines Östrogens der mittleren Potenz sollten mindestens 1 mg NET bzw. 2mg Medroxyprogesteronacetat (MPA) oder ein äquivalentes Gestagen in einer kontinuierlichen Therapie eingesetzt werden, mindestens 5 mg MPA oder ein äquivalentes Gestagen in einer sequentiellen Therapie mit ausreichend langer Gestagenphase (10-14 Tage).

5.1.2 FR 2021

Different treatments

(see also chapter 5.8 on cardiovascular risks and chapter 5.9 on cancer risks)

Au total, il est recommandé de privilégier le 17bêta-estradiol ou le valérate d'estradiol associés à la progestérone ou la dydrogestérone (grade B).

Chez la femme hystérectomisée, il est recommandé d'utiliser l'estradiol ou le valérate d'estradiol seul, sans progestérone ou progestatif associé (grade B).

Globalement, l'impact métabolique et le risque thromboembolique veineux du 17-bêta estradiol et du valérate d'estradiol donné par voie orale, sont moindres par rapport aux oestrogènes conjugués équins (NP2).

Le risque TEV est également influencé par le type de progestatifs avec une absence de sur-risque avec la progestérone, la dydrogestérone, l'acétate de chlormadinone et l'acétate de médrogestone. En revanche, le risque est majoré avec l'acétate de nomégestrol et la promégestone, même en association avec l'estradiol par voie cutanée en population générale (NP2).

De plus, le type de progestatif apparaît influencer le sur-risque de cancer du sein associé aux estroprogestatifs. Quatre études de cohorte européennes rapportent un sur-risque de cancer du sein plus faible chez les utilisatrices de progestérone ou dydrogestérone pour un traitement de 5 ans ou moins qu'avec les associations avec un progestatif de synthèse (NP2).

Le risque de cancer de l'endomètre est majoré avec les estrogènes seuls, ce risque étant annulé par l'addition du progestatif. La progestérone serait associée à une protection endométriale moindre que la dydrogestérone et les autres progestatifs de synthèse (NP3)

La tibolone n'est pas recommandée en première intention du fait d'une balance bénéfices-risques moins favorable que pour le THM classique sur le plan cardiovasculaire (grade B).

La tibolone apparaît moins efficace que le traitement hormonal combiné pour le contrôle des symptômes climatiques dans les études comparatives (NP1).

Certains essais suggèrent une meilleure efficacité sur la qualité de vie sexuelle et la libido par rapport au traitement hormonal classique (NP2).

La tibolone diminue de manière significative la perte osseuse densitométrique par rapport au placebo (NP1).

Il n'a pas été montré d'augmentation du risque d'infarctus du myocarde dans les essais sur la tibolone, tout en prenant en compte la faible incidence des événements (NP2). En revanche, une augmentation du risque d'accident vasculaire cérébral a été retrouvée chez les femmes de plus de 60 ans traitées par tibolone 1,25 mg par rapport au placebo.

Dans les deux essais randomisés LIFT et LIBERATE, la tibolone n'est pas associée à un sur-risque de MVTE par rapport au placebo, tout en prenant en compte la très faible incidence de ces événements dans ces deux essais (NP2), ce qui avait conduit à l'arrêt prématuré de cet essai.

Pour les femmes indemnes, le traitement par tibolone est associé à un sur-risque de cancer du sein comparable à celui du traitement hormonal de ménopause dans différentes études de cohorte (NP2).

Une étude randomisée chez des femmes en début de ménopause (étude THEBES) ne montre pas de différence concernant les cas d'hyperplasie endométriale ou de cancer de l'endomètre par rapport au traitement hormonal combiné par voie orale (NP2). Dans l'étude LIFT, chez des femmes âgées de plus de 60 ans il existe une augmentation du risque de cancer de l'endomètre chez les femmes traitées par tibolone en comparaison au placebo (NP1).

Route of administration

(see also chapter 5.8 on cardiovascular risks)

Au total, il est recommandé de privilégier la voie cutanée de l'estradiol en raison de l'absence de sur-risque veineux associé à cette voie d'administration (grade B).

Il existe un risque veineux lié à la prise des oestrogènes (toutes molécules) par voie orale lié au 1er passage hépatique (NP1). Au contraire, cet effet de 1er passage hépatique est très limité avec la voie cutanée de l'estradiol (aux doses utilisées dans le THM) et il n'a pas été montré de sur-risque veineux associé à une prise d'estradiol par voie cutanée en population générale (NP2).

Schema of administration

(see also chapter 5.9 on cancer risks)

Pour limiter le sur-risque de cancer du sein attribuable au traitement hormonal de la ménopause, il est recommandé de privilégier l'association des estrogènes avec la progestérone ou la dydrogestérone chez les femmes non hystérectomisées (grade B).

En cas d'hystérectomie, il n'y a pas de bénéfice mammaire à associer la progestérone ou un progestatif à l'estradiol (grade A).

Il est recommandé d'associer un progestatif pour la prévention du cancer de l'endomètre induit par les estrogènes (grade A) ; la durée recommandée de prise d'un progestatif dans les THM séquentiels doit être au minimum de 12 jours par mois (grade B) ou au mieux selon un schéma combiné (grade A).

Au total, il n'est pas possible de recommander un schéma thérapeutique particulier comme étant associé à la balance bénéfices-risques la plus favorable (grade B).

Un schéma combiné continu est à privilégier en cas de survenue de bouffées vasomotrices lors de la période d'arrêt, de symptômes liés aux variations hormonales (migraines) ou de difficultés d'observance d'un schéma séquentiel (avis d'expert).

Le choix entre schéma séquentiel ou combiné doit tenir compte du souhait de la patiente d'avoir ou non des héorragies de privation.

Le schéma d'administration le plus classiquement utilisé est le schéma combiné en raison de sa supériorité concernant le risque endométrial (NP1) et de la volonté de la plupart des patientes d'une absence d'hémorragie de privation (NP3).

Figure below shows the different HRT regimen as proposed by FR 2021

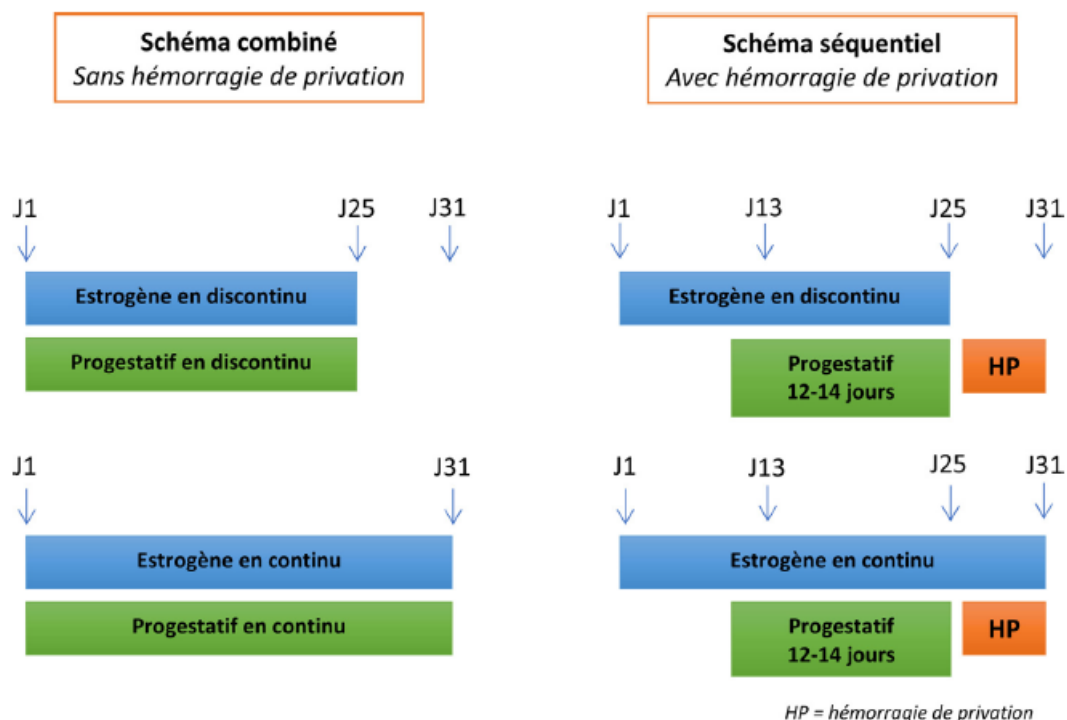


Fig. 1. Principaux schémas thérapeutiques combiné (continu ou discontinu) et séquentiel (continu ou discontinu).

Pour un schéma séquentiel, il est recommandé d'associer une dose de 200 mg de progestérone naturelle ou de 20 mg de dydrogestérone par jour pendant au moins 12 jours (grade B).

Pour un schéma combiné, il est possible d'utiliser la dose minimale de progestérone naturelle de 100 mg ou de 10 mg de dydrogestérone par jour à adapter à la dose d'estradiol et à la tolérance endométriale (grade B).

Chez les femmes hystérectomisées, il est recommandé d'utiliser les oestrogènes seuls (grade A)

Le traitement hormonal de la ménopause peut être initié à une dose minimale et doit par la suite être adapté au profil de la patiente, sa tolérance et son efficacité (avis d'expert).

Les doses d'oestrogènes standards sont :

- 17-bêta estradiol par voie orale : 2 mg/j
- 17-bêta estradiol par voie transdermique : 50 mg/j
- 17-bêta estradiol par voie percutanée : 1,5 mg/j.

Il existe un effet-dose des oestrogènes sur la plupart des tissus avec une hiérarchie de la sensibilité tissulaire des estrogènes, le sein, l'endomètre et le tissu osseux étant les plus estrogéno-dépendants. L'efficacité du THM sur les symptômes climatiques est également dose-dépendante.

5.1.3 NHG 2022

Oral estrogen

Het voordeel van hormoontherapie (oestrogeen, al dan niet gecombineerd met progestageen) is dat deze waarschijnlijk vasomotorische overgangsklachten (opvliegers en nachtelijke zweetaanvallen) vermindert en de kwaliteit van leven verbetert. Dit effect is iets sterker bij de dosering van 1 mg oraal estradiol per dag (of equivalent), maar ook bij de lagere dosering van 0,5 mg oraal estradiol per dag is het effect mogelijk nog klinisch relevant.

Transdermal estradiol

Bespreek de respectievelijke voor- en nadelen van orale en transdermale toediening van estradiol, en maak samen met de vrouw de keuze. (Low level of evidence)

- Er lijkt geen verschil in effectiviteit te zijn tussen orale en transdermale toediening
- Mogelijk is het risico op VTE lager bij transdermale toediening, maar robuust bewijs hiervoor ontbreekt vooralsnog.
- Er lijken geen relevante verschillen te zijn in andere ernstige bijwerkingen.
- Progestagenen zijn niet beschikbaar in transdermale vorm. Mogelijk zijn gebruiksgemak en therapietrouw bij een oraal combinatiepreparaat hoger dan bij een combinatie van transdermaal estradiol met oraal progestageen.
- Transdermale toediening kan specifieke bijwerkingen veroorzaken, zoals huidirritatie.

De kwaliteit van bewijs was laag tot zeer laag.

Preferred transdermal estradiol

- **Estradiolpleisters hebben de voorkeur.**
- Andere toedieningsvormen, zoals transdermale estradiolgel of estradiolspray, zijn beperkt onderzocht.

De in "Estradiol oraal of transdermaal" beschreven onderzoeken zijn voornamelijk uitgevoerd met estradiolpleisters. Of de bevindingen ook gelden voor andere transdermale toedieningsvormen (gel, spray) is niet duidelijk. Er is geen direct vergelijkend onderzoek gevonden naar de klinische effectiviteit tussen deze verschillende toedieningsvormen. Op basis van farmacokinetische gegevens worden met de gel globaal wat hogere en met de spray wat lagere serumspiegels bereikt dan met een estradiolpleister 50 microg:

- estradiol pleister 50 microg: gemiddelde estradiolconcentratie 44-55 pg/ml
- estradiol gel, applicatie met 1,5 mg estradiol, 2 applicaties: gemiddelde estradiolconcentratie 68,1 pg/ml. Geen informatie over 1 applicatie

- estradiol spray: gemiddelde estradiolconcentratie 17,8 pg/ml (1 spray), 28,2 pg/ml (2 sprays), 29,5 pg/ml (3 sprays)

Monotherapy estradiol or combination therapy estradiol with progestogen

(see also chapter 5.8 on cardiovascular risks and chapter 5.9 on cancer risks)

- Geef vrouwen met uterus combinatietherapie, ter vermindering van het risico op endometriumcarcinoom.
- Geef vrouwen zonder uterus en zonder endometriose monotherapie estradiol.
- Geef vrouwen zonder uterus, maar met endometriose, ook combinatietherapie.

Om het risico op endometriumcarcinoom te verminderen is bij vrouwen met uterus toevoeging van een progestageen aan oestrogeen noodzakelijk.

Hormoontherapie kan endometriose beïnvloeden. Oestrogeen monotherapie wordt ontraden bij postmenopauzale vrouwen met uterusextirpatie en endometriose in de voorgeschiedenis.

Type of progestogen

(see also chapter 5.8 on cardiovascular risks and chapter 5.9 on cancer risks)

- Dydrogesteron heeft de voorkeur omdat dit het kleinste risico op ernstige bijwerkingen geeft.
- Progesteron is tweede keuze.
- Overweeg bij gelijktijdige klachten van hevig menstrueel bloedverlies (bij perimenopauzale vrouwen) de hormoonspiraal met 52 mg levonorgestrel. Voor toepassing van de hormoonspiraal bij perimenopauzale vrouwen met anticonceptiewens zie perimenopauzale vrouwen met anticonceptiewens.

(Low recommendation, low level of evidence)

Van de in Nederland verkrijgbare progestagenen die voor endometriumprotectie kunnen worden gecombineerd met oestrogeen, lijkt dydrogesteron over het geheel van de onderzochte ernstige bijwerkingen het gunstigst, gevolgd door progesteron. De kosten van progesteron zijn wel hoger dan die van andere progestagenen.

Bovenstaande overwegingen maken dat de werkgroep een voorkeur heeft voor dydrogesteron. Als tweede keuze kan progesteron overwogen worden.

Alleen bij gelijktijdige klachten van hevig menstrueel bloedverlies (bij perimenopauzale vrouwen) kan de hormoonspiraal met levonorgestrel overwogen worden (zie NHG-Standaard Vaginaal bloedverlies). Deze geeft mogelijk een verhoogd risico op borstkanker.

De kwaliteit van bewijs is laag tot zeer laag.

Continuous or sequential progestogen

- Bij postmenopauzale vrouwen heeft continue (dagelijkse) toediening van progestageen de voorkeur. De eerste maanden is er kans op onregelmatig bloedverlies en spotting, maar doorgaans blijft bloedverlies op termijn achterwege bij continu gebruik.
- Bij perimenopauzale vrouwen geeft sequentiële toediening van progestageen (14 dagen per maand) maandelijks een onttrekkingsbloeding en geeft continue (dagelijkse) toediening van progestageen frequent en langdurig bloedverlies. Daarom ligt sequentiële

toediening voor deze groep het meest voor de hand. Overigens is hormoontherapie offlabel bij vrouwen bij wie de laatste menstruatie <6 maanden geleden is.

- **Bij vrouwen zonder uterus, maar met endometriose, ongeacht menopauzale status, heeft continue toediening van progestageen de voorkeur.**

Bij continue gecombineerde hormoontherapie zal gemiddeld na 3 tot 8 maanden een atrofisch endometrium ontstaan. Bij 12 tot 22% van de vrouwen die continue combinatietherapie gebruikten trad onregelmatig bloedverlies op bij gebruik gedurende een jaar.

Perimenopausal women with contraceptive desire

- **Hormoontherapie voor overgangsklachten heeft onvoldoende anticonceptieve werking.**
- **Bij vasomotorische klachten én anticonceptiewens zijn er 2 opties:**
 - **hormoonspiraal met 52 mg levonorgestrel in combinatie met transdermaal of oraal estradiol**
 - **orale anticonceptie (combinatiepreparaat)**
- **Houd bij de keuze rekening met contra-indicaties en weeg hierbij het vanwege de leeftijd hogere uitgangrisico op VTE, borstkanker en hart- en vaatziekten mee (zie NHG-Standaard Anticonceptie).**
- **Bespreek bij keuze voor orale anticonceptie het algemene advies om op de leeftijd van 52 jaar te stoppen met hormonale anticonceptie (zie NHG-Standaard Anticonceptie). Vanaf deze leeftijd geldt bij aanhoudende vasomotorische klachten het beleid voor postmenopauzale vrouwen (tenzij er nog een cyclus is).**

De werkgroep is van mening dat estradiol in combinatie met een hormoonspiraal overwogen kan worden bij perimenopauzale vrouwen met anticonceptiewens en hinderlijke vasomotorische klachten.

- *Estradiol in combination with a hormone IUD*

Voordelen: de hormoonspiraal met estradiol (oraal of transdermaal) is een vorm van continue combinatietherapie met anticonceptieve werking. De combinatie hormoonspiraal en transdermaal estradiol kan eventueel gebruikt worden na een gastric bypass.

Nadelen: continue combinatietherapie kan langdurig (3-12 maanden) onregelmatig bloedverlies of spotting veroorzaken. Mogelijk verhoogt estradiol in combinatie met een hormoonspiraal als vorm van continue combinatietherapie het risico op borstkanker. Onbekend is in welke mate gebruik van estradiol in combinatie met een hormoonspiraal als vorm van continue combinatietherapie het risico op VTE en hart- en vaatziekten verhoogt. De gebruikstermijn van een hormoonspiraal als progestageenadjuvans > 3 jaar is in Nederland offlabel.

Het advies is (vooralsnog) de hormoonspiraal te vervangen na die termijn.

- *Oral contraception (combination preparations)*

Voordelen: anticonceptieve werking. Het effect op opvliegers en/of aanvallen van nachtzweeten is nauwelijks onderzocht, een gunstig effect is wel aannemelijk. Gebruik leidt in de regel na 3 maanden tot gereguleerd, voorspelbaar bloedverlies.

Nadelen: mogelijk vasomotorische klachten tijdens de stopweek. Gebruik verhoogt het risico op VTE, hart- en vaatziekten en borstkanker. Bij vrouwen rond de menopauze of bij contra-indicaties is het

absolute risico mogelijk groter. Gebruik voor vasomotorische klachten alleen is offlabel. Het continueren van hormonale anticonceptie (combinatiepreparaten) na de leeftijd van 52 jaar voor overgangsklachten alleen wordt ontraden (zie [NHG-Standaard Anticonceptie](#)).

Vergelijkend onderzoek werd niet gevonden. Er is nauwelijks onderzoek gedaan naar estradiol in combinatie met een hormoonspiraal ter behandeling van vasomotorische klachten en naar gebruik van hormonale anticonceptie (combinatiepreparaten) voor deze indicatie.

Treatment options

Table below presents the different treatment options depending on women menopausal status and her wishes

Perimenopauzaal, geen anticonceptiewens	Combinatietherapie estradiol met progestageen sequentieel (onttrekkingsbloeding maandelijks)	
	Estradiol oraal	Combinatiepreparaat (kalenderverpakking met 14 tabletten met estradiol 1 mg en 14 tabletten met estradiol 1 mg + dydrogesteron 10 mg): 1 dd 1 tablet
		Tweede keuze: estradiol tablet 1 dd 1 mg + gedurende 14 opeenvolgende dagen per maand progesteron tablet 100 mg 1 dd 2 voor de nacht
	Estradiol transdermaal	Estradiol pleister 50 microg/24 uur 2 x per week vervangen*+ gedurende 14 opeenvolgende dagen per maand dydrogesteron tablet 1 dd 10 mg
		Tweede keuze: estradiol pleister 50 microg/24 uur 2 x per week vervangen*+ gedurende 14 opeenvolgende dagen per maand progesteron tablet 100 mg 1 dd 2 voor de nacht
	Combinatietherapie estradiol met hormoonspiraal (bij gelijktijdige klachten van hevig bloedverlies)	
Perimenopauzaal met anticonceptiewens	Zie Perimenopauzaal met anticonceptiewens	
	Combinatietherapie estradiol met hormoonspiraal	
	Estradiol oraal	Estradiol tablet 1 dd 1 mg + hormoonspiraal 52 mg levonorgestrel [†]
	Estradiol transdermaal	Estradiol pleister 50 microg/24 uur, 2 x per week vervangen*+ hormoonspiraal 52 mg levonorgestrel [†]
	Orale anticonceptie (combinatiepreparaat)*	
Postmenopauzaal	Zie NHG-Standaard Anticonceptie voor voorkeursmiddelen	
	Combinatietherapie estradiol met progestageen continu (bloedverlies op termijn afwezig)	
	Estradiol oraal	Combinatiepreparaat met estradiol 1 mg + dydrogesteron 5 mg: 1dd 1 tablet
		Tweede keuze: estradiol tablet 1 dd 1 mg + progesteron tablet 100 mg 1 dd 2 voor de nacht
		Optie lage dosering: [‡] combinatiepreparaat met estradiol 0,5 mg + dydrogesteron 2,5 mg: 1 dd 1 tablet
	Estradiol transdermaal	Estradiol pleister 50 microg/24 uur, 2 x per week vervangen*+ dydrogesteron tablet 1 dd 10 mg
		Tweede keuze: estradiol pleister 50 microg/24 uur, 2 x per week vervangen*+ progesteron tablet 100 mg 1 dd 2 voor de nacht
		Optie lage dosering: [‡] estradiol pleister 25 microg/24 uur (= halve pleister, offlabel), 2 x per week vervangen* + dydrogesteron tablet 1 dd 10 mg
Na uterusextirpatie (zonder endometriose)	Monotherapie estradiol	
	Estradiol oraal	Estradiol tablet 1 dd 1 mg
	Estradiol transdermaal	Estradiol pleister 50 microg/24 uur, 2 x per week vervangen*
Na uterusextirpatie (met endometriose)	Combinatietherapie estradiol met progestageen continu	
	Zie Postmenopauzaal	

* Pleister op droge, onbeschadigde huid plakken: buik, bovenbeen, bil, lage rugstreek, niet borsten. Toedieningsplaats afwisselen. Pleister mag nat worden, tijdens douchen, baden. Huiddeel met pleister niet blootstellen aan direct zonlicht.

[†] Gebruikstermijn voor deze indicatie 3 jaar. Zie [NHG-Standaard Anticonceptie](#) voor meer informatie over de hormoonspiraal.

[‡] Houd rekening met contra-indicaties en weeg hierbij het vanwege de leeftijd hogere uitgangrisico op VTE, borstkanker en hart- en vaatziekten mee (zie [NHG-Standaard Anticonceptie](#)). Bespreek bij keuze voor orale anticonceptie het algemene advies om op de leeftijd van 52 jaar te stoppen met hormonale anticonceptie. Vanaf deze leeftijd geldt bij aanhoudende vasomotorische klachten het beleid voor postmenopauzale vrouwen (tenzij er nog een cyclus is).

[§] Als de vrouw hierom vraagt.

5.1.4 NICE upd 2019

No specific recommendations or comments were provided regarding the different hormonal treatments in this guideline.

5.1.5 USPSTF 2022

Menopausal hormone therapy refers to the use of combined estrogen and progestin in persons with an intact uterus, or estrogen alone in persons who have had a hysterectomy, taken at or after the time of menopause. For this recommendation, the USPSTF considered evidence on the benefits and harms of systemic (ie, oral or transdermal) menopausal hormone therapy but not local formulations of hormone therapy, because these are not generally used for the primary prevention of chronic conditions.

Currently, evidence to determine whether different types, doses, or modes of delivery of hormone therapy affect its benefit-to-harm profile for the prevention of chronic conditions is limited.

...the USPSTF concludes that overall, both estrogen plus progestin and estrogen alone have no net benefit for the primary prevention of chronic conditions.

5.2 Treatment of menopausal symptoms

Vasomotor symptoms

AWMF 2020, FR 2021, NHG 2022 and NICE upd 2019 all recommend to offer HRT to women with VMS. They also specify to inform women and discuss the short- (up to 5 years) and long-term benefits and risks of HRT. (strong recommendations for all except NHG 2022: Low recommendation, low level of evidence)

Both AWMF 2020 and NICE upd 2019 recommend to not routinely offer serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line agents for VMS. According to AWMF 2020, gabapentin should not be routinely offered either. (strong recommendations)

According to FR 2021 serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, clonidine, gabapentin, genistein, yoga and hypnosis have been shown to be somewhat effective and can be proposed for the management of menopausal VMS (Grade B).

Genitourinary symptoms

(see also chapter 5.11 on phytotherapies and non-pharmacological treatments for recommendations about lubricants)

AWMF 2020, FR 2021, NHG 2022 and NICE upd 2019 all specify that low-dose systemic HRT does not always have a sufficient effect on the vaginal epithelium and that additional local therapy may be necessary. (strong recommendations)

FR 2021 recommends local vaginal treatment as 1st-line treatment for the management of genitourinary symptoms (Grade A). Lubricants and moisturizers are recommended 1-st, followed by low-dose vaginal hormone treatment as 2nd-line treatment (FR 2021, expert opinion). Low doses vaginal ET are effective against all genitourinary symptoms (FR 2021).

For urogenital atrophy, AWSM 2020, NHG 2022 and NICE upd 2019 recommend to offer women with symptomatic urogenital atrophy lubricants alone or together with vaginal ET.

AWMF 2020 recommend to use the therapy as long as necessary. (strong recommendations for all except NHG 2022: Low recommendation, low level of evidence)

According to NICE upd 2019 vaginal ET are to be considered for women in whom systemic HRT is contraindicated. However according to NHG 2022 the contraindications for vaginal ET are the same as for systemic ET.

AWMF 2020 also recommends to offer vaginal ET specifically for postmenopausal patients with urinary incontinence (with pelvic floor muscle training) (level of evidence 1a, recommendation grade A, consensus strength ++) and for overactive bladder (level of evidence 1b, consensus strength +++).

According to AWMF 2020, if urological disease has been ruled out in urge symptomatology, local ET can be offered. Micturition frequency and urge symptoms can be reduced (level of evidence 1b, recommendation grade 0, consensus strength ++).

In recurrent cystitis in postmenopausal women, vaginal ET should be performed before starting long-term antibiotic prevention (AWMF 2020) (level of evidence 2a, recommendation grade B, consensus strength ++).

Concerning sexual symptoms, AWMF 2020 adds that dyspareunia also affects other dimensions of experience such as libido, arousal and orgasm. Advice should be given on local treatment options but if women raise other sexual problems, a psychosexual exploration should be conducted.

If vaginal ET are used:

According to AWMF 2020:

- Preparations containing oestriol are to be preferred.
- When estradiol is applied vaginally, 0.1 mg per gram is supplied with the cream, which can lead to relevant systemically effective estradiol levels. These high dosages are to be avoided.
- There is no evidence that vaginal ET leads to endometrial hyperplasia. A combination with progestogens, is therefore not recommended (not formulated as formal recommendations).

According to NHG 2022, there are 2 equivalent choices:

- Estriol vaginal ovules or cream 1 dd 0.5 mg for 2 weeks. Then switch to 0.5 mg 2× per week.
- Or estradiol tablet for vaginal use 1 dd 10 microg. After 2 weeks, decrease to a maximum of 10 micrograms 2× per week

According to AWMF 2020 and NICE upd 2019 a dose increase may be considered if there is no improvement. (formal recommendation for NICE upd 2019 only)

Concerning oral, transdermal or vaginal testosterone:

FR 2021 mentions that given the current lack of evidence, these treatments are not recommended for the management of genitourinary symptoms (NP3).

Both AWMF 2020 (level of evidence 1b, recommendation grade 0, consensus strength ++) and NICE upd 2019 recommend to consider testosterone therapy in women with libido loss in the peri- and postmenopause, after psychosexual exploration and if HRT is not effective. Patients should be made aware that it concerns off-label use of testosterone.

Concerning vaginal DHEA:

FR 2021 mentions that EMA issued a favourable opinion for a marketing authorization for vaginal prasterone in the treatment of the genitourinary symptoms and that this product is effective in treating these symptoms (NP2). Vaginal prasterone can be offered to symptomatic patients but oral or transdermal DHEA is not recommended due to a low level of evidence (NP3).

Concerning oral tibolone:

FR 2021 mentions that data concerning the value of oral tibolone in the management of genitourinary symptoms are limited and of low level of evidence (NP3).

Women with cancer or with a history of cancer

See recommendations formulated in chapter 5.9 on the risks of cancer.

5.2.1 AWMF 2020

5.2.1.1 *Vasomotor symptoms*

Frauen mit vasomotorischen Beschwerden soll eine HRT angeboten werden, nachdem sie über die kurz- (bis zu 5 Jahren) und langfristigen Nutzen und Risiken informiert wurden. Für nichthysterektomierte Frauen kommt eine Östrogen-Gestagen-Therapie (EPT) mit adäquatem Gestagenanteil, für hysterektomierte Frauen eine ET in Betracht. (Evidenzgrad 1a, Empfehlungsgrad A, Konsensusstärke ++)

Serotonin-Wiederaufnahmehemmer (SSRIs), Serotonin-Noradrenalin-Wiederaufnahmehemmer (SNRIs), Clonidin und Gabapentin sollen nicht routinemäßig als Mittel erster Wahl gegen vasomotorische Symptome angeboten werden. (Evidenzgrad 3, Empfehlungsgrad A, Konsensusstärke ++)

Für nicht hysterektomierte Frauen ist eine Östrogen/Gestagentherapie (EPT) die effektivste Behandlung vasomotorischer Beschwerden. Darüber sollen Frauen aufgeklärt werden. Insbesondere bei erheblichen Beschwerden, die als belastend oder die Alltagsfunktionen beeinträchtigend erlebt werden, soll die HRT empfohlen werden.

Bei hysterektomierten Frauen kann eine Monotherapie mit Östrogenen (ET) durchgeführt werden.

5.2.1.2 *Genitourinary symptoms*

Sexual symptoms

Bei Frauen mit Libidoverlust in der peri- und Postmenopause kann nach psychosexueller Exploration ggf. eine Testosterontherapie erwogen werden, wenn eine HRT nicht wirksam ist. Auf den off-label-use soll hingewiesen werden. (Evidenzgrad 1b, Empfehlungsgrad 0, Konsensusstärke ++)

Bei peri- und postmenopausalen Frauen kann es zu Veränderung sexueller Funktionen kommen. In Beratungsgesprächen soll Frauen die Möglichkeit gegeben werden, über sexuelle Probleme zu sprechen. Es sollte erfragt werden, ob Scheidentrockenheit vorhanden ist und diese zu Beschwerden führt. Dyspareunien wirken sich auch auf andere Erlebensdimensionen wie Libido, Erregungs- und Orgasmusfähigkeit aus. Über die lokalen Behandlungsmöglichkeiten mit Lubrikans und hormonhaltigen Zubereitungen soll beraten werden. Wenn Frauen weitere sexuelle Probleme ansprechen, sollte eine psychosexuelle Exploration durchgeführt werden. Nachlassende Libido ist eine häufige Begleiterscheinung des Alterwerdens. Sinkende Östrogen- und Testosteronspiegel können dazu beitragen. Ein Testosteronmangel kann bei Frauen, deren Eierstöcke operativ entfernt wurden, ausgeprägter sein. Oft verbirgt sich hinter Libidoverlust ein komplexes Geflecht von Beziehungs-, Selbstwert-, gesundheitlichen und soziokulturellen Aspekten.

Urogenital atrophy

Frauen mit symptomatischer urogenitaler Atrophie soll die Anwendung von Befeuchtungs-, Gleitmitteln alleine oder zusammen mit einer vaginalen ET angeboten werden. Die Therapie kann so lange wie erforderlich angewendet werden. (Evidenzgrad 1b, Empfehlungsgrad A, Konsensusstärke +++)

In einer aktuellen Studie hat sich kein signifikanter Unterschied zwischen vaginaler

Östrogentablette (10 µg) plus Placebo-Gel, vaginaler Placebotablette plus speziellem Vaginalgleitmittel sowie vaginaler Placebotablette plus Placebo-Gel gezeigt.

Jede Form der Behandlung hat vulvovaginale Beschwerden wie Juckreiz, Schmerzen, Trockenheit, Irritation oder Schmerzen bei Penetration gelindert, auch unabhängig davon, dass nur die Östrogenbehandlung einen Einfluss auf den Reifungsindex der Vaginalepithelzellen und auf den pH-Wert hatte.

Frauen sollen ihrer Vorliebe entsprechend behandelt werden.

- *If using vaginal estrogen*

Wenn Östrogene vaginal angewendet werden, sind Östriol-haltige Präparate zu bevorzugen. Bei der vaginal-topischen Anwendung von Östradiol werden mit der Creme pro Gramm 0,1 mg zugeführt, die zu relevanten systemisch wirksamen Östradiolspiegeln führen können. Diese hohen Dosierungen sind zu vermeiden.

Aus klinischen Untersuchungen liegen keine Hinweise dafür vor, dass eine vaginale ET zu Endometriumhyperplasien führt. Eine Kombination mit Gestagenen, die bei systemischen ETs durchgeführt werden soll, wird daher nicht empfohlen.

Langzeitergebnisse (>1 Jahr) zur endometrialen Sicherheit der vaginalen ET liegen allerdings nicht vor (NAMS Position Statements 2013 und 2017).

Frauen mit lokaler ET wegen Beschwerden durch urogenitale Atrophie soll erklärt werden,

- dass bei ausbleibender Besserung eine Dosisanhebung erwogen werden kann
- dass eine niedrig dosierte systemische HRT nicht immer einen ausreichenden Effekt auf das Vaginalepithel hat und ggf. eine zusätzliche Lokaltherapie notwendig sein kann
- dass die Symptome häufig wiederkehren, wenn die Behandlung beendet wird
- dass Nebenwirkungen einer lokalen Östriolbehandlung sehr selten sind
- dass sie sich bei ihrem Frauenarzt* vorstellen sollen, wenn vaginale Blutungen auftreten

For use of vaginal ET for women with/after cancer see chapter 5.9 on the cancer risks

Stress urinary incontinence and overactive bladder

Eine vaginale ET kann eine Harninkontinenz bei postmenopausalen Frauen verbessern.

(Evidenzgrad 1a, Konsensusstärke ++)

Eine vaginale ET verbessert dagegen bei postmenopausalen Patientinnen vaginale Beschwerden und Symptome des unteren Harntraktes unabhängig davon, ob eine Atrophie der Vaginalhaut vorliegt.

Patientinnen sollen vor einer systemischen ET/EPT darüber informiert werden, dass diese zum Auftreten oder zur Verschlechterung einer Harninkontinenz führen kann. (Evidenzgrad 1a, Empfehlungsgrad A, Konsensusstärke ++)

Postmenopausalen Patientinnen mit Harninkontinenz sollen Beckenbodentraining und eine vaginale ET angeboten werden. (Evidenzgrad 1a, Empfehlungsgrad A, Konsensusstärke ++)

Eine vaginale ET kann bei überaktiver Blase (OAB) angeboten werden. (Evidenzgrad 1b, Konsensusstärke +++)

Wenn bei einer Drangsymptomatik urologische Erkrankungen ausgeschlossen wurden, kann eine lokale ET angeboten werden. Miktionsfrequenz und Drangsymptomatik können reduziert werden. (Evidenzgrad 1b, Empfehlungsgrad 0, Konsensusstärke ++)

Die Rolle der Östrogene bei der überaktiven Harnblase (OAB) ist ungeklärt. In Kombination mit Antimuskarinika scheint ein positiver Effekt zu bestehen. Miktionsfrequenz und Drangsymptomatik waren reduziert.

Recurrent urinary tract infections

Die Veränderung des Vaginalmilieus postmenopausaler Frauen disponiert zu Harnwegsinfektionen.

Es besteht eine positive Korrelation mit höherem Alter. (Evidenzgrad 2b, Konsensusstärke ++)

Bei rezidivierenden Zystitiden postmenopausaler Frauen sollte vor Beginn einer antibiotischen Langzeitprävention eine vaginale ET durchgeführt werden. (Evidenzgrad 2a, Empfehlungsgrad B, Konsensusstärke ++)

5.2.2 FR 2021

5.2.2.1 Vasomotor symptoms

Les troubles climatériques incluent les bouffées vasomotrices (BVM) et les sueurs nocturnes, les troubles du sommeil, les troubles de l'humeur, les douleurs ostéoarticulaires et le syndrome génito-urinaire de la ménopause (SGUM). Les BVM sont très fréquentes, affectant environ 80 % des femmes occidentales ménopausées, dont 25 % de façon très invalidante. Elles durent en moyenne 5 à 7 ans mais peuvent perdurer au-delà de 15 ans.

Pour corriger les bouffées vasomotrices, en fonction de leur intensité et de leur fréquence et en l'absence de contre-indication, il est recommandé de proposer la prise d'un THM en 1ère intention (grade A).

Les inhibiteurs de la recapture de la sérotonine, les inhibiteurs de la recapture de la sérotonine et de la noradrénaline, la clonidine, la gabapentine, la génistéine, le yoga et l'hypnose ont fait la preuve d'une certaine efficacité et peuvent être proposés pour la prise en charge des BVM de la ménopause (grade B).

Toutes les molécules à activité estrogénique sont efficaces pour diminuer la fréquence et l'intensité des BVM, quelle que soit la voie d'administration, cutanée ou orale (NP1).

L'efficacité est dose-dépendante comme sur la plupart des tissus avec une hiérarchie de la sensibilité tissulaire des estrogènes, le sein, l'endomètre et le tissu osseux étant les plus estrogéno-dépendants (NP1).

Toutes les doses d'estrogènes, y compris les faibles doses et tous les types de schéma thérapeutique (combiné ou séquentiel, continu ou discontinu) sont efficaces sur la fréquence et l'intensité des BVM (NP1).

5.2.2.2 Genitourinary symptoms

Sa prévalence varie selon les études de 27 % à 70 % et il associe trois types de symptômes :

- les symptômes vulvovaginaux : sécheresse, douleurs, brûlures, irritation, prurit
- les symptômes sexuels : c'est essentiellement la dyspareunie d'intromission, par manque de lubrification et parfois sténose orificielle
- les symptômes urinaires qui peuvent associer la pollakiurie, les urgences mictionnelles, les infections urinaires à répétition (brûlures urinaires).

Les symptômes cliniques du SGUM altèrent la qualité de vie et s'aggravent en fonction de l'âge, de la durée de la ménopause, mais diminuent lorsque la fréquence des rapports sexuels augmente. Les examens complémentaires (pH, biopsie de la muqueuse, évaluation du microbiote, etc.) ne sont pas utiles au diagnostic du SGUM (NP2).

Pour la prise en charge du SGUM, le traitement local par voie vaginale est recommandé en 1ère intention (grade A).

Pour la prise en charge du SGUM, il est recommandé de prescrire lubrifiants et hydratants en 1ère intention et de prendre le relais avec un traitement hormonal vaginal à faible dose en 2ème intention en fonction de l'évolution clinique (avis d'expert).

Dans l'attente d'une évaluation plus complète, il n'est pas recommandé d'utiliser un laser en 1ère intention pour la prise en charge des symptômes du SGUM (grade C).

Vaginal estrogen

La méta-analyse de Cody et al. en 2012 montre en parallèle de l'amélioration des symptômes liés à l'atrophie vulvaire une amélioration significative des signes d'hyperactivité vésicale et de l'incontinence urinaire par urgenturie après traitement par oestrogènes locaux en comparaison avec un placebo (ces données sont également basées sur des études de faible niveau de preuve). Plusieurs essais contrôlés randomisés contre placebo ont confirmé l'amélioration significative de la sécheresse vaginale et dyspareunie après application d'oestradiol faible dose (15 mg 2 fois par semaine).

Concernant la dose, l'efficacité de l'oestrogénothérapie locale sur les symptômes du SGUM a été démontrée lors de l'application de faibles doses, c'est-à-dire lors de l'application d'un anneau vaginal de 7,5 mg, d'ovule vaginal d'oestradiol à 10 mg et d'estriol 0,03 mg.

La prescription d'oestradiol par voie vaginale faible dose montre une augmentation des taux d'oestrogènes plasmatiques à l'initiation du traitement suivi d'une diminution rapide, restant en dessous des seuils habituels de la ménopause. Les données pharmacologiques concernant le promestriène ne sont pas décrites. Lors de la poursuite du traitement les dosages sont comparables à ceux habituellement retrouvés lors de la ménopause.

Il n'existe pas de données concernant l'utilisation d'oestrogènes locaux chez les femmes à risque thromboembolique.

La méta-analyse de 2016 de Lethaby et al. retrouve, quels que soient le type de produit et le mode d'administration, une efficacité significative des oestrogènes par voie vaginale contre placebo pour l'amélioration des symptômes du SGUM (NP2).

La North American Menopause Society (NAMS) et l'American College of Obstetrician and Gynecologist (ACOG) et l'EMAS ont déclaré l'oestrogénothérapie locale préférable à la thérapie systémique par oestrogènes en raison de son innocuité et de son efficacité. Les oestrogènes utilisés par voie locale à faible dose sont efficaces sur l'ensemble des symptômes du SGUM (NP2).

Lorsque le traitement est prescrit à faible dose il n'y a pas d'hyperplasie endométriale ni de carcinome de l'endomètre décrits à 52 semaines. D'après l'EMAS et la NAMS il n'y a donc pas d'indication de protection de l'endomètre par adjonction de progestérone lors de la prescription d'oestrogènes vaginaux à faible dose. Il n'y a cependant pas de données concernant l'impact sur l'endomètre au-delà d'un an.

Les données de tolérance à 1 an ne montrent pas d'effet indésirable important mais les données disponibles actuellement ne permettent pas de conclure pour les traitements de longue durée (NP2).

Vaginal DHEA

... ces traitements ont montré à partir d'une dose de 6,5 mg/jour une efficacité supérieure au placebo sur les paramètres cliniques de l'atrophie, sur la dyspareunie, et les critères intermédiaires (pH, IMV). Les effets apparaissent dès deux semaines de traitement.

D'autres études randomisées ont montré une efficacité significative de la DHEA contre placebo dans le cadre de la dysfonction sexuelle (amélioration du FSFI).

La comparaison avec l'oestrogénothérapie locale (oestrogènes conjugués équins 0,3 mg) n'a été faite que dans un seul essai avec des résultats identiques sur les paramètres de dyspareunie. En termes de tolérance, l'innocuité de la DHEA par voie vaginale a été établie au cours de plusieurs essais contrôlés par placebo et une étude ouverte à 52 semaines.

La DHEA n'augmente pas significativement les taux sériques d'oestradiol en raison de son métabolisme particulier (intracrinologie). Il n'y a pas d'impact sur l'endomètre avec un recul de 1 an de traitement.

L'Agence européenne des médicaments (EMA) a rendu un avis favorable en novembre 2017 pour une autorisation de mise sur le marché de la Prastérone 6,5 mg commercialisé en France sous le nom d'Intrarosa dans le cadre du traitement des symptômes du SGUM. Ce produit est efficace sur les symptômes du SGUM et peut être proposé chez les patientes symptomatiques (NP2).

Vaginal testosterone

Les données actuelles concernant la testosterone par voie vaginale sont de faible niveau de preuve et les études s'intéressent principalement à l'impact sur la fonction sexuelle et la dyspareunie.

Il semblerait exister un effet bénéfique pour la prise en charge des troubles de la fonction sexuelle, dyspareunie et sécheresse vaginale en lien avec le SGUM (NP3).

Compte tenu du manque actuel de données, ce traitement n'est pas recommandé pour la prise en charge du SGUM (NP3).

Oral treatments

De nombreuses études, dans leurs critères d'efficacité secondaires, montrent une amélioration significative sous THM de la sensation de sécheresse, d'irritation, de brûlure et de la dyspareunie en lien avec le SGUM dès 1 à 3 mois de traitement.

Concernant les symptômes urinaires, plusieurs essais randomisés ultérieurs se sont intéressés à la comparaison d'oestrogènes conjugués équins par voie orale ou d'oestradiol transdermique faible dose contre placebo. Les résultats suggèrent qu'il n'y a pas d'efficacité significative de ces traitements par rapport au placebo concernant les symptômes urinaires voire une aggravation. Bien que pouvant être efficace sur les symptômes du SGUM, le THM a un effet partiel et inconstant (NP2). En cas de persistance des symptômes malgré le traitement, un traitement local pourra être associé (NP3).

La tibolone 2,5 mg a obtenu l'AMM en 2000 pour la prise en charge des symptômes liés à la carence oestrogénique chez les femmes ménopausées. Les données concernant son intérêt pour la prise en charge du SGUM sont limitées et de faible niveau de preuve (NP3).

DHEA par voie orale ou transdermique : en raison d'un faible niveau de preuve, ce traitement n'est actuellement pas recommandé pour la prise en charge du SGUM (NP3).

Testostérone par voie orale ou transdermique : en l'absence de données solides, ce traitement n'est actuellement pas recommandé pour la prise en charge globale du SGUM (NP3).

Women with a history of breast cancer

(for recommendations for women with a history of cancer see chapter 5.9 on cancer risks)

5.2.3 NHG 2022

5.2.3.1 Vasomotor symptoms

Overweeg hormoontherapie voor vasomotorische klachten bij vrouwen met hinderlijke beperkingen in het dagelijks leven. (Low recommendation, low level of evidence)

Hormoontherapie van vasomotorische klachten bestaat uit:

- estradiol ter vermindering van de vasomotorische klachten
- progestageen ter verlaging van het risico op endometriumhyperplasie of -carcinoom bij estradiolgebruik (niet nodig bij vrouwen zonder uterus, tenzij zij in het verleden endometriose hadden)

Hormoontherapie leidt tot klachtenvermindering, maar kan ook leiden tot een kleine (soms onzekere) risicoverhoging van zeldzame, maar ernstige aandoeningen (borstkanker, myocardinfarct, beroerte, endometriumcarcinoom, VTE). Dit heeft geleid tot een zwakke aanbeveling voor hormoontherapie bij vrouwen met hinderlijke overgangsklachten.

In aparte details wordt verder ingegaan op de keuze voor toedieningsvorm van oestrogeen en type progestageen.

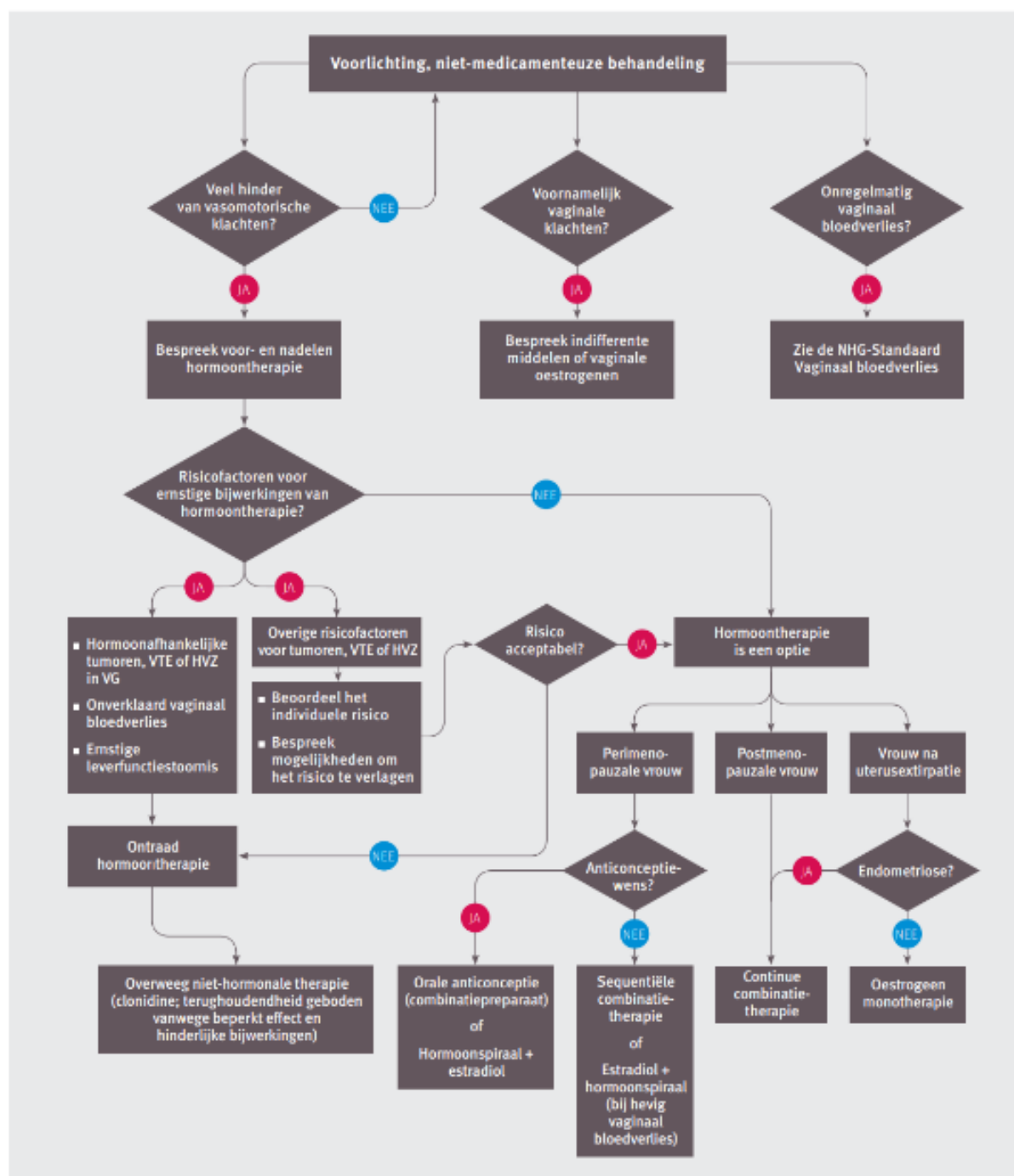
De kwaliteit van bewijs voor de effectiviteit was redelijk tot laag.

Bespreek de voor- en nadelen van hormoontherapie:

- Na 3 maanden hormoontherapie is het globaal te verwachten effect op het aantal opvliegers en/of nachtelijke zweetaanvallen, als een vrouw bij aanvang ongeveer 10 opvliegers en/of nachtelijke zweetaanvallen per dag heeft:
 - met placebobehandeling: ongeveer 5 opvliegers/nachtelijke zweetaanvallen minder per dag
 - met hormoontherapie: ongeveer 8 opvliegers/nachtelijke zweetaanvallen minder per dag
- Hormoontherapie verbetert mogelijk de kwaliteit van leven.
- Hormoontherapie beïnvloedt de stemming en het seksueel functioneren waarschijnlijk niet of nauwelijks.
- Hormoontherapie kan leiden tot een kleine toename van het risico op in deze leeftijdsgroep weinig voorkomende, maar ernstige aandoeningen (VTE, myocardinfarct, beroerte, borstkanker, endometriumcarcinoom). Het absolute risico op deze ernstige bijwerkingen is afhankelijk van het individuele risico en neemt toe met de duur van het gebruik.
- De belangrijkste en meest voorkomende niet-ernstige bijwerkingen zijn onregelmatig vaginaal bloedverlies, hoofdpijn en pijnlijke en gespannen borsten.

Figure below shows the management of menopausal symptoms as proposed by NHG 2022.

Beleid overgangsklachten



Figuur. Samenvatting beleid bij overgangsklachten

5.2.3.2 Genitourinary symptoms

De stemming en het seksueel functioneren worden door hormoontherapie niet of nauwelijks beïnvloed.

Bij klachten van vaginale atrofie kunnen zowel indifferente middelen (vochtinbrengende gel, crème met hyaluronzuur) als vaginaal oestrogeen overwogen worden. (Low recommendation, low level of evidence)

Bij vaginaal oestrogeen kan het tot 2 maanden duren voordat het effect optimaal is. Vaginaal oestrogeen kan de eerste dagen een branderig gevoel veroorzaken.

Zowel vaginale oestrogenen als indifferente middelen (zoals vochtinbrengende gel, crème met hyaluronzuur) leiden tot een vermindering van klachten van vaginale atrofie. Bij beide zijn we onzeker over de bijwerkingen, maar op theoretische gronden is niet te verwachten dat er ernstige bijwerkingen optreden.

Het voordeel van oestrogeentherapie is dat deze mogelijk bij een groter percentage van de vrouwen (ongeveer 80-90%) leidt tot subjectieve verbetering van de vaginale klachten dan placebo of niet-hormonale therapie.

Behandeling van vaginale atrofie heeft geen effect op seksuele klachten. Bij indifferente middelen is er een directe, maar kortdurende klachtenvermindering.

Over de nadelen zijn we onzeker, maar er zijn geen aanwijzingen dat het risico op borstkanker na langdurig gebruik verhoogd is. Overige bijwerkingen zijn niet goed onderzocht, maar in de meeste onderzoeken kwamen op de korte termijn (8-12 weken, voor sommige onderzoeken 52 weken) alleen lichte bijwerkingen voor in beide groepen.

De kwaliteit van bewijs is over het algemeen laag.

If choosing vaginal oestrogen

- Er zijn 2 gelijkwaardige keuzes:
 - estriol vaginale ovules of crème 1 dd 0,5 mg gedurende 2 weken. Ga daarna over op 2 × per week 0,5 mg.
 - estradiol tablet voor vaginaal gebruik 1 dd 10 microg. Bouw na 2 weken af tot maximaal 10 microgram 2 × per week.
- Instrueer de vrouw contact op te nemen bij vaginaal bloedverlies.
- De contra-indicaties voor vaginale oestrogenen zijn dezelfde als voor systemische oestrogenen
- Er is echter geen bewijs dat vaginale oestrogenen bij gebruik < 10 jaar meer kans op borstkanker geven. Voor VTE en HVZ is dit onbekend. Bespreek dit met de patiënt.

5.2.4 NICE upd 2019

The main short-term menopausal symptoms that were the focus of this question were:

- frequency of VMS

- anxiety and low mood (excluding clinical depression) as aspects of psychological wellbeing; depression in the context of this review question referred to low mood, as no clinical diagnosis was made and this term (low mood) is used across the review
- frequency of sexual intercourse as a measure of sexual function
- joint and muscle aches and pains as indicators of musculoskeletal symptoms.

Anxiety and low mood are discussed in the chapter 5.7 concerning neurological and psychological effects of HRT.

Joint and muscle aches and pains are discussed in the chapter 5.6 concerning musculoskeletal effects of HRT.

5.2.4.1 Vasomotor symptoms

Treatment for VMS may include hormone replacement therapy (HRT), since symptoms occur at a time when oestrogen levels are dropping and 'replacement' leads to relief. HRT comprises synthetic hormones that may be identical to those produced from the ovaries during the reproductive years (oestradiol and progesterone) although other similar compounds (such as conjugated equine oestrogens, oestradiol valerate and several synthetic progestogens) are widely used. Tibolone belongs to the group of normethyltestosterone progestogen derivatives: it has metabolites that exhibit estrogenic, progestogenic and androgenic effects, and has been in clinical use since the early 1990s for treatment of menopausal symptoms.

Adapt a woman's treatment as needed, based on her changing symptoms.

Offer women HRT for vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of preparations as follows:

- oestrogen and progestogen to women with a uterus
- oestrogen alone to women without a uterus.

Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone.

Two of the most critical factors determining the choice and appropriateness of treatments for relief of menopausal symptoms are whether a woman has a uterus or not and whether she has a history of breast cancer (or other hormone sensitive conditions or other contraindications to hormone therapies), since the side effect profiles of hormonal treatments are different for these groups of women.

- For women with a uterus, oestrogen plus progestogen (transdermal) was found to be the most effective treatment to relieve VMS, with a significantly lower discontinuation rate compared with all the other available treatments (hormonal, non-hormonal and non-pharmacological). There was evidence that oestrogen plus progestogen (oral) may be more effective to relieve VMS than placebo, but this did not rank as highly as transdermal oestrogen plus progestogen in the hierarchy of the best treatment options for this outcome.
- For the outcome of VMS in women without a uterus, the NMA results were not helpful in decision-making owing to lack of evidence on the most clinically relevant hormonal treatment of oestrogen alone (progesterone is not required for women without a uterus).

However, the direction of effects of non-hormonal treatments was the same for both groups of women (with and without a uterus). The group extrapolated the evidence from the network of women with a uterus for their decision-making by selecting the most clinically effective hormonal treatment option for relief of menopausal symptoms in women without a uterus, keeping in mind the limitations on this generalisation. This recommendation was supported by the group's clinical experience.

5.2.4.2 Genitourinary symptoms

Sexual function

Menopausal women may experience problems with sexual intercourse. This can be a complex issue that has both physical and psychological elements. The vaginal dryness resulting from urogenital atrophy can lead to pain during intercourse which can impact on libido. Loss of libido may also be a result of declining levels of oestrogen and testosterone as the ovaries fail; the lack of testosterone can be more marked in women who have their ovaries removed by surgery. Vaginal dryness tends to increase in severity with time since menopause. Topical treatment may be offered, both hormonal and non-hormonal.

Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective. In November 2015, this was an off-label use.

In relation to the other short-term outcomes, limited data was found for the outcome of frequency of satisfying sexual intercourse, but testosterone (10 mg/day; gel) was found to significantly increase frequency compared with placebo although the majority of women included in these trials were surgically menopausal. The other evidence identified comparing tibolone versus oestrogen plus progestogen did not show a significant difference in the frequency of satisfying sexual activities. Given the limited availability of evidence, the group incorporated their clinical experience to decide that testosterone, although unlicensed for this indication in women, should only be offered as an option of improving low sexual desire for women in menopause when HRT is not effective.

Urogenital atrophy

It is estimated that symptoms caused by vulvovaginal atrophy can affect up to 50% of all postmenopausal women. The most common symptoms affecting the vulva and vagina include dryness, pain on intercourse, vaginal itching and vaginal discharge. There is increased vulnerability to inflammation, trauma and infection. Urogenital atrophy can also result in urinary symptoms, such as urgency to urinate and urinary tract infections.

Symptoms typically become apparent 4 to 5 years after the menopause transition, due to the long-term reduction in oestrogen levels. This results in thinning and loss of elasticity of the vulval and vaginal skin and loss of vaginal lubrication.

Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms.

Consider vaginal oestrogen for women with urogenital atrophy in whom systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause.

If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause.

Explain to women with urogenital atrophy that:

- **symptoms often come back when treatment is stopped**
- **adverse effects from vaginal oestrogen are very rare**
- **they should report unscheduled vaginal bleeding to their GP.**

Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy.

Both short-term outcomes (efficacy, safety, acceptability) and long-term outcomes (safety, acceptability) of urogenital atrophy were considered in this review question.

In terms of short-term symptoms, the measurement of vaginal pH, maturation index (for parabasal, intermediate and superficial cells) and women's subjective assessment of symptom improvement relating to atrophy, dryness, dyspareunia (painful intercourse), itching and discomfort were considered the most important outcomes. Short-term outcomes were measured at the 3-month timepoint to allow detection of the treatment effect. Safety outcomes included an assessment of endometrial stimulation, breast pain (as a surrogate marker for systemic absorption), blood oestradiol levels, adverse events (including withdrawal due to adverse events), acceptability and adherence to treatment. In terms of long-term outcomes, endometrial hyperplasia or cancer, long-term relief of symptoms and impact on health-related quality of life were considered.

The evidence showed that local vaginal oestrogen was beneficial for improving short-term outcomes (vaginal pH, maturation index, patients' symptomatic improvement) for menopausal women when compared with placebo. Furthermore, no difference in the experience of adverse events was found between those women treated with local vaginal oestrogen and those on placebo. In terms of long-term outcomes, although a significant improvement was found for women who used local vaginal oestrogens compared with placebo groups in relieving vaginal dryness symptoms, dyspareunia and itching or discomfort, there was also a case of endometrial hyperplasia (although the difference in this outcome was not significant) among those who used local oestrogen treatment compared with placebo.

The Guideline Development Group concluded that given the effectiveness of vaginal local oestrogen in relieving symptoms of urogenital atrophy and the reasonable safety profile, it should be considered as a treatment for this condition for women in menopause (including those who take systemic HRT but experience persistent urogenital symptoms).

The group discussed duration of treatment and concluded that local oestrogen can be used in the long term to provide symptom relief; since systemic absorption of oestrogen from recommended doses is very small, it is unlikely to be associated with the adverse effects reported with the use of systemic HRT.

The group considered that it would be a safe option to increase the dose, noting that vaginal tablets of oestradiol are available only at a dose of 10 micrograms and that a dose of 20 micrograms may be required, as supported by the reviewed evidence. However, the group concluded that the most appropriate way to manage persistent symptoms would be to obtain advice from a healthcare professional with expertise in this area.

The group discussed the role of local oestrogens for women in whom systemic HRT is contradicted, for example women with a history of breast cancer, and concluded that local oestrogen should still be considered for relieving symptoms of urogenital atrophy in these women, as there is minimal systemic absorption of local preparations, although this decision should be discussed with a healthcare professional with expertise in the field as even very small amounts of oestradiol may decrease the effect of aromatase inhibitors which are used in the treatment of breast cancer.

The majority of evidence was of moderate to very low quality. Different dosages of local oestrogens were used but data were too limited to allow further subgroup analyses. There was a paucity of information for any long-term follow-up data longer than 1 year of treatment, therefore the results of the included studies should be interpreted with caution given the unknown long-term efficacy and safety of this treatment.

5.2.5 USPSTF 2022

No specific recommendations or comments were provided regarding menopausal symptoms in this guideline.

The recommendation from USPSTF does not apply to persons who are considering hormone therapy for the management of perimenopausal symptoms, such as hot flushes or vaginal dryness.

Urinary incontinence

Two trials reported on incident urinary incontinence (self-reported) in persons taking estrogen plus progestin; both found increased risk.

5.3 Initiation, discontinuation and follow-up of HRT

Starting HRT

FR 2021 recommends not to start HRT until the post-menopausal phase (12 months of amenorrhoea) has been confirmed. The guideline recommends HRT be started less than 10 years after confirmation of the menopause (Grade B).

NHG 2022 specifies that hormone therapy has not been studied in perimenopausal women whose last menstrual period was less than 6 months ago and that hormone therapy is therefore not authorized for these women. Although efficacy, safety and side effects have not been studied in this group, and it is not known whether protection of the endometrium is adequate, the study group does not believe that this should prevent the use of hormone therapy for these women and formulated treatment option propositions for perimenopausal women with and without contraception needs (see chapter 5.1 on different hormonal therapies, dosages and schema of administration).

When starting HRT, NHG 2022 and NICE upd 2019 recommend to inform patients about several aspects of menopause including different stages, symptoms and their duration, other ageing symptoms, social changes, general health and wellbeing... AWMF 2020, NHG 2022 and NICE upd 2019 also formerly recommend to discuss the advantages and the short- and long-term risks of HRT. NICE upd 2019 also recommends to discuss other non-hormonal and non-pharmacological treatments.

Follow up

FR 2021 (Grade B) and NHG 2022 recommend to clinically assess the effectiveness of menopausal hormone treatment on vasomotor symptoms. The absence of a reduction in vasomotor symptoms after adaptation of HRT modalities raises the possibility of atypical flushing (FR 2021, expert opinion).

After starting HRT, women should initially see their gynaecologist after 3 months to check the effectiveness and the tolerability of the therapy and then regularly (AWMF 2020, NHG 2022, NICE upd 2019). All the guidelines recommend to reassess the rationale (benefit-risk balance, new contraindication) for the HRT on a yearly basis.

Women should be informed about the importance of recommended cancer screening (AWMF 2020).

According to AWMF 2020 and FR 2021 it could be necessary to adjust the therapy (change of dose, switch to another therapy measure, etc.). FR 2021 recommends to reassess HRT doses on a yearly basis (expert opinion). According to NHG 2022 increasing the dose of estradiol is not recommended (formal recommendation).

According to FR 2021, current data do not allow to recommend an optimal duration of treatment (expert opinion). NHG 2022 rather aims for use < 5 years because of gradually increasing risks.

Vaginal ET for vaginal atrophy

NHG 2022 recommends to evaluate the result of treatment after 3 months and to check the treatment annually or with higher frequency in accordance with women depending on the symptoms.

For AWMF 2020 and NICE upd 2019 women should be explained that adverse effects from vaginal ET are very rare. Women should consult in case of vaginal bleeding.

Routine vaginal ultrasonography to measure endometrial thickness should not be performed for vaginal atrophy.(AWMF 2020, NICE upd 2019) (formal recommendation against for NICE upd 2019 only)

Stopping HRT

Women should be advised before starting treatment that vasomotor symptoms may recur after stopping HRT (AWMF 2020). If that is the case, restart of hormonal menopause treatment is possible (FR 2021).

Two options may be offered for discontinuing HRT: immediate discontinuation or gradual tapering. According to FR 2021 the available data do not allow to recommend one over the other (Grade B). NICE upd 2019 recommends to offer the choice between gradually or immediate reduction to women. According to NHG 2022 hormone therapy does not need to be tapered.

AWMF 2020 specifies that after gradual tapering off, symptoms may recur less frequently in the short term. In the long term, the recurrence of symptoms is independent of whether the hormones are stopped slowly or suddenly. NICE upd 2019 agrees with this and recommends to inform the patient about this.

FR 2021 recommends to maintain specific medical monitoring, including screening for and active management of vascular and metabolic risk factors, annual gynaecological check-ups and screening tests for the various gynaecological cancers (particularly breast cancer), in post-menopausal women once HRT has been discontinued (expert opinion).

According to FR 2021, it is possible to resume menopausal hormone treatment in women without contraindications, taking into account the individual benefit-risk balance and after informing the patient. Priority should be given to minimum doses effective in correcting climacteric symptoms (expert opinion).

Vaginal ET for vaginal atrophy

NHG 2022 states to discuss and consider stopping in consultation with the women.

For AWMF 2020 and NICE upd 2019 women should be explained that symptoms often come back when treatment is stopped.

HRT for patients with risk factors

(see also HRT for patient with cancer or with a history of cancer in chapter 5.9 on cancer risks, and recommendation on cardiovascular risks in chapter 5.8.

NHG 2022 has formulated specific recommendations to discourage HRT for patients with:

- previously diagnosed hormone-dependent tumours, such as breast cancer or endometrial carcinoma
- previously diagnosed VTE, with or without thrombophilia (this does not apply to women taking anticoagulation)

- previously diagnosed cardiovascular disease
- unexplained vaginal bleeding (perform additional diagnostics before starting, see NHG Standard Vaginal bleeding)
- severe liver function disorders

For other situations, NHG 2022 recommends to discuss the number, nature and severity of risk factors when assessing individual risk of:

- cardiovascular disease (see NHG Standard Cardiovascular risk management)
- VTE (see NHG Standard Deep vein thrombosis and pulmonary embolism)
- breast cancer (see NHG Standard Breast Cancer). In familial burden of breast cancer, the increase in risk due to hormone therapy has not been sufficiently studied.

NHG 2022 recommends to weigh the pros and cons of treatment together with the woman and also to discuss options to reduce individual risk, such as quitting smoking, reducing alcohol consumption, increasing exercise and losing weight. Moderating the consumption of alcohol can also have a beneficial effect on the number of hot flashes.

5.3.1 AWMF 2020

Follow up

Nach Beginn einer HRT sollten sich Frauen regelmäßig bei ihrem Frauenarzt vorstellen (initial nach 3 Monaten), um die Wirksamkeit und Verträglichkeit der Therapie zu überprüfen.

Eine Anpassung der Therapie (Dosisveränderung, Umstellung auf eine andere Therapiemaßnahme etc.) kann im Verlauf der verschiedenen Phasen der Peri- und Postmenopause notwendig werden und muss individuell entschieden werden. Wenn nicht aus anderen Gründen ein vorzeitiger Arztbesuch nötig wird, sind jährliche Wiedervorstellungen anzustreben.

Besonderes Augenmerk sollte hierbei auf neu aufgetretene Kontraindikationen gelegt werden.

Frauen sollen über die Bedeutung der empfohlenen Krebsfrüherkennungsuntersuchungen informiert werden. Unter lokaler ET soll keine routinemäßige Vaginalsonographie zur Messung der Endometriumdicke durchgeführt werden.

Discontinuation

Frauen sollten vor Beginn der Behandlung darauf hingewiesen werden, dass nach dem Absetzen der HRT vasomotorische Beschwerden wieder auftreten können.

Für das Absetzen der HRT können zwei Optionen angeboten werden: sofortiges Absetzen oder allmähliches Ausschleichen.

Nach allmählichem Ausschleichen treten die Symptome kurzfristig möglicherweise seltener wieder auf. Langfristig ist das Wiederauftreten von Symptomen unabhängig davon, ob die Hormone langsam oder plötzlich abgesetzt werden.

5.3.2 FR 2021

Initiation of HRT

Il est recommandé de ne pas débuter le THM avant d'avoir affirmé la réalité de la phase post-ménopausique (12 mois d'aménorrhée) (grade B).

Il est recommandé de débuter le THM moins de 10 ans après confirmation de la réalité de la ménopause (grade B).

La mise en place du THM à distance de l'installation de la ménopause est par ailleurs associée à des risques variables carcinologiques et cardiovasculaires.

Lorsque le THM est débuté dans les 10 ans suivant l'installation de la ménopause physiologique, il n'a pas été montré en population générale, d'augmentation significative du risque coronarien (NP1)

Il a été montré dans plusieurs analyses poolées, un bénéfice sur la mortalité globale et les maladies coronariennes chez les femmes débutant un traitement dans les 10 ans suivant l'installation de la ménopause.

A l'inverse plusieurs études suggèrent un moindre risque de cancer du sein lorsqu'il est débuté plus de 3 à 5 ans après l'installation de la ménopause (NP2-3).

Follow up

La gestion du THM en pratique sous-tend l'évaluation de son efficacité sur ses deux principales indications (syndrome climatérique et prévention de l'ostéoporose) tout comme de la durée de traitement.

Il est recommandé d'évaluer cliniquement l'efficacité du traitement hormonal de la ménopause sur les symptômes vasomoteurs (grade B).

L'absence de diminution de la symptomatologie vasomotrice après adaptation des modalités du THM fait évoquer la possibilité de BVM atypiques (avis d'expert)

Le THM diminue la fréquence et l'intensité des bouffées vasomotrices, respectivement de 75 et 87 % et de manière significative par rapport au placebo dans un délai de 2 à 6 semaines dans les essais randomisés (NP1).

L'amélioration des symptômes climatériques tout comme la présence d'hémorragie de privation (lorsque le schéma est séquentiel) n'est pas corrélée à l'effet osseux du THM (NP2).

See also efficacy evaluation for THM used to prevent fractures in chapter 5.6 On musculoskeletal effects.

Treatment duration

Une patiente bénéficiant d'un THM peut être amenée à arrêter un THM pour trois raisons principales:

- par choix personnel de la patiente ;
- en raison de la survenue d'une pathologie qui contre-indique la poursuite du THM ;
- la balance bénéfices-risques n'est plus jugée aussi favorable que lors de l'initiation du THM.

La dose minimale efficace peut varier avec le temps (NP2) et il est nécessaire de réévaluer la posologie du THM mais aussi le bien-fondé de la prescription annuellement (avis d'expert).

Les données actuelles ne permettent pas de recommander une durée optimale de traitement hormonal de ménopause qui doit prendre en compte l'indication initiale du traitement comme sa balance bénéfices–risques (avis d'expert).

Il est recommandé de délivrer une information complète et de réévaluer annuellement la balance bénéfices–risques du traitement hormonal de ménopause, en s'adaptant au terrain et au type de traitement hormonal (grade A).

La question de la durée de prise « minimale » d'un THM est une vraie problématique clinique et il n'existe pas d'étude spécifique. Cette problématique a fait l'objet de recommandations nationales et internationales basées sur une balance bénéfices-risques individuelle, c'est-à-dire discutée au cas par cas.

En France, la HAS recommande une durée la plus courte possible tant que durent les symptômes climatériques avec réévaluation régulière de la balance bénéfices–risques du THM, celle-ci conditionnant la possibilité de le poursuivre ou au contraire, son arrêt.

La réduction du risque fracturaire est démontrée pour une durée de THM d'au moins 5 ans (NP1) et toutes les études montrent que le bénéfice anti-fracturaire est maintenu avec la durée du THM (NP1). *(See also chapter 5.6 on musculoskeletal effects for treatment duration for osteoporosis prevention)*

C'est notamment l'augmentation du risque de cancer de sein au-delà d'une certaine durée d'utilisation qui justifie de réévaluer la balance bénéfices–risques individuelle de ce traitement en tenant compte des indications du THM (symptomatologie climatérique et/ou prévention du risque fracturaire).

Discontinuation of HRT

Les données disponibles ne permettent pas de recommander l'arrêt progressif du traitement hormonal de ménopause par rapport à son interruption immédiate (grade B).

Les modalités de l'arrêt (immédiat ou progressif en diminuant les posologies estrogéniques) ne semblent pas conditionner la reprise des manifestations climatériques (NP2).

Pour les femmes qui ne présentent pas de contre-indication au traitement hormonal de ménopause, il est possible de reprendre un traitement hormonal de ménopause en tenant compte de la balance bénéfices–risques individuelle et après information de la patiente, en privilégiant les doses minimales efficaces pour corriger les symptômes climatériques (avis d'expert).

Les principaux symptômes rapportés par les femmes ayant arrêté le THM étaient les suivants (NP2) : récurrence des bouffées vasomotrices et/ou sudations nocturnes (21,2 %), arthralgies/myalgies (36,8 %), asthénie (21,6 %), troubles du sommeil (17,6 %), syndrome dépressif (10,5 %), symptomatologie vaginale (sécheresse (9,8 %), irritation/inconfort (4,5 %)).

Une diminution globale de la qualité de vie était observée chez les patientes ayant interrompu leur THM (NP3). L'analyse en sous-groupe d'âge a mis en évidence que cette diminution de qualité de vie secondaire à l'arrêt de ce traitement concernait surtout les femmes âgées de 65 à 75 ans (NP3).

Pour les femmes qui ont arrêté leur THM en raison de la survenue d'une contre-indication métabolique, vasculaire ou carcinologique, il sera nécessaire d'envisager les alternatives au THM en tenant compte de chacun des symptômes associés à une altération de la qualité de vie ;

Après l'arrêt d'un THM, il est nécessaire de maintenir un suivi médical spécifique comprenant entre autres le dépistage et la prise en charge active des facteurs de risque vasculaires et métaboliques chez les femmes ménopausées (avis d'expert).

Les auteurs ont constaté une augmentation significative de la mortalité cardiovasculaire dans l'année suivant l'arrêt du THM, mais en revanche une diminution significative au-delà d'une année d'interruption (NP2). Les conclusions de ces deux études, qui doivent être confirmées par d'autres travaux, doivent inciter les prescripteurs à maintenir une certaine vigilance, en particulier chez les femmes présentant des facteurs de risque de pathologie athéromateuse.

Une étude de méthodologie équivalente portant sur le suivi longitudinal d'une population de 432 775 femmes finlandaises ayant interrompu leur THM entre 1994 et 2013 a confirmé cette augmentation du risque cardiovasculaire par AVC ou pathologie cardiaque à l'arrêt du THM, bien que l'augmentation ne fût significative que dans la sous-population des femmes âgées de moins de 60 ans au moment de l'arrêt (NP2).

Dans un essai contrôlé randomisé concernant 240 femmes ménopausées prenant un THM, Pettersen et al. ont mis en évidence que l'arrêt d'un THM induisait des modifications délétères du profil lipidique (augmentation significative du cholestérol et du LDL-cholestérol) en comparaison aux femmes qui l'avaient poursuivi (NP2). En revanche, ces dernières étaient considérablement minimisées par les

mesures hygiéno-diététiques préventives (contrôle, voire perte de poids, activité physique régulière, équilibre nutritionnel) (NP3).

Après l'arrêt d'un THM, il est nécessaire de maintenir un suivi médical spécifique comprenant entre autres un suivi gynécologique annuel mais aussi la réalisation des examens de dépistage des différents cancers gynécologiques (en particulier pour le cancer du sein) en fonction des facteurs de risque individuels de chaque patiente (avis d'expert).

Le cancer du sein est vraisemblablement le cancer qui serait le plus influencé par la durée de prise d'un THM. Après l'arrêt du THM, l'incidence du cancer du sein rejoindrait celui des femmes jamais traitées dans les 2 ans pour l'essai WHI (NP1) et dans les 10 ans pour la méta-analyse la plus récente (NP2).

Il existe un certain nombre de données qui semblent indiquer que le THM puisse être associé à une augmentation modeste mais significative avec la durée du traitement de développer certaines tumeurs ovariennes cancéreuses. Le surrisque de cancer de l'ovaire disparaît après 5 ans d'arrêt du THM chez les femmes traitées moins de 5 ans (NP2). Pour les femmes ayant pris un THM plus de 5 ans, le surrisque persiste au-delà de 5 ans (NP3).

Dans l'état actuel des connaissances, il n'existe pas d'étude spécifique sur l'influence de l'arrêt du THM sur l'incidence des autres cancers.

5.3.3 NHG 2022

Treatment initiation

Geef voorlichting over de volgende aspecten van de overgang.

- De overgang is een fysiologisch proces met grote variaties in het beloop en de hinder van klachten, dat vaak samengaat met andere verouderingsverschijnselen en met sociale veranderingen.
- Door hormonale veranderingen verandert de menstruatie. Bij de meeste vrouwen treden opvliegers en nachtelijke zweetaanvallen op. Ook kunnen vaginale klachten optreden.
- Het duurt gemiddeld 4-6 jaar voordat de menstruatie definitief wegblijft.
- Het valt niet te voorspellen in welke mate een vrouw klachten van de overgang zal krijgen.
- De duur van de opvliegers en/of nachtelijke zweetaanvallen kan variëren van 3-7 jaar. Het beloop varieert per persoon en is niet goed te voorspellen.
- Klachten van moeheid, sombere gevoelens en slapeloosheid kunnen een gevolg zijn van nachtelijke zweetaanvallen. Ook andere omstandigheden of veranderingen in het leven kunnen deze klachten veroorzaken.
- Het algemene advies is om op de leeftijd van 52 jaar te stoppen met hormonale anticonceptie. De kans op zwangerschap is na deze leeftijd erg klein. Afhankelijk van de situatie kan men afwachten of na het staken de cyclus nog terugkeert en of er vasomotorische klachten optreden (zie NHG-Standaard Anticonceptie).
- Bespreek bij klachten van dyspareunie het belang van adequate stimulatie en opwinding voor voldoende lubricatie (zie Klachten tijdens de overgang en NHG-Standaard Seksuele klachten).

Hormone therapy at last menstruation < 6 months ago

- Uit productinformatie van geregistreerde hormoonpreparaten (zoals dydrogesteron/estradiol continu en cyclisch) volgt dat deze zijn onderzocht bij, en geregistreerd voor gebruik door (Geneesmiddeleninformatiebank, geraadpleegd maart 2022):

- vrouwen die ≥ 6 maanden geleden hun laatste menstruatie hebben gehad (in de productinformatie benoemd als 'vrouwen die tenminste 6 maanden in de menopauze zijn')
- vrouwen die ≥ 12 maanden geleden hun laatste menstruatie hebben gehad, dat wil zegen postmenopauzale vrouwen
- Hieruit volgt dat hormoontherapie niet is onderzocht bij, en geregistreerd voor gebruik door, perimenopauzale vrouwen bij wie de laatste menstruatie < 6 maanden geleden was. Hormoontherapie is dus offlabel voor deze vrouwen; effectiviteit, veiligheid en bijwerkingen zijn in deze groep niet onderzocht.
- Het is niet bekend of endometriumprotectie bij deze groep vrouwen, die een hoger niveau van eigen aanmaak van oestrogeen hebben dan de hierboven genoemde groepen vrouwen, afdoende is. De werkgroep verwacht niet dat dit in de praktijk de toepassing van hormoontherapie bij deze groep vrouwen in de weg hoeft te staan. (*see proposed table with treatment options in chapter 5.1 different hormonal therapies, dosages and schema of administration*).

HRT for patients with risk factors

See also recommendations after cancer in chapter 5.9 on cancer risks and in case of cardiovascular risks in chapter 5.8 on cardiovascular risks.

- **Ontraad hormoontherapie bij:**
 - eerder vastgestelde hormoonafhankelijke tumoren, zoals borstkanker of endometriumcarcinoom
 - eerder vastgestelde VTE, met of zonder trombofilie (dit geldt niet voor vrouwen die antistolling gebruiken)
 - eerder vastgestelde hart- en vaatziekten
 - onverklaard vaginaal bloedverlies (verricht aanvullende diagnostiek alvorens te starten, zie **NHG-Standaard Vaginaal bloedverlies**)
 - ernstige leverfunctiestoornissen
- **Bespreek bij overige situaties het aantal, de aard en de ernst van de risicofactoren bij de beoordeling van het individuele risico op:**
 - hart- en vaatziekten (zie **NHG-Standaard Cardiovasculair risicomanagement**)
 - VTE (zie **NHG-Standaard Diepveneuze trombose en longembolie**)
 - borstkanker (zie **NHG-Standaard Borstkanker**). Bij familiale belasting met borstkanker is de toename van het risico door hormoontherapie onvoldoende onderzocht.
- Weeg samen met de vrouw de voor- en nadelen van de behandeling af.
- Bespreek ook mogelijkheden om het individuele risico te verlagen, zoals stoppen met roken, minderen met alcoholgebruik, meer bewegen en afvallen. Matigen van het gebruik van alcohol kan ook een gunstig effect hebben op het aantal opvliegers.

Follow up

- *Hormone therapy for vasomotor complaints*
- **Evalueer na 3 maanden het effect van behandeling op vasomotorische klachten en kwaliteit van leven.**
- **Vraag naar:**

- (hinder van) vasomotorische klachten bij het dagelijks functioneren thuis, op het werk of in de vrije tijd
- bijwerkingen: onregelmatig, onverwacht vaginaal bloedverlies dat optreedt of aanhoudt > 3 maanden na de start van de behandeling (zie Verwijzing)
- therapietrouw: met name bij gebruik van transdermaal estradiol in combinatie met oraal dydrogesteron
- Ophogen van de dosering estradiol wordt niet aanbevolen.
- Controleer de behandeling in ieder geval jaarlijks. Spreek eventueel in samenspraak met de vrouw een hogere frequentie af afhankelijk van de klachten, bijvoorbeeld halfjaarlijks.
- Evalueer jaarlijks het gebruik en het al dan niet continueren van de behandeling, de risicofactoren voor VTE, hart- en vaatziekten en borstkanker. Bespreek, als hierin verandering is opgetreden, de consequenties voor het vervolgbeleid.

Bij onvoldoende werking dient te worden nagegaan of er opnameverminderende medicatie wordt gebruikt, zoals anti-epileptica of Sint-Janskruid. Overwogen kan worden een ander middel te proberen. Ophogen van de dosering wordt niet aanbevolen.

- *Drug therapy for vaginal atrophy*
- Evalueer na 3 maanden het resultaat van de behandeling.
- Instrueer de vrouw contact op te nemen bij vaginaal bloedverlies.
- Controleer de behandeling in ieder geval jaarlijks bij gebruik van vaginaal oestrogeen. Spreek eventueel in samenspraak met de vrouw een hogere frequentie af afhankelijk van de klachten, bijvoorbeeld halfjaarlijks.

Referral

- Bij veel hinder van vasomotorische klachten en contra-indicaties voor medicamenteuze behandeling: consulteer of verwijs naar een gynaecoloog.
- Bij problemen op het werk door overgangsklachten: adviseer contact op te nemen met de bedrijfsarts.
- Verwijs bij vroegtijdige overgang (menopauze < 40 jaar) voor diagnostiek naar oorzaak (auto-immuunziekte, genetische afwijking) en advies.

Duration of treatment

- *Hormone therapy for vasomotor complaints*
- Streef naar gebruik < 5 jaar vanwege de geleidelijk oplopende risico's.
- Hormoontherapie hoeft niet te worden afgebouwd.
- *Drug therapy for vaginal atrophy*
 - Bespreek en overweeg stoppen in samenspraak met de vrouw.

Discontinuation of HRT

Er is weinig bekend over wat de beste manier van stoppen van hormoontherapie is: direct stoppen of afbouwen.

Er is mogelijk geen verschil in effect op terugkeer van vasomotorische klachten na direct stoppen of afbouwen van hormonale therapie bij vrouwen die langdurig hormonale therapie gebruiken. De kwaliteit van bewijs was laag tot zeer laag.

Onderzoek met als uitkomstmaten herstarten van de behandeling en aanvaardbaarheid werd niet gevonden.

Er zijn zeer beperkte aanwijzingen dat in het eerste jaar na stoppen met hormoontherapie de risico's op sterfte aan coronaire hartziekten en beroerte verhoogd zijn. Bij vrouwen < 60 jaar waren deze risico's hoger. Na > 1 jaar was het risico niet meer verhoogd. Gegevens over aanwezige cardiovasculaire risicofactoren, zoals eerder vastgestelde hart- en vaatziekten en roken, ontbraken. De kwaliteit van bewijs was zeer laag.

5.3.4 NICE upd 2019

Starting treatment

Give information to menopausal women and their family members or carers (as appropriate) that includes:

- an explanation of the stages of menopause
- common symptoms (see recommendation 8) and diagnosis
- lifestyle changes and interventions that could help general health and wellbeing
- benefits and risks of treatments for menopausal symptoms
- long-term health implications of menopause.

Explain to women that as well as a change in their menstrual cycle they may experience a variety of symptoms associated with menopause, including:

- vasomotor symptoms (for example, hot flushes and sweats)
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (for example, low mood)
- urogenital symptoms (for example, vaginal dryness)
- sexual difficulties (for example, low sexual desire).

Give information to menopausal women and their family members or carers (as appropriate) about the following types of treatment for menopausal symptoms:

- hormonal, for example hormone replacement therapy (HRT)
- non-hormonal, for example clonidine
- non-pharmaceutical, for example cognitive behavioural therapy (CBT).

Give information on menopause in different ways to help encourage women to discuss their symptoms and needs.

Give information about contraception to women who are in the perimenopausal and postmenopausal phase. See guidance from the Faculty of Sexual & Reproductive Healthcare on contraception for women aged over 40 years.

Follow up and referral

Discuss with women the importance of keeping up to date with nationally recommended health screening.

Review each treatment for short-term menopausal symptoms:

- **at 3 months to assess efficacy and tolerability**
- **annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).**

Refer women to a healthcare professional with expertise in menopause if treatments do not improve their menopausal symptoms or they have ongoing troublesome side effects.

Consider referring women to a healthcare professional with expertise in menopause if:

- **they have menopausal symptoms and contraindications to HRT or**
- **there is uncertainty about the most suitable treatment options for their menopausal symptoms.**

Following the decision to start treatment for menopause symptoms, initial review is required to assess effectiveness and side effects.

Once treatment is established, review is necessary to assess changes in risk due to new or pre-existing health problems, to carry out basic health checks, such as measurement of weight and blood pressure, and to inform and engage women in national screening programmes.

If hormonal therapy was initiated in the perimenopause, change from cyclical to continuous combined hormone replacement therapy (HRT) should be discussed at review and with longer duration of therapy a reduction in the dosage of oestrogen in the HRT may be considered.

Information provision and discussion of longer term risks and benefits is important. Regular review of the effectiveness and safety of non-hormonal treatment is also required.

No clinical evidence was found for this review question. The recommendations were based on the Guideline Development Group members' expert opinions.

Discontinuation of HRT

Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment.

Explain to women that:

- **gradually reducing HRT may limit recurrence of symptoms in the short term**
- **gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term.**

In recent years, many women were advised to stop HRT after 2–5 years of use or at the age of 60, although the evidence for this advice is uncertain.

The options for discontinuation are either for the woman to stop treatment immediately or to gradually wean off treatment by decreasing the dose or number of days per week that HRT is taken.

The discontinuation process can range from several weeks to several months.

Given that no strong evidence was found to suggest harm nor indicate an improvement in outcomes, they concluded that both methods could be used and this decision should be based on the woman's preference. In addition, the data didn't suggest a specific duration for the tapering method discontinuation so this may vary depending on the women's personal circumstances and needs. They noted that tapering methods may involve either cutting the dose or administering HRT less often and that the discontinuation process may last anywhere from a couple of weeks to several months.

The quality of the evidence supporting these recommendations was generally of low to very low quality due to the high risk of bias (most studies were unblinded) and lack of precision associated with the estimates of effect. In fact, most of the outcomes did not provide measures of variation in the effect estimates. Because these outcomes were reported only in narrative summaries where, in

some cases, the level of statistical significance was the only data presented, these results should be interpreted with caution. There

The recommendations were based on both the clinical evidence reviewed and the expert opinion of Guideline Development Group members.

5.3.5 USPSTF 2022

« Timing Hypothesis »

It has been hypothesized that the benefits and harms of menopausal hormone therapy might differ based on participants' age or timing of initiation of therapy with respect to menopause. Accordingly, the WHI trials reported on outcomes stratified by decade of age and by time since menopause. Of note, the analyses of outcomes by time since menopause were post hoc. For most outcomes, there were no differences based on these parameters.

The WHI reported no statistically significant differences in risk of coronary heart disease based on age or time since menopause. One analysis of the WHI estrogen plus progestin trial reported a statistically significant trend for risk of myocardial infarction (a secondary trial outcome) by time since menopause, with significantly higher risk in persons 20 or more years after menopause, while a second analysis found no difference in coronary risk between early (<5 years) vs late (≥5 years) initiation of hormone therapy with respect to menopause.

The WHI estrogen-alone trial reported statistically significant trends by decade of age for the outcomes of myocardial infarction, colorectal cancer, and all-cause mortality, with lower risk in younger persons and higher risk in older persons, although the confidence intervals in all age groups included the null, with the exception of colorectal cancer, for which risk was significantly increased in 70- to 79-year-old persons.

Other studies have reported on the effect of timing on the benefits and harms of menopausal hormone therapy, but they are limited by study quality or other issues as well.

5.4 Short-term side effects

NHG 2022 specifies that about 1-10% of users experience non-serious side effects, such as irregular bleeding, headache, gastrointestinal complaints, painful and tense breasts.

NICE upd 2019 recommends to inform women that unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment. All the guidelines also recommend to report it if it occurs. According to FR 2021, abnormal uterine bleeding under HRT is one of the main factors in poor compliance. However, there is insufficient evidence to recommend how the HRT treatment regimen should be adapted in the event of abnormal uterine bleeding (Grade C).

AWMF 2020 recommends to inform patients before systemic ET/EPT that it may lead to the occurrence or worsening of urinary incontinence. (level of evidence 1a, recommendation grade A, consensus strength ++)

FR 2021 recommends providing information on the effect of HRT on breast pain syndrome when it is prescribed, because of the link with the risk of breast cancer (Grade B).

FR 2021 and NHG 2022 further provide formal recommendations on how to manage abnormal uterine bleeding. In addition, the FR 2021 guideline provides recommendations on the management of breast pain or mass. See full text for these recommendations.

NHG 2022 mentions that the non-serious side effects (see above) of transdermal administration appear broadly similar to oral administration. However, itching and rash at the administration site also occur frequently after transdermal administration. They are uncertain about most serious side effects, but the risk of VTE may be lower with transdermal administration than with oral administration.

NHG 2022 also specifies that vaginally administered ET does not lead to supraphysiological levels at the usual doses and forms of administration and therefore on theoretical grounds that endometrial safety should not be an issue. AWMF 2020 and FR 2021 mention that side effects of local oestriol treatment are very rare, however, long-term results (>1 year) on the endometrial safety of vaginal ET are not available. NICE upd 2019 formally makes a recommendation to inform women that adverse effects from vaginal ET are very rare. AWMF 2020, NHG 2022 and NICE upd 2019 recommend women to report unscheduled vaginal bleeding.

5.4.1 AWMF 2020

Patientinnen sollen vor einer systemischen ET/EPT darüber informiert werden, dass diese zum Auftreten oder zur Verschlechterung einer Harninkontinenz führen kann. (Evidenzgrad 1a, Empfehlungsgrad A, Konsensusstärke ++)

Ein Jahr nach systemischer ET verdoppelt sich bei kontinenten Frauen die Prävalenz der Harninkontinenz im Vergleich zur Placebogruppe, unabhängig davon, ob eine Hysterektomie vorausging. Bei harninkontinenten Frauen besteht nach systemischer ET im Vergleich zu Placebo eine 30%-ige Wahrscheinlichkeit, dass sich die Inkontinenz verschlechtert. Bei einer EPT verschlechtert sich die Harninkontinenz ebenfalls, aber in geringerem Ausmass als bei einer ET.

Frauen, die nicht hysterektomiert sind, soll erklärt werden, dass Blutungsstörungen unter einer HRT auftreten können, insbesondere in den ersten Monaten der Therapie

Auch wenn diese meist harmlos sind, sollten Blutungsstörungen Anlass für eine Konsultation des Gynäkologen sein. Frauen sollen dem Gynäkologen bei dem Kontrolltermin nach 3 Monaten über Zwischenblutungen berichten. Wenn Blutungsstörungen nach 3 Monaten auftreten, sollten sie sofort ihre Gynäkologen aufsuchen.

Zu den unerwünschten Begleiterscheinungen gehören Brustspannen, Ödeme, Gelenkschmerzen und psychische Symptome. Als ernsthafte Ereignisse wurden in den HRT-Gruppen Thrombosen und Brustkrebs beobachtet.

5.4.2 FR 2021

Side effects

Les saignements utérins anormaux (SUA) sous traitement hormonal de ménopause (THM) sont un des principaux facteurs de mauvaise compliance.

Les SUA survenant sous THM correspondent (FIGO 2011) :

- à des saignements survenant en dehors de la période d'arrêt dans le traitement séquentiel
- ou des saignements survenant lors des schémas combinés continus.

L'hémorragie de privation est normale et attendue dans la période d'arrêt du traitement séquentiel mais son abondance et/ou sa durée peut (vent) être anormale(s). La durée moyenne des saignements pendant la période de privation est de $5,4 \pm 2$ jours.

Les données sont insuffisantes pour recommander des modalités d'adaptation du schéma thérapeutique du THM en cas de saignement utérin anormal (grade C).

L'aménorrhée sous THM combiné continu augmente significativement au-delà de 6 mois de traitement (NP2). La progestérone micronisée en traitement séquentiel offre un profil de saignement meilleur qu'un THM séquentiel utilisant de la MPA (NP1).

Le THM séquentiel offre un profil de saignement plus régulier versus THM combiné continu qui se modifie peu avec le temps. Plus de 2/3 des patientes présentent des saignements uniquement pendant la période de privation.

La posologie en estrogènes influence l'incidence des saignements. Une posologie faible en estrogènes (0,5 mg d'estradiol) en traitement combiné continu diminue de façon significative l'incidence des saignements avec la durée du traitement.

La posologie du progestatif influe sur l'incidence des saignements. Des doses élevées d'acétate de médroxyprogestérone (MPA) (5 mg) offrent un profil de saignement meilleur en comparaison à des doses plus faibles (2 mg). De plus, en associant le progestatif à doses élevées aux estrogènes à faible dose, le profil de saignement est amélioré.

Le traitement combiné estradiol/acétate de noréthistérone (NETA) en continu diminue de manière significative les saignements en comparaison à l'association estrogènes conjugués équinés (ECE)/MPA.

Une information concernant l'effet du traitement hormonal de ménopause sur le syndrome douloureux mammaire doit être donnée lors de sa prescription en raison de la relation avec le risque de cancer du sein (grade B).

Une information concernant l'amélioration spontanée du SDM avec l'avancée en âge doit être donnée aux femmes symptomatiques lors de la consultation de suivi.

La prévalence du SDM chez les femmes ménopausées diminue de manière significative avec l'âge (NP1).

La prévalence du syndrome douloureux mammaire (SDM) chez les femmes ménopausées diminue significativement moins avec l'âge chez les femmes prenant un THM (NP1) que chez les femmes non traitées.

La prévalence du SDM chez les femmes ménopausées augmente significativement chez les femmes prenant un THM à base d'ECE associé à un progestatif (NP1).

La prévalence du SDM n'augmente pas chez les femmes récemment ménopausées prenant un THM à dose modérée ou standard à base d'E et de P micronisée (NP3).

Les données publiées confirment le lien entre SDM et risque de cancer du sein. Ainsi les femmes rapportant un SDM avant de débiter un THM ou pendant l'utilisation d'un THM ont un risque de cancer du sein significativement augmenté comparativement aux femmes ne souffrant pas de SDM. Le risque est majoré en cas de SDM modéré à intense. (NP1)

In case of vaginal bleeding

En cas de saignement utérin anormal chez une femme ménopausée prenant un traitement hormonal de ménopause, il est recommandé de rechercher une cause organique (grade A) ; il est proposé de réaliser une échographie pelvienne (grade A), en fin de séquence progestative en cas de THM séquentiel ou quelle que soit la période en cas de traitement hormonal de ménopause combiné (avis d'expert) ; lors d'un épisode unique de saignement utérin anormal et lorsque l'échographie estime l'épaisseur de l'endomètre inférieure ou égale à 4 mm, il est possible de surseoir à une exploration utérine complémentaire (avis d'expert). En cas de saignements utérins anormaux récidivants ou lorsque l'épaisseur de l'endomètre est supérieure à 4 mm chez une femme ménopausée, des explorations utérines complémentaires (hystérocopie et histologie) sont recommandées (grade B).

Les principales causes fonctionnelles de SUA chez une femme prenant un THM sont la reprise de l'activité ovarienne, une observance médiocre et les troubles trophiques de l'endomètre (NP3). Ils sont dépendants du type de THM (NP2).

L'ajout de progestatifs, sous forme de régimes combinés continus ou séquentiels permet de prévenir l'apparition d'une hyperplasie de l'endomètre et le développement d'un cancer de l'endomètre (NP1). En cas de saignements, le diagnostic de cancer de l'endomètre est moins souvent porté sous THM que sans.

In case of painful breast syndrome

Devant un syndrome douloureux mammaire bilatéral (sans anomalie à l'examen clinique), il est proposé de ne pas modifier les indications habituelles de dépistage du cancer du sein ou ses modalités (avis d'expert).

Il n'y a pas non plus d'indication à réaliser une biopsie en cas de SDM diffus (avis d'experts).

Devant un syndrome douloureux mammaire bilatéral chez une femme récemment ménopausée, il est proposé de réduire, voire d'interrompre, le traitement hormonal de la ménopause (avis d'expert).

Devant un SDM focal, une imagerie diagnostique doit être réalisée (grade B).

A decision chart detailing these procedures is shown in the figure below.

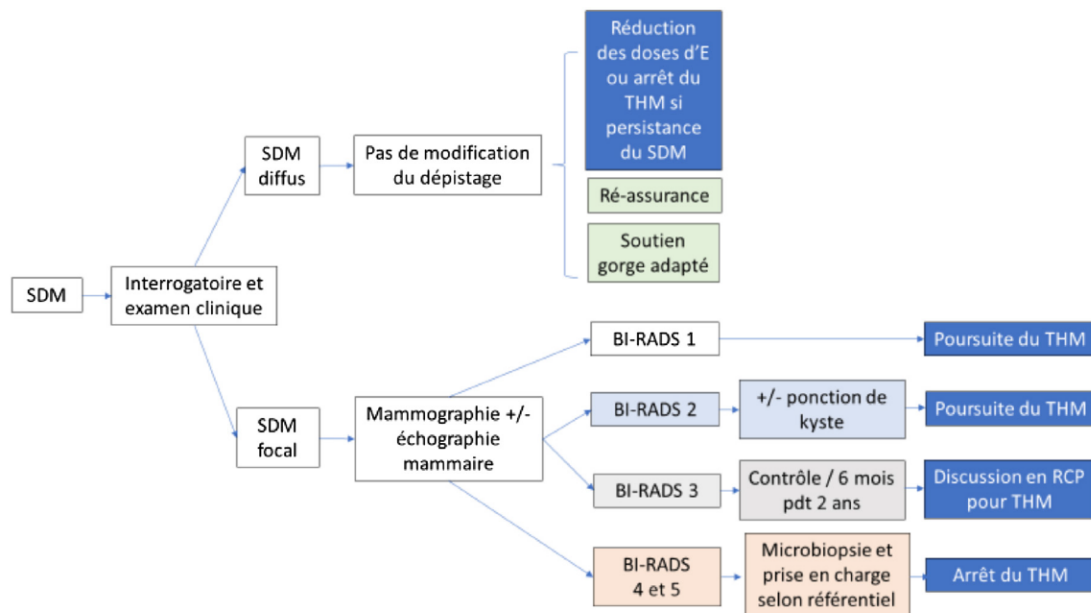


Fig. 1. Prise en charge d'un syndrome douloureux mammaire (SDM) sous THM.

In case of breast mass

En cas de découverte d'une masse mammaire chez une femme ménopausée prenant un traitement hormonal de la ménopause, il est recommandé de suspendre le traitement hormonal de la ménopause le temps de la démarche diagnostique (grade A).

En cas de découverte clinique d'une masse mammaire, il est recommandé de réaliser une imagerie du sein comprenant une mammographie et une échographie mammaire (grade B).

Il est recommandé d'utiliser la terminologie BI-RADS pour décrire les différentes anomalies mammaires visualisées sur l'imagerie (grade C). La conduite à tenir diagnostique doit être proposée selon cette catégorie lésionnelle BI-RADS.

La prise en charge diagnostique des masses classées BI-RAD 4 et 5 repose sur la réalisation de prélèvements percutanés au premier rang desquels se situe la microbiopsie. La prise en charge diagnostique des microcalcifications classées BI-RAD 4 et 5 repose sur la réalisation de macrobiopsie sous stéréotaxie.

Four radioclinical situations must be distinguished in the case of a clinical mass (see figure below).

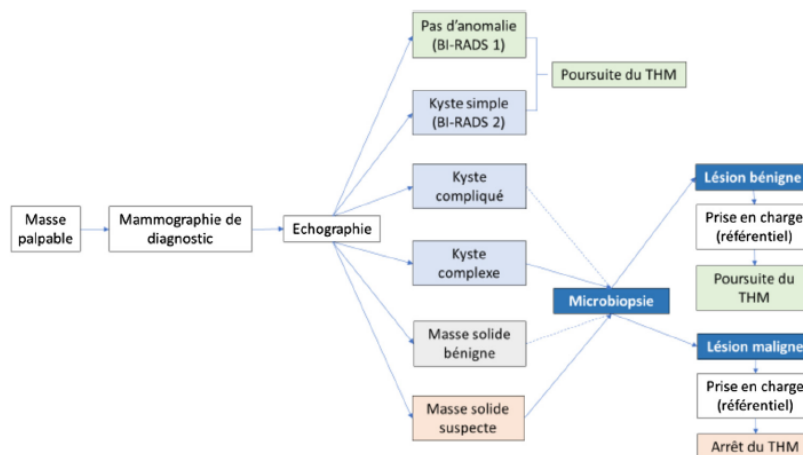


Fig. 1. Arbre décisionnel concernant la poursuite du THM chez une femme consultant pour une masse clinique (selon 4 situations radiocliniques : absence d'anomalie, masse liquidienne, masse solide bénigne et masse solide maligne).

Si la taille de la masse clinique reste stable, il n'y a pas d'argument pour contre-indiquer le THM et la poursuite du dépistage mammaire systématique est recommandée. Si la taille de la masse clinique augmente, une biopsie tissulaire doit être effectuée, la poursuite du THM devant tenir compte des résultats de cette biopsie.

En cas de kyste simple, il n'y a pas d'argument pour contre-indiquer le THM et la poursuite du dépistage mammaire systématique est recommandée. En cas de kyste compliqué ou complexe, si une biopsie tissulaire est effectuée, la poursuite du THM doit tenir compte des résultats de cette biopsie.

En cas de tumeurs mammaires bénignes, il n'y a pas de contre-indication à poursuivre le THM.

En cas de découverte d'une lésion maligne, (in situ ou invasive), le traitement hormonal de la ménopause doit être interrompu définitivement, quels que soient le statut des récepteurs hormonaux, le caractère invasif ou in situ de la tumeur du sein (grade A).

5.4.3 NHG 2022

Ongeveer 1-10% van de gebruikers heeft last van niet-ernstige bijwerkingen, zoals onregelmatig bloedverlies, hoofdpijn, maagdarmklachten, pijnlijke en gespannen borsten. Hormoontherapie heeft daarnaast mogelijk zeldzame, maar ernstige bijwerkingen. Het risico hierop kan enigszins verschillen, afhankelijk van de methode (oestrogeen monotherapie, sequentiële combinatietherapie of continue combinatietherapie), het type progestageen en de toedieningsvorm van het oestrogeen (oraal of transdermaal).

De niet-ernstige bijwerkingen van de verschillende progestagenen komen globaal overeen, maar verschillen enigszins in frequentie van voorkomen

Bij transdermale toediening lijken de niet-ernstige bijwerkingen globaal vergelijkbaar, maar daarnaast komt bij transdermale toediening frequent jeuk en huiduitslag op de toedieningsplaats voor. Over de meeste ernstige bijwerkingen zijn we onzeker, maar mogelijk is het risico op VTE lager bij transdermale toediening dan bij orale toediening.

...al geeft tibolon mogelijk minder kans op onregelmatig bloedverlies. Ook bij gebruik van tibolon kunnen er ernstige bijwerkingen op de lange termijn optreden, zoals borstkanker en endometriumcarcinoom; deze zijn minder goed onderzocht dan die van hormoontherapie met oestrogeen.

Voor tibolon gelden dezelfde contra-indicaties als voor hormoontherapie, dus het is niet breder toepasbaar dan hormoontherapie (KNMP Kennisbank, geraadpleegd juli 2020).

Vaginaal toegediende oestrogenen kunnen de eerste nachten van het gebruik een pijnlijk en branderig gevoel geven. In 1 onderzoek werd na 1 jaar gebruik geen verschil in endometriumdikte gevonden tussen oestrogeentabletten en placebotabletten. Geen enkel onderzoek keek naar het optreden van bijwerkingen over een periode > 1 jaar. Omdat vaginaal toegediende oestrogenen bij de gebruikelijke doseringen en toedieningsvormen niet tot suprafysiologische spiegels leiden (≤ 120 pmol/l) is er op theoretische gronden weinig reden om aan te nemen dat de veiligheid in het geding is.

In case of vaginal bleeding

- Verwijs naar een gynaecoloog voor beoordeling van het endometrium bij onregelmatig vaginaal bloedverlies dat optreedt of aanhoudt > 3 maanden na de start van continue combinatietherapie terwijl cervixpathologie en een chlamydia-infectie uitgesloten zijn.
- Transvaginale echografie in eigen beheer volstaat in deze situatie niet, want de endometriumdikte bij hormoontherapie is vaak > 4 mm
- Verwijs naar een gynaecoloog bij onverklaard vaginaal bloedverlies bij gebruik van vaginaal oestrogeen.

Bij combinatietherapie in de postmenopauze wordt onregelmatig onverwacht bloedverlies dat optreedt of aanhoudt > 3 maanden na de start van de behandeling beschouwd als abnormaal vaginaal bloedverlies. De termijn van 3 maanden voor verwijzing voor aanvullende diagnostiek is enigszins arbitrair.

Als aanvullend onderzoek dient er bij postmenopauzale vrouwen die onregelmatig bloedverlies hebben bij gebruik van combinatietherapie altijd een cervixuitstrijkje te worden verricht en dient een chlamydia-infectie te zijn uitgesloten.

5.4.4 NICE upd 2019

In order to capture the spectrum of adverse events that may be associated with different treatments used for the relief of menopausal related symptoms, vaginal bleeding and discontinuation of treatment due to side-effects were selected as the most representative measures of women's experience of adverse events in the short term.

Oral HRT

Explain to women with a uterus that unscheduled vaginal bleeding is a common side effect of HRT within the first 3 months of treatment but should be reported at the 3-month review appointment, or promptly if it occurs after the first 3 months (see recommendations on endometrial cancer in the NICE guideline on suspected cancer).

With hormonal therapy, unscheduled bleeding is common in the first 3 months and adjustment of dosage or formulation may be considered if there are persistent side effects such as bloating, nausea and breast discomfort.

In the absence of relevant evidence, the Guideline Development Group's recommendations were based on their clinical experience and expert opinion, and on existing guidance.

Local estrogen:

Explain to women with urogenital atrophy that:

- **symptoms often come back when treatment is stopped**
- **adverse effects from vaginal oestrogen are very rare**
- **they should report unscheduled vaginal bleeding to their GP.**

With regard to adverse events, the group wished to inform women who may opt for this local treatment that adverse events are considered rare, but, as is the case with systemic HRT, unscheduled vaginal bleeding should be reported to a healthcare professional. A separate recommendation was drafted to highlight this guidance.

No conclusive points could be made for the outcome of vaginal bleeding for women with a uterus given the limited data for this outcome and the lack of inclusion of several interventions in the network.

5.4.5 USPSTF 2022

USPSTF 2022 only formulated recommendations for risk of chronic conditions. No recommendation or information were related to short term side effects.

5.5 Chronic conditions

“Chronic conditions” are broadly defined as conditions that last 1 or more years and require ongoing medical attention, limit activities of daily living, or both. The following are classified as major chronic diseases by the Centers for Disease Control and Prevention because they are leading drivers of death, disability, and healthcare costs: heart disease, cancer, chronic lung disease, stroke, Alzheimer’s disease, diabetes, and chronic kidney disease. These conditions all have multiple risk factors, such as lack of physical activity, poor nutrition, tobacco use, and others.

The USPSTF 2022 recommends against the use of combined estrogen and progestagen for the primary prevention of chronic conditions in postmenopausal persons and against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy. (Grade D, moderate certainty)

5.5.1 USPSTF 2022

“Chronic conditions” are broadly defined as conditions that last 1 or more years and require ongoing medical attention, limit activities of daily living, or both. The following are classified as major chronic diseases by the Centers for Disease Control and Prevention because they are leading drivers of death, disability, and healthcare costs: heart disease, cancer, chronic lung disease, stroke, Alzheimer’s disease, diabetes, and chronic kidney disease. These conditions all have multiple risk factors, such as lack of physical activity, poor nutrition, tobacco use, and others.

Before 2002, hormone therapy was believed to help prevent some of these conditions based on evidence from observational studies.

Prior to 2002, menopause was viewed as a risk factor for several chronic conditions attributable primarily to two (related) bodies of evidence:

- 1) large observational studies showing an increased risk of chronic conditions in relationship to age at natural menopause (as well as increased incidence of biomarkers associated with chronic conditions, such as elevated lipid levels)

- 2) several observational studies and meta-analyses suggesting that hormone therapy including estrogen was beneficial for the prevention of chronic diseases such as coronary heart disease, osteoporosis, dementia, and all-cause mortality.

Before the publication of randomized, controlled trials (RCTs) of hormone therapy in postmenopausal persons, guidelines advocated for the use of hormone therapy for prevention of chronic diseases, and it was commonly prescribed for primary prevention of these conditions and others such as osteoporosis in persons without menopausal symptoms. After the publication of RCTs, the indication for hormone treatment shifted toward menopausal symptom management in the earlier stages of menopause.

The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons. (Grade d)

The US Preventive Services Task Force (USPSTF) concludes **with moderate certainty** that the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons with an intact uterus has no net benefit.

The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy. (Grade d)

The USPSTF concludes **with moderate certainty** that the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal persons who have had a hysterectomy has no net benefit.

Overall, trials reported several statistically significant benefits of treatment.

- For women using estrogen only, risk of fractures (388 fewer cases per 10,000 women over 7.2 years [95% CI, 489 to 277 fewer]) and diabetes (134 fewer cases per 10,000 women over 7.1 years [95% CI, 237 to 18]) were statistically significantly reduced compared with women taking placebo. The risk of breast cancer was numerically reduced but did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]).
- Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years [95% CI, 9 to 51]), fractures (230 fewer cases per 10,000 women over 5.0 years [95% CI, 372 to 66 fewer]), and diabetes (78 fewer cases per 10,000 women over 5.6 years [95% CI, 133 to 15 fewer]) compared with women in the placebo groups.

Long-term followup studies of the WHI showed that most beneficial effects dissipated after stopping hormone therapy. An exception was the risk of invasive breast cancer in women who received estrogen-only therapy. The risk reduction became statistically significant during cumulative (trial and postintervention phase) follow-up (median 13 years: HR, 0.79 [95% CI, 0.65 to 0.97]; 67 median 20.7 years: HR, 0.78 [95% CI, 0.65 to 0.93] [87]). Likewise, after 13.2 years of cumulative followup, the risk for endometrial cancer became statistically significantly lower in women who were on estrogen plus progestin therapy (HR, 0.65 [95% CI, 0.48 to 0.89]).

Results of trials and our meta-analyses indicate several important harms for hormone therapy. They differ by treatment formulation (i.e., estrogen only or estrogen plus progestin).

- Women receiving estrogen-only therapy had statistically significantly increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years [95% CI, 234 to 540]), stroke (79 more cases per 10,000 women over 7.2 years [95% CI, 15 to 159]), urinary incontinence (885 more cases per 10,000 women over 1 year [95% CI, 659 to 1,135]), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years [95% CI, 19 to 153]).
- For women receiving estrogen plus progestin therapy, risk of invasive breast cancer (51 more cases per 10,000 women over 5.6 years [95% CI, 6 to 106]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 212]), gallbladder disease (260 more cases per 10,000 women over 5.6 years [95% CI, 169 to 364]), stroke (52 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104]), urinary incontinence (562 more cases per 10,000 women over 1 year [95% CI, 412 to 726]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185]) were statistically significantly increased compared with women taking placebo (Figure 4).

We did not find any evidence on other harms or on the effect of harms on functional capacity.

Global mortality:

A pooled analysis of 3 trials (n=?19,580) showed no significant difference in all-cause mortality between persons taking estrogen and progestin therapy and those taking placebo (RR, 1.01 [95% CI, 0.88-1.16]) during 3.2 to 5.6 years of follow-up.

Similarly, a pooled analysis of 3 trials (n=11,587) showed no significant difference in all-cause mortality between persons receiving estrogen alone and those receiving placebo (RR, 1.04 [95% CI, 0.89-1.21]) during a mean follow-up of 7.1 years.

5.6 Musculoskeletal effects

NHG 2022 does not provide specific recommendations or comments regarding musculoskeletal effects/risks.

Osteoporosis

AWMF 2020, FR 2021 and NICE upd 2019 all agree that HRT leads to a significant reduction in the risk of osteoporosis and or associated fractures. This effect is independent of the duration of use (i.e. already detectable after < 1 year of use) and the age at the start of therapy. This effect is maintained during treatment but decreases once treatment stops and may continue for longer if treatment is taken longer.

NICE upd 2019 recommends to give women advice on bone health, explain to women that the baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another, and to discuss these issues at review appointments.

In women at risk of fracture, FR 2021 recommends that at the start of the menopause, menopausal hormone therapy should be offered as the first-line treatment to prevent osteoporosis (Grade A). The proposed threshold for intervention is a T-score (vertebral or femoral) of less than -2. Other clinical risk factors for fracture and the individualized benefit-risk balance of HRT should be taken in to account (Grade C).

FR 2021 states that, given the inter-individual variability of the bone response to estrogens, it is not possible to recommend a single standard dose for the prevention of bone loss in all women (grade B), which justifies individual assessment of the bone impact of HRT prescribed for the prevention of osteoporosis (expert opinion).

Monitoring of bone effect (FR 2021)

- The management of HRT in practice implies the evaluation of its efficacy in its two main indications (climacteric syndrome and prevention of osteoporosis).
- In practice, there is insufficient data to recommend systematic estradiol measurement to monitor the efficacy of HRT on bone (Grade B).
- It is suggested that women taking HRT for the prevention of osteoporosis should have their lumbar and femoral BMD measured again (using the same DXA measurement system) after 2 years of HRT (expert opinion).
- In menopausal women taking HRT to prevent osteoporosis, measurement of a bone remodeling marker (plasma CTX) may be suggested (expert opinion):
 - in the event of difficulty in interpreting the densitometric variation between two examinations
 - to assess the bone effect of HRT at an earlier stage in special cases (patients at increased risk of fracture, doubts about compliance with HRT, a priori insufficient doses of estrogen, etc.).
- In practice, there is currently no consensus on the definition of a bone response to HRT based on the measurement of bone remodeling markers. Criteria can be identified based on what

has been proposed for bisphosphonate (expert opinion, see full recommendations from FR 2021 for more details).

When HRT is prescribed to prevent the risk of fracture in a woman at increased risk, FR 2021 also suggests that a BMD measurement be taken when the HRT is stopped, considering possible changes in management (possible replacement by another osteoporosis treatment and/or hygienic and dietary measures) (expert opinion).

AWMF 2020 specifies that the duration of a specific osteoporosis therapy depends primarily on the current estimated fracture risk and in most cases is at least 3-4 years. They mention that the clinical follow-up is essential, because adherence to therapy is a major problem. According to current studies, more than one in two patients discontinues the drug within 1-2 years.

According to FR 2021 the question of the optimal duration of HRT for the prevention of osteoporosis remains governed by the increased risk of breast cancer and must also consider the availability of other osteoporosis treatments. They suggest the following:

“HRT should be considered first and foremost as the 1st step in a long-term fracture prevention strategy for women at risk of osteoporosis at the start of the menopause. Indeed, while the risk of fracture at this age remains moderate, it will increase with age, justifying the use of osteoporosis treatments (raloxifene, bisphosphonates, denosumab, teriparatide) later on, which have above all demonstrated their efficacy in women at high risk of fracture after the menopause. The role of HRT is therefore to enable genuine primary prevention of fracture risk, which involves preventing bone loss and micro-architectural abnormalities at the start of the menopause rather than reducing fracture risk, which is still moderate in younger women.”

Muscle mass

NICE recommends to explain to women that there is limited evidence suggesting that HRT may improve muscle mass and strength and that muscle mass and strength is maintained through, and is important for, activities of daily living.

5.6.1 AWMF 2020

Eine HRT führt zu einer signifikanten Erniedrigung für das Risiko für Osteoporose-assoziiierter Frakturen. (Evidenzgrad 1a, Konsensusstärke +++)

Der frakturvermindernde Einfluss einer HRT war unabhängig von der Einnahmedauer (d.h. bereits nach einer kurzen < 1-jährigen Einnahme nachweisbar) und des Alters bei Therapiebeginn.

Zusätzlich scheint der frakturvermindernde Effekt nach Beendigung einer HRT in geringerem Maße weiter zu bestehen. (Evidenzgrad 2a, Konsensusstärke ++)

Die Wirksamkeit einer EPT bzw. einer ET zur Primärprävention osteoporotischer Frakturen wurde in multiplen älteren Beobachtungsstudien, Fall-Kontroll sowie RCTs hinreichend belegt. Dabei konnte auch bei Frauen ohne erhöhtes Frakturrisiko eine signifikante Risikoreduktion für Schenkelhals-, Wirbelkörper- sowie nicht-vertebrale Frakturen nachgewiesen werden. Diese Ergebnisse flossen in diverse Meta-Analysen sowie Empfehlungen internationaler Fachgesellschaften ein.

In der aktuellen Version (2017) der SIII-Leitlinie des DVO ist die Prävention oder Behandlung der Osteoporose mittels einer HRT bei postmenopausalen Frauen mit hohem Risiko möglich, wenn

Wechseljahrsbeschwerden bzw. eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Medikamenten besteht. Bei aus anderen Gründen durchgeführter HRT in einer Standarddosis ist auch bei hohem Frakturrisiko kein weiteres spezifisches.

Zusätzlich scheint der frakturreduzierende Effekt auch nach Beendigung einer HRT weiter zu bestehen.

Grundsätzlich ist aufgrund der chronischen Natur der Erkrankung der Osteoporose von einer Langzeittherapie auszugehen. Hierbei richtet sich die Dauer einer spezifischen Osteoporosetherapie vor allem nach dem aktuellen geschätzten Frakturrisiko beträgt in den meisten Fällen primär jedoch mindestens 3-4 Jahre. Hierbei sind klinische Verlaufskontrollen essentiell, weil die Therapietreue ein großes Problem darstellt. Aktuelle Studien zur Folge setzt mehr als jede zweite Patientin das Medikament innerhalb von 1-2 Jahren ab.

5.6.2 FR 2021

HRT for prevention of osteoporosis

Chez la femme à risque fracturaire, il est recommandé de proposer en début de ménopause, la prise d'un traitement hormonal de ménopause en 1^{re} intention pour prévenir l'ostéoporose (grade A).

Le THM diminue le risque de fracture à tous les sites osseux y compris chez les femmes à faible risque de fracture (NP1).

Le seuil d'intervention proposé est un T-score (vertébral ou fémoral) inférieur à -2 (avis d'expert).

Cette décision devra prendre en compte les autres facteurs cliniques de risque de fracture et la balance bénéfice-risque individualisée du traitement hormonal de ménopause (grade C).

En prévention de l'ostéoporose, le THM peut être proposé chez les femmes qui abordent la ménopause avec une diminution de la DMO plus ou moins associée à des facteurs de risque de fracture. Compte tenu du taux moyen de perte osseuse en début de ménopause, il a été montré que les femmes dont le T-score était supérieur à -2 avaient moins de 10 % de risque d'évoluer vers l'ostéoporose densitométrique dans les 10 ans (valeur prédictive négative de 90 %) (NP2).

Le THM garde sa place dans les 10 premières années de la ménopause chez une femme ayant une ostéoporose fracturaire et/ou densitométrique à côté des autres traitements de l'ostéoporose tel que défini par les recommandations du GRIO.

Néanmoins, compte tenu de la variabilité inter-individuelle de la réponse osseuse aux estrogènes, il n'est pas possible de recommander une dose standard unique pour la prévention de la perte osseuse chez toutes les femmes (grade B), ce qui justifie l'évaluation individuelle de l'impact osseux du THM prescrit pour la prévention de l'ostéoporose (avis d'expert).

L'effet du THM en prévention de la perte osseuse et des anomalies de la micro-architecture osseuse du début de la ménopause est largement démontré (NP1).

Il existe un effet-dose des estrogènes tant sur les variations de DMO que sur le pourcentage de non-répondeurs au THM (NP1) avec un taux de non-répondeurs plus élevé pour les doses les plus faibles (NP1).

Il n'est pas possible de recommander un schéma thérapeutique standard pour la prévention de l'ostéoporose et du risque fracturaire chez toutes les femmes (grade B).

Dans cette indication, le recours à un suivi individuel de l'effet osseux du THM est justifié (avis d'expert).

La voie d'administration des estrogènes n'influence pas la réponse osseuse au THM (NP1). Le type de schéma thérapeutique et l'addition de la progestérone ou d'un progestatif de synthèse (à l'exception de l'acétate de norethistérone) n'influencent pas la réponse osseuse au THM (NP1-2). Aucune étude randomisée contrôlée ne permet de répondre à la question de l'efficacité anti-fracturaire des faibles doses d'estrogènes. Dans l'étude WHI, l'efficacité anti-fracturaire du THM était comparable avec les estrogènes conjugués seuls ou en association avec l'acétate de médroxyprogestérone. Dans les études de cohorte E3N et MWS, il n'y avait aucune différence en termes d'efficacité anti-fracturaire du THM selon le type du progestatif associé aux estrogènes (NP2).

Evaluation of HRT efficacy for osteoporosis

La gestion du THM en pratique sous-tend l'évaluation de son efficacité sur ses deux principales indications (syndrome climatérique et prévention de l'ostéoporose) tout comme de la durée de traitement.

Une étude a montré l'absence de corrélation entre le degré d'efficacité clinique (score de Kupperman) et le gain de masse osseuse à 3 ans. L'étude de Rodgers et Miller a également montré l'absence de corrélation entre les symptômes climatériques, le taux d'estradiolémie et la prévention de la perte osseuse. La présence d'hémorragie de privation dans le cadre de traitement séquentiel n'était pas significativement corrélée à la réponse osseuse dans l'étude de Ribot et al.

En pratique, il n'y a pas de donnée suffisante pour recommander un dosage systématique de l'estradiolémie pour le suivi de l'efficacité osseuse du THM (grade B).

Pour la voie transdermique, la concentration maximale plasmatique d'estradiol est atteinte entre 2 et 8 heures après application du patch. Ce même taux se maintiendra à un niveau relativement constant pendant trois à quatre jours.

Les études pharmacocinétiques des traitements par voie orale montrent une importante variabilité circadienne et interindividuelle qui ne permet pas au dosage d'être reproductible et informatif. En pratique, le dosage de l'estradiolémie peut donc s'envisager uniquement pour les traitements par voie cutanée, 8 à 12 heures après l'application de gel ou 48 heures environ après l'application d'un patch. Il existe cependant des difficultés inhérentes au dosage de l'estradiolémie puisque les variations circadiennes et inter-individuelles sont très importantes.

Un seuil ≥ 50 pg/mL serait associé à une réponse osseuse satisfaisante quel que soit le mode d'administration de l'estrogène. Néanmoins, ces données sont parcellaires et la qualité méthodologique des études est médiocre.

Il est proposé pour une femme prenant un traitement hormonal de ménopause pour la prévention de l'ostéoporose, de répéter la mesure de la DMO lombaire et fémorale (sur le même système de mesure de DXA) après 2 ans de THM. (avis d'expert)

L'absence de perte osseuse à 2 ans représente l'objectif thérapeutique d'un THM prescrit pour la prévention de l'ostéoporose en début de ménopause.

Chez une femme ménopausée prenant un traitement hormonal de ménopause pour la prévention de l'ostéoporose, le recours au dosage d'un marqueur du remodelage osseux (CTX plasmatique) peut être proposé (avis d'expert) :

- en cas de difficulté à interpréter la variation densitométrique entre deux examens
- pour évaluer plus précocement l'effet osseux du THM dans des cas particuliers (patiente à risque fracturaire majoré, doute sur l'observance du THM, doses d'estrogènes a priori insuffisantes...)

En pratique, il n'y a pas à ce jour de consensus sur la définition d'une réponse osseuse au THM basée sur le dosage des marqueurs du remodelage osseux. Si l'on se base sur ce qui a été proposé pour les bisphosphonates par voie orale on peut identifier deux critères de réponse (avis d'expert) :

- une baisse minimale du taux de CTX à 3 mois et/ou 6 mois par rapport au taux préthérapeutique, le seuil retenu étant au minimum de 30 %, ce qui correspond à la plus petite variation significative tenant compte de la variabilité inhérente à la technique de dosage (NP2)
- le retour aux valeurs moyennes de la femme non ménopausée (notamment lorsque les valeurs avant traitement ne sont pas disponibles) (NP2).

Le dosage des marqueurs du remodelage osseux offre l'avantage d'une variation plus précoce et plus ample (par rapport à la reproductibilité de la méthode) que l'évolution densitométrique et peut être complémentaire de la mesure de DMO dans certaines situations.

Treatment duration

(see also chapter 5.3 for more general recommendations.)

L'impact du THM pour prévenir la perte osseuse post-ménopausique est rapide et peut être documenté après 6 mois de traitement par la mise au repos de l'activité du remodelage osseux et 12 à 18 mois par la stabilité des valeurs de DMO (NP1). Cet effet perdure avec la durée du THM (NP1). En termes de risque fracturaire, l'étude WHI a montré qu'une durée de 5 ans de THM était associée à une réduction significative du risque de fracture (NP1). Toutes les études montrent de plus que le bénéfice anti-fracturaire est maintenu avec la durée du THM (NP1).

Néanmoins, la question de la durée optimale du THM pour la prévention de l'ostéoporose reste sous-tendue par l'augmentation du risque de cancer de sein au-delà d'une certaine durée de traitement qui justifie de réévaluer régulièrement la balance bénéfices-risques individuelle du THM. Cette question doit également prendre en compte la disponibilité des autres traitements de l'ostéoporose. À ce jour, l'ostéoporose post-ménopausique reste considérée comme une pathologie chronique avec un risque de fracture qui ne fera qu'augmenter avec l'avancée en âge.

Le THM doit donc être avant tout envisagé comme une 1ère étape d'une stratégie de prévention à long terme du risque fracturaire pour les femmes à risque d'ostéoporose en début de ménopause. En effet, si le risque fracturaire à cet âge reste modéré, il ne fera que se majorer avec l'âge justifiant de privilégier plus tard les traitements de l'ostéoporose (raloxifène, bisphosphonates, dénosumab, téraparatide) qui ont avant tout démontré leur efficacité chez les femmes à haut risque de fracture et à distance de la ménopause. Le rôle du THM est ainsi de permettre une véritable prévention primaire du risque fracturaire qui passe plus par la prévention de la perte osseuse et des anomalies micro-architecturales du début de la ménopause que par la réduction d'un risque fracturaire qui reste encore modéré chez les femmes les plus jeunes.

Treatment discontinuation for women with increased risk receiving THM for fractures prevention

(see also chapter 5.3. for more general recommendations.)

Quand le THM est prescrit pour la prévention du risque fracturaire chez une femme à risque majoré, il est proposé de faire une mesure de DMO à l'arrêt du THM, en vue d'une prise en charge adaptée (relais possible par un autre traitement de l'ostéoporose et/ou mesures hygiénodietétiques) (avis d'expert).

Dans toutes ces études, l'arrêt du traitement est associé à un phénomène de perte osseuse intéressant l'ensemble du squelette (NP1).

Cette perte osseuse est comparable à ce que l'on observe en début de ménopause (NP2). Après 5 ans d'arrêt en moyenne, il n'apparaît habituellement plus de différence de DMO entre les anciennes utilisatrices et les non-utilisatrices du THM (NP2). L'effet du THM sur la DMO et la micro-architecture osseuse disparaît rapidement à l'arrêt de celui-ci du fait de la reprise d'une perte osseuse liée au retour du remodelage osseux à son niveau de base (NP1). De façon parallèle, le risque de fracture revient progressivement à un taux équivalent à celui de femmes n'ayant jamais reçu de THM (NP2). Il n'y a pas à l'arrêt du THM, de phénomène de rebond avec un risque fracturaire qui dépasserait le risque physiologique lié à l'âge (NP1). Le retour à un niveau de risque fracturaire comparable à celui de femmes de même âge n'ayant jamais été traitées se fait dans un délai plus ou moins court, entre 1 à 5 ans pour les études d'observation et selon la durée préalable du THM (NP2) et après 5 ans dans l'essai WHI (NP1). Le risque de fracture est proportionnel à la valeur de T-score mesurée à l'arrêt du THM (NP2). Chez les femmes à risque, le relais du traitement hormonal par un bisphosphonate permet de bloquer la reprise de la perte osseuse associée à l'arrêt du THM (NP2).

5.6.3 NHG 2022

No specific recommendations or comments were provided regarding musculoskeletal effect or risk this guideline.

5.6.4 NICE upd 2019

5.6.4.1 Loss of muscle mass ('sarcopenia')

Explain to women that:

- **there is limited evidence suggesting that HRT may improve muscle mass and strength**
- **muscle mass and strength is maintained through, and is important for, activities of daily living.**

The group considered the change in muscle strength (knee extension torque and strength, flexion, handgrip strength and adductor pollicis) to be the most important outcome for their decision-making. Change in muscle mass was assessed using either cross-sectional lean tissue area or appendicular skeletal muscle mass.

Loss of function relating to ageing was not considered for this review question.

Interventions that slow sarcopenia (such as exercise and good nutrition) are important as they enable postmenopausal women to maintain independent living.

The evidence reviewed was not consistent in terms of producing benefit for improving skeletal support for women in menopause taking HRT. The only significant result from randomised evidence was for the outcomes of quadriceps muscle cross-sectional area and adductor pollicis for postmenopausal women on HRT compared with the group who had not received treatment.

The group also discussed the role of an integrated approach to improve skeletal support for postmenopausal women, such as dietary strategies, nutritional supplementation and physical exercise; however, preventing and treating sarcopenia was not the focus of this review, although the group discussed its importance in improving women's muscle strength outcomes.

For this review question the group focused on the impact of HRT on the risk of developing sarcopenia and did not consider primary treatment for that condition. For this reason, exercise that increases muscle strength was not considered as a focus in this section.

The quality of the randomised evidence ranged from moderate to very low due to high risk of bias of some of the included studies (due to unclear randomisation or allocation concealment) and to imprecision.

5.6.4.2 Osteoporosis

Give women advice on bone health and discuss these issues at review appointments (see the NICE guideline on osteoporosis: assessing the risk of fragility fracture).

Using table 4, explain to women that the baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies from one woman to another.

Using table 4, explain to women that their risk of fragility fracture is decreased while taking HRT and that this benefit:

- **is maintained during treatment but decreases once treatment stops**
- **may continue for longer in women who take HRT for longer.**

Consistent evidence from both randomised and cohort studies demonstrated that the risk of any fragility fracture and non-vertebral fracture was significantly lower for women currently taking HRT (either oestrogen alone or for the combination of oestrogen plus progestogen) compared with non-users. The risk of hip fracture was also found to be significantly lower for those women on HRT treatment compared with the no treatment group, but this finding was only supported by the prospective cohort studies.

The effect of duration of HRT use on the risk of fractures was investigated in both randomised and observational data. No change in the direction of observed protective effect of HRT on the risk of any fracture was found when different HRT durations (short-term duration of less than 1 year, up to 5 years, 5 to 10 years or more than 10 years) were examined in RCTs. However, the observational evidence on non-vertebral and hip fracture showed that the effect of HRT on lowering the risk of this type of fracture was only apparent for HRT durations more than 10 years.

Subgroup analysis was undertaken on the role of different age profiles when the risk of osteoporosis was examined in relation to HRT use; randomised evidence did not support any differences in the direction of effects based on age.

Evidence from cohort studies also showed that the protective effect of HRT on the risk of fractures is not influenced by the time since stopping HRT, implying that protection may be preserved after HRT is stopped.

The Guideline Development Group concluded that current use of HRT treatment compared with non-use for women in menopause is associated with a significantly lower risk of fragility fracture and this lower risk is preserved when HRT is discontinued, although magnitude of difference between groups is smaller. Age and HRT duration may not produce any change in the direction of these conclusions. The majority of evidence from RCTs was rated moderate to low quality with imprecision the domain mainly affected in the quality assessment. All women included in the RCTs were postmenopausal and aged 40 to 65 years old.

5.6.5 USPSTF 2022

USPSTF only formulated general recommendations for all chronic conditions considered together. Evidence were provided separately for fractures but are not reported in this document.

5.7 Neurological and psychological effects

NHG 2022

No specific recommendations or comments were provided regarding neurological or psychological effects.

Cognitive function, dementia and Alzheimer's disease.

AWMF 2020 (level of evidence LLA, recommendation grade A, consensus strength +++) and NICE upd 2019 recommend that menopausal women should be informed that it is unclear whether HRT before the age of 65 influences the risk of dementia. The data from the available low-quality studies show that there is no strong evidence to support a conclusion regarding a protective or negative effect of HRT.

FR 2021 does not recommend starting HRT for the sole purpose of preventing Alzheimer's disease (Grade C), as well as for the sole purpose of preventing cognitive decline (Grade B). Concerning cognitive decline FR 2021 further states that according to the WIHMS study, starting HRT late is harmful, and adding medroxyprogesterone is even more so.

FR 2021 recommends against prescribing menopausal hormone therapy to women with Alzheimer's disease (Grade C).

Mood disorder, anxiety and depression

AWMF 2020 adds that HRT may be considered for the treatment of mood disorders if the psychological symptoms occur as a result of menopause or worsen in relation to menopause (not formulated as formal recommendation).

NICE upd 2019 recommends to consider HRT to alleviate low mood that arises as a result of the menopause. Also consider cognitive behavioural therapy to alleviate low mood or anxiety that arise as a result of the menopause.

Ensure that menopausal women and healthcare professionals involved in their care understand that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression (NICE upd 2019).

AWMF 2020 states that there is insufficient evidence to recommend HRT or psychotherapy for the treatment of perimenopausal depression. The indication for pharmacological treatment of depression in perimenopause should follow the general treatment guidelines (no direct efficacy studies in perimenopause). AWMF 2020 adds that there is currently no firm evidence of differential efficacy of antidepressants depending on menopausal status (level of evidence LLA, recommendation grade A, consensus strength ++).

5.7.1 AWMF 2020

Dementia

Frauen in der Peri- und Postmenopause sollen darüber beraten werden, dass es unklar ist, ob eine HRT vor dem 65. Lebensjahr das Demenzrisiko beeinflusst. (Evidenzgrad LLA, Empfehlungsgrad A, Konsensusstärke +++)

Es gibt keine Daten mit starker Evidenz für ein erhöhtes Demenzrisiko oder für einen vorteilhaften Effekt hinsichtlich Demenz bei Frauen mit natürlicher Menopause, die eine peri- oder postmenopausale HRT vor dem 65. Lebensjahr anwenden.

Lediglich in einer der untersuchten Studien, einer retrospektiven Kohortenstudie an >10000 Frauen, fand sich ein signifikant reduziertes Demenzrisiko nach Anwendung einer HRT gegenüber keiner HRT in der Eigenanamnese. Daten aus der WHI-Studie legen nahe, dass bei Beginn einer HRT nach dem 65. Lebensjahr das Risiko einer Demenz signifikant erhöht ist. Die Daten aus den vorliegenden Studien von geringer Qualität belegen, dass keine starke Evidenz vorliegt eine Aussage bzgl. eines protektiven oder negativen Effekts einer HRT zu unterstützen.

Mood disorder

Eine HRT kann zur Behandlung von Stimmungsschwankungen in Betracht gezogen werden, wenn die psychischen Symptome als Folge der Menopause auftreten oder sich in zeitlichem Zusammenhang mit der Menopause verschlechtern.

Depression

Die Indikation zur pharmakologischen Behandlung von Depressionen in der Perimenopause soll den allgemeinen Behandlungsleitlinien folgen (es liegen keine direkten Wirksamkeitsstudien in der Perimenopause vor). Es gibt derzeit keine sicheren Hinweise auf eine unterschiedliche Wirksamkeit von Antidepressiva in Abhängigkeit vom Menopausenstatus. Es liegt keine ausreichende Evidenz zur Empfehlung einer HRT oder Psychotherapie zur Behandlung perimenopausaler Depressionen vor. (Evidenzgrad LLA, Empfehlungsgrad A, Konsensusstärke ++)

Zur Wirksamkeit einer HRT bei Frauen mit peri- und postmenopausaler Depression liegen nur einzelne Studien mit widersprüchlichen Ergebnissen vor. Die North American Menopause Society kommt zu folgenden Schlüssen: Bewährte therapeutische Optionen für Depressionen (Antidepressiva, Psychotherapie) sind auch die Behandlungsoptionen der ersten Wahl für perimenopausale Depression.

Es existieren zwar keine expliziten Wirksamkeitsstudien bzgl. einer antidepressiven Behandlung in der Peri- und Postmenopause, verschiedene Studien untersuchten jedoch den Einfluss des Menopausenstatus auf die Wirkung antidepressiver Pharmakotherapien. Während in früheren Studien ein schlechteres Ansprechen auf SSRIs bei älteren im Vergleich zu jüngeren Frauen berichtet wurde, bzw. ein besseres Therapieansprechen bei älteren Frauen, wenn neben SSRIs auch eine HRT erfolgte, wird dies durch die Ergebnisse neuerer großer Studien nicht bestätigt.

5.7.2 FR 2021

Les connaissances sur les relations entre THM et fonction cognitive sont limitées par le peu d'essais randomisés contrôlés disponibles et la quasi-absence d'études comparatives entre les différents estrogènes et progestatifs.

Alzheimer's disease

Un lien épidémiologique est suggéré entre le risque de démence et la durée d'exposition aux estrogènes. L'ovariectomie avant la ménopause augmente le risque de démence ; si elle survient

avant 38 ans, le risque de maladie d'Alzheimer (MA) est multiplié par 3 et une estrogénothérapie substitutive, au moins jusqu'à 50 ans annulerait ce surrisque (NP2).

- *Women with Alzheimer's disease*

Il est recommandé de ne pas prescrire le traitement hormonal de la ménopause à des femmes atteintes de MA (grade A).

Chez des femmes souffrant de MA, le traitement hormonal de la ménopause aggrave les troubles cognitifs (NP1).

- *Primary prevention of Alzheimer's disease*

Il n'est pas recommandé de débiter un traitement hormonal de la ménopause dans le seul but de prévenir la maladie d'Alzheimer (grade C).

Une étude ancillaire de l'étude WHI concernant des femmes de plus de 65 ans rapporte une augmentation du déclin cognitif associé à la fois à la combinaison ECE + MPA et aux ECE donnés seuls (NP1).

Plusieurs études d'observation suggèrent qu'un THM débuté précocement en début de ménopause n'a pas d'effet délétère (NP2), voire pourrait limiter le risque de MA (NP3), alors que lorsqu'il est débuté à distance de la ménopause, une aggravation du risque pourrait être observé (NP2).

La prise d'E2td (au contraire des ECE) était associée à une réduction significative des dépôts de protéine bêta amyloïde (bA), particulièrement chez les femmes porteuses de l'allèle ApoEε4 (allèle qui confère à ces femmes un risque particulier pour la MA) (NP1). Bien plus, ces femmes traitées par E2td avaient une diminution significativement moindre du volume du cortex préfrontal dorsolatéral (impliqué dans la MA), et ce, corrélé à un moindre dépôt de bA. Cette étude suggère que l'impact cérébral des E2 administrés par voie transdermique ne serait pas le même que pour les ECE par voie orale (NP2).

Cognitive impairment

Il n'est pas recommandé de débiter un traitement hormonal de la ménopause dans le seul but de prévenir un déclin cognitif (grade B). De plus, instaurer un THM tardivement est délétère selon la WHIMS, et l'ajout de la médroxyprogestérone l'est encore davantage.

La notion de fenêtre d'intervention, bien établie pour le risque CV, n'est donc pas retrouvée pour le déclin cognitif, la réserve cognitive permettant le maintien d'une cognition normale même en présence de lésions cérébrales (NP1).

Pour les essais randomisés réalisés chez des femmes jeunes, en début de ménopause ou plus à distance, les données ne montrent majoritairement aucun bénéfice, ni aucune dégradation des fonctions cognitives associées au THM (ECE ou estradiol associés à la progestérone) (NP1).

Aucun bénéfice, ni aucun effet délétère n'ont été retrouvés 7 ans après l'arrêt du traitement hormonal qu'il s'agisse des ECE seuls ou de ECE + MPA (NP2).

En conclusion, la prise d'un THM en début de ménopause, dans la fenêtre d'intervention, fenêtre bénéfique pour le système cardiovasculaire n'a pas d'effet délétère sur le déclin cognitif ou l'apparition d'une démence (NP1). Il n'y a néanmoins, à ce jour, pas d'effet bénéfique démontré.

5.7.3 NHG 2022

No specific recommendations or comments were provided regarding neurological or psychological effects this guideline.

De stemming en het seksueel functioneren worden door hormoontherapie niet of nauwelijks beïnvloed.

5.7.4 NICE upd 2019

Dementia

Explain to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown.

The only small RCT included for this topic showed that there is no significant difference in dementia as assessed by different measurements for postmenopausal women who received HRT for 2 years and those who did not. In contrast, the evidence from prospective cohort studies was not consistent, mainly due to the heterogeneity of data included. The majority of studies, which looked at different ways to assess dementia, showed no significant difference in the development of dementia between those women who had current or prior use of HRT and those who had not.

The group considered the spectrum of both randomised and cohort evidence and concluded that there was no strong evidence base to support the protective or negative effect of HRT on the risk of dementia for women experiencing a 'normal', as opposed to premature, menopause.

There is some indication that there may be a window of opportunity for lowering the risk of dementia with HRT use for women with specific preconditions, such as higher baseline risk if they have first-line relatives with dementia, or for women who have premature ovarian insufficiency (POI).

However, the group did not feel confident to extrapolate from this evidence and their clinical experience on whether a consistent direction of HRT impact on dementia exists for women going through a normal menopause.

The group concluded that it would be important to advise women in the menopause that the evidence on HRT and the risk of dementia is yet to be firmly established either way (protective or harmful effect).

However, the randomised evidence was of low to very low quality as it included just 1 small RCT study of high risk of bias (selection and performance bias) which was also downgraded for imprecision. In addition, its population had a younger age profile (below 60 years) and the follow-up was too short (2 years) to allow any observation of the effect of HRT on the outcome of dementia. The quality of the evidence on comparative cohort studies varied from low to very low quality.

Anxiety and low mood

Depression and mood change is common at times of hormonal change, such as during the menstrual cycle, after pregnancy and in the perimenopausal period. In some instances this may lead to clinical depression, although this is not the focus of this part of the guideline. Women often complain of anxiety and feeling low around the time of the menopause, having mood swings and feeling frustrated. Women are often distressed at these changes and feel that they are out of character. Some women will feel much better with HRT, particularly if the mood change is associated with fatigue due to VMS.

Consider HRT to alleviate low mood that arises as a result of the menopause.

Consider CBT to alleviate low mood or anxiety that arise as a result of the menopause.

Ensure that menopausal women and healthcare professionals involved in their care understand that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression (see the NICE guideline on depression in adults).

The main short-term menopausal symptoms that were the focus of this question were:

- ...
- anxiety and low mood (excluding clinical depression) as aspects of psychological wellbeing; depression in the context of this review question referred to low mood, as no clinical diagnosis was made and this term (low mood) is used across the review
- ...

Psychological symptoms are commonly experienced by women in menopause and these can impact on their personal, social and professional quality of life. The group reviewed the limited evidence available, which showed that low mood can be ameliorated by hormonal replacement therapy (oestrogen alone) and psychological therapies, such as CBT, but not from the other non-pharmacological treatments reviewed, such as herbal treatments. For the outcome of anxiety, psychosocial therapies, such as CBT, genistein and red clover, were found to significantly reduce anxiety for women in menopause when compared with placebo or usual care.

The discussion behind this recommendation was that low mood may be the result of hormonal changes occurring at the perimenopause and antidepressant medication may not be the most appropriate treatment for all women in the absence of clinical depression. However, the group discussed that clinical depression is a different entity and was not assessed as an outcome in this question, therefore any conclusion was made only in relation to the outcome of low mood.

For the outcome of low mood, there is some evidence that HRT and CBT may improve low mood for women in menopause.

5.7.5 USPSTF 2022

USPSTF only formulated general recommendations for all chronic conditions considered together. Evidence were provided separately for dementia but are not reported in this document.

5.8 Cardiovascular risks

FR 2021 points out that almost all of the trials were done using the combination of oral conjugated equine estrogen (CEE), with or without medroxyprogesterone acetate (MPA).

The baseline cardiovascular risk of menopausal women varies greatly depending on the risk factors. All the guidelines recommend to optimally control cardiovascular risk factors so that they do not constitute a contraindication for HRT.

Patients with risk factors

At menopause FR 2021 recommends individual assessment of the cardiovascular risk (grade A).

FR 2021 recommends not starting HRT after a myocardial infarction or ischaemic stroke (Grade B).

AWMF 2021 states that vascular risk factors should be assessed and treated before starting HRT.

NHG 2022 recommends to discourage HRT in case of previously diagnosed VTE, with or without thrombophilia (this does not apply to women taking anticoagulation) or previously diagnosed cardiovascular disease and recommends to discuss options to reduce individual risk, such as quitting smoking, reducing alcohol consumption, increasing exercise and losing weight. Moderating the consumption of alcohol can also have a beneficial effect on the number of hot flashes.

In the case of a personal history of VTE, obesity or biological thrombophilia (factor V Leiden mutation, prothrombin G20210A mutation), FR 2021 recommends against the use of oral estrogens (Grade A). In these situations, it may be proposed to use cutaneous estradiol combined with progesterone depending on the individualized benefit-risk balance of HRT (Grade C). Similarly, NICE upd 2019 recommends to consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m² and to consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Starting HRT

“Timing hypothesis”: FR 2021 recommends starting HRT within the first 10 years of physiological menopause (Grade B). AWMF 2020 recommends that HRT should be started for the treatment of menopausal symptoms before the age of 60 (level of evidence 2b, recommendation grade A, consensus strength ++).

FR 2021 recommends to favour the combination of cutaneous estradiol and progesterone to limit the risk of ischemic CVA attributable to HRT (Grade B).

AWMF 2020 and NICE upd 2019 also make specific recommendations to inform women about different risks:

- Regarding cardiovascular risk:
 - HRT does not increase cardiovascular risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease (NICE upd 2019).

- EPT does not increase or only slightly increases cardiovascular risk and that ET does not increase or decrease cardiovascular risk (AWMF 2020, level of evidence 2b, recommendation grade A, consensus strength ++).
- Regarding TVE risk:
 - The risk of thromboembolism is increased with oral HRT (ET and EPT) and is higher than with transdermal application (AWMF 2020, level of evidence 2a, recommendation grade A, consensus strength ++ and NICE upd 2019).
 - The risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk (NICE upd 2019).
- Regarding cerebrovascular events:
 - Oral EPT may increase the risk of ischaemic cerebrovascular events but not transdermal ET (AWMF 2020, level of evidence 2b, recommendation grade A, consensus strength ++ and NICE upd 2019)
- Regarding coronary heart disease:
 - The baseline risk of coronary heart disease and stroke for women around menopausal age varies according to the presence of cardiovascular risk factors (NICE upd 2019).
 - HRT with ET alone is associated with no, or reduced, risk of coronary heart disease and EPT is associated with little or no increase in the risk of coronary heart disease (AWMF 2020, NICE upd 2019).
 - HRT is unsuitable for the prevention of coronary heart disease (AWMF 2020, level of evidence 2b, recommendation grade A, consensus strength ++).

Thromboembolism

NHG 2022 agrees that EPT and ET monotherapy possibly leads to an increased risk of VTE (especially with oral estrogen).

AWMF 2020 reports that no evidence of an increased risk of thromboembolism was found with transdermal forms. FR 2021 (NP2) and NICE upd 2019 both state that cutaneous estradiol does not appear to increase the risk of VTE in the general population.

The use of vaginal estradiol in the treatment of vulvovaginal atrophy does not appear to increase the risk of VTE (FR 2021, NP3). This is unknown according to NHG 2022.

According to FR 2021, the risk of VTE appears to be higher with CEE than with 17-b-estradiol (FR 2021, NP2).

In obese women or in women with a personal history of VTE, V Leiden mutation or a G20210A prothrombin mutation, HRT with oral ET therapy increases the risk of VTE recurrence (NP1). HRT with cutaneous ET therapy appears to be neutral with regard to the risk of recurrence of VTE (NP3) (FR 2021).

Cerebrovascular events

NICE upd 2019 concludes that there is no clear evidence of harm in terms of stroke in menopausal women who are taking HRT and aged under 65 years when HRT is terminated.

NHG 2022 states that EPT possibly leads to an increased risk of stroke, especially with continuous combination therapy; with sequential combination therapy, the risk seems less increased. ET monotherapy also potentially leads to an increased risk of stroke (with oral ET).

Transdermal ET therapy combined with natural progesterone does not appear to be associated with the risk of ischaemic stroke. (AWMF 2020; FR 2021, NP3).

In practice, the question arises whether this high risk of stroke under HRT also applies to women who start HRT in the first ten years after the onset of menopause (AWMF 2020).

Coronary heart disease

NICE upd 2019 concluded that there is no clear evidence of harm in terms of coronary heart disease in menopausal women who are taking HRT and aged under 65 years when HRT is terminated. There were limited data indicating that there may be a significant increase in coronary heart disease found in current HRT users with pre-existing conditions. According to NICE upd 2019 this evidence was not compelling enough to draft a negative recommendation for information giving.

FR 2021 mentions that there is no increase in the risk of MI associated with the use of CEE regardless of the duration of use (NP1). However, there is an increased risk of a first event during the first year of use (NP2). There is also an increased risk of recurrent MI associated with the use of a CEE and MPA in the first year of use (NP2). According to them the risk of MI is significantly reduced when HRT is used less than 10 years after the menopause (NP2) and may be reduced when HRT is used before the age of 60 (NP3). AWMF 2020 also concludes that the effects differ in women who started HRT in the first 10 years or later, and in the age groups under and over 60.

There does not appear to be any difference between the route of ET administration on the risk of myocardial infarction, but only one small randomized trial is available (AWMF 2020; FR 2021, NP3).

There is no difference in the risk of myocardial infarction according to the type of ET (FR 2021, NP2).

NHG 2022 states that EPT possibly leads to an increased risk of coronary heart disease especially with continuous combination therapy; with sequential combination therapy, the risk seems less increased. The risk of myocardial infarction may be reduced when HRT is used before the age of 60 (AWMF 2020, FR 2021).

Tibolone

No increase in the risk of myocardial infarction was shown in the tibolone trials, taking into account the low incidence of events (NP2). Tibolone is not associated with an increased risk of VTE, taking into account the very low incidence of these events in these two trials (NP2). However, an increased risk of stroke was found in women over 60 treated with tibolone 1.25 mg compared with placebo (FR 2021).

Differences between progestogens

Progesterone: NHG 2022 is uncertain about the risk of coronary heart disease, stroke and VTE. FR 2021 mentions that the risk of VTE is also influenced by the type of progestogen, with no increased risk with progesterone.

Dydrogesterone: NHG 2022 is uncertain about the risk of coronary heart disease, stroke and VTE (although the little available research does not seem to indicate increased risk). FR 2021 mentions that the risk of VTE is also influenced by the type of progestogen, with no increased risk with dydrogesterone.

Chlormadinone acetate and medrogestone acetate: FR 2021 mentions that the risk of VTE is also influenced by the type of progestogen, with no increased risk with chlormadinone acetate and medrogestone acetate (NP2).

Nomegestrol acetate and pomegestone: The risk of VTE is increased with nomegestrol acetate and pomegestone, even in combination with cutaneous estradiol in the general population (FR 2021, NP2).

Medroxyprogesterone: NHG 2022 reports that medroxyprogesterone may lead to an increased risk of VTE and according to AWMF 2020, it has possibly a particularly high risk. NHG 2022 is uncertain about the risk of coronary heart disease and stroke.

Norethisterone: According to NHG 2022, it may lead to an increased risk of VTE coronary heart disease and stroke.

NHG 2022 found no studies on serious side effects of drospirenone and lynestrenol.

According to FR 2021, there is no difference in the risk of myocardial infarction according to the type of progestogen associated with ET therapy (NP3). AWMF 2020 mentions that so far, the effects of the progestogens have not been sufficiently tested in randomized intervention studies concerning the risk of coronary heart disease.

According to NICE upd 2019 findings for different types of progestogens in combined HRT were inconclusive regarding the VTE risk.

Hormonal IUD

NHG 2022 specifies that it is unknown to which extent the use of estradiol in combination with a hormone IUD as a form of continuous combination therapy increases the risk of VTE and cardiovascular disease.

5.8.1 AWMF 2020

Das kardiovaskuläre Basisrisiko peri- und postmenopausaler Frauen variiert sehr stark in Abhängigkeit von den Risikofaktoren. Sie sollten optimal kontrolliert sein, damit sie keine Kontraindikation für eine HRT darstellen. Deshalb sollten die vaskulären Risikofaktoren vor Beginn einer HRT abgeklärt und behandelt werden. (Evidenzgrad 2b, Empfehlungsgrad B, Konsensusstärke ++)

Eine HRT wurde peri- und postmenopausalen Frauen lange Zeit mit der Absicht der Prävention von Herz-Kreislauf-Erkrankungen verordnet. Dies beruhte auf der einfachen Vorstellung, dass Der Vorteil der Frau gegenüber dem Mann hinsichtlich kardiovaskulärer Erkrankungen großteils durch den höheren Östrogenspiegel bedingt sei. Die großen randomisierten Interventionsstudien haben dies nicht bestätigt, sondern wiesen auf einen neutralen oder sogar negativen Effekt einer HRT in der Postmenopause hin. Die Analysen der durchgeführten großen Studien sowie Daten neuerer Studien weisen auf notwendige Vorsicht hin, aber auch Auf W ege einer individualisierten Therapie mit wenig Risiko oder sogar kardiovaskulärem Vorteil.

5.8.1.1 Thromboembolism

Frauen sollen darüber informiert werden, dass das Thromboembolierisiko unter oraler ET und EPT erhöht ist und höher ist als bei transdermaler Applikation. (Evidenzgrad 2a, Empfehlungsgrad A, Konsensusstärke ++)

Östrogene und Gestagene haben thrombogene Effekte, die sowohl dosisabhängig sind als auch substanzspezifisch und entsprechend dem Zuführungsmodus variieren.

- Sie sind zu Therapiebeginn am stärksten ausgeprägt und bei erhöhtem Basisrisiko absolut größer als bei Frauen mit geringem Ausgangsrisiko.
- Bei niedrig dosierter transdermaler Therapie wurden vermutlich aufgrund fehlender Anflutung höherer Östrogenmengen in der Leber keine Hinweise auf ein erhöhtes Thromboembolierisiko ermittelt.

Die höchsten vaskulären Risiken einer oralen HRT sind venöse Thrombosen und Thromboembolien. Sie verdoppeln sich durch HRT um etwa zwei Fälle pro 1000 behandelte Frauen pro Jahr. Eine ET bzw. eine EPT haben in Studien zur Primärprävention vaskulärer Ereignisse eine vergleichbare Risikoerhöhung ergeben wie in solchen zur Sekundärprävention mit Anwendung einer EPT.

Difference between treatments

Die vergleichbare Risikoerhöhung durch eine ET oder eine EPT weist darauf hin, dass der Auswahl des Gestagens vermutlich nur untergeordnete Bedeutung zukommt. Das deckt sich mit Ergebnissen eines sehr großen englischen Registers, das keinen Unterschied für HRT-Formen mit und ohne Gestagen für die Häufigkeit von Thromboembolien bei 23.505 Fällen gezeigt hat.

Das Thromboserisiko steigt offenbar mit der Östrogendosis. Dennoch sei erwähnt, dass möglicherweise Medroxyprogesteronacetat ein besonders hohes Risiko zukommt, während mikronisiertes Progesteron und die 17- Hydroxyprogesteronderivate wie beispielsweise Dydrogesteron und Medrogeston sowie Nortestosteronderivate wie z.B. Norethisteronacetat sich nicht zusätzlich zum Effekt des Östrogens auswirken.

Risk factors

Bekanntermaßen hängt das individuelle Risiko für venöse Thrombosen von Faktoren wie Alter, Gewicht und genetischer Prädisposition mit dem höchsten Risiko bei Homozygotie für Faktor V Leiden ab.

In Beobachtungsstudien wie auch Interventionsstudien war das Risiko für Thrombosen in den ersten ein bis zwei Jahren am höchsten und fiel vom 3- bis 4-fachen gleichbleibend auf das 2-fache in den Folgejahren.

Route of administration

Vor dem Hintergrund dieses beachtlichen Risikos einer oralen HRT sind Beobachtungsstudien zu transdermalen Applikationsformen vielversprechend, aber Ohne Beweischarakter. Vermutlich Aufgrund fehlender Anflutung höherer Östrogenmengen in der Leber und damit Vermeiden der

Stimulation der Synthese von Gerinnungsfaktoren wurde kein Hinweis auf ein erhöhtes Thromboembolierisiko ermittelt.

5.8.1.2 Cerebrovascular events

Frauen sollen darüber informiert werden, dass eine orale EPT das Risiko für ischämische zerebrovaskuläre Ereignisse möglicherweise erhöht, nicht aber eine transdermale ET. Das absolute Risiko für einen Schlaganfall ist bei jüngeren Frauen sehr niedrig. (Evidenzgrad 2b, Empfehlungsgrad A, Konsensusstärke ++)

Schlaganfälle sind die zweithäufigsten und sehr ernstesten Risiken einer oralen HRT. Es kann lebenslange schwerste Behinderung mit Störung des Sprachvermögens und des Sprachverständnisses nach sich ziehen.

Das Risiko für einen ischämischen Schlaganfall steigt unter oraler ET oder EPT gleichermaßen, nach WHI und einer Meta-Analyse der Daten von 40.000 Probandinnen einschließlich kleinerer Studien um mindestens 30%, in absoluten Zahlen um einen Fall pro 1000 behandelter Frauen pro Jahr.

Das Risiko besteht nur während der Einnahmedauer und normalisiert sich nach Absetzen vollkommen.

Kein erhöhtes Risiko wurde für hämorrhagische Schlaganfälle detektiert.

Bezüglich zerebrovaskulärer Mortalität zeigt die Analyse der WHI für alle Altersstufen weder in der Interventionsphase noch nach 18 Jahren Nachbeobachtung einen signifikanten Effekt einer ET oder EPT.

« Timing Hypothesis »

Für die Praxis stellt sich die Frage, ob dieses hohe Schlaganfallrisiko unter HRT auch für Frauen gilt, die in den ersten zehn Jahren nach Eintritt der Menopause oder in dem entsprechenden Alter von etwa 50-59 Jahren mit einer HRT beginnen. Unter einer oralen EPT muss bei 1000 Frauen möglicherweise mit etwa 5 zusätzlichen Schlaganfällen innerhalb von zehn Jahren gerechnet werden. Allerdings war dieser Risikoanstieg in der Subgruppe mit Beginn der HRT früh in der Postmenopause nicht signifikant ebenso wie in einer Cochrane Meta-Analyse von 19 randomisierten Interventionsstudien mit 40.410 Probandinnen.

Route of administration :

Zu transdormaler HRT liegen leider keine Daten von randomisierten Interventionsstudien zum Schlaganfallrisiko vor. Eine Meta-Analyse von Beobachtungsstudien mit nur einer Fall-Kontroll-Studie ergab für eine orale HRT ein um das 1,24-fach höheres Schlaganfallrisiko verglichen mit dem Risiko unter transdormaler HRT.

Die Fall-Kontroll-Studie ermöglichte auch den Vergleich von transdormaler HRT mit niedrig und hoch dosierten Östrogenen. Nur für Östrogendosen bis 50µg ergab sich kein Risiko, während sich für über 50µg ein um 90% erhöhtes Risiko ergab. Durch Anwendung einer transdermalen HRT könnte also eine Erhöhung des Schlaganfallrisikos vermeidbar sein, allerdings nur bis zu einer Dosis von 50 µg. Keine ausreichenden Daten liegen allerdings für den Fall nach ischämischem Schlaganfall oder TIA vor, sodass diese Konstellation weiterhin als Kontraindikation gelten muss.

5.8.1.3 Coronary heart disease

Frauen sollen darüber informiert werden, dass eine EPT das kardiovaskuläre Risiko nicht oder nur geringfügig erhöht bzw. Eine ET das kardiovaskuläre Risiko nicht erhöht oder verringert.

Unter Berücksichtigung dieser Evidenz und der Risiken für Thromboembolien und ischämische Schlaganfälle ist eine HRT zur Prävention der Koronaren Herzkrankheit ungeeignet und sollte zur

Behandlung klimakterischer Beschwerden vor dem 60. Lebensjahr begonnen werden. (Evidenzgrad 2b, Empfehlungsgrad A, Konsensusstärke ++)

Das Risiko für koronare Ereignisse unter HRT wird häufig und kontrovers diskutiert. Den Studienergebnissen zufolge spielt es keine oder nur eine untergeordnete Rolle. Weder für die ET noch für die EPT wurde in der WHI als Primärpräventionsstudie oder der HERS Studie als Sekundärpräventionsstudie ein signifikanter Einfluss auf das koronare Risiko gefunden. Dies änderte sich auch nicht unter Berücksichtigung einer hormonfreien Zeit nach der Interventionsperiode von insgesamt 13 Jahren.

Auch die kardiovaskuläre und gesamt mortalität wurde nicht berührt.

« Timing Hypothesis »

Allerdings findet diese Meta-Analyse unterschiedliche Effekte bei Frauen, die innerhalb der ersten 10 Jahre mit einer HRT begonnen haben oder später, wie sie sich schon in der WHI und in einer früheren Meta-Analyse zu den Altersgruppen unter und über 60 Jahren bei Beginn einer HRT andeuteten. Danach geht eine HRT, die in den ersten 10 Jahren der Postmenopause begonnen wurde, mit einer verminderten Mortalität und geringeren koronaren Ereignisrate einher. Allerdings wird nicht zwischen einer ET und einer EPT unterschieden.

In der Cochrane Meta-Analyse zeigte sich kein signifikanter Effekt einer HRT auf das kardiale Risiko bei Beginn jenseits von 10 Jahren nach der Menopause (Boardman et al. 2015). Das stimmt weitgehend mit den Ergebnissen der WHI überein, wobei die WHI eine signifikante Risikoerhöhung durch eine EPT bei Beginn 20 Jahre und mehr nach der Menopause gefunden hat.

Differences between treatment

Da in der WHI das durchschnittliche kardiovaskuläre Risiko unter einer ET in allen Altersklassen günstiger als unter kombinierter Therapie lag, möchte man annehmen, dass das kardiovaskuläre Risiko in hohem Maße vom Gestagenanteil abhängt. Medroxyprogesteronacetat wie in der WHI in hoher Dosis kontinuierlich eingenommen, könnte aufgrund der vasokonstriktiven Wirkung kardiovaskulär ungünstiger sein als andere Gestagene. Aber bisher sind die heute gebräuchlichen Gestagene in ihrer Wirkung durch randomisierte Interventionsstudien nur ungenügend geprüft.

5.8.2 FR 2021

Le risque cardiovasculaire a fait l'objet de nombreuses publications chez les femmes ménopausées utilisant un THM. En effet, la prévention du risque coronaire a été longtemps le principal bénéfice escompté de ce traitement en raison des résultats favorables de l'ensemble des études de cohorte et cas témoins. La publication des essais randomisés initialement chez les femmes ayant déjà eu un accident artériel (prévention secondaire : étude HERS), puis en prévention primaire chez les femmes saines et, notamment, la Women's Health Initiative (WHI) a largement remis en cause ce bénéfice, ce qui s'est traduit par une diminution majeure de l'utilisation des différents THM. En effet, les premiers résultats montraient une augmentation de tous les événements cardiovasculaires (IDM, AVCI mais également MTEV et EP) rendant la balance bénéfice-risque non favorable pour le THM évalué dans cette étude (estrogènes conjugués équinés associés à l'acétate de médroxyprogestérone [MPA]) Ces premiers résultats ont été très discutés, et différentes analyses ultérieures émettent des hypothèses intéressantes sur la relation entre THM, selon sa nature, et le risque cardiovasculaire.

En dehors des événements veineux, dont l'utilisation de la voie transdermique de l'estradiol, combinée à la progestérone, semble neutre sur le risque thromboembolique veineux, les études

analysent principalement le risque d'accidents vasculaires cérébraux ischémiques (AVCI) et d'infarctus du myocarde (IDM).

Il est à noter que la quasi-totalité de ces essais concernaient l'association d'estrogènes conjugués équins (ECE) par voie orale, associés ou non à l'acétate de médroxyprogestérone (MPA).

Lors d'une consultation de ménopause, il est recommandé d'évaluer de manière individuelle le risque cardiovasculaire (grade A).

Il est recommandé de ne pas débiter un THM après un infarctus du myocarde ou après un accident vasculaire cérébral ischémique (grade B).

Si un THM est nécessaire, il est recommandé de le débiter dans les 10 premières années de la ménopause physiologique (grade B) et de privilégier l'association d'estradiol par voie cutanée et de progestérone pour limiter le risque d'AVCI attribuable au THM (grade B)

En cas d'antécédent personnel de MVTE, d'obésité ou de thrombophilie biologique (mutation du facteur V Leiden, mutation G20210A de la prothrombine), il est recommandé de ne pas utiliser les estrogènes par voie orale (grade A) ; dans ces situations, il peut être proposé d'utiliser l'estradiol cutané associé à la progestérone en fonction de la balance bénéfice–risque individualisée du THM (grade C).

5.8.2.1 Thromboembolic diseases

Les différentes sociétés savantes internationales recommandent l'évaluation du risque de MVTE avant la prescription d'un THM sans recommander systématiquement la recherche de thrombophilie biologique. Ce risque doit impérativement être évalué lors de la 1^{re} consultation avant d'initier un THM.

Le THM associant une molécule d'estrogène par voie orale avec ou sans progestatif augmente le risque de MVTE d'environ 70 %.

Le risque de MVTE associé au THM composé d'une estrogéno-thérapie par voie orale a tendance à diminuer avec la durée d'utilisation tout en restant significativement augmenté par rapport aux non-utilisatrices.

Route of administration

Les résultats épidémiologiques sont biologiquement plausibles avec une absence d'activation de la coagulation chez les utilisatrices de THM composé d'estradiol par voie cutanée et une activation chez les utilisatrices de THM composé d'une estrogénothérapie par voie orale.

Il existe également une augmentation du risque de MVTE chez les utilisatrices d'un THM composé d'une estrogénothérapie par voie orale par rapport à un THM composé d'une estrogénothérapie par voie cutanée dans une sous-population de femmes sans FDR de MVTE : OR : 1,80 (1,35–2,39).

L'estradiol par voie cutanée ne semble pas augmenter le risque de MVTE en population générale (NP2).

Difference between estrogens

Les femmes étaient majoritairement utilisatrices d'estrogènes conjugués équins (ECE).

Les estrogènes (ECE et estradiol) par voie orale augmentent le risque de MVTE en population générale de 1,7 par rapport au placebo (NP1).

Le risque semble plus important avec les ECE par rapport au 17-b-estradiol (NP2).

Difference between progestogens

Le THM associe un estrogène à un progestatif lorsque l'utérus est en place.

Le risque de MVTE semble être modulé en fonction du type de progestatif combiné du THM. Le

risque de MVTE associé à l'utilisation d'un THM composé d'estradiol par voie cutanée semble neutre

chez les utilisatrices de progestérone micronisée et dérivés pregnanes et augmentéchez les utilisatrices de dérivés norpregnanes en population générale (NP2).

Le risque TEV est également influencé par le type de progestatifs avec une absence de sur-risque avec la progestérone, la dydrogestérone, l'acétate de chlormadinone et l'acétate de médrogestone.

En revanche, le risque est majoré avec l'acétate de nomégestrol et la promégestone, même en association avec l'estradiol par voie cutanée en population générale (NP2).

Women wit risk factors

Chez les femmes ayant un antécédent personnel de MVTE (TVP ou EP), le THM composé d'une estrogénothérapie par voie orale augmente le risque de récurrence de MVTE (NP1). Le THM avec estrogénothérapie par voie cutanée semble neutre vis-à-vis du risque de récurrence de MVTE (NP3). Chez les femmes porteuses d'une mutation du facteur V Leiden ou d'une mutation G20210A de la prothrombine, le THM composé d'une estrogénothérapie par voie orale augmente le risque de MVTE (NP1). Le THM composé d'une estrogénothérapie par voie cutanée semble neutre vis-à-vis du risque de MVTE (NP3).

L'utilisation d'un THM composé d'une estrogénothérapie par voie orale chez les femmes obèses majore le risque de MVTE (NP1). Chez les utilisatrices d'estradiol par voie cutanée, il ne semble pas exister d'augmentation du risque de MVTE quel que soit le BMI (NP2).

Les données publiées ne permettent pas d'évaluer le risque de MVTE chez les utilisatrices de THM ayant un antécédent familial de MVTE.

The figure below shows proposition of the FR 2021 concerning initiation of HRT depending on the VTE risks.

Proposition de conduite à tenir pour l'instauration d'un THM en fonction du risque de MVTE.

Niveau de risque	Situations cliniques	THM
Pas de risque	Absence de facteur de risque	THM autorisé en privilégiant une estrogénothérapie par voie cutanée en 1 ^{re} intention en association à de la progestérone micronisée. Un THM composé d'une estrogénothérapie par voie orale n'est pas contre-indiqué
Faible risque	-Thrombophilie mineure (FVL hétérozygote ou FII hétérozygote) -TVP distale avec un délai > à 6 mois, quel que soit le facteur déclenchant associé ou non à une thrombophilie mineure -TVP proximale ou EP provoquée (hors contexte hormonal) avec un délai > à 1 an -ATCD familiaux de MVTE unique associés ou non à une thrombophilie mineure	THM contenant : Estradiol par voie cutanée et progestérone micronisée est autorisé En cas de doute, ne pas hésiter à demander l'avis d'une RCP
Risque modéré	-Obésité sans autre facteur de risque vasculaire -Thrombophilie modérée (déficit en PC, PS, déficit combiné, déficit en AT de type HBS) -Site de MVTE particuliers (TVC, thrombose porte...) -MVTE dans contexte hormonal ou idiopathique (hors TVP distale) > à un 1 an -MVTE récidivante distale -ATCD de MVTE et anticoagulation au long cours (hors SAPL) -ATCD familiaux multiples < 50 ans -TVP proximale ou EP associé à un autre facteur de risque (obésité, thrombophilie biologique)	À discuter en RCP au cas par cas
Haut risque	-Facteurs de risque vasculaire veineux multiples -TVP distale < à 6 mois -MVTE (hors TVP distale) < à 1 an -SAPL (avec ou sans anticoagulant ou antiagrégant) -Déficit en AT documenté hors déficit HBS	Contre-indication à un THM, quelle que soit sa voie d'administration

FVL : mutation du facteur V Leiden ; FII : mutation du facteur II ; RCP : réunion de concertation pluridisciplinaire ; THM : traitement hormonal de ménopause ; TVP : thrombose veineuse profonde ; EP : embolie pulmonaire ; ATCD : antécédents ; MVTE : maladie veineuse thromboembolique ; PC : protéine C ; PS : protéine S ; TVC : thrombose veineuse cérébrale ; FDR : facteurs de risque ; SAPL : syndrome des antiphospholipides ; AT : antithrombine.

Vaginal estrogens (treatment of vulvovaginal atrophy)

Aucun évènement thromboembolique veineux n'est rapporté, mais les données sont limitées avec des essais randomisés dont l'objectif principal n'est pas d'évaluer le risque de MVTE. Les données biologiques sont rassurantes avec des concentrations d'estradiol plasmatique inférieures à 20 pg/mL chez les utilisatrices de l'anneau vaginal et similaires aux concentrations des utilisatrices d'un

traitement placebo. Cela témoigne d'un probable faible passage plasmatique d'estradiol chez les utilisatrices de cet anneau vaginal. Dans l'étude récente de Vinogradova et al., l'utilisation d'une crème composée d'ECE ou d'un anneau vaginal composé d'estradiol n'était pas associée à une augmentation du risque de MVTE.

L'utilisation d'estradiol par voie vaginale dans le cadre du traitement de l'atrophie vulvovaginale ne semble pas augmenter le risque de MVTE (NP3).

Chez les femmes à risque de MVTE (antécédent personnel de MVTE et/ou thrombophilie biologique), les données sont également limitées.

5.8.2.2 Cerebrovascular events

Concernant ce risque, les études, quel que soit le niveau de preuve (observationnelles ou randomisées), sont assez concordantes.

Elles montrent une augmentation significative du risque d'AVCI associé à l'utilisation d'un THM par voie orale (1,32 [1,12–1,56]).

Le risque d'accident vasculaire cérébral ischémique est significativement augmenté lors de l'utilisation d'une THM utilisant des estrogènes par voie orale seuls ou combinés à un progestatif (NP2).

Route of administration

Il existe cependant une très probable plausibilité biologique. En effet, les estrogènes par voie orale, en raison du premier passage hépatique, induisent une augmentation de la production hépatique d'angiotensinogène (substrat de la rénine), puis une augmentation secondaire des taux plasmatiques d'angiotensine I et II. Ainsi, la voie transdermique semble de meilleure sécurité d'emploi que la voie orale.

L'utilisation d'une estrogénothérapie par voie transdermique associée à la progestérone naturelle ne semble pas associée au risque d'accident vasculaire cérébral ischémique (NP3).

5.8.2.3 Coronary heart disease

Secondary prevention

Il existe une augmentation du risque de récurrence d'infarctus du myocarde associé à l'utilisation d'un traitement associant estrogènes conjugués équins par voie orale et acétate de méthoxyprogestérone, la première année d'utilisation (NP2).

Primary prevention

Aucune augmentation de risque d'IDM lié à l'utilisation d'estrogènes conjugués équins n'est observée sans tenir compte de la durée d'utilisation (NP1).

En revanche, il existe une augmentation du risque de premier événement lors de la première année d'utilisation (NP2).

Route of administration

Il ne semble pas exister de différence de la voie d'administration des estrogènes sur le risque d'IDM mais seul un essai randomisé de petite taille est disponible (NP3).

Age of introduction

Les effets de l'âge d'introduction du THM après la ménopause nécessitent l'analyse d'un nombre important de femmes pour atteindre une puissance statistique suffisante pour pouvoir interpréter les résultats. C'est bien sûr le cas de l'étude WHI. Ainsi, les auteurs en regroupant l'essai analysant ECE + MPA et l'essai analysant les ECE seuls montrent un impact légèrement différent en fonction de l'âge ($p = 0,08$) en faveur de l'utilisation du THM avant 60 ans. Aucune différence n'est observée après 60 ans.

Le risque d'IDM pourrait être diminué lorsque le THM est utilisé avant 60 ans (NP3).

« Timing Hypothesis »

Le risque d'IDM est significativement diminué lorsque le THM est utilisé moins de 10 ans après la ménopause (NP2).

Differences between estrogens

Il n'existe pas de différence de risque d'IDM en fonction du type d'estrogènes (NP2).

Differences between progestogens

Il n'existe pas de différence de risque d'IDM en fonction du type de progestatif associé à l'estrogénothérapie (NP3).

Il n'existe aucun essai randomisé analysant l'utilisation de la progestérone.

5.8.2.4 Global mortality

Tout âge confondu, le traitement hormonal de la ménopause n'augmente ni la mortalité globale ni celle liée aux maladies cardio-vasculaires ou au cancer du sein (NP2). Le THM pourrait même exercer un effet protecteur sur le taux de mortalité lorsqu'il est initié dans les 10 premières années de la ménopause (NP2).

5.8.2.5 Tibolone

Il n'a pas été montré d'augmentation du risque d'infarctus du myocarde dans les essais sur la tibolone, tout en prenant en compte la faible incidence des événements (NP2). En revanche, une augmentation du risque d'accident vasculaire cérébral a été retrouvée chez les femmes de plus de 60 ans traitées par tibolone 1,25 mg par rapport au placebo.

Dans les deux essais randomisés LIFT et LIBERATE, la tibolone n'est pas associée à un sur-risque de MVTE par rapport au placebo, tout en prenant en compte la très faible incidence de ces événements dans ces deux essais (NP2), ce qui avait conduit à l'arrêt prématuré de cet essai.

5.8.3 NHG 2022

Daarnaast leidt combinatietherapie mogelijk tot een verhoogd risico op coronaire hartziekten en beroerte (beide met name bij continue combinatietherapie; bij sequentiële combinatietherapie lijkt het risico minder verhoogd) en VTE (met name bij oraal oestrogeen). Dit zijn in deze leeftijdsgroep relatief weinig voorkomende, maar ernstige bijwerkingen.

Vrouwen zonder uterus komen in aanmerking voor oestrogeen monotherapie. Ook dit leidt mogelijk tot een verhoogd risico op beroerte en VTE (bij oraal oestrogeen). Deze bijwerkingen komen relatief weinig voor in deze leeftijdsgroep, maar zijn wel ernstig. Op het risico op borstkanker en hart- en vaatziekten heeft oestrogeen monotherapie niet of nauwelijks invloed.

De kwaliteit van bewijs voor de bijwerkingen was laag tot zeer laag, alleen redelijk voor de bijwerking 'coronaire hartziekten' bij oestrogeen monotherapie.

Progestogens

- Progesteron : We zijn onzeker over het risico op coronaire hartziekten, beroerte en VTE.

- Dydrogesteron: Over het risico op coronaire hartziekten, beroerte en VTE zijn we onzeker (al lijkt het weinige beschikbare onderzoek niet op een verhoogd risico te wijzen).
- Ook medroxyprogesteron en norethisteron ...maar leiden mogelijk tot een verhoogd risico op borstkanker en VTE; daarnaast verhoogt norethisteron mogelijk het risico op coronaire hartziekten en beroerte (over medroxyprogesteron zijn we onzeker).
- Er is geen onderzoek gevonden naar ernstige bijwerkingen van drospirenon en lynestrenol.

De kwaliteit van bewijs is laag tot zeer laag.

IUD

De hormoonspiraal met levonorgestrel : Andere uitkomstmaten zijn niet onderzocht.

Onbekend is in welke mate gebruik van estradiol in combinatie met een hormoonspiraal als vorm van continue combinatietherapie het risico op VTE en hart- en vaatziekten verhoogt. De gebruikstermijn van een hormoonspiraal als progestageenadjuvans > 3 jaar is in Nederland offlabel.

Vaginal estrogen

Er is echter geen bewijs dat vaginale oestrogenen bij gebruik < 10 jaar meer kans op borstkanker geven. Voor VTE en HVZ is dit onbekend. Bespreek dit met de patiënt.

Patients with risk factors

(See also other recommendation for patient with risk factors in chapter..... initiation, discontinuation and follow-up of HRT)

Ontraad hormoontherapie bij:

- eerder vastgestelde VTE, met of zonder trombofilie (dit geldt niet voor vrouwen die antistolling gebruiken)
- eerder vastgestelde hart- en vaatziekten
- *Increased cardiovascular risk, smoking and cardiovascular disease*
- De Richtlijn Management rondom menopauze stelt in de module over vrouwen met een verhoogd uitgangrisico dat hormoontherapie voor overgangsklachten een bescheiden plaats heeft bij vrouwen met cardiovasculaire risicofactoren, gezien het ontbreken van goede evidence over de veiligheid. Transdermale toediening heeft de voorkeur als er een indicatie is (zeer lage kwaliteit van bewijs, op basis van 1 observationeel onderzoek naar beroerte). Als voorwaarde wordt genoemd dat de betreffende cardiovasculaire risicofactoren behandeld worden. Er werd geen onderzoek gevonden naar het effect van transdermale toediening op ischemische hartziekten bij vrouwen met een verhoogd cardiovasculair risico.
- In een recente narratieve review wordt op basis van internationale richtlijnen geadviseerd geen hormoontherapie voor overgangsklachten voor te schrijven aan vrouwen met eerder vastgestelde hart- en vaatziekten of een hoog cardiovasculair risico, vanwege een negatief effect van oestrogenen op beschadigd endotheel.
- *Thrombophilia and deep vein thrombosis/long embolism*
- De Richtlijn Antitrombotisch beleid ontraadt orale hormoontherapie voor overgangsklachten aan vrouwen met eerdere VTE of met een positieve eerstegraadsfamilieanamnese voor VTE – met of

zonder trombofilie. Vrouwen met een eerdere VTE hebben een sterk verhoogd risico op een recidief als zij orale hormoontherapie gebruiken.

- De Richtlijn Management rondom menopauze sluit aan bij de NIV-richtlijn. Hormoontherapie kan worden overwogen bij aanhoudende ernstige overgangsklachten die niet verbeteren met een niet-hormonale behandeling. Bij vrouwen met BMI > 30 kan transdermale toediening overwogen worden (zeer lage kwaliteit van bewijs: 1 observationeel onderzoek, beperkt aantal cases). Transdermale therapie kan eveneens worden overwogen bij vrouwen met een protrombinemutatie (zeer lage kwaliteit van bewijs: observationeel onderzoek, beperkt aantal cases). Bij goede instelling op antistolling is het risico op VTE niet verhoogd.

5.8.4 NICE upd 2019

Ensure that menopausal women and healthcare professionals involved in their care understand that HRT:

- **does not increase cardiovascular disease risk when started in women aged under 60 years**
- **does not affect the risk of dying from cardiovascular disease.**

Be aware that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.

Table below present the summary of the risks and the benefices during or after HRT use according to NICE upd 2019.



Table 1: Summary of HRT risks and benefits* during current use and current use plus post-treatment from age of menopause up to age 69 years, per 1000 women with 5 years or 10 years use of HRT

	Risks over 5 years use (with no use or 5 years current HRT use)		Total risks up to age 69 (after no use or after 5 years HRT use [†])			Risks over 10 years (with no use or 10 years current HRT use)		Total risks up to age 69 (after no use or after 10 years HRT use [†])	
	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT		Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT	Cases per 1000 women with no HRT use	Extra cases per 1000 women using HRT
Risks associated with combined estrogen-progestogen HRT									
Breast cancer	13	+8	63	+17		27	+20	63	+34
Sequential HRT	13	+7	63	+14		27	+17	63	+29
Continuous combined HRT	13	+10	63	+20		27	+25	63	+40
Endometrial cancer	2	-	10	-		4	-	10	-
Ovarian cancer	2	+ <1	10	+ <1		4	+1	10	+1
Venous thromboembolism (VTE) [‡]	5	+7	26	+7		8	+13	26	+13
Stroke	4	+1	26	+1		8	+2	26	+2
Coronary heart disease (CHD)	14	-	88	-		28	-	88	-
Fracture of femur	1.5	-	12	-		1	-	12	-
Risks associated with estrogen-only HRT									
Breast cancer	13	+3	63	+5		27	+7	63	+11
Endometrial cancer	2	+4	10	+4		4	+32	10	+32
Ovarian cancer	2	+ <1	10	+ <1		4	+1	10	+1
Venous thromboembolism (VTE) [‡]	5	+2	26	+2		10	+3	26	+3
Stroke	4	+1	26	+1		8	+2	26	+2
Coronary heart disease (CHD)	14	-	88	-		28	-	88	-
Fracture of femur	0.5	-	12	-		1	-	12	-

*Menopausal symptom relief is not included in this table, but is a key benefit of HRT and will play a major part in the decision to prescribe HRT.

[†]Best estimates based on relative risks of HRT use from age 50 (see [table 2](#) for relative risks). For breast cancer this includes cases diagnosed during current HRT use and diagnosed after HRT use until age 69 years; for other risks, this assumes no residual effects after stopping HRT use.

[‡]Latest evidence suggests that transdermal HRT products have a lower risk of VTE than oral preparations.

5.8.4.1 *Venous thromboembolism*

Explain to women that:

- the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk
- the risk of VTE associated with HRT is greater for oral than transdermal preparations
- the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk.

Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m².

Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Overall, evidence from both RCTs and observational studies was largely consistent with regard to the increased risk of VTE associated with current oral HRT use compared with nonuse for women in menopause.

The Guideline Development Group concluded that current oral HRT use was associated with a significant increase in risk of developing VTE compared with non-use. Conversely, the risk of VTE was not found to be significantly different with transdermal HRT use compared with non-use.

However, the group still wanted to draw attention to women's baseline risk of VTE and the recommendation explicitly states that transdermal HRT does not further increase the risk of VTE above the individual baseline risk.

Furthermore, due to the well-known VTE risk associated with obesity, the group emphasized that the use of transdermal HRT is not contraindicated for those with a high BMI (over 30 kg/m²).

The evidence showed that the increase in the VTE risk occurs rapidly after starting HRT and continues until treatment is discontinued

For women who had experienced previous episodes of VTE, observational evidence found no significant difference between HRT users and non-users. However, the group considered that there may be special considerations for this set of menopausal women before they start HRT and concluded that a referral to a haematologist should be offered.

The group considered that a referral should be made to a haematologist for all women with a significant increase in risk of DVT, for example a previous thromboembolic episode or a hereditary thrombophilia (Factor V Leiden). The decision whether to offer HRT or not to these women is complex and therefore the group decided that the involvement of a haematologist is necessary in order to contribute expertise to a woman's thrombophilia risk assessment before considering HRT unless she is already on anticoagulant therapy.

Findings for different types of progesterone and progestogens in combined HRT were inconclusive. Some observational studies showed an increased risk for some specific preparations of progesterone or progestogen when combined with oestrogen, while other studies found no significant difference. Therefore, the group decided not to differentiate the direction of their decision-making based on HRT type.

The group also discussed the management of women who use HRT and are considered for elective surgery. Since transdermal HRT has little or no impact on coagulation and is not associated with an increased risk of VTE, the group did not consider that there is a need for HRT to be discontinued prior to elective surgery, especially when the surgery is minor and will not involve immobility. However, the group felt that this is a discussion that should take place between the woman, her surgeon and her anaesthetist.

Evidence from this review was assessed as being of moderate to very low quality

5.8.4.2 Cerebrovascular events and coronary heart disease

Using tables 1 and 2, explain to women that *(see the summary table above for the risks and the benefices during or after HRT use according to NICE upd 2019.)*

- **the baseline risk of coronary heart disease and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors**
- **HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease**
- **HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.**

Explain to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke. Also explain that the baseline population risk of stroke in women aged under 60 years is very low (see table 2).

The population included in this review was women who have initiated treatment with HRT before age 65 years. Randomised evidence from several thousand women aged between 45 and 58 years consistently showed that the risk of stroke and MI is not significantly different between menopausal women who received HRT (either as oestrogen alone or as a combination of oestrogen plus progestogen) and those who received no treatment and the group decided to recommend that menopausal women and healthcare professionals involved in their care understand that HRT doesn't increase the cardiovascular disease risk when started in women aged under 60 years.

The group placed importance on the following results from the observational studies when they were drafting the recommendations: • The risk of CHD was significantly lower for women using HRT compared with no treatment across different follow-up periods (4, 10, 16 and 20 years) and different HRT durations (1, 2, 5 or 10 years) although the risk seemed to significantly increase in current users with pre-existing heart disease. • Conflicting results were found as to whether the risk of CVD or CHD is reduced or is similar in current HRT users compared with non-users. • Some observational data found that the risk of stroke may be higher for women aged under 55 years who are on HRT compared with non-users, whereas other evidence found no difference in the outcome of stroke among users of any route of HRT with different duration of use and long-term follow-up (16, 20 years) when compared with non-users. • Weak data suggesting transdermal HRT administration may be associated with a lower risk of stroke than oral.

The group considered in detail the synthesis of evidence and they concluded that there is no clear evidence of harm in terms of CHD or stroke in menopausal women who are taking HRT and aged under 65 years when HRT is terminated. Therefore, there is enough evidence to support healthcare professionals in advising women of the absence of or low risk in CVD outcomes associated with the use of HRT. In addition, although there were limited data indicating that there may be a significant

increase in CHD found in current HRT users with pre-existing conditions compared with nonusers, the group did not feel that this evidence was compelling enough to draft a negative recommendation for information giving.

The group discussed how this review did not consider any potential differences in outcome related to different types and dosage of HRT, although there was weak evidence suggesting that transdermal preparations may be associated with a lower risk of stroke than oral, consistent with the finding of lower VTE risk. The expert opinion of the group suggests that there may be differential effects and further research in this area is needed.

This review question looked at the impact on the risk of CVD of HRT use, duration, timing since stopping and age, but did not consider any potential differences in outcome related to the different formulations or the type and dosage of HRT in the preparations, although the clinical experience of the group members suggests that there may be differential effects and further research in this area is needed.

The majority of RCT evidence was low to very low quality, largely due to high risk of bias (mainly due to unblinding of study design) and the lack of confidence in the direction of effect size (imprecision).

5.8.5 USPSTF 2022

USPSTF only formulated general recommendations for all chronic conditions considered together. Evidence were provided separately for coronary heart disease, thromboembolic events, and stroke but are not reported in this document.

5.9 Cancer risks

FR 2021 recommends that the risk of different cancers be taken into account in the assessment of the individualized benefit-risk balance and in the shared decision (Grade B). According to them HRT appears to be associated with an increased risk of breast cancer (NP1) and serous/endometrioid ovarian cancer (NP2), and a reduced risk of colorectal cancer (NP2), pancreatic cancer (NP2), oesophageal and stomach cancer (NP2) and liver cancer (NP3).

Regarding the selection of the type of progestogen, the FR 2021 recommendation specifically states that it is recommended that ET be combined with progesterone or dydrogesterone in order to limit the increased risk of breast cancer attributable to HRT (Grade B).

FR 2021 recommends to associate progestogens to ET in order to prevent ET-induced endometrial cancer (Grade A). (see also recommendations on administration regimens in chapter 5.1). In the case of hysterectomy, there is no benefit of combining progestogen with estradiol for the risk of breast cancer (Grade A).

In regard to the risk of endometrial cancer, all the guidelines formulate recommendations for combination with progestogens (see also chapter 5.1). (strong recommendations)

AWMF 2020 and NICE upd 2019 recommend to inform women about different cancer risks:

- Regarding breast cancer:
 - The baseline risk of breast cancer for women around menopausal age varies from one woman to another (NICE upd 2019).
 - HRT with ET alone is associated with little or no change in the risk of breast cancer and EPT can be associated with an increase in the risk of breast cancer (NICE upd 2019).
 - HRT (EPT/ET) may lead to little or no increase in the risk of breast cancer (AWMF 2020).
 - The increase in risk depends on the composition of HRT, the duration of treatment and is reduced after discontinuation of HRT (AWMF 2020, level of evidence 1a, recommendation grade A, consensus strength ++, NICE upd 2019).
- Regarding ovarian cancer:
 - HRT (ET/EPT) may increase the risk of ovarian cancer. The effect can already occur with periods of use of less than 5 years and is reduced after discontinuation of the therapy (AWMF 2020, level of evidence 2a, recommendation grade A, consensus strength ++).
- Colorectal cancer:
 - HRT can reduce the risk of colorectal cancer. This does not result in an indication for the preventive use of HRT (AWMF 2020, Level of evidence 2a, recommendation grade A, consensus strength +++).

Breast cancer

According to AWMF 2020 both ET and EPT can be associated with an increased risk of breast cancer. NHG 2022 and NICE upd 2019 report that EPT may lead to an increased risk of breast cancer and that this risk gradually increases with longer use depending on the type of progestogen added. NICE upd 2019 reports that HRT with ET alone is associated with little or no change in the risk of breast cancer. FR 2021 specifies that there is no increased risk of breast cancer with CEE alone in WHI study (NP1) and that the risk of breast cancer attributable to HRT is higher with EPT than with ET in large European observational studies (NP1).

There is evidence that continuous combined EPT leads to a higher risk increase than sequential EPT. (AWMF 2020, FR 2021, NP2).

FR 2021 adds that the type of progestogen appears to influence the excess risk with a lower excess risk of breast cancer in users of progesterone or dydrogesterone for treatment of 5 years or less than with combinations with a synthetic progestogen (NP2).

Evidence shows that current use increases the risk of breast cancer but this risk decreases within a few years (5 to 10 years) of stopping therapy and is no longer different from that of non-users (AWMF 2020, FR 2021 NP1, NICE upd 2019).

According to AWMF 2020, women who started hormone therapy at or shortly after menopause age showed a higher increase in risk than those who started hormone therapy more than 5 years after menopause. There exists controversy about when the increase in breast cancer risk starts after the start of hormone treatment.

According to AWMF 2020, there is evidence that EPT with progesterone leads to a small increase in risk. NHG 2022 reports that progesterone does not seem to increase the risk of breast cancer. Concerning dydrogesterone NHG 2022 mentions that it may lead to a little or no increased risk of breast cancer when used <5 years. According to FR 2021, the over-risk of breast cancer is lower with progesterone or dydrogesterone than synthetic progestogens.

FR 2021 states that mortality from breast cancer is not increased in women receiving HRT (NP1).

Endometrial cancer

AWMF 2020 (Level of evidence 2, consensus strength +++), FR 2021 (NP1) and NHG 2022 agree that HRT with ET alone without progestogen protection is a risk factor for the occurrence of endometrial carcinoma in non-hysterectomized women. The effect depends on the duration of use.

FR 2021 (NP1) and NHG 2022 mentions that the over-risk of endometrial cancer with HRT is no longer observed with the combination of a progestogen and estrogen therapy.

AWMF 2020 states that a reduction in the risk of endometrial cancer was observed with continuous combined HRT with CEE and medroxyprogesterone acetate as a progestogen with an average duration of use of 5.6 years (Level of evidence 2, consensus strength ++). They conclude that continuous combined HRT with <5 years of use can be considered safe with regard to the risk of endometrial cancer (Level of evidence 2, consensus strength +++). FR 2021 summarizes that this over-risk of endometrial cancer with HRT is reduced for combined regimens for durations < 10 years (NP1).

AWMF 2020 states that sequential-combined HRT may increase the risk of developing endometrial cancer. The effect depends on the duration, type and dose of progestogen use (Level of evidence 3, consensus strength ++). Sequential combined HRT with a duration of use of less than 5 years and using a synthetic progestogen can be considered safe with regard to the risk of endometrial carcinoma (Level of evidence 3, consensus strength +++). FR 2021 mentions that there is no increase in the risk of endometrial cancer, provided the progestogen is taken for at least 12 days a month (NP2).

According to NHG 2022 the progestogen can be administered sequentially (for 14 days per month) or continuously.

AWMF 2020 states that the use of progesterone or dydrogesterone as part of continuous combined HRT may increase the risk of developing endometrial cancer (Level of evidence 4, consensus strength +). NHG 2022 reports similar observation for progesterone and adds that because endometrial carcinoma is relatively rare, the absolute risk increase is limited when used <5 years. For dydrogesterone NHG 2022 reports that it does not appear to increase the risk of endometrial carcinoma. FR 2021 specifies that synthetic progestogens may be more effective than progesterone and dydrogesterone (to be confirmed) and that progesterone may be associated with less endometrial protection than dydrogesterone (NP3). For NHG 2022, even medroxyprogesterone and norethisterone appear to increase the risk of endometrial carcinoma only slightly or not at all, up to 5 years of use.

According to AWMF 2020, long-term use of continuous combined HRT > 6 years or > 10 years may lead to an increased risk of endometrial cancer (Level of evidence 3, consensus strength ++).

Ovarian cancer

According to AWMF 2020 ET or EPT may increase the risk of ovarian cancer. They specify that significant differences were found for histological subtypes.

AWMF 2020 and FR 2021 specify that the effect is related to the duration of use, can already occur with periods of use of less than 5 years and is reduced after discontinuation of the therapy.

Details of the associations between HRT and the risks of different digestive cancers are reported in the full text.

Tibolone

According to FR 2021, treatment with tibolone is associated with an increased risk of breast cancer comparable to that of hormonal menopause treatment in various cohort studies (NP2).

NHG 2022 similarly specifies that serious long-term side effects, such as breast cancer and endometrial carcinoma, can also occur when using tibolone; these are less well studied than those of hormone therapy with estrogen. The same contraindications apply to tibolone as to hormone therapy.

Vaginal ET

Vaginal ET can lead to an increase in systemically effective estrogen levels (AWMF 2020). It is not known whether this leads to an increased risk of breast cancer (AWMF 2020, NHG 2022).

There is no evidence from clinical studies that vaginal ET leads to endometrial hyperplasia. However, long-term results (>1 year) on the endometrial safety of vaginal ET are not available (AWMF 2020).

Hormonal IUD

According to NHG 2022, the hormone IUD containing levonorgestrel may lead to an increased risk of breast cancer. They are uncertain about the risk of endometrial carcinoma, although the very limited

results do not suggest an increased risk. Other outcome measures have not been studied. It is also possible that estradiol combined with a hormonal IUD as a form of continuous combination therapy increases the risk of breast cancer.

At-risk patients

Breast cancer:

AWMF 2020 concludes that HRT may increase the risk of recurrence after treated breast cancer (Level of evidence 2b, consensus strength +++) and recommends that HRT should not be given to women who have had breast cancer. It may be considered on a case-by-case basis after failure of non-hormonal treatments and in the event of a significant reduction in quality of life (Level of evidence 2b, recommendation grade A, consensus strength +++). Similarly, NHG 2022 recommends to discourage hormone therapy in previously diagnosed hormone-dependent tumours, such as breast cancer or endometrial carcinoma. NHG 2022 also adds that for familial burden of breast cancer, the increase in risk due to hormone therapy has not been sufficiently studied. FR 2021 specifies that given the risk of recurrence, the use of HRT is contraindicated in women with a history of breast cancer, but does not make a formal recommendation (NP1).

Women who have or have had breast cancer should also not be given progestogens or tibolone (not formulated as a formal recommendation by AWMF 2020).

FR 2021 also mentions that SERMs are not contraindicated in Europe for women with a history of breast cancer, but they are not approved by the FDA. In the absence of solid data, SERMs are not currently recommended for the management of genitourinary symptoms in women with a history of breast cancer (not formulated as a formal recommendation, NP3).

NICE upd 2019 recommends to offer menopausal women with, or at high risk of, breast cancer: information on all available treatment options, referral to a healthcare professional with expertise in menopause and information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen. FR 2021 has issued a similar recommendation against fluoxetine, paroxetine and sertraline in the specific case of postmenopausal women being treated for breast cancer with tamoxifen and suffering from flushing due to interaction with cytochrome P450 2D6 (grade B)

Endometrial cancer:

AWMF 2020 specifies that the risk associated with HRT after treated endometrial cancer has not been adequately studied (Level of evidence 2b, consensus strength +++). They recommend that HRT may be considered in patients with treated endometrial cancer, in the case of menopausal symptoms with significant limitations in quality of life and in the case of failure of non-hormonal alternatives (Level of evidence 2b, recommendation grade: expert consensus, consensus strength ++).

NHG 2022 recommends to discourage hormone therapy in previously diagnosed hormone-dependent tumours, such as breast cancer or endometrial carcinoma.

Ovarian cancer

AWMF 2020 was not able to formulate a reliable statement on the safety of HRT after treatment of ovarian cancer (Level of evidence 2b, consensus strength ++) and concludes that HRT can be administered to women after treatment of an ovarian carcinoma after appropriate information (Level of evidence 2b, recommendation grade 0, consensus strength +++).

Vaginal ET:

Concerning vaginal application, AWMF 2020 states that despite local application, ET are not necessarily safer and can be absorbed. According to AWMF 2020 treatment with ultralow-dose oestrinol (0.03 mg, 3 applications per week) seems to be acceptable.

According to FR 2021 local estrogens may be prescribed for women with a history of breast cancer whose symptoms persist despite non-hormonal treatment, taking into account the risk factors specific to the disease (NP3).

For patients who have undergone treatment for endometrial cancer and having symptoms of atrophic vaginitis, AWMF 2020 recommends that these symptoms should be treated primarily with lubricating gels or inert creams (Level of evidence 4, recommendation grade A, consensus strength ++). Local ET after primary therapy for endometrial cancer may be considered after unsatisfactory treatment with inert lubricating gels or creams (Expert consensus, consensus strength ++).

AWMF 2020 and FR 2021 (NP2) also add that in women with a history of breast cancer, non-hormonal regimens are an important first-line therapy for the symptoms of genitourinary symptoms.

According to FR 2021, in the current state of knowledge, neither vaginal DHEA nor vaginal testosterone can be recommended for women with a history of breast cancer (not formulated as a formal recommendation, NP3).

In the full recommendation, FR2021 also reports a table with the international recommendation for the treatment of genitourinary symptoms after breast cancer.

Non-hormonal approaches:

AWMF 2020 mentions that acupuncture, CBT (cognitive behavioural therapy), St. John's wort are safe treatment approaches according to the current state of knowledge because they do not have an estrogen-like effect. AWMF 2020 also specifies that In the NICE network meta-analysis, St. John's wort is found to be the best option for hot flushes in women after breast cancer, followed by gabapentin. In the case of Cimicifuga (black cohosh), it is controversial whether the effect occurs via estrogen receptors or not.

NICE upd 2019 specifically formulated recommendations concerning St John's wort to inform women with a history of, or at high risk of, breast cancer. Although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about: appropriate doses, persistence of effect, variation in the nature and potency of preparations, and potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).

5.9.1 FR 2021 recommends that phytoestrogens not be used in post-menopausal women being monitored for breast cancer or for the treatment of menopausal flushing (Grade A). AWMF 2020 also proposes that women who have or have had breast cancer should also not be given phytoestrogens (not formulates as a formal recommendation). AWMF 2020

5.9.1.1 Breast cancer

Frauen, die eine HRT erwägen, sollen darüber aufgeklärt werden, dass eine HRT (EPT/ET) zu einer geringen oder keiner Erhöhung des Brustkrebsrisikos Führen ann. Die mögliche Risikoerhöhung ist abhängig von der Zusammensetzung der HRT, der Behandlungsdauer und reduziert sich nach Absetzen der HRT. (Evidenzgrad 1a, Empfehlungsgrad A, Konsensusstärke ++)

Oestrogen-progestogen therapy

Die Anwendung einer EPT kann das Brustkrebsrisiko erhöhen. Dies wurde in einer Reihe von Metaanalysen, die Fallkontrollstudien, Kohortenstudien und RCTs einbezogen haben, nachgewiesen. Das relative Risiko einer EPT-Anwendung liegt in der WHI, einer RCT, bei 1,26. Dies entspricht 8 zusätzlichen invasiven Mammakarzinomen pro 10.000 Frauen pro Anwendungsjahr.

- *After stopping the treatment*

In RCTs und Beobachtungsstudien konnte gezeigt werden, dass die derzeitige Anwendung das Brustkrebsrisiko zwar erhöht, dieses allerdings nach Absetzen der Therapie innerhalb von wenigen Jahren sinkt und nicht mehr unterschiedlich von dem der Nichtanwenderinnen ist.

- *“Timing theory”*

Der Beginn einer HRT im Verhältnis zum Menopausealter hat einen Effekt auf das Ausmaß des Risikos. Dies wurde in der WHI als RCT und mehreren größeren Beobachtungsstudien gezeigt. Frauen, die die Therapie im oder kurz nach dem Menopausealter begonnen haben, zeigten eine höhere Risikosteigerung als diejenigen, die die Therapie über 5 Jahre nach der Menopause begonnen hatten.

- *Treatment duration*

Die Anwendungszeiten, die zur Risikosteigerung führen, werden kontrovers diskutiert.

Für eine EPT wird überwiegend eine 5-jährige Anwendungsdauer als Mindestzeit für einen statistisch signifikanten risikosteigernden Effekt der EPT angesehen. Eine jüngere Studie der WHI, die Daten von therapieadhärenten Anwenderinnen analysierte, zeigte Bereits nach 3-jähriger EPT eine Risikosteigerung. Beobachtungsstudien berichten über Mindestanwendungszeiten von 2 bis 5 Jahren.

- *Difference between treatments*

Aus Kohortenstudien liegen Anhaltspunkte dafür vor, dass eine kontinuierlich kombinierte EPT zu einer höheren Risikosteigerung führt als eine sequentielle EPT.

Es liegen Hinweise dafür vor, dass eine EPT mit Progesteron zu einer geringen Risikosteigerung führt. Natürliches Progesteron hat allerdings im Vergleich zu synthetischen Gestagenen einen schwächeren antiproliferativen Effekt auf das Endometrium.

Estrogen alone

Im Gegensatz zu einer Vielzahl von Beobachtungsstudien zeigte die WHI eine Senkung des Risikos für ein Mammakarzinom bei ET- im Vergleich zu Placebo-Anwenderinnen.

Die 3 weiteren RCTs haben wesentlich geringere Probandenzahlen und kürzere Anwendungszeiten zwischen 2 und 2,8 Jahren geprüft. In diesen 3 Studien fand sich kein signifikanter Unterschied im Brustkrebsrisiko zwischen Placebo- und ET- Anwenderinnen.

Die o.a. Einschränkungen machen zuverlässige Aussagen dieser Studien nicht möglich.

Die Beobachtungsstudien zeigen alle eine geringere Brustkrebsrisikosteigerung bei Anwendung einer ET im Vergleich zu einer EPT.

Die Dauer der ET, die zur Risikosteigerung führt, wird kontrovers beurteilt. Anwendungszeiten von > 5, 10 bzw. 20 Jahren werden diskutiert.

Zusammenfassend kann festgehalten werden, dass eine HRT (sowohl ET als auch EPT) mit einem erhöhten Brustkrebsrisiko verbunden sein kann. Die Risikoerhöhung ist allerdings gering und muss aber in die Nutzen-Risikobewertung bei der Behandlung klimakterischer Symptome mit einer HRT einbezogen werden.

Vaginal estrogens

Die vaginale ET kann zu einem Anstieg der systemisch wirksamen Östrogenspiegel führen. Es ist nicht bekannt, ob dies zu einem erhöhten Brustkrebsrisiko führt. Bereits eine ultraniedrigdosierte vaginale ET (0,03 mg Östriol 2 – 3 mal pro Woche) führt zu guten Therapieresultaten. Es ist unwahrscheinlich, dass diese selbst bei chronischer Anwendung einen Einfluss auf das Brustkrebsrisiko hat.

5.9.1.2 After breast cancer

Eine HRT kann das Risiko für ein Rezidiv nach behandeltem Mammakarzinom steigern.

(Evidenzgrad 2b, Konsensusstärke +++)

Eine HRT soll bei Frauen nach einem Mammakarzinom nicht durchgeführt werden. Im Einzelfall kann sie nach Versagen nichthormonaler Therapien und bei erheblicher Einschränkung der Lebensqualität erwogen werden. (Evidenzgrad 2b, Empfehlungsgrad A, Konsensusstärke +++)

Bei Frauen, die an hormonabhängigen Tumoren erkrankt sind, kann es Kontraindikationen gegen Sexualhormone und hormonartige Wirksubstanzen geben.

Vasomotorische Beschwerden können vor allem für Frauen, die mit Antiöstrogenen, Aromatasehemmern und/oder GnRH-Analoga behandelt werden, zu deutlichen Einschränkungen der Lebensqualität führen. Dasselbe gilt für Frauen mit irreversiblen ablativen Behandlungen wie beidseitiger Ovariectomie oder Radiatio der Ovarien.

Frauen, die an Brustkrebs erkrankt sind oder waren, sollen keine Östrogene, keine Gestagene, kein Tibolon und keine Phytoöstrogene (z.B. Isoflavone, Genistein, Rheum rhapontikum, Rotklee) zur Behandlung ihrer vasomotorischen Symptome bekommen.

Metaanalysen, die Beobachtungsstudien und RCTs einbezogen haben, konnten kein erhöhtes Rezidivrisiko nach behandeltem Mammakarzinom durch die Anwendung einer HRT nachweisen. Diese Studien weisen allerdings erhebliche methodische Schwächen auf (z.B. geringe Fallzahl, kurzes Follow-up). Zu der Fragestellung liegen auch 3 RCTs mit kontroversen Ergebnissen vor.

Vaginal estrogens

Frauen mit einer Brustkrebsdiagnose, deren Primärtherapie beendet wurde oder die sich unter einer laufenden adjuvanten endokrinen Therapie befinden, leiden nicht selten unter vaginalen Symptomen.

Trotz der lokalen Anwendung ist diese nicht zwingend sicherer.

Es wurde gezeigt, dass vaginal applizierte Östrogene insbesondere bei Vorhandensein einer Vaginalatrophie resorbiert werden und teilweise zu deutlichen Steigerungen der Serumöstrogenkonzentrationen führen

Eine Behandlung mit ultraniedrigdosiertem Östriol (0,03 mg, 3 Applikationen pro Woche) scheint vertretbar zu sein, dennoch sollten zunächst nichthormonale Alternativen genutzt werden.

Non hormonal treatments

Akupunktur, CBT (Kognitive Verhaltenstherapie), Johanniskraut stellen nach dem heutigen Wissenstand sichere Behandlungsansätze dar, weil sie keine östrogenartige Wirkung entfalten. Allerdings sind bei Johanniskraut Interaktionen mit anderen Arzneimitteln bekannt, zum Beispiel mit Docetaxel, Antikoagulantien und Midazolam. Das Interaktionspotential ist abhängig von der Johanniskrautdosis und dem Hyperforingehalt.

Bei Cimicifuga ist Es umstritten, ob die Wirkung über Östrogenrezeptoren erfolgt oder nicht. Als Wirkmechanismen werden SERM-ähnliche, antioxidative, anti-inflammatorische und serotonerge Effekte diskutiert. Früher noch vermutete östrogenartige Effekte an Brust und Gebärmutter können aufgrund aktueller klinischer und experimenteller Daten für Cimicifuga-Arzneimittel ausgeschlossen werden.

5.9.1.3 Endometrial cancer

Eine ET soll nur bei hysterektomierten Frauen durchgeführt werden. Eine kombinierte EPT bei nicht hysterektomierten Frauen soll eine mindestens 10-, besser 14-tägige Gestagenanwendung pro Behandlungsmonat enthalten. (Evidenzgrad LLA, Empfehlungsgrad A, Konsensusstärke ++)

Oestrogen-progestogen therapy

For general administration schema (see also chapter 5.1 Different hormonal therapies, dosages and schema of administration)

Bei einer kontinuierlich kombinierten HRT mit konjugierten equinen Östrogenen und Medroxyprogesteronacetat als Gestagen mit durchschnittlich 5,6 Jahren Anwendungsdauer wurde eine Reduktion des Endometriumkarzinomrisikos beobachtet. (Evidenzgrad 2, Konsensusstärke ++)

Eine kontinuierlich-kombinierte HRT mit <5 Jahren Anwendungsdauer kann hinsichtlich des Endometriumkarzinomrisikos als sicher angesehen werden. (Evidenzgrad 2, Konsensusstärke +++)

Die sequentiell-kombinierte HRT kann das Risiko der Entstehung eines Endometriumkarzinoms erhöhen. Der Effekt ist von der Dauer, Art und Dosis der Gestagenanwendung abhängig. (Evidenzgrad 3, Konsensusstärke ++)

Die sequentiell-kombinierte HRT mit einer Anwendungsdauer unter 5 Jahren und unter Verwendung eines synthetischen Gestagens kann hinsichtlich des Endometriumkarzinomrisikos als sicher angesehen werden. (Evidenzgrad 3, Konsensusstärke +++)

Die EPT wird entweder sequentiell oder kontinuierlich kombiniert durchgeführt. Eine sequentielle EPT mit einer mindestens 10-tägigen Anwendung eines Gestagens pro Behandlungsmonat erhöhte das Endometriumkarzinomrisiko bei Anwendungszeiten von bis zu ca. 5 Jahren nicht. Eine längerfristige sequentielle EPT kann das Endometriumkarzinomrisiko erhöhen. Die Reduktion der Anwendungsdauer des Gestagens von unter 10 Tagen pro Monat erhöht das Endometriumkarzinomrisiko ebenfalls (RR 3,0-4,4).

Bei Einnahme eines Östrogens der mittleren Potenz sollten mindestens 1 mg NET bzw. 2mg Medroxyprogesteronacetat (MPA) oder ein äquivalentes Gestagen in einer kombiniert kontinuierlichen Therapie eingesetzt werden, mindestens 5 mg MPA oder ein äquivalentes Gestagen in einer sequentiellen Therapie mit ausreichend langer Gestagenphase (10-14 Tage).

- *Difference between treatments*

Die Verwendung von Progesteron oder Dydrogesteron im Rahmen einer kontinuierlich-kombinierten HRT kann das Risiko der Entstehung eines Endometriumkarzinoms erhöhen. (Evidenzgrad 4, Konsensusstärke +)

- *Treatment duration*

Die Langzeitanwendung einer kontinuierlich-kombinierten HRT > 6 Jahre bzw. > 10 Jahre kann zu einem erhöhten Endometriumkarzinomrisiko führen. (Evidenzgrad 3, Konsensusstärke ++)

Estrogene alone

Eine alleinige HRT mit Östrogenen ohne Gestagenschutz ist bei nicht Hysterektomierten Frauen ein Risikofaktor für das Auftreten eines Endometriumkarzinoms. Der Effekt ist von der Dauer der Anwendung abhängig. (Evidenzgrad 2, Konsensusstärke +++)

Eine ET kann bei postmenopausalen, nicht hysterektomierten Frauen zu einem erhöhten Endometriumkarzinomrisiko führen. Dieser Effekt ist zeit- und dosisabhängig. Bei Anwendung von Standard Dosen (z. B. 2 mg Östradiol, 0,625 mg CEE) ist das RR bei mehr als 3-jähriger Anwendung bis zu 5-fach erhöht, bei 10-jähriger Anwendung bis 10-fach. Diese Risikoerhöhung persistiert für mehrere Jahre nach Absetzen der ET.

Vaginal estrogen

Aus klinischen Untersuchungen liegen keine Hinweise dafür vor, dass eine vaginale ET zu Endometriumhyperplasien führt. Eine Kombination mit Gestagenen, die bei systemischen ETs durchgeführt werden soll, wird daher nicht empfohlen.

Langzeitergebnisse (>1 Jahr) zur endometrialen Sicherheit der vaginalen ET liegen allerdings nicht vor (NAMS Position Statements 2013 und 2017).

5.9.1.4 After endometrial carcinoma

Das Risiko einer HRT nach behandeltem Endometriumkarzinom ist nicht ausreichend untersucht. (Evidenzgrad 2b, Konsensusstärke +++)

Bei Patientinnen mit behandeltem Endometriumkarzinom kann eine HRT bei klimakterischen Beschwerden mit erheblichen Einschränkungen der Lebensqualität und Versagen nicht hormonaler Alternativen erwogen werden. (Evidenzgrad 2b, Empfehlungsgrad EK, Konsensusstärke ++)

Dennoch kann trotz der limitierten Evidenz gefolgert werden, dass insbesondere in den Frühstadien des Endometriumkarzinoms eine HRT zumindest nicht zu einer relevanten Risikosteigerung führt, sodass sie bei eingeschränkter Lebensqualität und Versagen nicht-hormonaler Alternativen erwogen werden kann.

Vaginal estrogens

Symptome einer atrophen Vaginitis bei Patientinnen nach Therapie eines Endometriumkarzinoms sollen primär mit inerten Gleitgelen oder Cremes behandelt werden. (Evidenzgrad 4, Empfehlungsgrad A, Konsensusstärke ++)

Eine lokale ET nach Primärtherapie eines Endometriumkarzinoms kann nach nicht zufriedenstellender Behandlung mit inerten Gleitgelen oder Cremes erwogen werden. (Expertenkonsens, Konsensusstärke ++)

Da ein erhöhtes Rezidivrisiko durch eine vaginale ET nicht ausgeschlossen werden kann, sollen bei symptomatischer atropher Vaginitis nichtöstrogenhaltige Feuchthaltemittel und Emollentien (auf Wasser- Glycerin- oder Silikonbasis) und/oder Befeuchtungscremes empfohlen werden. Als besonders wirksam haben sich pH-stabilisierende Präparate mit einem pH-Wert von 4-4,5 (Milchsäure) erwiesen. Eine lokale ET kann Symptome einer Vaginalatrophie nach Radiotherapie der Vagina günstig beeinflussen. Dies wirkt sich positiv auf die Sexualfunktion aus. Es wurde gezeigt, dass lokal applizierte Östrogene resorbiert und somit systemisch wirksam werden können. In retrospektiven Kohorten- und Fallkontroll-Studien konnte keine erhöhte Rezidivrate nach einer ET bei Patientinnen im Stadium I und II nachgewiesen werden. Wie bei der systemischen HRT ist die Datenlage dennoch zu schwach, um die onkologische Sicherheit dieser Maßnahme zu belegen. Bei

Patientinnen nach Therapie eines Endometriumkarzinoms mit östrogenmangelbedingten und postaktinischen Beschwerden der Vagina soll vor Anwendung lokaler Östrogene das möglicherweise erhöhte Rezidivrisiko gegenüber den Vorteilen der Hormonanwendung abgewogen und im Sinne eines „informed consent“ mit der Patientin besprochen werden.

5.9.1.5 Ovarian cancer

Frauen, die eine HRT erwägen, sollen darüber aufgeklärt werden, dass eine ET bzw. EPT das Ovarialkarzinomrisiko erhöhen können. Die Wirkung kann bereits bei Anwendungszeiten von unter 5 Jahren auftreten und reduziert sich nach Absetzen der Therapie. (Evidenzgrad 2a, Empfehlungsgrad A, Konsensusstärke ++)

Die Kenntnisse zum Zusammenhang zwischen HRT und Ovarialkarzinomrisiko wurden ganz überwiegend in Beobachtungsstudien generiert.

Bei den derzeitigen Anwenderinnen war das Risiko bereits bei Anwendungszeiten von unter 5 Jahren erhöht (RR 1,43; 95% CI 1,31 – 1,56, $p < 0,001$). Wurden die Daten von derzeitigen Anwenderinnen und Frauen analysiert, die die HRT unter 5 Jahren vor der Diagnosestellung des Ovarialkarzinoms abgesetzt hatten, war das Risiko weiterhin erhöht (RR 1,37; 95% CI 1,29 – 1,46, $p < 0,001$). Das Risiko war sowohl bei ET- als auch bei EPT-Anwendung erhöht. Es fanden sich allerdings deutliche Unterschiede für histologische Subtypen.

5.9.1.6 After ovarian cancer

Zur Sicherheit einer HRT nach Behandlung eines Ovarialkarzinoms kann keine zuverlässige Aussage gemacht werden. (Evidenzgrad 2b, Konsensusstärke ++)

Eine HRT kann bei Frauen nach Behandlung eines Ovarialkarzinoms nach entsprechender Aufklärung durchgeführt werden. (Evidenzgrad 2b, Empfehlungsgrad 0, Konsensusstärke +++)

Zur Behandlung von klimakterischen Beschwerden oder Prävention östrogenabhängiger Erkrankungen wird daher bei Frauen nach behandeltem Ovarialkarzinom nicht selten eine HRT erwogen. Es liegen nur wenige Studien vor, in denen die Sicherheit einer HT bei Patientinnen nach Ovarialkarzinombehandlung geprüft wurde.

Da jedoch alle Studien zeigen, dass kein risikosteigernder Effekt sondern eher eine Risikoreduktion vorliegt, scheint eine HRT bei erheblichen Einschränkungen der Lebensqualität durch klimakterische Symptome vertretbar. Insbesondere bei jungen Frauen, die iatrogen postmenopausal wurden, besteht ein erhöhtes Mortalitätsrisiko durch das Auftreten einer koronaren Herzkrankheit, so dass bei diesen eine HRT sinnvoll erscheint.

5.9.1.7 Colorectal carcinoma

Frauen sollen darüber aufgeklärt werden, dass eine HRT das Risiko für kolorektale Karzinome senken kann. Daraus ergibt sich keine Indikation für einen präventiven Einsatz der HRT. (Evidenzgrad 2a, Empfehlungsgrad A, Konsensusstärke +++)

Der überwiegende Anteil zeigt eine Risikoreduktion nach HRT Anwendung. Eine Metaanalyse, in die Daten aus RCTs und Beobachtungsstudien einbezogen wurden, zeigte, dass die jemalige Anwendung einer EPT und einer ET zu einem reduzierten Risiko für kolorektale Karzinome führte (RR 0,74; 95% CI 0,68-0,81 bzw. RR 0,79; 95% CI 0,69-0,91). Die derzeitige Anwendung einer ET war mit einem reduzierten Risiko verbunden (RR 0,70; 95% CI 0,57-0,85). Es bestanden keine Unterschiede zwischen ET- und EPT-Anwenderinnen.

Eine Bewertung von Effekten verschiedener Gestagene, Applikationsformen und langfristiger (>10 Jahre) HRTs ist nicht möglich.

5.9.2 FR 2021

Le traitement hormonal de la ménopause apparaît associé à une augmentation du risque de cancer du sein (NP1) et de l'ovaire de type séreux et endométrioïde (NP2) et à une diminution des risques de cancer du colorectal (NP2), du pancréas (NP2), de l'oesophage et de l'estomac (NP2) et du foie (NP3), qu'il est recommandé de prendre en compte dans l'évaluation de la balance bénéfices–risques individualisée et dans la décision partagée (grade B).

Tout âge confondu, le traitement hormonal de la ménopause n'augmente ni la mortalité globale ni celle liée aux maladies cardio-vasculaires ou au cancer du sein (NP2). Le THM pourrait même exercer un effet protecteur sur le taux de mortalité lorsqu'il est initié dans les 10 premières années de la ménopause (NP2).

Tibolon

Pour les femmes indemnes, le traitement par tibolone est associé à un sur-risque de cancer du sein comparable à celui du traitement hormonal de ménopause dans différentes études de cohorte (NP2). Une étude randomisée chez des femmes en début de ménopause (étude THEBES) ne montre pas de différence concernant les cas d'hyperplasie endométriale ou de cancer de l'endomètre par rapport au traitement hormonal combiné par voie orale (NP2). Dans l'étude LIFT, chez des femmes âgées de plus de 60 ans il existe une augmentation du risque de cancer de l'endomètre chez les femmes traitées par tibolone en comparaison au placebo (NP1).

5.9.2.1 *Breast cancer*

Pour limiter le sur-risque de cancer du sein attribuable au traitement hormonal de la ménopause, il est recommandé de privilégier l'association des estrogènes avec la progestérone ou la dydrogestérone chez les femmes non hystérectomisées (grade B).

En cas d'hystérectomie, il n'y a pas de bénéfice mammaire à associer la progestérone ou un progestatif à l'estradiol (grade A).

- WHI :

- pas d'augmentation du risque de cancer du sein avec ECE seuls (NP1) ;
- RR de cancer du sein attribuable au THM [ECE + MPA] $\approx$ 1,25 après 5 ans de traitement (NP1). Le risque absolu estimé: 2 cas supplémentaires de cancer du sein pour 1000 femmes traitées pendant 5 ans et 6 cas supplémentaires pour 1000 femmes traitées pendant 10 ans.

- Études observationnelles européennes montrent que le risque de cancer du sein attribuable au THM est :
 - plus élevé avec traitements estroprogestatifs qu'avec estrogènes seuls (NP1) ;
 - dépendant du type de progestatif utilisé! non augmenté avec associations E2 et progestérone micronisée ou dydrogestérone pour durée < 5 ans (NP2) ;
 - non influencé par la voie d'administration des estrogènes (NP2).

Disparition du surrisque de cancer du sein à l'arrêt pour des durées d'arrêt de 5 à 10 ans (NP1).

Une augmentation du risque relatif apparaît pour des durées plus longues (NP3).

Il n'existe pas de donnée concernant le surrisque de cancer du sein et la dose des estrogènes.

Les schémas combinés continus seraient associés à un surrisque plus élevé de cancer du sein que les schémas séquentiels (NP2).

La mortalité par cancer du sein n'est pas augmentée chez les femmes recevant un THM que cela soit dans les essais randomisés ou les études d'observation et quel que soit le type de THM (NP1). De plus, le type de progestatif apparaît influencer le sur-risque de cancer du sein associé aux estroprogestatifs. Quatre études de cohorte européennes rapportent un sur-risque de cancer du sein plus faible chez les utilisatrices de progestérone ou dydrogestérone pour un traitement de 5 ans ou moins qu'avec les associations avec un progestatif de synthèse (NP2).

5.9.2.2 Endometrial cancer

Il est recommandé d'associer un progestatif pour la prévention du cancer de l'endomètre induit par les estrogènes (grade A) ; la durée recommandée de prise d'un progestatif dans les THM séquentiels doit être au minimum de 12 jours par mois (grade B) ou au mieux selon un schéma combiné (grade A).

E2 systémiques utilisés seuls ! au risque d'hyperplasie et de cancer de l'endomètre (augmente avec la durée du traitement) (NP1).

Ce sur-risque de cancer de l'endomètre sous THM :

- n'est plus observé avec l'association d'un progestatif à l'estrogénothérapie (NP1) ;
- est diminué pour les schémas combinés pour des durées < 10 ans (NP1) ;
- pour les schémas séquentiels : pas d'augmentation du risque de cancer de l'endomètre sous réserve d'une durée minimale de prise du progestatif de 12 jours/mois (NP2).

Dans le cadre d'une association estro-progestative, le type de progestatif pourrait influencer le risque endométrial (NP3) : les progestatifs de synthèse seraient peut-être plus efficaces que la progestérone et la dydrogestérone (à confirmer). La progestérone serait associée à une protection endométriale moindre que la dydrogestérone.

5.9.2.3 Ovarian cancer

La plupart des études d'observation rapportent ↑ risque des cancers séreux de l'ovaire associé au THM (NP2), liée à la durée d'utilisation du THM.

Pas d'augmentation de ce risque de cancer ovarien dans la WHI pour une durée de THM de moins de 5 ans.

Une méta-analyse rapporte RR de cancer de l'ovaire ≈ 1,5 (NP2) :

- quel que soit le type de THM : E2 seuls et associations estro-progestatives ;
- quelle que soit la durée du THM ; _
- sur-risque attribuable ≈ 1 cas supplémentaire pour 8000 femmes traitées
- concerne essentiellement les cancers séreux et endométrioïdes.

5.9.2.4 Gastrointestinal cancer

Colorectal :

La très grande majorité des études et méta-analyses rapportent une diminution du risque de cancer colorectal associée à la prise d'un THM (NP2) :

- influence de la voie d'administration des oestrogènes : voie transdermique > voie orale (NP2) ;
- pas d'influence des progestatifs (NP3).

Dans l'essai randomisé WHI, l'association d'ECE et de MPA, était associée à ↓ du risque de cancer du colorectal (NP2).

Pancréas :

- ↓ risque de cancer du pancréas chez les femmes utilisant un THM (NP2) ;

- effet bénéfique de la durée du THM (NP3) ;
- effet bénéfique plus important avec estrogènes seuls qu'avec les associations oestroprogestatives (NP3).

Oesophage :

- ↓ risque de cancer de l'oesophage sous THM, quel que soit son type histologique (épidermoïde, adénocarcinome) (NP2).

Foie :

Peu d'études sur les relations entre THM et cancer du foie sont disponibles. Une seule large étude de cohorte réalisée en Europe du Nord rapporte une diminution de pratiquement 20 % du risque de cancer du foie chez les femmes utilisant un THM (NP2). Cette diminution du risque est associée à la prise d'estradiol seul ou combiné avec un progestatif (quel qu'en soit son type), les schémas combinés étant associés à une diminution du risque plus importante que les schémas séquentiels (NP3).

5.9.2.5 Women with cancer

Dans le cas particulier des femmes ménopausées suivies pour un cancer du sein et souffrant de bouffées vasomotrices :

- **en cas de traitement adjuvant du cancer du sein par tamoxifène, il est recommandé de ne pas utiliser la fluoxétine, la paroxétine ou la sertraline pour la prise en charge des BVM de la ménopause du fait de l'interaction avec le cytochrome P450 2D6 (grade B)**
- **chez les femmes ménopausées suivies pour un cancer du sein, il est recommandé de ne pas utiliser les phytoestrogènes pour le traitement des BVM de la ménopause (grade A).**

Compte tenu du risque de récurrence, l'utilisation du THM est contre-indiquée chez les femmes avec antécédent de cancer du sein (NP1).

Chez les femmes avec antécédent de cancer du sein, les schémas non hormonaux sont une thérapie de première ligne importante pour les symptômes du SGUM (NP2).

SERM : Ces produits pourraient être intéressants du fait de leur effet anti-oestrogénique (SERM) in vitro et chez la souris, mais il n'y a pas d'étude centrée spécifiquement chez la femme ayant un antécédent de cancer du sein. Ainsi, les SERMs ne sont pas contre-indiqués en Europe dans cette indication mais non approuvés par la FDA. En l'absence de données solides, ce traitement n'est actuellement pas recommandé pour la prise en charge du SGUM chez les femmes avec antécédent de cancer du sein (NP3).

Plusieurs essais ont démontré l'importance des techniques non médicamenteuses telles que l'accompagnement, la rééducation pelvienne, l'utilisation de dilateurs vaginaux sur l'amélioration de la fonction sexuelle et d'inconfort vulvovaginal.

Vaginal treatments

Chez les femmes avec antécédent de cancer du sein, les schémas non hormonaux sont une thérapie de première ligne importante pour les symptômes du SGUM (NP2).

Les données actuelles à court terme ne semblent pas montrer de risque de récurrence de cancer du sein lors de l'administration d'oestrogènes locaux faible dose. Il n'est cependant pas possible de conclure à l'innocuité d'un tel traitement puisque la majorité des études concernent seulement l'effet du traitement sur le taux d'estradiol circulant (NP3). La prescription des oestrogènes locaux est envisageable pour les femmes avec antécédent de cancer du sein ayant une persistance des

symptômes malgré un traitement non hormonal, en tenant des facteurs de risques propres à la maladie (NP3).

En l'état actuel des connaissances, la prescription de DHEA vaginale ne peut pas être recommandée chez les femmes avec antécédent de cancer du sein (NP3).

En l'état actuel des connaissances, la prescription de testostérone vaginale ne peut pas être recommandée chez les femmes avec antécédent de cancer du sein (NP3).

Figure below reports the international recommendations for genitourinary symptoms treatment after breast cancer as translated by FR 2021 guideline.

Tableau 15A

Recommandations internationales de la prise en charge du SGUM après cancer du sein (traduction française depuis [101]).

Recommandations générales

Les traitements doivent être individualisés et tenir compte du risque de récurrence, de la sévérité des symptômes, l'impact sur la qualité de vie et le choix de la patiente

Les lubrifiants et hydratants locaux, les vibromasseurs et les dilateurs vaginaux sont des traitements de 1^{re} ligne

L'accord de l'oncologue doit être demandé avant d'initier une hormonothérapie locale

L'Ospémifène et les SERMS n'ont pas été étudiés chez la femme à haut risque de cancer du sein et ne sont pas recommandés par la FDA dans ce contexte

La testostérone vaginale et l'estriol ne sont pas recommandés

Le laser doit être proposé aux femmes qui préfèrent une approche non hormonale

Femmes à haut risque de cancer du sein

L'hormonothérapie locale est une option raisonnable chez les femmes pour qui le traitement non hormonal est un échec

Les études ne semblent pas montrer un risque augmenté de cancer du sein tant pour l'hormonothérapie locale que générale

Femmes présentant une tumeur hormonodépendante traitée par Tamoxifène

Le Tamoxifène est un SERM dont le rôle est d'antagoniser les RE présents dans le tissu mammaire ; de faibles concentrations sanguines d'hormones ont été constatées chez les patientes utilisant une hormonothérapie locale

Les patientes présentant une symptomatologie sévère persistante, malgré l'utilisation de traitement non hormonal, et présentant un faible risque de récurrence sont éligibles au traitement hormonal local

Femmes présentant une tumeur hormonodépendante traitée par anti-aromatases

Les anti-aromatases bloquent la conversion des androgènes en œstrogènes, à l'origine d'un taux indétectable d'œstrogènes circulants

Le SGUM est plus sévère chez ces patientes

Les patientes présentant une symptomatologie sévère non améliorée par les traitements non hormonaux, peuvent tout de même bénéficier d'un traitement hormonal local après avis et accord de l'oncologue, et après avoir discuté d'un éventuel changement d'hormonothérapie pour le Tamoxifène

Femme présentant une tumeur dite « triple négative »

En théorie, l'utilisation d'un traitement hormonal local semble raisonnable et donc possible chez ces patientes mais la littérature manque de données à ce sujet

Femme présentant une atteinte métastatique de la pathologie

La qualité de vie et le confort doivent rester des priorités chez patientes

L'utilisation d'une hormonothérapie locale dans ce cas et de son impact sur la survie doit être appréhendée différemment quand la qualité de vie est la priorité

5.9.3 NHG 2022

Omdat oestrogeen monotherapie het risico op endometriumcarcinoom sterk verhoogt, komen de meeste vrouwen in aanmerking voor combinatietherapie van een oestrogeen met een progestageen.

Combinatietherapie leidt vermoedelijk niet tot een verhoogd risico op endometriumcarcinoom. Het progestageen kan sequentieel (gedurende 14 dagen per maand) of continu (alle dagen) worden toegediend. Bij perimenopauzale vrouwen leidt continu toegediend progestageen frequent tot onregelmatig vaginaal bloedverlies, waardoor hiervoor alleen postmenopauzale vrouwen in aanmerking komen.

Combinatietherapie leidt mogelijk tot een verhoogd risico op borstkanker; dit risico loopt geleidelijk op als de combinatietherapie langer wordt gebruikt. Het risico hangt af van het type progestageen dat wordt toegevoegd (zie Type progestageen).

Vrouwen zonder uterus komen in aanmerking voor oestrogeen monotherapie. Ook dit leidt mogelijk tot een verhoogd risico op beroerte en VTE (bij oraal oestrogeen). Deze bijwerkingen komen relatief weinig voor in deze leeftijdsgroep, maar zijn wel ernstig. Op het risico op borstkanker en hart- en vaatziekten heeft oestrogeen monotherapie niet of nauwelijks invloed.

De kwaliteit van bewijs voor de bijwerkingen was laag tot zeer laag.

(Voir aussi chapitre 5.1. Different hormonal therapies, dosages and schema of administration)

Progestagens

Progestagenen verlagen het risico op endometriumcarcinoom bij gebruik van oestrogeen. De verschillende progestagenen verschillen echter enigszins in zowel het risico op endometriumcarcinoom als het risico op andere ernstige bijwerkingen.

- Progesteron lijkt het risico op endometriumcarcinoom enigszins te verhogen, maar omdat endometriumcarcinoom relatief weinig voorkomt, is de absolute risicotoename beperkt bij gebruik < 5 jaar. Progesteron lijkt het risico op borstkanker niet te verhogen.
- Dydrogesteron lijkt het risico op endometriumcarcinoom niet te verhogen, en leidt daarnaast mogelijk tot een niet of nauwelijks verhoogd risico op borstkanker bij gebruik < 5 jaar.
- Ook medroxyprogesteron en norethisteron lijken het risico op endometriumcarcinoom tot een gebruik van 5 jaar niet of nauwelijks te verhogen.
- Er is geen onderzoek gevonden naar ernstige bijwerkingen van drospirenon en lynestrenol.
- De niet-ernstige bijwerkingen van de verschillende progestagenen komen globaal overeen, maar verschillen enigszins in frequentie van voorkomen.

De kwaliteit van bewijs is laag tot zeer laag.

IUD

De hormoonspiraal met levonorgestrel leidt mogelijk tot een verhoogd risico op borstkanker. Over het risico op endometriumcarcinoom zijn we onzeker, al wijzen de zeer beperkte resultaten niet op een verhoogd risico. Andere uitkomstmaten zijn niet onderzocht.

Mogelijk verhoogt estradiol in combinatie met een hormoonspiraal als vorm van continue combinatietherapie het risico op borstkanker.

Tibolon

Ook bij gebruik van tibolon kunnen er ernstige bijwerkingen op de lange termijn optreden, zoals borstkanker en endometriumcarcinoom; deze zijn minder goed onderzocht dan die van hormoontherapie met oestrogeen.

Voor tibolon gelden dezelfde contra-indicaties als voor hormoontherapie, dus het is niet breder toepasbaar dan hormoontherapie (KNMP Kennisbank, geraadpleegd juli 2020).

Vaginal estrogen

Er is echter geen bewijs dat vaginale oestrogenen bij gebruik < 10 jaar meer kans op borstkanker geven. Voor VTE en HVZ is dit onbekend. Bespreek dit met de patiënt.

Patients with risk factors

(see also other recommendations for patients with risk factors in chapter 5.3. Initiation, discontinuation and follow-up of HRT)

Bij eerder vastgestelde borstkanker geldt een absolute contra-indicatie voor hormoontherapie bij overgangsklachten. Dit sluit aan op de aanbeveling in de Richtlijn Borstkanker.

Er is vrijwel geen onderzoek naar hormoontherapie bij vrouwen met een verhoogd risico op borstkanker. In een cohort van vrouwen met een BRCA1- of BRCA2-mutatie is het risico op borstkanker bij gebruik van hormoontherapie onderzocht. Er waren te weinig vrouwen die geen BPO ondergingen maar wel hormoontherapie gebruikten om hiervoor een HR te kunnen berekenen. De auteurs concludeerden dat hormoontherapie het beschermende effect van BPO op het borstkankerrisico niet tenietdoet.

- **Ontraad hormoontherapie bij:**
 - eerder vastgestelde hormoonafhankelijke tumoren, zoals borstkanker of endometriumcarcinoom
- **Besprek bij overige situaties het aantal, de aard en de ernst van de risicofactoren bij de beoordeling van het individuele risico op:**
 - borstkanker (zie NHG-Standaard Borstkanker). Bij familiale belasting met borstkanker is de toename van het risico door hormoontherapie onvoldoende onderzocht.
- **Weeg samen met de vrouw de voor- en nadelen van de behandeling af.**
- **Besprek ook mogelijkheden om het individuele risico te verlagen, zoals stoppen met roken, minderen met alcoholgebruik, meer bewegen en afvallen. Matigen van het gebruik van alcohol kan ook een gunstig effect hebben op het aantal opvliegers.**

5.9.4 NICE upd 2019

Using table 3, explain to women around the age of natural menopause that: *(see the summary table of the risks and the benefices during or after HRT use presented in chapter on the cancer risks.)*

- **the baseline risk of breast cancer for women around menopausal age varies from one woman to another according to the presence of underlying risk factors**
- **HRT with oestrogen alone is associated with little or no change in the risk of breast cancer**
- **HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer**
- **any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.**

There was insufficient evidence to demonstrate whether mortality from breast cancer was significantly different between those who currently or had ever used HRT and those women who never been treated with HRT and the GDG did not formulate a recommendation regarding this outcome.

The included evidence from both randomised and cohort studies showed that there may be risk of developing breast cancer during treatment associated with oestrogen plus progestogen compared with no HRT use, but this risk does not seem to be the same for those women treated with oestrogen or progestogen taken alone.

The Guideline Development Group discussed the importance of these findings which may suggest that HRT stimulates the development of cancer from occult lesions already present and that the natural history of the disease is not changed.

The group considered that the decision to offer HRT for women in menopause should be individualised, taking into account personal (baseline) risk factors for breast cancer that include

genetic predisposition and lifestyle factors, such as diet, exercise, alcohol consumption, smoking and reproductive history.

HRT with oestrogen and progestogen may be associated with an increased risk of breast cancer. Any increased risk of breast cancer associated with HRT is low and should be taken in the context of the overall benefit and risk ratio in using HRT for treating menopausal symptoms. In addition, this risk seems to be lost when HRT is discontinued, as demonstrated in the studies on the low risk of breast cancer for past HRT users.

The impact of oestrogen on breast cancer risk is currently considered to be a class effect. There are emerging but as yet insufficient data to suggest that different progestogens may impact to a different degree and therefore these have not been considered separately.

Low to very low quality evidence from both randomised and comparative cohort studies was considered for this review question and evidence was presented by HRT type when data were available.

Women with a history of cancer

Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about:

- **appropriate doses**
- **persistence of effect**
- **variation in the nature and potency of preparations**
- **potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).**

For advice on the treatment of menopausal symptoms in women with breast cancer or at high risk of breast cancer, see section 1.13 of the NICE guideline on early and locally advanced breast cancer and section 1.7 of the NICE guideline on familial breast cancer.

Offer menopausal women with, or at high risk of, breast cancer:

- **information on all available treatment options**
- **information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen**
- **referral to a healthcare professional with expertise in menopause.**

Two of the most critical factors determining the choice and appropriateness of treatments for relief of menopausal symptoms are whether a woman has a uterus or not and whether she has a history of breast cancer (or other hormone sensitive conditions or other contraindications to hormone therapies), since the side effect profiles of hormonal treatments are different for these groups of women. For these reasons, evidence from the NMA was synthesized separately for women with and without a uterus and for women with a history of breast cancer.

For women with breast cancer, there was limited evidence from the NMA assessing the efficacy of different treatments for relief of VMS and the tolerability of these interventions. For the outcome of VMS, only SSRIs/SNRIs, gabapentin, isoflavones and St John's Wort were included in the network. None of these treatments were found to be significantly better than placebo in relieving VMS for women with a history of, or at high risk of, breast cancer, although St John's Wort had the highest probability of being the best treatment to achieve this outcome compared with all the other treatments included in the network.

In addition, the group discussed thoroughly that women with a history of, or at high risk of, breast cancer should be offered information about all the available treatment options for menopausal symptoms, information that the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen and referred to a specialist with an interest in menopause for further advice.

For women with breast cancer, St John's Wort appeared to be the most cost-effective alternative treatment, with an ICER of £13,435 relative to the next best non-dominated treatment alternative. This is reflected in a recommendation that women should be advised that St John's Wort could be considered as a treatment option, while highlighting the uncertainty about appropriate dosages, persistence of effect, variation in the nature and potency of preparations and that there is a possibility for it to interact with other medicines.

There was relatively limited evidence available for women with breast cancer or history of breast cancer.

5.9.5 USPSTF 2022

USPSTF only formulated general recommendations for all chronic conditions considered. Evidence were provided separately for breast and colorectal cancers but are not reported in this document.

5.10 Metabolic effects

NICE upd 2019 recommends to explain women that taking HRT (orally or transdermally) is not associated with an increased risk of developing type 2 diabetes.

For women with preexisting type 2 diabetes, NICE upd 2019 recommends to ensure that these women and all healthcare professionals involved in their care are aware that HRT is not generally associated with an adverse effect on blood glucose control. They also recommend to consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.

AWSM 2020 specifies that the literature data regarding an influence of HRT on the incidence of type 2 diabetes are not consistent, and that based on the published data, pre-existing type 2 diabetes is not a contraindication for HRT but doesn't formulate any specific recommendation.

AWMF 2020 also specifies that female sex hormones influence lipid metabolism in many ways but no formal recommendation was formulated.

FR 2021 and NHG 2022 have not formulated specific recommendations regarding metabolic effects of HRT.

5.10.1 AWMF 2020

5.10.1.1 Diabetes

Risk of developing diabetes

Die Literaturdaten hinsichtlich einer Beeinflussung der Inzidenz von Diabetes mellitus (DM) Typ 2 durch eine HRT sind nicht einheitlich.

Effect on preexisting diabetes

Ein vorbestehender DM Typ 2 stellt daher aufgrund der publizierten Daten keine Kontraindikation für eine HRT dar. Studien zu den Effekten einer HRT auf einen vorbestehenden DM Typ 1 liegen nicht vor. In einem Fallbericht führte die Anwendung eines Gestagens bei einer Patientin mit DM Typ 1 zu einer akuten diabetischen Entgleisung.

5.10.1.2 Lipid metabolism

Weibliche Sexualhormone beeinflussen den Lipidstoffwechsel auf vielfältige Weise. Bei der oralen Östrogen-Applikation steigt die Triglyceridfraktion an.

Die Cholesterinfraktion sinkt ab, wobei es zu einer relativen Verschiebung zugunsten des HDL kommt. Ebenso sinkt Lp(a) unter einer HRT ab. Der günstige Effekt von Östrogenen auf den Lipidmetabolismus wird durch die Induktion von LDL-Rezeptoren in der Leber erklärt.

Bei einer transdermalen Applikation von Östrogenen wird der Lipidmetabolismus allerdings kaum beeinflusst. Es zeigt sich lediglich in der LDL-Cholesterinfraktion eine Verschiebung hin zu größeren Partikeln. Diese gelten als weniger pathogen für die Atherosklerose als kleinere LDL-Partikel.

Gestagene mit einer androgenen Partialwirkung können die Östrogen-induzierten Effekte auf den Cholesterinstoffwechsel antagonisieren.

5.10.2 FR 2021

No specific recommendations or comments were provided regarding metabolic effect or risk in this guideline.

5.10.3 NHG 2022

No specific recommendations or comments were provided regarding metabolic effect or risk in this guideline.

5.10.4 NICE upd 2019

Thus, maintaining physiological oestrogen levels in postmenopausal women could be hypothesised to decrease the incidence of abnormal glucose tolerance, T2DM and associated dyslipidaemia with the potential to improve cardio-metabolic risk.

Explain to women that taking HRT (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes.

Although evidence from randomised studies showed no significant difference in risk of developing T2DM associated with HRT compared with placebo, evidence from large cohort studies found that current HRT users have a significantly lower risk of T2DM compared with non-users. This protective effect of HRT on the risk of developing T2DM seems to disappear when the HRT treatment stops, as was found when data were compared between past HRT users and non-users. Data from post hoc subgroup analyses of different durations of HRT consistently indicated a protective effect of HRT on T2DM risk. Route of administration also did not seem to change HRT's protective effect against T2DM.

The Guideline Development Group concluded that HRT administration is not associated with an increased risk of developing T2DM.

The evidence informing these recommendations included 1 RCT and 3 comparative cohort studies. All of the subgroup analyses presented by the cohort studies should be interpreted with caution due to the risk of type II errors. The main reasons for downgrading the quality of the studies were the high and very high risk of bias due to selection, performance and attrition bias. Quality of evidence was also downgraded due to imprecision in the estimates of relative effects.

Ensure that women with type 2 diabetes and all healthcare professionals involved in their care are aware that HRT is not generally associated with an adverse effect on blood glucose control.

Consider HRT for menopausal symptoms in women with type 2 diabetes after taking comorbidities into account and seeking specialist advice if needed.

Weak evidence showed that although treatment with conjugated equine oestrogen alone may be linked with a significant decrease in blood glucose levels at 6 months for HRT users with T2DM, this direction of effect was not found when the impact of either sequential or continuous combined HRT on diabetic control was examined (for either 3 or 6 months outcomes). No significant change in the direction of above effects was found for either oral or transdermal HRT preparation. The Guideline Development Group discussed the interpretation of these results and concluded that the lack of any significant differences between the HRT and no HRT groups would be expected given the trials' short duration (as it would take longer for any effect on blood glucose levels to be observed).

In addition, supplementary evidence from a large cross-sectional study showed that HRT may have a positive impact on diabetes/glycaemic control in menopausal women taking HRT for a longer

duration (2 years) compared with menopausal women who did not take HRT as the percentage of HbA1c was significantly reduced.

The Guideline Development Group concluded that HRT does not exert a negative or positive impact on diabetic/glucose control for women with T2DM. However, the evidence base for this topic had flaws and the generalisation of results should be interpreted with caution.

The quality of evidence included for this question was considered to be low to very low.

5.10.5 USPSTF 2022

USPSTF only formulated general recommendations for all chronic conditions considered together.

Evidence were provided separately for diabetes but are not reported in this document.

5.11 Phytotherapies and non-pharmacological treatments

Phytoestrogens

AWMF 2020 recommends that CBT, isoflavones and Cimicifuga (black cohosh) preparations can be used for vasomotor symptoms (Level of evidence 1b, recommendation grade 0, consensus strength ++). AWMF 2020 further adds a recommendation to distinguish the cimicifuga preparations. Approved Cimicifuga medicinal products, unlike other Cimicifuga products (e.g. food supplements), have proven their benefit. Therefore, only approved Cimicifuga medicinal products should be recommended (recommendation grade: A (isopropanolische Cimicifuga-Arzneimittel), B (ethanolische Cimicifuga-Arzneimittel); Level of Evidence: 1b (isopropanolische Cimicifuga-Arzneimittel), 2b (ethanolische Cimicifuga-Arzneimittel)).

NICE upd 2019 recommends to explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms, multiple preparations are available, their safety is uncertain, different preparations may vary and interactions with other medicines have been reported.

NICE upd 2019 further recommends to explain to women that the efficacy and safety of unregulated compounded bioidentical hormones (defined as unregulated plant-derived hormonal combinations that are chemically similar or structurally identical to human hormones that are compounded by pharmacies to the specification of the prescriber) are unknown and to explain to women who wish to try complementary therapies that the quality, purity and constituents of these products may be unknown.

According to FR 2021, the data in the literature do not allow to recommend the use of phytoestrogen extracts for the management of menopausal flushing (Grade B). FR 2021 states that genistein, yoga and hypnosis (+ some pharmacological treatments) have been shown to be somewhat effective and may be proposed for the management of menopausal hot flushes (Grade B). FR 2021 also adds that due to the low level of evidence, these treatments (phytotherapies) are not currently recommended for the management of genitourinary symptoms (NP3).

NHG 2022 does not recommend black cohosh and phytoestrogens in women with hot flushes and/or night sweats (Strong recommendation against, very low level of evidence).

- According to NICE upd 2019, limited evidence showed that low mood can be ameliorated by HRT (ET alone), but not from the other non-pharmacological treatments reviewed, such as herbal treatments.
- According to NHG 2022, phytoestrogens may reduce the number of hot flushes compared with placebo or no intervention. But there are many different phytoestrogens on the market in many different doses. Side effects have hardly been studied. There is little research on long-term use of specific phytoestrogens, so their effectiveness and side effects remain uncertain.
- Genistein in a dose of 30-60 mg/d shows the most reliable effect according to AWMF 2020. FR 2021 concludes that high doses of genistein (> 30 mg per day) significantly improves the frequency of hot flushes (NP2). According to NICE upd 2019, genistein was found to significantly reduce anxiety. Because of concerns of unknown safety for genistein, NICE upd 2019 decided that HRT and CBT are preferable treatment options for low mood.

- According to AWMF 2020, isoflavones lead to a significant reduction of hot flushes (>30 mg/d isoflavones are effective in some studies, but not in others). FR 2021 mentions that the studies published do not allow to determine with certainty the effect of isoflavone extracts on the frequency and severity of hot flushes. NICE upd 2019 concludes that isoflavones were shown to be more effective than placebo in relief of VMS for women with a uterus, but not significantly better than EPT. They specify that isoflavones may improve anxiety for women with menopausal symptoms but there is a lack of consistency between isoflavones. NICE upd 2019 also expresses a concern around safety issues of isoflavones and highlights that there may be unknown risks.
- According to FR 2021 and NHG 2022, evaluation of the use of black cohosh show no significant differences in the frequency or severity of hot flushes. In addition, black cohosh is associated with significant liver toxicity and should therefore be avoided (FR 2021, NHG 2022). AWMF 2020 rather concludes that cimicifuga (black cohosh) has a similar effect as phytoestrogens (reduction of the frequency of hot flushes, but not night sweats). Similarly, NICE upd 2019 concludes that black cohosh was shown to be more effective than placebo in relief of VMS for women with a uterus, but not significantly better than EPT. They also express a concern around safety issues of black cohosh and highlight that there may be unknown risks.
- According to FR 2021 (NP2) and AWMF 2020 evaluation of the use of Chinese medicinal herbs show no significant differences in the frequency or severity of hot flushes. AWMF 2020 also adds that the safety of treatment with Chinese medicinal herbs has not been sufficiently investigated.
- According to NICE upd 2019, red clover was found to significantly reduce anxiety. Because of concerns of unknown safety for red clover, they decided that HRT and CBT are preferable treatment options for low mood. FR 2021 mentions that the use of red clover does not appear to reduce the frequency of hot flushes compared with placebo (NP2).
- Regarding flax seeds, FR 2021 concludes that assessments of the use of lignans (including flax seeds) have produced conflicting results and highly heterogeneous studies of poor methodological quality. AWMF 2020 mentions that flax seeds at least 100 mg/d are possibly effective.
- According to AWMF 2020, equol 10 mg/d and Rheum raphanistrum are possibly effective.
- According to AWMF 2020, most studies found no differences between phytoestrogens and control groups regarding drug safety. There was no significant increase in endometrial thickness in any of the studies.

Ginseng

AWMF 2020 reports that there is too little data to make a statement on ginseng while FR 2021 reports that the use of ginseng does not appear to have any effect on the frequency of hot flushes or on women's quality of life scores (NP2).

Vitamin E

According to FR 2021, the data available to assess the efficacy of vitamin E in the treatment of hot flushes is poor and inconsistent. No recommendation can therefore be made.

Beta-alanine

The HAS concluded that this compound "has no place in the therapeutic strategy for menopausal hot flushes". The data available to assess the efficacy of beta-alanine in the treatment of hot flushes are insufficient to make a recommendation. (FR 2021)

Omega-3

According to FR 2021, the use of omega-3 does not appear to be effective in managing hot flushes in perimenopausal or postmenopausal women (NP2).

Pollen extracts

FR 2021 mentions that few studies have been carried out, there is only one randomized trial evaluating the efficacy of pollen extracts on vasomotor symptoms. It showed a significant reduction in hot flushes compared with placebo, but was based on only 54 women (NP3).

Primerose oil

Primerose oil does not appear to be effective in reducing the frequency of hot flushes (FR 2021, NP2).

Aromatherapy

Very few studies have evaluated the effectiveness of aromatherapy or massage with essential oils hot flushes. The favourable results of a crossover trial need to be confirmed by other randomized trials (FR 2021).

Vaginal lubricants

(see also chapter 5.2 Treatment of menopausal symptoms, for more recommendations on vaginal atrophy.)

AWMF 2020 recommends to offer women with symptomatic urogenital atrophy lubricants alone or together with vaginal ET. Therapy can be used for as long as necessary (Level of evidence 1b, recommendation grade A, consensus strength +++).

Similarly, NHG 2022 recommends to consider both indifferent agents (moisturizing gel, cream with hyaluronic acid) and vaginal ET for complaints of vaginal atrophy (Low recommendation, low level of evidence).

FR 2021 recommends lubricants and moisturizers 1-st, followed by low-dose vaginal hormone treatment as 2nd-line treatment (expert opinion).

NICE upd 2019 recommends to advise women with vaginal dryness that moisturizers and lubricants can be used alone or in addition to vaginal ET.

FR 2021 specifies that several varieties are commercially available, based on water, silicone, glycerin, mineral or vegetable oil. They only have a temporary effect and do not improve vaginal trophicity in the long term. There is no evidence that any one lubricant is superior to the others. They propose that lubricants and moisturizers can be offered to women with moderate genitourinary symptoms but are less effective than local ET therapy (NP3). Vaginal hyaluronic acid is associated with a significant improvement in genitourinary symptoms (NP3).

CBT and mindfulness-based therapy

AWMF 2020 recommends that CBT can be used for vasomotor symptoms.

NHG 2022 recommends to consider mindfulness-based therapy or referral for a stress-reducing psychological intervention (such as cognitive behavioural therapy) in women with hot flushes and/or night sweats who are open to a psychological intervention and who are unable or unwilling to use hormone therapy (Low recommendation, low level of evidence).

NICE upd 2019 recommends to consider CBT to alleviate low mood or anxiety that arise as a result of the menopause. According to them, there was some evidence suggesting that CBT was more effective than usual care in reducing anxiety and low mood.

FR 2021 proposes yoga and hypnosis (+ some pharmacological treatments) that have been shown to be somewhat effective, for the management of menopausal hot flushes (Recommendation Grade B). They mention that hypnosis (NP2) and yoga (NP3) appear to significantly reduce the frequency and severity of hot flushes and that behavioural therapies appear to significantly reduce the severity of hot flushes but have little influence on their frequency (NP2).

According to FR 2021, relaxation has no significant effect on the frequency of hot flushes (NP2). AWMF 2020 mentions that the data are not sufficient to make a statement about the effectiveness of deep relaxation on vasomotor complaints.

FR 2021 also mentions that the small number of published studies does not allow to conclude that reflexology is effective in reducing hot flushes.

Acupuncture

The results vary depending on the comparator used (AWMF 2020, FR 2021). Studies show an efficacy on the frequency and severity of hot flushes when compared to waiting list (AWMF 2020, FR 2021 NP3). Acupuncture does not reduce the frequency of hot flushes compared to sham acupuncture (AWMF 2020).

Electro-acupuncture and deep relaxation showed no difference in effect (AWMF 2020).

HRT was superior to the above methods in reducing the frequency of hot flushes. However, no differences were found between HRT and acupuncture in influencing the intensity of hot flushes (AWMF 2020).

Sport

In general, NHG 2022 states that physical activity has an overall positive health effect (Low level of evidence). Accordingly, FR 2021 recommends low-to-moderate levels of regular physical activity and the fight against sedentary lifestyles to reduce mortality and cardiovascular risk after menopause (Grade A).

FR 2021 also mentions that in the prevention of osteoporosis and fractures, the benefit is smaller, particularly at the start of the menopause, given the strong estrogen-dependency of bone loss and/or when the risk of fracture is already increased. However, they add that after the menopause and in cases where there is a risk of osteoporosis, it is advisable to avoid a sedentary lifestyle and to engage

in physical activity combining weight-bearing exercises with impact and muscle strengthening to reduce the risk of fracture (Grade B).

No significant effects were found regarding sport on hot flushes (AWMF 2020, FR 2021, NHG 2022). Sport is significantly inferior to HRT (AWMF 2020). However, there are too few studies of good quality to be able to exclude an effect with certainty. The effect of exercise in previous years on vasomotor symptoms in peri- and post-menopause has also not been studied. Adverse effects and desirable effects on other health effects on other health parameters were not evaluated (AWMF 2020).

Nutrition

NHG 2022 states that weight reduction can have a positive health effect in overweight or obese women, but weight reduction has not been shown to help reduce hot flushes or night sweats (Very low level of evidence).

FR 2021 further recommends a moderate reduction in energy intake in overweight postmenopausal women, combined with a sufficient intake of protein to reduce body fat and try to counteract the loss of lean body mass, and physical activity (Grade C). FR 2021 also suggests for post-menopausal women to have a sufficient and diversified intake of protein, a sufficient intake of calcium, giving preference to dietary calcium (dairy products) and a sufficient intake of vitamin D, 80% of which is provided by skin synthesis of vitamin D under the effect of ultraviolet light (Grade C). They provide a table with general recommendations for nutritional prevention during the menopause (see full FR 2021 recommendation text)

For the use of phytotherapy and non-pharmacological treatments for women with cancer or with a history of cancer see chapter 5.9 on cancer risks.

5.11.1 AWMF 2020

Kognitive Verhaltenstherapie (CBT), Isoflavone und Cimicifuga präparate können bei vasomotorischen symptomten angewendet werden. (Evidenzgrad 1b, Empfehlungsgrad 0, Konsensusstärke ++)

Frauen, die Phytotherapeutika anwenden möchten, soll erklärt werden:

- dass es eine vielzahl von zubereitungen gibt und deren Sicherheit unklar ist.
- dass unterschiedliche Zusammensetzungen unterschiedlich wirken können.
- dass Interaktionen mit anderen medikamenten berichtet wurden.

5.11.1.1 Lubricants

Frauen mit symptomatischer urogenitaler atrophie soll die anwendung von befeuchtungs-, gleitmitteln alleine oder zusammen mit einer vaginalen ET angeboten werden. Die Therapie kann so lange wie erforderlich angewendet warden. (Evidenzgrad 1b, Empfehlun gsgrad A, Konsensusstärke +++)

In einer aktuellen Studie hat sich kein signifikanter Unterschied zwischen vaginaler Östrogentablette (10 µg) plus Placebo-Gel, vaginaler Placebotablette plus speziellem Vaginalgleitmittel sowie vaginaler Placebotablette plus Placebo-Gel gezeigt.

5.11.1.2 *Cimicifuga racemosa* (black cohosh)

Zugelassene Cimicifuga-Arzneimittel haben im Gegensatz zu sonstigen Cimicifuga-Produkten (z. B. Nahrungsergänzung) ihren Nutzen nachgewiesen. Daher sollten nur zugelassene Cimicifuga-Arzneimittel empfohlen werden.

(Empfehlungsgrad: A (isopropanolische Cimicifuga-Arzneimittel), B (ethanolische Cimicifuga-Arzneimittel); Level of Evidence: 1b (isopropanolische Cimicifuga-Arzneimittel), 2b (ethanolische Cimicifuga-Arzneimittel)).

Die Sicherheit vieler Präparate mit Cimicifuga und Phytoöstrogenen ist ungewiss. Die Zubereitung kann Unterschiede aufweisen. Es wurden Interaktionen mit anderen Arzneimitteln berichtet. Nutzerinnen von Cimicifuga-Produkten sollten registrierte Arzneimittel verwenden. So vermeiden sie Risiken, die mit der Anwendung ungeprüfter oder gar gepanschter Produkte vorhanden sind. Der Cochrane Review von Leach et al. (2012) hat 16 Studien mit 2017 Probandinnen eingeschlossen. Die Autoren kommen zu dem Schluss, dass die Wirksamkeit von Cimicifuga nicht gesichert ist, weil es nicht genügend gut durchgeführte Studien gibt. Im Vergleich zu Placebo zeigen mehrere Studien zwar eine Tendenz zur Wirksamkeit, aber keine Signifikanz. UAW waren selten, mild und reversibel. Am häufigsten wurden gastrointestinale Beschwerden, Muskel- und Gelenksbeschwerden berichtet. Einzelne Fälle von Hepatitis, Leberversagen, Gesichtssödemen und Vaskulitiden der Haut wurden weltweit beschrieben, aber es ist unklar, ob ein kausaler Zusammenhang zur Cimicifuga-Einnahme besteht.

Anders als der Cochrane-Review findet die Netzwerkanalyse von NICE einen signifikanten Therapieeffekt von Cimicifuga in der Reduktion von Hitzewallungen (MR 0.4; 95% CI 0.17-0.9).

5.11.1.3 Phytoestrogen

Von den Phytoöstrogenen zeigt Genistein in einer Dosis von 30-60mg/d die zuverlässigste Wirkung. >30 mg/d Isoflavone sind in manchen Studien wirksam, in anderen nicht. Von den übrigen Phytoöstrogenen sind Leinsamen, mindestens 100 mg/d, Equol 10 mg/d und Rheum raphanistrum möglicherweise wirksam. Bezüglich der Arzneimittelsicherheit finden die meisten Studien keine Unterschiede zwischen Interventions- und Kontrollgruppen. In einigen Studien treten unter Phytoöstrogenen mehr unerwünschte Begleiterscheinungen auf als unter Placebo. Eine signifikante Zunahme der Endometriumdicke findet sich in keiner Studie, zwei Studien weisen einen Effekt auf den Reifegrad des Vaginalepithels nach. In einem systematischen Review wurden 62 Studien mit 6653 Probandinnen erfasst. Der Einfluss von Phytoöstrogenen (Soja- und Rotkleeisoflavone u.a.), Cimicifuga und chinesischen und anderen Kräutern auf Hitzewallungen, nächtliche Schweißausbrüche und vaginale Trockenheit wurde untersucht. Phytoöstrogene reduzieren signifikant die Frequenz von Hitzewallungen, nicht aber nächtliche Schweißausbrüche. Cimicifuga hat einen ähnlichen Effekt, während chinesische Kräuter keinen signifikanten Effekt auf Hitzewallungen haben. Eine Metaanalyse untersuchte u.a. den Effekt von Leinsamen auf Hitzewallungen in 9 Studien mit 1392 Teilnehmerinnen. Die täglich aufgenommene Menge enthält 45 - 410 mg Lignane. Es lässt sich zwar eine tendenzielle Verbesserung der Hitzewallungen feststellen, die aber nicht signifikant ist. Über die Sicherheit der Behandlung können die Studien keine Aussage machen. Die Netzwerkanalyse von NICE zeigt, dass Isoflavone zu einer signifikanten Reduktion von Hitzewallungen führen (MR 0.62; 95% CI 0.44-0.87).

5.11.1.4 Ginseng

Die Meta-Analyse von Lee et al. erfasste 10 RCTs mit insgesamt 925 Teilnehmerinnen. Nur zwei Studien mit insgesamt 98 Frauen untersuchen den Einfluss von Koreanischem Ginseng auf Hitzewallungen. Eine Studie zeigt eine signifikante Verbesserung der Frequenz von Hitzewallungen, die andere nicht. Es liegen zu wenige Daten vor, um eine Aussage zu machen.

5.11.1.5 St. John's wort (*Hypericum perforatum*)

In beiden Studien wurde eine Reduktion der Hitzewallungen festgestellt.

Die Aussagekraft ist wegen der kleinen Fallzahl sehr begrenzt. In der NICE Netzwerk-Metaanalyse wird Johanniskraut als beste Option gegen Hitzewallungen bei Frauen nach Brustkrebs gefunden, gefolgt von Gabapentin.

5.11.1.6 Acupunctur

In dem Cochrane Review von Dodin et al. wurden 16 Studien mit 1155 Teilnehmerinnen analysiert.

Akupunktur reduzierte die Häufigkeit von Hitzewallungen im Vergleich zur Warteliste, aber nicht im Vergleich zur Scheinakupunktur. Akupunktur verringert die Intensität von Hitzewallungen, sowohl im Vergleich zur Scheinakupunktur als auch im Vergleich zur Warteliste.

Elektroakupunktur und Tiefenentspannung weisen keine Wirkunterschiede auf.

Die HRT war in der Reduktion der Häufigkeit von Hitzewallungen o.a. Methoden überlegen. Es fanden sich jedoch keine Unterschiede zwischen HRT und Akupunktur in der Beeinflussung der Intensität von Hitzewallungen.

5.11.1.7 Deep relaxation

Die Studien zeigten keinen signifikanten Effekt. Die Daten reichen nicht aus, um eine Aussage über die Wirksamkeit von Tiefenentspannung auf vasomotorische Beschwerden zu machen. Die Studien dauerten 4 Wochen bis drei Monate. Tiefenentspannungsmethoden müssen über einen längeren Zeitraum erlernt und regelmäßig angewendet werden, um den größtmöglichen Effekt zu erzielen. Insofern ist die Aussage dieses Studiendesigns begrenzt.

5.11.1.8 Sport

Es zeigten sich keine signifikanten Effekte. Im Vergleich zur HRT ist Sport signifikant unterlegen. Es gibt aber zu wenig gute Studien, um einen Effekt sicher ausschließen zu können.

Auch die Auswirkung von Sport in vorausgegangenen Jahren auf vasomotorische Beschwerden in der Peri- und Postmenopause wurde nicht untersucht. Unerwünschte Effekte sowie erwünschte Effekte auf andere Gesundheitsparameter wurden nicht ausgewertet.

5.11.1.9 Chinese herbal medicine

Insgesamt wurden 91 verschiedene Kräuter eingesetzt, 11 davon regelmäßig.

Es konnte nicht nachgewiesen werden, dass chinesische Kräuter in der Therapie vasomotorischer Beschwerden wirksamer sind als Placebo. Dafür können methodische Aspekte wie eine Vielzahl verschiedener Kräuter und unterschiedliche Outcome-Parameter verantwortlich sein.

Die vorhandenen Studien zeigen keine konsistenten Daten zu UAW. Die Sicherheit der Behandlung mit CHM ist nicht ausreichend untersucht.

5.11.1.10 *Cognitive brain therapy*

Alle Methoden zeigten eine signifikante Reduktion der Beeinträchtigung durch Hitzewallungen sowie begleitender menopausaler Beschwerden. Eine Subgruppenanalyse der Frauen mit therapieinduzierter Menopause bestätigte die Wirksamkeit auch bei diesen Frauen nach Brustkrebs. CBT kann als Einzeltherapie, in Gruppen oder als Selbsthilfe angeboten werden.

5.11.2 FR 2021

5.11.2.1 *Vitamin E*

La vitamine E est une vitamine liposoluble présente principalement dans les huiles végétales. Elle agit comme antioxydant. Quelques essais randomisés ont évalué son efficacité dans le traitement des BVM.

Les données disponibles pour évaluer l'efficacité de la vitamine E dans le traitement des BVM sont pauvres et discordantes. Aucune recommandation ne peut donc être proposée.

5.11.2.2 *Bêta-alanine*

Un seul essai clinique en double aveugle versus placebo a été publié en 1991. D'importants problèmes méthodologiques (44 % des femmes non ménopausées et non-description des méthodes statistiques utilisées) ne permettent pas d'apprécier une quelconque efficacité thérapeutique de cette molécule dans la prise en charge des BVM. Ainsi, la HAS concluait que cette molécule « n'a pas de place dans la stratégie thérapeutique des bouffées de chaleur de la ménopause »

Les données disponibles pour évaluer l'efficacité de la bêta-alanine dans le traitement des BVM sont insuffisantes pour émettre une recommandation.

5.11.2.3 *Omega 3*

Cette thérapeutique a été proposée en prévention secondaire de l'infarctus du myocarde, en association aux traitements de référence, avec des résultats contradictoires. Elle a été testée dans le traitement des BVM et a fait l'objet d'une récente méta-analyse.

L'utilisation d'oméga 3 n'apparaît pas efficace pour gérer les BVM chez les femmes en péri-ménopause ou ménopausées (NP2).

5.11.2.4 *Phytoestrogens*

Les données de la littérature ne permettent pas de recommander l'utilisation des extraits des phytoestrogènes pour la prise en charge des bouffées vasomotrices de la ménopause (grade B).

Les inhibiteurs de la recapture de la sérotonine, les inhibiteurs de la recapture de la sérotonine et de la noradrénaline, la clonidine, la gabapentine, la génistéine, le yoga et l'hypnose ont fait la preuve d'une certaine efficacité et peuvent être proposés pour la prise en charge des BVM de la ménopause (grade B).

Chez les femmes ménopausées suivies pour un cancer du sein, il est recommandé de ne pas utiliser les phytoestrogènes pour le traitement des BVM de la ménopause (grade A).

Les phytoestrogènes peuvent donc être séparés en plusieurs catégories principalement :

- Les isoflavones :
ces molécules sont présentes dans de nombreuses légumineuses principalement le soja mais aussi dans d'autres plantes.
On peut ainsi distinguer :

- Les produits à base de soja (soja alimentaire et extraits de soja présentés sous diverses formes, poudres, boissons et comprimés ou gélules) :
 - L'analyse des essais évaluant les phytoestrogènes alimentaires montre des résultats discordants et des études très hétérogènes de faible qualité méthodologiques.
 - Les études publiées ne permettent pas de déterminer de façon certaine l'effet des extraits d'isoflavones (extrait de soja en comprimés ou en gélules) sur la fréquence et de la sévérité des BVM.
- La génistéine, la daidzéine sont les flavonoïdes de soja les plus étudiés.
L'utilisation de génistéine à fortes doses (> 30 mg par jour) améliore significativement la fréquence des BVM (NP2).
- Le trèfle rouge ou red clover :
L'utilisation du trèfle rouge ne semble pas diminuer la fréquence des BVM comparativement au placebo (NP2).
- Le black cohosh ou actée à grappes noires (*cimicifuga racemosa*)
 - L'évaluation de l'utilisation de black cohosh versus placebo ne montre aucune différence significative de la fréquence et de la sévérité des BVM (NP2).
 - Il faut souligner de plus que cette molécule est associée à une importante toxicité hépatique. Son utilisation doit, de ce fait, être évitée.
- Les lignanes contenus dans les fruits, plantes, graine de lin, céréales complètes :
Concernant cette catégorie de phytoestrogènes, il est aussi difficile d'effectuer une synthèse compte tenu des différents produits utilisés (graines de lin, houblon. . .).
L'évaluation de l'utilisation de lignanes montre des résultats discordants et des études très hétérogènes de faible qualité méthodologique.
- Les flavonones contenus dans le houblon et la bière. . . ;
- Les coumestanes contenus dans certaines plantes (luzerne, trèfle. . .),
- Les herbes médicinales chinoises :
Il existe de nombreux essais randomisés évaluant sur différents symptômes l'utilisation des herbes médicinales chinoises, mais ces produits ne sont pas disponibles en France.
L'évaluation de l'utilisation d'herbes médicinales chinoises ne montre aucune différence significative de la fréquence des BVM comparativement au placebo (NP2).

Les femmes asiatiques ont habituellement un syndrome climatérique nettement moins marqué que les Américaines/ Européennes d'où l'idée d'un rôle possible de l'alimentation riche en soja. Il existe actuellement une hypothèse selon laquelle les Asiatiques pourraient avoir un métabolisme de ces substances différent de celui des Occidentaux, peut-être lié à une exposition ancestrale, et qui conduirait à un métabolisme distinct lié à d'autres bactéries intestinales. Il est donc difficile d'extrapoler l'impact des phytoestrogènes alimentaires retrouvés chez les femmes asiatiques à d'autres populations. Par ailleurs, les larges variations selon les quantités, la forme, la qualité des apports des phytoestrogènes évalués rendent difficile l'interprétation de l'ensemble des études.

En raison d'un faible niveau de preuve, ces traitements (phytothérapies) ne sont actuellement pas recommandés pour la prise en charge du SGUM (NP3).

5.11.2.5 Pollen extracts

Les extraits de pollen purifiés associent pollen, extraits de pistils provenant d'une plante de la famille Poaceae et vitamine E. Ils possèdent un fort pouvoir antioxydant. Il n'existe pas d'effet estrogénique selon une étude préclinique de Hellstrom et al. en 2012.

L'élimination d'allergènes potentiels permet l'utilisation chez des patientes allergiques au pollen. Ils ont, cependant, fait l'objet de peu d'études.

Il n'existe qu'un essai randomisé ayant évalué l'efficacité des extraits de pollens sur les BVM. Il montre une diminution significative des BVM comparativement au placebo mais il n'est basé que sur 54 femmes (NP3).

5.11.2.6 *Primerose oil*

Cette huile provient des graines d'une plante de la famille des onagraceae (onagre). Elle contient des acides gras de la famille des omégas 6.

L'huile de primerose ne semble pas efficace sur la fréquence des BVM (NP2).

5.11.2.7 *Ginseng*

L'utilisation de ginseng ne semble pas efficace sur la fréquence des BVM et le score de qualité de vie des femmes (NP2).

5.11.2.8 *Aromatherapy*

Une étude en crossover en double aveugle a évalué chez 100 femmes l'effet d'inhalation d'extraits de lavande sur 12 semaines comparativement à un placebo. Les auteurs observent une diminution significative du nombre de BVM comparativement au groupe placebo.

D'autres essais en Iran semblent montrer l'efficacité de massages à base d'huiles essentielles comparativement à de simples massages sur certains symptômes de ménopause en particulier les BVM mais les auteurs ne fournissent que peu d'information méthodologique de ces études.

Très peu d'études ont évalué l'efficacité de l'aromathérapie ou des massages aux huiles essentielles sur les BVM. Les résultats favorables d'un essai en crossover nécessitent une confirmation par d'autres essais randomisés.

5.11.2.9 *Vaginal lubricants*

Les lubrifiants sont utilisés pour soulager la sécheresse et l'inconfort vaginal au cours de l'activité sexuelle, en réduisant la friction contre les tissus génitaux amincis. Plusieurs variétés sont disponibles dans le commerce, à base d'eau, de silicone, de glycérine, d'huile minérale ou végétale. Ils ont une action uniquement temporaire et n'apportent pas d'amélioration de la trophicité vaginale à long terme. Les données ne démontrent pas de supériorité d'un des lubrifiants sur les autres.

L'OMS préconise d'utiliser les lubrifiants en association avec les préservatifs et recommande par ailleurs que l'osmolalité d'un lubrifiant ne dépasse pas 380 mOsm/kg, afin de minimiser les risques de lésions épithéliales mais une limite supérieure de 1200 mOsm/kg est considérée comme acceptable. Le pH devrait être compris entre 3,8 et 4,5.

Les hydratants vaginaux sont utilisés pour le traitement de la sécheresse vaginale au quotidien ou pendant l'activité sexuelle. Ils ont pour objectif une amélioration des symptômes à long terme. Ils abaissent le pH vaginal et adhèrent à la muqueuse imitant ainsi les sécrétions vaginales naturelles. Ils sont disponibles sous forme de polymères synthétiques ou à base de plantes. Les études concernant les hydratants/lubrifiants sont de courte durée et de faible niveau de preuve.

Les lubrifiants et hydratants pourront être proposés chez les femmes ayant des symptômes modérés du SGUM, l'efficacité étant inférieure à celle de l'oestrogénothérapie locale (NP3). L'acide hyaluronique par voie vaginale est associé à une amélioration significative des symptômes du SGUM (NP3).

5.11.2.10 *Acupuncture*

De nombreux essais randomisés ont analysé l'effet de l'acupuncture sur les BVM.

Les résultats sont différents en fonction du comparateur utilisé.

Notons que ces essais sont globalement de qualité modérée avec une grande hétérogénéité (définition non standardisée de ménopause, durée d'intervention variable, population de femmes ovariectomisées ou atteintes de cancer du sein, différentes méthodes d'acupuncture). La difficulté d'évaluation de ce type de procédure doit être soulignée compte tenu de l'absence de placebo réellement utilisable.

L'évaluation de l'efficacité de l'acupuncture sur les BVM est rendue difficile en raison de l'absence de groupe placebo réellement utilisable.

Les essais montreraient une efficacité sur la fréquence et la sévérité des BVM lorsqu'il n'existe aucun comparatif (NP3).

5.11.2.11 *Physical activity*

L'activité physique doit être adaptée au profil de risque de chaque patiente en sachant que les bénéfices d'une activité modérée seront les plus importants chez une femme à risque cardiovasculaire (NP1).

En prévention de l'ostéoporose et des fractures, le bénéfice est moindre, particulièrement en début de ménopause compte tenu de la forte estrogéno-dépendance de la perte osseuse (NP1) et/ou lorsque le risque fracturaire est déjà majoré (NP2). Elle est par ailleurs, de nature à amplifier le bénéfice osseux du traitement hormonal de ménopause (NP1).

Les effets bénéfiques cardiométaboliques sont bien démontrés, ce qui justifie de promouvoir l'activité physique dès le début de la ménopause.

Les études observationnelles réalisées chez la femme ménopausée mettent en évidence les bénéfices associés à un temps passé assis faible mais aussi ceux liés à une réduction du temps passé assis chez les femmes ayant un temps assis élevé (NP2). Il est fortement suggéré de suivre ces recommandations.

- *Vasomotor flushes :*

L'exercice physique n'a pas d'effet significatif sur les BVM (NP2).

- *Global mortality and cardiovascular risk*

Après la ménopause, une activité physique régulière faible à modérée tout comme la lutte contre la sédentarité est recommandée pour diminuer la mortalité et le risque cardiovasculaire (grade A).

L'AP régulière diminue significativement la mortalité globale et cardiovasculaire chez la femme ménopausée. Elle est efficace en prévention primaire comme en prévention secondaire et tertiaire (NP1). L'AP régulière diminue en moyenne de 30 % le risque de survenue de maladies cardiovasculaires, ce qui correspond aux chiffres retrouvés en population générale (NP1). Il s'agit d'une AP d'intensité modérée, mais la plupart des études montrent aussi le rôle de l'AP de faible intensité qui reste l'AP principale chez les femmes avançant en âge [70 ans ou plus] (NP2).

Quel que soit l'âge, il est aussi important de diminuer les comportements sédentaires (NP1).

Ces effets sont indépendants de l'alimentation. D'autres études seront nécessaires pour définir pour ces derniers points les seuils/durées minimales à respecter.

- *Osteoporosis and muscle mass*

Après la ménopause et en cas de risque d'ostéoporose, il est recommandé de lutter contre la sédentarité et d'avoir une activité physique associant exercices en charge avec impact et renforcement musculaire pour diminuer le risque de fracture (grade B).

Les exercices combinés associant exercices en charge avec impacts et principalement les impacts aléatoires et les impacts de forte intensité associés à du renforcement musculaire, avec une durée 30 à 60 min par session, à raison de 3 j/sem sur une durée moyenne de 10 mois sont les plus efficaces pour préserver/augmenter la densité minérale osseuse au niveau du rachis, du col fémoral, du trochanter et de la hanche chez la femme ménopausée, tout en diminuant le risque de fractures (NP1).

Il reste à déterminer les relations dose-effet en fonction du temps écoulé depuis la date de la ménopause.

L'AP régulière de type endurance/aérobie (au moins 3 fois par semaine, minimum 30 minutes par session d'AP, durée moyenne 30 à 60 min) diminue la masse grasse totale de façon significative mais modérée (en moyenne - 3 %) et plus particulièrement la masse grasse abdominale sous-cutanée et viscérale, et ceci en l'absence de restriction alimentaire. Il faut noter que toutes les études réalisées portaient le plus souvent chez des femmes en surpoids ou obèses et dans tous les cas chez des femmes ayant préalablement un niveau d'AP insuffisant. Les effets de l'AP sur la diminution de masse grasse viscérale sont observés quel que soit l'IMC, en l'absence de RC, pour des exercices de type endurance/ aérobie (NP1) et/ou combinés (NP2).

Pour la masse musculaire, seuls le renforcement musculaire ou les entraînements de type combiné (aérobie/endurance + renforcement musculaire) ont montré leur efficacité pour freiner la perte de masse musculaire voire pour l'augmenter (NP1). Mais dans ce dernier cas les programmes ont inclus des entraînements de type combiné avec des charges élevées pour le renforcement musculaire [70 et 80 % d'1 répétition maximale], et avec des durées de 30 minutes pour les exercices d'aérobie, 3 fois par semaine, non accessibles à toutes les femmes.

La durée minimale de l'AP est de 12 à 24 semaines et elle doit être poursuivie pour que les effets se maintiennent sur le long terme.

Cependant, il manque des études ayant mesuré en parallèle l'évolution de la force musculaire rapportée au kg de masse musculaire : une AP peut induire un gain de force musculaire sans gain de masse musculaire.

- *To reduce sedentary lifestyles:*

Les recommandations reposent sur deux objectifs complémentaires : réduire le temps total quotidien passé en position assise et rompre les périodes prolongées passées en position assise par quelques minutes de mouvements. Le temps quotidien assis peut être remplacé par une AP d'intensité modérée mais aussi par une AP de faible intensité. Pour atteindre ce second objectif, il est proposé de se lever une minute toutes les heures ou 5 à 10 minutes toutes les 90 minutes, et par exemple, de marcher. Ces recommandations s'ajoutent aux recommandations d'activité physique.

- *Physical activity recommendations :*

Chez la femme ménopausée, une combinaison d'activités à impacts (course à pied, saut, danse, exercices sur plateforme de vibration, etc.) (75 min/semaine en 2 à 3 fois si intensité élevée et 150 min/semaine si intensité modérée, en cinq fois) et de renforcement musculaire (résistance élevée) semble nécessaire, au moins 2 fois/semaine. Si l'AP avec impacts est impossible, la marche garde ses effets bénéfiques cardiométaboliques. La pratique des escaliers (montée et descente) est considérée comme une AP avec impacts.

- *Risks associated with physical activity*

Aucune étude n'a rapporté d'incident majeur lié à la pratique d'une AP d'intensité modérée à élevée telle qu'elle est recommandée dans ce chapitre. Néanmoins, certaines précautions doivent être respectées (progressivité, régularité, adaptation à chaque personne), la principale étant vis-à-vis du risque cardiovasculaire.

En l'absence de pathologie connue : un avis médical (médecin traitant) n'est pas nécessaire pour débuter une AP de type marche ou vélo d'intensité faible à modérée. Ces recommandations sont à adapter en fonction de l'âge de la personne.

En présence d'une pathologie connue : dans la plupart des cas, l'AP fait alors partie de la prise en charge non thérapeutique de la pathologie.

En présence de facteurs de risques cardiovasculaires non stabilisés, ou d'une pathologie évolutive, une consultation auprès du médecin traitant est indiquée. Il ne s'agit pas de contre-indications à la pratique d'une AP. La pathologie devra être stabilisée (exemple : tension artérielle stabilisée si HTA...) et l'AP deviendra une indication dans la prise en charge en tant que thérapeutique non médicamenteuse.

Pour toute AP de faible intensité ou d'intensité modérée en l'absence de symptomatologie de repos ou d'effort, il n'y a pas d'indication à demander un avis cardiologique. Si une activité de forte intensité ou de compétition est prévue, une consultation cardiologique est nécessaire.

5.11.2.12 *Other behavioural, psychological or spiritual therapies*

L'hypnose semble réduire de façon significative la fréquence et la sévérité des BVM (NP2).

Le yoga semble réduire de façon significative la fréquence et la sévérité des BVM (NP3).

Les thérapies comportementales semblent diminuer de façon significative la sévérité des BVM (NP2) mais ont peu d'influence sur leur fréquence.

La relaxation n'a pas d'effet significatif sur la fréquence des BVM (NP2).

Le faible nombre d'études publiées ne permet pas de conclure sur une quelconque efficacité de la réflexologie sur la diminution des BVM (NP3).

5.11.2.13 *Nutrition*

Chez les femmes ménopausées en surpoids, il est conseillé une diminution modérée de l'apport énergétique associée à un apport protidique suffisant pour réduire la masse grasse et tenter de s'opposer à la perte de masse maigre, et d'y associer une activité physique (grade C).

Les études longitudinales montrent que la prise de poids débute bien avant la ménopause et se poursuit après celle-ci avec une grande variabilité inter-individuelle. Les facteurs favorisants font intervenir la balance énergétique. Le rôle des dépenses est primordial et l'excès d'apports est donc à la fois relatif et absolu. Seule une balance chroniquement positive peut favoriser une prise de poids, ce qui signifie que seuls les excès répétés et/ou un déséquilibre chronique quantitatif et qualitatif de l'alimentation peuvent être en cause. Les causes de ces excès et/ou de ce déséquilibre incluent le déficit de sommeil et plus largement, les perturbations des rythmes de vie, le stress et ses conséquences sur l'alimentation, l'inactivité physique et la sédentarité, les conditions socioéconomiques et les facteurs psychologiques

Chez les femmes ménopausées, il est proposé d'avoir des apports suffisants diversifiés en protéines, un apport suffisant en calcium, en privilégiant le calcium alimentaire (les produits laitiers) et un apport suffisant en vitamine D qui est fourni à 80 % par la synthèse cutanée de vitamine D sous l'effet des ultraviolets (grade C).

Compte tenu du déterminisme hormonal de la perte osseuse, l'impact préventif des mesures nutritionnelles en début de ménopause est relativement limité même si des déficits sont susceptibles d'amplifier la perte osseuse post-ménopausique ; son bénéfice, à distance du début de la ménopause dans la prévention des fractures, pourrait justifier la mise en place de mesures nutritionnelles en association avec la lutte contre l'inactivité physique (NP2).

La nutrition intervient dans la prévention du risque cardiovasculaire des femmes ménopausées au même titre qu'en population générale.

Table below reports general recommendations for nutritional prevention during the menopause as given by FR 2021

Recommandations générales pour une prévention nutritionnelle lors de la ménopause.

- Prévention du surpoids par une surveillance du poids et surtout par une balance énergétique équilibrée grâce à une activité physique régulière et une lutte contre la sédentarité.
- Modération des apports excessifs en aliments sucrés. Éviction des boissons sucrées si possible.
- Choix d'aliments de faible index glycémique (légumes secs, fruits notamment).
- Apports élevés en aliments sources de fibres alimentaires : céréales complètes et pain complet quotidiennement, légumes secs (2 fois par semaine), fruits et légumes. . .
- Apport élevé en fruits et légumes : au moins 400–500 g/jour, variés, colorés, crus et cuits, sous toutes les formes avec cependant une modération des jus de fruits.
- Apport régulier d'oléagineux (noix, amandes) sans excès cependant (20–25 g/jour).
- Apport tri-quotidien de produits laitiers variés, dont un produit laitier fermenté (yaourt nature si possible).
- Apport quotidien d'une source de protéines animales (indépendamment de l'apport en produits laitiers) : viande (volaille en particulier), œufs, poisson.
- Apport régulier en protéines végétales (légumes secs, soja. . .) avec environ 2 à 4 repas végétariens par semaine.
- Apport bihebdomadaire de poisson dont une fois du poisson gras (maquereau, sardine, anchois, hareng, saumon. . .).
- Modération de l'apport en sel visible ou caché en deçà de 6 g/jour.
- Modération de l'apport en viande rouge (< 500 g (cuit)/semaine) et en charcuterie (< 50 g/jour).
- Variété des modes de cuisson et limitation des produits grillés. Éviter la cuisson au barbecue.
- Modération de l'apport d'alcool (2 unités par jour maximum).
- Éviter les régimes amaigrissants restrictifs et les régimes d'exclusion non justifiés (sans lait, végétalien).

5.11.3 NHG 2022

Niet-medicamenteuze behandeling bij opvliegers en/of nachtzweeten heeft in het algemeen geen tot matig effect.

5.11.3.1 *Weight reduction*

Gewichtsreductie kan een positief gezondheidseffect hebben bij vrouwen met overgewicht of obesitas, maar het is niet aangetoond dat gewichtsreductie bijdraagt aan het verminderen van opvliegers of nachtelijke zweetaanvallen. (Very low level of evidence)

Er is onvoldoende aangetoond dat gewichtsreductie effect heeft op overgangsklachten. Wel heeft gewichtsreductie een algemeen gezondheidsbevorderend effect bij vrouwen met overgewicht of obesitas. De vrouw kan na uitleg zelf haar keuze bepalen. Dit moment kan aangegrepen worden om het cardiovasculair risicoprofiel in kaart te brengen.

De kwaliteit van bewijs is zeer laag.

5.11.3.2 *Physical activity*

Lichaamsbeweging heeft een algemeen positief gezondheidseffect, maar draagt niet bij aan het verminderen van opvliegers of nachtelijke zweetaanvallen. (Low level of evidence)

Het is niet aangetoond dat lichaamsbeweging vermindering geeft van het aantal en de hinder van opvliegers en/of nachtelijke zweetaanvallen. Ook lijkt er geen invloed te zijn op stemmingsklachten en seksuele klachten in het kader van de overgang. Daarom is het niet zinvol om lichaamsbeweging te adviseren specifiek met het oog op vermindering van overgangsklachten. Dit moment kan wel aangegrepen worden om het cardiovasculair risicoprofiel in kaart te brengen. De vrouw kan na uitleg zelf haar keuze maken.

De kwaliteit van bewijs is over het algemeen laag.

5.11.3.3 *Psychological therapy*

5.11.3.4 Overweeg op mindfulness gebaseerde therapie of verwijzing voor een stressreducerende psychologische interventie (zoals cognitieve gedragstherapie) bij vrouwen met opvliegers en/of nachtelijke zweetaanvallen die openstaan voor een psychologische interventie en die geen hormoontherapie kunnen of willen gebruiken. (Low recommendation, low level of evidence)

Het globaal te verwachten effect van een stressreducerende psychologische interventie bij een vrouw met 8 opvliegers per dag is ongeveer 3 opvliegers minder per dag (ter vergelijking: in de controlegroepen was dit ongeveer 1 opvlieger minder per dag).

Op andere uitkomsten (hinder van opvliegers, kwaliteit van leven, stemming, seksuele klachten en slaap) zijn echter slechts kleine verbeteringen te zien, die niet klinisch relevant zijn. Er zijn geen bijwerkingen te verwachten. De interventie kan ook worden toegepast bij vrouwen met een contra-indicatie voor hormoontherapie.

De kwaliteit van bewijs is redelijk tot laag.

5.11.3.5 Phytotherapies

We bevelen zilverkaars (*black cohosh*) niet aan bij vrouwen met opvliegers en/of nachtelijke zweetaanvallen. (Strong recommendation against, very low level of evidence)

Er lijkt niet of nauwelijks verschil te zijn in aantal of ernst van opvliegers tussen de groepen die zilverkaars gebruikten en de placebogroepen. In onderzoek waarin zilverkaars werd vergeleken met hormoontherapie leken aantal en ernst van opvliegers minder te zijn in de groepen die hormoontherapie kregen. Op andere uitkomstmaten werden geen klinisch relevante voordelen van zilverkaars gevonden.

Bijwerkingen zijn nauwelijks onderzocht, de beperkte gegevens uit de RCT's geven geen aanwijzingen voor verschillen tussen de groepen.

In de literatuur worden gevallen van hepatotoxiciteit genoemd. Dit kwam niet terug in de RCT's, maar de aantallen zouden daarvoor ook te klein zijn. Eén RCT onderzocht de leverfunctie en vond daarin geen veranderingen (of verschillen tussen zilverkaars en placebo) gedurende 12 weken gebruik. Ook kan geen uitspraak worden gedaan over interacties met geneesmiddelen (waaronder die gemedieerd door cytochroom-P450-enzymen).

Daarnaast varieert de samenstelling en kwaliteit van de preparaten en wordt deze niet gecontroleerd. Deze overwegingen hebben geleid tot een sterke aanbeveling tegen zilverkaars. Voor de effecten is de kwaliteit van bewijs over het algemeen laag, voor de bijwerkingen zeer laag.

We bevelen fyto-oestrogenen niet aan bij vrouwen met opvliegers en/of nachtelijke zweetaanvallen. (Strong recommendation against, very low level of evidence)

Voordeel: fyto-oestrogenen verminderen mogelijk het aantal opvliegers vergeleken met placebo of geen interventie.

Nadeel: er zijn veel verschillende fyto-oestrogenen op de markt in veel verschillende doseringen. Bijwerkingen zijn nauwelijks onderzocht (de RCT's zijn daarvoor niet geschikt), maar uit case-reports en meldingen bij Lareb zijn er aanwijzingen dat deze wel degelijk kunnen optreden. We zijn onzeker over het effect op borstkanker, endometriumhyperplasie en cardiovasculair risico. In theorie kan het risico verhoogd zijn, omdat het toch om oestrogenen (zonder toegevoegd progestageen) gaat. Er is weinig onderzoek naar langdurig gebruik van specifieke fyto-oestrogenen, zodat de effectiviteit en de bijwerkingen ervan onzeker blijven. Daarnaast varieert de samenstelling en kwaliteit van de preparaten en wordt deze niet gecontroleerd. Deze overwegingen hebben geleid tot een sterke aanbeveling tegen fyto-oestrogenen.

De kwaliteit van bewijs was over het algemeen zeer laag.

5.11.3.6 Lubricants

5.11.3.7 Bij klachten van vaginale atrofie kunnen zowel indifferente middelen (vochtinbrengende gel, crème met hyaluronzuur) als vaginaal oestrogeen overwogen worden. (Low recommendation, low level of evidence)

Indifferente middelen geven een directe, maar kortdurende klachtenvermindering.

5.11.4 NICE upd 2019

Explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms. However, explain that:

- multiple preparations are available and their safety is uncertain
- different preparations may vary
- interactions with other medicines have been reported.

Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown. *Compounded bioidentical hormones is defined by NICE upd 2019 as* unregulated plant-derived hormonal combinations that are chemically similar or structurally identical to human hormones that are compounded by pharmacies to the specification of the prescribe

Explain to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown.

Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about:

- appropriate doses
- persistence of effect
- variation in the nature and potency of preparations
- potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants).

Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.

Vasomotor symptoms

Isoflavones and black cohosh were also shown to be more effective than placebo in relief of VMS for women with a uterus, but not significantly better when compared with combined oestrogen plus progestogen. However, the group expressed a concern around safety issues of isoflavones and black cohosh and they highlighted that there may be unknown risks regarding their safety profile.

There is also some evidence to suggest that isoflavones and black cohosh may be beneficial for this outcome. The group decided to extrapolate the evidence from this population to women without a uterus.

Low mood and anxiety

The group reviewed the limited evidence available, which showed that low mood can be ameliorated by hormonal replacement therapy (oestrogen alone) and psychological therapies, such as CBT, but not from the other non-pharmacological treatments reviewed, such as herbal treatments

For the outcome of anxiety, psychosocial therapies, such as CBT, genistein and red clover, were found to significantly reduce anxiety for women in menopause when compared with placebo or usual care. Because of concerns of unknown safety for genistein and red clover, the group decided that HRT and CBT are preferable treatment options for low mood for some women in menopause. In addition, CBT can be considered for the treatment of anxiety for women in menopause. However, the group wanted to draw to the attention of both healthcare professionals and women in menopause that SSRIs/SNRIs should not be a first-line treatment to alleviate low mood for women in menopause who are not diagnosed with clinical depression, owing to their adverse side-effect profiles, and referred them to the relevant NICE guideline on [depression](#) for further advice.

In relation to anxiety, it was shown that CBT, isoflavones and red clover may improve anxiety for women with menopausal symptoms but there is a lack of consistency between the constituents of herbal preparations, isoflavones and phytoestrogens.

There was some evidence suggesting that CBT was more effective than usual care in reducing anxiety and low mood. CBT is not generally available for treatment of low mood in the perimenopausal woman and the Guideline Development Group felt that development of psychosocial services such as CBT should be considered given this evidence of benefit.

Urogenital atrophy

While the group did not review the clinical effectiveness and safety of the various moisturisers and lubricants, they discussed that these are widely used and generally considered to be a safe option for the relief of symptoms of urogenital atrophy.

Safety

Finally, the Guideline Development Group expressed concern regarding the wide variety of over-the-counter preparations available and the lack of information on quality control, efficacy and safety of herbal preparations and complementary therapies. The group noted previous reports of fatal adverse events from herbal preparations. Therefore, a separate recommendation was drafted to ensure that women who wish to try complementary therapies are aware that the quality, purity and constituents of these products may be unknown. They also discussed that both healthcare professionals and women should be aware of a registration scheme known as the Traditional Herbal Registrations scheme which provides evidence of quality assurance of each of these products in regard to purity rather than the efficacy of a preparation. Preparations registered with the Medicines and Healthcare Product Regulatory Authority (MHRA) that have the traditional herbal registrations certificate should be preferred.

5.11.5 USPSTF 2022

No specific recommendations or comments were provided regarding metabolic effect or risk in this guideline.

6 Hormone therapy for the treatment of menopausal symptoms. Summary and conclusions from the literature review

6.1 Estrogen vs placebo for vasomotor symptoms

Estrogen vs placebo for vasomotor symptoms			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Archer 2003(10), Archer 2012(11), Archer 2013(12), Bacchi-Modena 1997(13), Bachmann (d) 2007(14), Bachmann 2010(15), Baerug 1998(16), Baksu 2009(17), Baumgardner 1978(18), Bayer Healthcare (SIP) 2005*, Bayer Healthcare (SIP) 2007*, Bech 1998(19), Berlex (SIP) 2003*, Buster 2008(20), Campbell 1977(21), Chung 1996(22), Cohen 1999(23), Coope 1981(24), Crisafulli 2004(25), de Vrijer 1999(26), DeAloysio 2000(27), Derman 1995(28), Duramed (SIP) 2004*, Endrikat 2007(29), Gambacciani 2003(30), Gast 2009(31), Gelfand 2003(32), Good 1996(33), Haines 2009(34), Hassa 2010(35), Hedrick 2009(36), Lee 2007(37), Lin 2011(38), Liu 2011(39), Liu 2012(40), Martin 1971(41), Newton 2006(42), Nielsen 2006(43), Notelovitz 2000(44) ;(45) ;(46);, Novartis (SIP) 2005*, Panay 2007(47), Pinkerton 2013(48), Polisseni 2013(49), Polo-Kantola 1999(50), Rebar 2000(51), Rovati 2000(52), Rozenbaum 2002(53), Schurmann 2004(54), Shulman 2002(55), Simon 2001(56), Simon 2006(57), Simon 2007(58), Speroff 1996(59), Speroff 2000(60), Speroff 2006(61), Speroff 2003(62), Stevenson 2010(63), Strickler 2000(64), Studd 1999(65), Utian 2001(66), Utian 2004(67), Utian 2009(68), Veerus 2008(69), Vestergaard 2003(70), von Holst 2000(71), von Holst 2002(72), Welton 2008(73), Wiklund 1993(74), Yang 2004(75)			
*reference not available			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Vasomotor symptoms	(standard dose) N= 39 n= 9316 12-260 weeks	SMD -0.64 (95%CI -0.74 to -0.53) SS in favour of estrogens Tau ² = 0.0818	⊕⊕⊕⊖ MODERATE Study quality: -1; uncertain or inadequate randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok
Vasomotor symptoms	(high dose) N= 9 n= 1399 12-52 weeks	SMD -0.50 (95%CI -0.61 to -0.39) SS in favour of estrogens Tau ² = 0	⊕⊕⊕⊖ MODERATE Study quality: -1; uncertain or inadequate randomization and allocation concealment; great loss to follow-up or differential loss to follow-up in half of studies Consistency: ok Directness: ok Imprecision: ok
Vasomotor symptoms	(low/ultralow dose) N= 53 n= 11694	SMD -0.55 (95%CI -0.61 to -0.48) SS in favour of estrogens	⊕⊕⊕⊖ MODERATE Study quality: -1; uncertain or inadequate randomization and allocation concealment Consistency: ok

	Tau ² = 0.0344	Directness: ok Imprecision: ok
12-104 weeks		

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

39 RCTs were found that compared a standard dose estrogen therapy to placebo to alleviate vasomotor symptoms.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Oral mestranol + norethisterone

Oral quinestrol

Transdermal patch estradiol +/- norethisterone or levonorgestrel

Oral estradiol +/- norethisterone or dienogest

Intranasal estradiol +/- MPA or progesterone

Transdermal estradiol gel

Oral CEE +/- MPA or bazedoxifene

Oral synthetic conjugated estrogen

The majority of studies were of poor methodological quality. The most important methodological problems were uncertain randomization and allocation concealment.

9 RCTs were found that compared a high dose estrogen therapy to placebo to alleviate vasomotor symptoms.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Oral mestranol + norethisterone

Oral quinestrol

Oral CEE

Oral synthetic conjugated estrogen

Oral estradiol

Transdermal patch estradiol

Intranasal spray estradiol + MPA

Vaginal ring estradiol + progestin

The majority of studies were of poor methodological quality. The most important methodological problems were uncertain randomization and allocation concealment, as well as a great loss to follow-up or differential loss to follow-up in half of studies.

53 RCTs were found that compared a low or ultralow dose estrogen therapy to placebo to alleviate vasomotor symptoms.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Oral quinnestrol

Oral piperazine estrone

Transdermal estradiol patch +/- levonorgestrel

Oral estradiol +/- norethisterone or levonorgestrel or norgestimate or drospirenone or dydrogesterone

Intranasal estradiol +/- MPA or progesterone

Oral esterified estrogen +/- methyltestosterone

Oral CEE +/- MPA or bazedoxifene

Oral synthetic conjugated estrogen

Transdermal estradiol gel or cream or spray

The majority of studies were of poor methodological quality. The most important methodological problems were uncertain randomization and allocation concealment.

In menopausal women, a standard dose estrogen resulted in greater alleviation of vasomotor symptoms compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In menopausal women, a high dose estrogen resulted in greater alleviation of vasomotor symptoms compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In menopausal women, a low to ultralow dose estrogen resulted in greater alleviation of vasomotor symptoms compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

6.2 Estrogen vs placebo for quality of life

Estrogen vs placebo for quality of life			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Alexandersen 2000(76), Bacchi-Modena 1997(13), Bachmann 2010(15), Baerug 1998(16), Baksu 2009(17), Bech 1998(19), Brunner 2005(77), Chung 1996(22), de Vrijer 1999(26), DeAloysio 2000(27), Derman 1995(28), Gelfand 2003(32), Haines 2003(78), Hassa 2010(35), Hays 2003(79), Jensen 1983(80), Jirapinyo 2003(81), Panay 2007(47), Pinkerton 2013(48), Polisseni 2013(49), Rebar 2000(51), Rigano 2001(82), Rovati 2000(52), Rozenbaum 2002(53), Saletu 1995(83), Simon 2007(58), Soares 2001(84), Speroff 2003(62), Stevenson 2010(63), Strickler 2000(64), Studd 1999(65), Utian 2009(68), von Holst 2000(71), von Holst 2002(72), Welton 2008(73), Wiklund 1993(74), Yang 2004(75)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
QoL	(standard dose) N= 26 n= 31263 12-104 weeks	SMD 0.55 (95%CI 0.41 to 0.69) SS in favour of estrogen Tau ² = 0.0954	⊕⊕⊕⊖ LOW Study quality: -1 uncertain or inadequate randomization and allocation concealment Consistency: ok Directness: -1 majority of participants CEE+/-MPA; postmenopausal Imprecision: ok
QoL	(high dose) N= 5 n= 789 12-104 weeks	SMD 0.76 (95%CI 0.48 to 1.03) SS in favour of estrogen Tau ² = 0.0148	⊕⊕⊕⊖ MODERATE Study quality: -1 uncertain randomization, blinding and allocation concealment Consistency: ok Directness: ok Imprecision: ok
QoL	(low/ultralow dose) N= 17 n= 3507 12-104 weeks	SMD 0.36 (95%CI 0.27 to 0.45) SS in favour of estrogen Tau ² = 0.0628	⊕⊕⊕⊖ MODERATE Study quality: -1 uncertain allocation concealment Consistency: ok Directness: ok Imprecision: ok

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

26 RCTs were found that compared a standard dose estrogen therapy to placebo to improve quality of life.

Different forms of estrogen and estrogen/progestogen were used in these trials:

transdermal estradiol patch+/- levonorgestrel

oral estradiol +/- norethisterone

intranasal estradiol +/- MPA spray

oral piperazone estrone + norethisterone

transdermal estradiol patch

oral CEE +/- MPA

oral CEE + bazedoxifene

The majority of participants came from the large WHI and the WISDOM studies, both of which compared CEE or CEE+MPA to placebo.

The majority of participants came from the large WHI and the WISDOM studies, both of which included only post-menopausal women.

The majority of smaller studies were of poor methodological quality. The most important methodological problems were uncertain allocation concealment.

5 RCTs were found that compared a high dose estrogen therapy to placebo to improve quality of life.

Different forms of estrogen and estrogen/progestogen were used in these trials:

oral estradiol,

oral estriol + norethisterone;

transdermal estradiol patch,

intranasal estradiol +MPA spray,

vaginal ring estradiol +progestin.

The majority of studies were of poor methodological quality. The most important methodological problems were uncertain randomization, allocation concealment and blinding.

17 RCTs were found that compared a low or ultralow dose estrogen therapy to placebo to improve quality of life.

Different forms of estrogen and estrogen/progestogen were used in these trials:

oral estriol +/- norethisterone;

intranasal estradiol +/- MPA spray,

oral piperazine estrone + norethisterone,

transdermal estradiol patch,

oral estradiol + norgestimate;

transdermal estradiol gel,

oral CEE + bazedoxifene;

oral estradiol + dydrogesterone

The majority of studies were of poor methodological quality. The most important methodological problems were uncertain allocation concealment.

In **menopausal women**, a standard dose **estrogen** resulted in **greater improvement of quality of life** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **menopausal women**, a high dose **estrogen** resulted in **greater improvement of quality of life** compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **menopausal women**, a low to ultralow dose **estrogen** resulted in **greater improvement of quality of life** compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

6.3 Estrogen vs placebo for global psychological well-being

Estrogen vs placebo for global psychological well-being			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Wiklund 1993(74), Derman 1995(28), Baerug 1998(16), Rozenbaum 2002(53), Speroff 2003(62), Haines 2003(78), Gelfand 2003(32), Yang 2004(75), Nielsen 2006(43), Simon 2007(58), Utian 2009(68), Bachmann 2010(15), Demetrio 2011(85), Pinkerton 2013(48)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
global psychological well-being	N= 14 n= 3386 12-104 weeks	SMD -0.26 (95%CI -0.40 to -0.13) SS in favour of estrogen Tau ² = 0.0395	⊕⊕⊖⊖ LOW Study quality: -1 uncertain allocation concealment, Consistency: ok Directness: -1 few perimenopausal Imprecision: ok

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

14 RCTs were found that compared some form of estrogen therapy to placebo to improve global psychological well-being.

Different forms of estrogen and estrogen/progestogen were used in these trials:

*Oral estradiol +/- norethisterone;
oral estradiol + norgestimate;
estradiol transdermal patch;
estradiol nasal spray +/- progesterone;
vaginal ring estradiol + progestin;
oral CEE + MPA;
estradiol transdermal gel;
oral CEE + bazedoxifene.*

The majority of the women included in the studies were postmenopausal.

8 studies were assessed to be of poor methodological quality. 6 studies were assessed to be of fair methodological quality.

The most important methodological problems were uncertain allocation concealment.

In **menopausal women**, **estrogen** resulted in **greater improvement of global psychological well-being** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.4 Estrogen vs placebo for depressive symptoms

Estrogen vs placebo for depressive symptoms			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Campbell 1977(21), Coope 1981(24), Wiklund 1993(74), Derman 1995(28), Saletu 1995(83), Bech 1998(19), Polo-Kantola 1999(50), Soares 2001(84), Speroff 2003(62), Gambacciani 2003(30), Rudolph 2004(86), Yang 2004(75), Onalan 2005(87), Pefanco 2007(88), Baksu 2009(17), Hassa 2010(35), Demetrio 2011(85), Polisseni 2013(49)			
Additional RCT: Gordon 2018(89)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Depressive symptoms	N= 18 n= 3386 12-156 weeks	SMD -0.36 (95%CI -0.53 to -0.20) SS in favour of estrogen Tau² = 0.0734	⊕⊕⊕⊖ MODERATE Study quality: -1 uncertain or inadequate randomization and allocation concealment. Consistency: ok Directness: ok Imprecision: ok
Clinically significant depressive symptoms	N=1 N=172 12 months	OR: 2.5 (95% CI 1.1 to5.7) SS in favour of estrogen	⊕⊕⊖⊖ LOW Study quality: -2 single study with inadequate allocation concealment, unbalanced dropout and selective reporting Consistency: ok Directness: ok Imprecision: ok

An AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

18 RCTs were found that compared some form of estrogen therapy to placebo to alleviate depressive symptoms.

Different forms of estrogen and estrogen/progestogen were used in these trials:

oral CEE +/- MPA,

oral piperazine estrone,

transdermal estradiol patch,

oral estradiol + norethisterone or dienogest or progesterone,

transdermal estradiol gel,

vaginal ring estradiol + progestin.

The majority of studies were of poor methodological quality : the most important problems were uncertain randomization and allocation concealment.

In menopausal women, estrogen resulted in greater improvement of depressive symptoms compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

An additional RCT by Gordon 2018 included perimenopausal and early postmenopausal women without current major depressive disorder; and evaluated the incidence of clinically significant depressive symptoms with transdermal estradiol plus intermittent micronized progesterone compared to placebo.

The study had serious methodological problems that limit our confidence in the results: the allocation concealment was inadequate (the active and placebo patches were not identical), there was a large and uneven drop-out (19.8% in the placebo group and 26.7% in the estradiol+ progesterone group) and there was a risk of bias due to selective reporting.

In menopausal women, estrogen resulted in lower incidence of clinically significant depressive symptoms compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.5 Estrogen vs placebo for the treatment of depression in perimenopausal women

Estrogen versus placebo for the treatment of depression in perimenopausal women			
Bibliography: Zhang 2023(90)			
Including: Schmidt 2000(91), De Novaes Soares 2001(92), Morgan 2005(93), Kulkarni 2018(94), Schmidt 2021(95)			
Outcomes	N° of studies	Results	Quality of the evidence

	(n° of participants) Follow up		(GRADE)
Depressive mood	N= 5 n= 177 6-24 weeks	Std. Mean Difference -1.18 (-1.16 to -0.75) SS in favour of estrogen $I^2 = 38\%$	⊕⊕⊖⊖ LOW Study quality: -1 very small sample size Consistency: ok Directness: -1; short duration of studies, estrogen as add-on to antidepressant medication Imprecision: ok

This systematic review and meta-analysis by Zhang 2023 searched for all RCTs that compared estrogen therapy to placebo in women with depression. Subanalyses were made for studies in perimenopausal and postmenopausal women.

5 RCTs were found that compared estrogen therapy to placebo for depression in perimenopausal women.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Transdermal estradiol patch

Tibolone

Conjugated estrogen

In two of the trials, estrogen was used as an add-on treatment to antidepressants (estrogen + antidepressant versus placebo + antidepressant).

There are some methodological problems that limit our confidence in the estimate of the results: all of the individual studies had very small sample sizes ($n < 50$) and were of short duration (6-24 weeks).

In perimenopausal women with depression, estrogen resulted in greater alleviation of depressive mood compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.6 Estrogen vs placebo for the treatment of depression in postmenopausal women

Estrogen versus placebo for the treatment of depression in postmenopausal women			
Bibliography: Zhang 2023(90)			
Including: Berlenga 2003(96), Morrison 2004(97), Rudolph 2004(98), Rasgon 2007(99), Karsidag 2012(100)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)

Depressive mood	N= 5 n= 360	Std. Mean Difference -0.40 (-0.92 to 0.11)	⊕⊖⊖⊖ VERY LOW Study quality: -1; 1 study with high risk of bias due to deviation from the intended interventions, 3 studies with very small sample sizes Consistency: -1 great heterogeneity Directness: -1; short duration of studies, estrogen as add-on to antidepressant medication Imprecision: ok
	8-24 weeks	NS I ² = 78%	

This systematic review and meta-analysis by Zhang 2023 searched for all RCTs that compared estrogen therapy to placebo in women with depression. Subanalyses were made for studies in perimenopausal and postmenopausal women.

5 RCTs were found that compared estrogen therapy to placebo for depression in postmenopausal women.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Transdermal estradiol patch

Tibolone

Oral estradiol + dienogest

Oral estradiol + norethisterone

In two of the trials, estrogen was used as an add-on treatment to antidepressants (estrogen + antidepressant versus placebo + antidepressant).

There are some methodological problems that limit our confidence in the estimate of the results: 3 of the individual studies had very small sample sizes (n<50) and all were of short duration (6-24 weeks). One study was judged to have a very high risk of bias due to deviation from the intended intervention.

In postmenopausal women with depression, estrogen resulted in no difference for alleviation of depressive mood compared to placebo.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

6.7 Estrogen vs placebo for urogenital atrophy

Estrogen vs placebo for urogenital atrophy			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Bachmann (d) 2009(101), Bachmann 2009(102), Bachmann 2008(103), Bech 1998(19), Cano 2012(104), Casper 1999(105), Chung 1996(22), Eriksen 1992(106), Foidart 1991(107), Freedman 2009(108), Haines 2009(34), Lee 2007(37), Lin 2011(38), Parsons 2003(109), Raghunandan 2010(110), Rozenbaum 2002(53), Schurmann 2004(54), Simon (SIP) 2008*, Simon 2007(58), Simunic 2003(111), Speroff 2003(62), Vestergaard 2003(70), von Holst 2000(71), Welton 2008(73)			
*reference not available			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Urogenital atrophy	(Vaginal estrogens vs placebo) N= 12 n= 3419 12-52 weeks	SMD -0.64 (95%CI -1.03 to -0.26) SS in favour of vaginal estrogen Tau ² = 0.1056	⊕⊕⊕⊖ MODERATE Study quality: -1 ; overall studies with uncertain randomization, allocation concealment Consistency: ok Directness: ok Imprecision: ok
Urogenital atrophy	(Nonvaginal estrogens (standard dose) vs placebo) N= 6 n= 3600 12-260 weeks	SMD -0.32 (95%CI -0.47 to -0.18) SS in favour of estrogen Tau ² = 0.0159	⊕⊕⊕⊖ MODERATE Study quality: -1; uncertain or inadequate randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok
Urogenital atrophy	nonvaginal estrogens (low/ultralow dose) vs placebo N= 8 n= 1541 12-16 weeks	SMD -0.41 (95%CI -0.53 to -0.30) SS in favour of estrogens Tau ² = 0.0016	⊕⊕⊕⊖ MODERATE Study quality: -1 uncertain or inadequate randomization and allocation concealment. Consistency: ok Directness: ok Imprecision: ok

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

12 RCTs were found that compared vaginal estrogen therapy to placebo to treat urogenital atrophy.

Different forms of estrogen and estrogen/progestogen were used in these trials:

estriol gel or vaginal pessary,
estradiol vaginal tablet or gel,
conjugated estrogen vaginal cream,
estradiol + progestin vaginal ring.

The majority of the women included in the studies were postmenopausal.

The majority of studies were of poor methodological quality: the most important problems were uncertain randomization and allocation concealment.

6 RCTs were found that compared a standard dose of nonvaginal estrogen therapy to placebo to treat urogenital atrophy.

*Different forms of estrogen and estrogen/progestogen were used in these trials:
oral estradiol +/- norethisterone,
estradiol transdermal patch,
nasal spray,
oral CEE+MPA.*

The majority of the women included in the studies were postmenopausal.

The majority of studies were of poor methodological quality: the most important problems were uncertain or inadequate randomization and allocation concealment. One large study (comprising half of participants) was assessed to be of good methodological quality.

8 RCTs were found that compared a low or ultralow dose of nonvaginal estrogen therapy to placebo to treat urogenital atrophy.

*Different forms of estrogen and estrogen/progestogen were used in these trials:
oral estradiol + drospirenone,
estradiol transdermal gel or patch,
estradiol nasal spray,
oral CEE.*

The majority of the women included in the studies were postmenopausal.

The majority of studies were of poor methodological quality: the most important problems were uncertain or inadequate randomization and allocation concealment.

In menopausal women, vaginal estrogen resulted in greater improvement of urogenital atrophy compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **menopausal women**, a **standard dose nonvaginal estrogen** resulted in **greater improvement of urogenital atrophy** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **menopausal women**, a **low or ultralow dose nonvaginal estrogen** resulted in **greater improvement of urogenital atrophy** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.8 Estrogen vs placebo for dyspareunia

Estrogen vs placebo for dyspareunia			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including: Campbell 1977(21), Eriksen 1992(106), Casper 1999(105), Vestergaard 2003(70), Speroff 2003(62), Simunic 2003(111), Parsons 2003(109), Dessole 2004(112), Simon (SIP) 2008*, Bachmann (Study 1) 2009(102), Freedman 2009(108), Gast 2009(31), Bachmann (Study 2) 2009(101), Cano 2012(104)			
<i>*reference not available</i>			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Dyspareunia	(Vaginal estrogens vs placebo) N= 10 n= 3205 12-52 weeks	SMD -0.54 (95%CI -0.73 to -0.34) SS in favour of vaginal estrogens Tau ² = 0.0726	⊕⊕⊖⊖ LOW Study quality: -1 overall studies with inadequate or uncertain randomization, allocation concealment Consistency: ok Directness: -1 mostly postmenopausal women, use of conjugated estrogen in 4 studies Imprecision: ok
Dyspareunia	(oral estrogens vs placebo) N= 4 n= 1661 12-260 weeks	SMD -0.22 (95%CI -0.35 to -0.09) SS in favour of oral estrogens Tau ² = 0.0063	⊕⊕⊖⊖ LOW Study quality: -1 overall studies with inadequate or uncertain randomization, allocation concealment Consistency: ok Directness: -1 mostly postmenopausal women, use of conjugated estrogen in 2 studies Imprecision: ok

Dyspareunia	(all estrogens vs placebo) N= 14 n= 4866 12-260 weeks	SMD -0.45 (95%CI -0.61 to -0.29) SS in favour of estrogens Tau ² = 0.0699	⊕⊕⊖⊖ LOW Study quality: -1 overall studies with inadequate or uncertain randomization, allocation concealment Consistency: ok Directness: -1 mostly postmenopausal women, use of conjugated estrogen in 6 studies Imprecision: ok

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

14 RCTs were found that compared some form of estrogen therapy to placebo to treat dyspareunia.

Different forms of estrogen and estrogen/progestogen were used in these trials:

Oral CEE with or without MPA;

oral estradiol + norethisterone acetate;

vaginal estriol gel or ovules;

vaginal estradiol gel, tablets or ring;

vaginal conjugated estrogen cream.

The majority of the women included in the studies were postmenopausal.

The majority of studies were of poor methodological quality: the most important problems were inadequate or uncertain randomization and allocation concealment.

In menopausal women, oral estrogen resulted in **greater alleviation of dyspareunia** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In menopausal women, vaginal estrogen resulted in **greater alleviation of dyspareunia** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In menopausal women, oral or vaginal estrogen resulted in **greater alleviation of dyspareunia** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.9 Estrogen vs placebo or no intervention for sexual function

Estrogen versus placebo or no intervention for sexual function			
Bibliography: Meziou 2023(113)			
Including: Bumphenkiatikul 2020(114), Cruz 2015(115), Haines 2009(34), Hirschberg 2020(115), Lillemon 2022(116), Mac Bride 2014(117), MsFLASH VHT(118);(119);(120);(121), MsFLASH VMS(122);(123), REJOICE(124), Speroff 2003(62), Sun 2016(125), Verghese 2020(126), Wiklund 1993(127), Dayal 2005(128), Simon 2007(58), Strickler 2000(64)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Sexual function composite score	(estrogen versus control) N= 16 n= 2925 12 weeks- 52 weeks	Std. Mean Difference 0.16 (0.02 to 0.29) SS in favour of estrogen therapy $I^2 = 59\%$	⊕⊕⊖⊖ LOW Study quality: -2 more than half of studies have moderate to high risk of bias due to missing outcome data Consistency: ok Directness: ok Imprecision: ok
Sexual function composite score	(systemic estrogen therapy vs control) N= 6 n= 1095 12 weeks -	Std. Mean Difference 0.21 (0.02 to 0.41) SS in favour of estrogen therapy $I^2 = 56\%$	⊕⊕⊕⊖ MODERATE Study quality: -1; unclear randomization or allocation concealment in half of studies; 2 studies with high risk of incomplete outcome data Consistency: ok Directness: ok Imprecision: ok
Sexual function composite score	(vaginal estrogen therapy vs control) N= 10 n= 1830	Std. Mean Difference 0.12 (-0.07 to 0.31) NS $I^2 = 63\%$	⊕⊖⊖⊖ VERY LOW Study quality: -2 majority of studies have moderate to high risk of bias due to missing outcome data Consistency: ok Directness: -1; only one study in 67 participants included perimenopausal patients, all others postmenopausal Imprecision: ok

This systematic review and meta-analysis by Meziou 2023 searched for all RCTs that compared estrogen therapy, estrogen plus progestogen therapy, tibolone, or SERM to placebo or no intervention in peri- and postmenopausal women for the outcome of sexual function.

16 RCTs were found that compared estrogen therapy to control for a sexual function composite score. 6 RCTs compared systemic estrogen therapy to control, and 10 RCTs compared vaginal estrogen therapy to control.

Different forms of estrogen were used in these trials:

Vaginal tablet conjugated estrogen

Vaginal tablet estradiol

Vaginal cream estradiol

Vaginal cream estriol

Oral CEE

Oral estradiol

Transdermal patch microdose estradiol

Vaginal gel estriol

Vaginal ring estradiol

Vaginal gel capsule estradiol

Transdermal estradiol gel

Vaginal cream promestriene

Vagina pessary estradiol

Transdermal estradiol patch

Almost all studies with vaginal estrogen included postmenopausal women only.

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were a large amount of studies with moderate to high risk of bias due to missing outcome data. Additionally, many studies have unclear randomization or allocation concealment.

In **menopausal women**, **estrogen** resulted in **greater improvement of sexual function** compared to placebo or no intervention.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **menopausal women**, systemic **estrogen** resulted in **greater improvement of sexual function** compared to placebo or no intervention.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **menopausal women**, vaginal **estrogen** resulted in **no difference in improvement of sexual function** compared to placebo or no intervention.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

Update of the literature search

Due to the postponement of the consensus conference, an additional literature search was performed. A new Cochrane systematic review was identified (Lara 2023(129)) that compared estrogen or SERM to placebo for sexual function in peri-and postmenopausal women. This Cochrane systematic review performed a similar analysis as Meziou 2023(113). No new RCT's were identified. Given that there were no important differences in results and conclusions, we did not report the results of the Cochrane review here.

6.10 Estrogen plus progestogen vs placebo or no intervention for sexual function

Estrogen plus progestogen versus placebo or no intervention for sexual function			
Bibliography: Meziou 2023(113)			
Including: Davison 2013(130), KEEPS-Sexual(131), Nielsen 2006(43), Olmez 2017(121), Czarnecka 2000(132), Osmanagaoglu 2006(133), WISDOM(134)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Sexual function composite score	N= 7 n= 2432	Std. Mean Difference 0.11 (- 0.07 to 0.29)	⊕⊕⊕⊖ MODERATE Study quality: -1; larger studies with high risk of bias due to missing outcome data Consistency: ok Directness: ok Imprecision: ok
	12 weeks- 2years	NS I ² = 65%	

This systematic review and meta-analysis by Meziou 2023 searched for all RCTs that compared estrogen therapy, estrogen plus progestogen therapy, tibolone, or SERM to placebo or no intervention in peri- and postmenopausal women for the outcome of sexual function.

7 RCTs were found that compared estrogen plus progestogen therapy to control for a sexual function composite score.

Different forms of estrogen plus progestogen were used in these trials:

Oral estradiol + norethisterone

Oral estradiol + MPA

Oral estradiol + drospirinone

Oral estradiol + dienogest

Oral CEE + progesterone

Oral CEE+ MPA

Transdermal estradiol patch + oral progesterone

Intranasal spray estrogen + micronized progestogen

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were the longer and larger studies with high risk of bias due to missing outcome data.

In **menopausal women, estrogen plus progestogen** resulted in **no difference in improvement of sexual function** compared to placebo or no intervention.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Update of the literature search

Due to the postponement of the consensus conference, an additional literature search was performed. A new Cochrane systematic review was identified (Lara 2023(129)) that compared estrogen plus progesterone or SERM to placebo for sexual function in peri-and postmenopausal women. This Cochrane systematic review performed a similar analysis as Meziou 2023(113). No new RCT's were identified. Given that there were no important differences in results and conclusions, we did not report the results of the Cochrane review here.

6.11 Intravaginal DHEA vs placebo in postmenopausal women for vulvovaginal atrophy symptoms

Intravaginal DHEA vs placebo in postmenopausal women			
Labrie 2009(135), Archer 2015(136), Labrie 2015(137), Labrie 2016(138)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Change in severity score of most bothersome symptom* <i>*self-reported most bothersome symptom among vaginal dryness, vaginal and/or vulvar itching, and vaginal pain associated with sexual activity</i> <i>(severity score 0-3)</i>	N= 1 n= 108 12 weeks	Placebo: -0.6 ± 0.13 DHEA: -1.5 ± 0.14 P <0.0001 SS in favour of DHEA	⊕⊕⊕⊖ LOW Study quality: -2 small single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: NA Directness: ok Imprecision: ok
Severity of dyspareunia (PO)	N= 1 n= 187	Placebo: -1.71 ± 0.11 DHEA 0.5%: -1.36 ± 0.12	⊕⊕⊕⊖ MODERATE

(severity score 0-3)	12 weeks	p 0.013 SS in favour of DHEA	Study quality:-1; high exclusions in one study, selective reporting in other study Consistency: ok Directness: ok Imprecision: ok
	N= 1 n= 482	Placebo: -1.06 DHEA: -1.42	
	12 weeks	p 0.0002 SS in favour of DHEA	
Sexual function (Change in Female Sexual Function Index total score)	N= 1 n= 482	Placebo: 6.28 ±0.68 DHEA: 8.85 ±0.45 p 0.0006 SS in favour of DHEA	⊕⊕⊖⊖ LOW Study quality: -2 single study with high exclusion Consistency: NA Directness: ok Imprecision: ok
Participants with at least one adverse event	N= 1 n= 255	Placebo: 43.8% 0.50% DHEA: 52.9%	Insufficient evidence
	12 weeks	No statistical analysis	

	N= 1 n= 482	Placebo: 42.8% DHEA: 47.9%	
	12 weeks	No statistical analysis	

We found 4 publications of 3 trials (Labrie 2009, Archer 2015, Labrie 2015, Labrie 2016) that compared intravaginal DHEA (prasterone) 0.5% therapy to placebo in postmenopausal women to alleviate symptoms of vulvovaginal atrophy.

There are some methodological problems that limit our confidence in the estimate of the results: there was a risk of bias of selective reporting, and unclear randomization and allocation concealment in one of the studies.

In postmenopausal women, intravaginal DHEA resulted in greater alleviation of the most bothersome vulvovaginal atrophy symptom compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In postmenopausal women, intravaginal DHEA resulted in greater alleviation of dyspareunia compared to placebo.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **postmenopausal women**, **intravaginal DHEA** resulted in **greater improvement of sexual function** compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

*We had **insufficient evidence** to assess whether intravaginal DHEA resulted in more participants with at least one adverse event compared to placebo.*

6.12 Different routes of estrogens for the treatment of symptoms of menopause

Oral versus transdermal estrogen (+/- progestagen) for symptoms of menopause			
Bibliography: SR Grant 2015 (AHRQ)(1)			
Including : Good 1999(139); Parsey 2000(140); Polvani 1991(141); Serrano 2006(142); Studd 1995(143)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Vasomotor symptoms	N= 4 n= 823 12-52 weeks	NS (no meta-analysis performed; results of all individual RCTs were NS)	⊕⊕⊕⊕ LOW Study quality: -1 overall studies with uncertain randomization and allocation concealment Consistency: ok Directness: -1 CEE only Imprecision: ok
Quality of life	N= 1 n= 300 26 weeks	Std. Mean Difference -0.03 (-0.23 to 0.18) NS	⊕⊕⊕⊕ VERY LOW Study quality: -2 single unblinded study with uncertain randomization and allocation concealment and great or unbalanced loss to follow-up Consistency: NA Directness: -1 CEE only Imprecision: ok
Global psychological well-being	N= 1 n= 104 52 weeks	Std. Mean Difference -0.00 (-0.39 to 0.39) NS	⊕⊕⊕⊕ LOW Study quality: -1 single small study with uncertain allocation concealment Consistency: NA Directness: -1 CEE only Imprecision: ok
Sexual function	N= 1 n= 104 52 weeks	Std. Mean Difference 0.35 (-0.04 to 0.74) NS	⊕⊕⊕⊕ LOW Study quality: -1 single small study with uncertain allocation concealment Consistency: NA Directness: -1 CEE only Imprecision: ok

This AHRQ systematic review and meta-analysis by Grant 2015 searched for all RCTs that compared hormone therapies (including estrogen and estrogen/progestogen therapy administered by oral, transdermal, vaginal or nasal route), nonhormone therapies (such as SSRI/SNRIs, clonidine, etc.), or nonprescriptions therapies (such as isoflavones, black cohosh) with placebo or to each other in perimenopausal or postmenopausal women without pre-existing conditions in primary care settings.

5 RCTs were found that directly compared oral estrogen (with or without progestogen) to a similar dosage of transdermal estrogen (with or without progestogen) to treat symptoms of menopause.

In all of the trials, conjugated equine estrogen +/- MPA or dydrogesterone was used for the oral route.

In all of the trials, an estradiol patch (+/- MPA or dydrogesterone) was used for the transdermal route.

All of the studies were of poor methodological quality: the most important problems were inadequate or uncertain randomization and allocation concealment.

*In **menopausal women**, oral estrogen (with or without progestogen) to resulted in **no difference in vasomotor symptoms** compared to a similar dosage of transdermal estrogen (with or without progestogen).*

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

*In **menopausal women**, oral estrogen (with progestogen) to resulted in **no difference in quality of life** compared to a similar dosage of transdermal estrogen (with progestogen).*

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

*In **menopausal women**, oral estrogen (with progestogen) to resulted in **no difference in global psychological well-being** compared to a similar dosage of transdermal estrogen (with progestogen).*

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

*In **menopausal women**, oral estrogen (with progestogen) to resulted in **no difference in sexual function** compared to a similar dosage of transdermal estrogen (with progestogen).*

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.13 Tibolone vs placebo in post-menopausal women

Note: this table contains information on the prevention/risk of chronic conditions, see chapter 8

Tibolone vs placebo: short and long term effects			
Bibliography: Formoso 2016(144) (Short-term and long-term effects of tibolone in postmenopausal women)			
including Benedek-Jaszmann 1987(145), Berning 2000(146), Bouchard 2012(147), Cumming 2008(148), Gallagher 2001(149), Hudita 2003(150), Jacobsen 2012(151), Kenemans 2009(152), Kroiss 2015(153), Kubista 2007(154), Landgren 2002(155), Langer 2006(156), Meeuwssen 2002(157), Morais-Socorro 2012(158), Swanson 2006(159), Vieira 2009(160), Wender 2004(161), Ziaei 2010(162)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Vasomotor symptoms	N= 7 n= 1657	SMD (95% CI): -0.99 (-1.10 to -0.89) SS in favour of tibolone	⊕⊕⊕⊕ LOW Study quality: -1 Consistency: -1 Directness: ok Imprecision: ok Most of the studies with unclear selection bias, reporting bias, unclear or high attrition bias, 1 study with inappropriate blinding, high heterogeneity.
Vaginal dryness and painful sexual intercourse	N= 3 n= 3348	SMD (95% CI): -0.66[-0.9,-0.43] SS in favour of tibolone	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: -1 Directness: -1 Imprecision: ok 2 studies with unclear selection bias and reporting bias, high attrition bias in 1 study, inappropriate blinding in 1 study, high heterogeneity, most of the participants having had surgery for breast cancer.
Unscheduled bleeding	N= 9 n= 7814	617/3953 vs 242/3861 31% to 44% vs 18% OR (95 % CI): 2.79 (2.10 to 3.70) SS in favour of placebo	⊕⊕⊕⊕ LOW Study quality: -1 Consistency: ok Directness:-1 Imprecision: ok Most of the studies with unclear selection bias, several studies with unclear reporting bias, unclear or high attrition bias, most of the participants having had surgery for breast cancer or having 60-85 y with low BMD or

			vertebral fractures, 1 study with mean time from menopause =11 years.
Endometrial hyperplasia	N= 4 n = 4518	5/2485 vs 2/2033 OR (95% CI): 1..20 (0.23 to 6.25) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-1 Imprecision: -1 1 study with high attrition bias, 3 studies with unclear selection bias and reporting bias, most of the participants having 60-85 y with low DMD or vertebral fractures, low event rate
Endometrial cancer	N=9 n= 8504	16/4486 vs 5/4018 OR (95 % CI): 2.04 (0.79 to 5.24) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-1 Imprecision: -1 Most of the studies with unclear selection bias, several studies with unclear reporting bias, unclear or high attrition bias, most of the participants having had surgery for breast cancer or having 60-85 y with low BMD or vertebral fractures, 1 study with mean time from menopause =11 years, wide CI, low event rate
Breast cancer	N= 4 n= 5500	11/2808 vs 23/2692 OR (95 % CI): 0.52 (0.221 to 1.25) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-1 Imprecision: -1 3 studies with unclear selection bias and reporting bias, most of the participants having 60-85 y with low BMD or vertebral fractures, 1 study with mean time from menopause =11 years, wide CI, low event rate
Venous thromboembolic events	N= 5 n= 9176	12/5054 vs 12/ 4122 OR (95%CI): 0.85 (0.37 to 1.97) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-1 Imprecision: -1 3 studies with unclear selection bias and reporting bias, most of the participants having had surgery for breast cancer or having 60-85 y with low BMD or vertebral fractures, 1 study with mean time from menopause =11 years, low event rate
Cardiovascular events	N= 4 n= 8401	37/4202 vs 27/4199 OR (95 % CI): 1.38 (0.84 to 2.27) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-1

			Imprecision: -1 2 studies with unclear selection bias, 1 study with unclear reporting bias, 1 study with unclear blinding, 1 study with high attrition bias, all participants having had surgery for breast cancer, having more than 70y and living in community or having 60-85 y with low BMD or vertebral fractures, 1 study with mean time from menopause =11 years, low event rate
Cerebrovascular events	N= 4 n= 7930	35/3967 vs 20/3963 OR (95 % CI): 1.74 (0.99 to 3.04) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness:-2 Imprecision: -1 2 studies with unclear selection bias, 1 study with unclear reporting bias, 1 study with unclear blinding, 1 study with high attrition bias, all participants having had surgery for breast cancer, having more than 70y and living in community or having 60-85 y with low BMD or vertebral fractures, 1 study stopped for risk of stroke, 1 study with mean time from menopause =11 years, low event rate
Mortality	N= 4 n= 8242	98/4125 vs 93/4117 OR (95% CI): 1.06 (0.79 to 1.41) NS	⊕⊕⊕⊕ LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: ok 2 studies with unclear selection bias and reporting bias, most of the participants having had surgery for breast cancer or having 60-85 y with low BMD or vertebral fractures, 1 study with mean time from menopause =11 years, low event rate

The systematic review and meta-analysis by Formoso 2016 searched for RCTs that evaluated tibolone effectiveness and safety in peri and post-menopause.

All the RCTs that were found included post-menopausal women (surgical or spontaneous menopause) and in most of the studies, all or some participants had menopausal symptoms.

18 RCTs have compared tibolone to placebo.

Doses of oral tibolone ranging from 0.625 mg to 5 mg daily were pooled, usually 2.5 mg/d.

Three RCTs specifically studied individuals with breast cancer and were included in the MA.

Two of the largest RCTs, which strongly influenced results on several outcomes, included very specific populations (patients with breast cancer or those with osteoporosis). Findings of these studies are of limited applicability to general population of women taking tibolone for menopausal symptoms.

Follow up in available RCTs varies from 12 weeks to 3 years.

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were poor reporting of study methods. In most of the studies allocation concealment, randomization and reporting of outcomes was unclear. The risk of attrition bias and conflict of interest were high/or unclear in most of the studies as well.

Quality of the evidence was downgraded for lack of directness when patients with breast cancer or those 60 to 85 y having osteoporosis were predominant in term of included population. The same applies to studies including patients aged over 70 y living in the community or patients whose mean time since menopause is 11 years. The data observed in these populations are not applicable to the more general population of menopausal women. The quality of evidence related to some adverse events was also downgraded in case of low or very low event rates leading to imprecision.

For cerebrovascular events, there is an additional concern on the estimate (which is at the limit of statistical significance), as result the RCT that provided most of the data was stopped prematurely for increased risk of stroke with 1.25 mg/d of tibolone and has selected osteoporotic women aged 60 to 85 years. This evidence was downgraded by 2 levels for directness.

In post-menopausal women tibolone resulted in greater improvement of vasomotor symptoms (occurrence or through scale) compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In post-menopausal women tibolone resulted in greater improvement of vaginal dryness and painful sexual intercourse compared to placebo.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

In post-menopausal women tibolone resulted in more unscheduled vaginal bleeding compared to placebo.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was no significant difference between tibolone and placebo for endometrial hyperplasia in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **endometrial cancer** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **breast cancer** in post-menopausal women without history of breast cancer.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **venous thromboembolic events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **cardiovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **cerebrovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **mortality** in post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

6.14 Tibolone vs estrogens in post-menopausal women

Tibolone vs estrogens: short- and long-term effects

Bibliography: Formoso 2016(144) (Short-term and long-term effects of tibolone in postmenopausal women) including Gupta 2013(163), Mendoza 2000(164)

Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Vasomotor symptoms	N= 2 n= 108	6/54 vs 5/54 OR (95 % CI): 1.23 (0.35 to 4.34) NS	⊕⊖⊖⊖ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 Both studies with inappropriate blinding, and high attrition bias. Selection bias and reporting bias are also unclear, all participants hysterectomized, two small study with low event rate

The systematic review and meta-analysis by Formoso 2016 searched for RCTs that evaluated tibolone effectiveness and safety in peri and post-menopause.

All the RCTs that were found included post-menopausal women (surgical or spontaneous menopause) and in most of the studies, all or some participants had menopausal symptoms.

Only 3 small studies were found. 2 of these were suitable for analysis and only included women with surgical menopause which is of limited applicability for general population of post-menopausal women.

Tibolone was used at a dose of 2.5 mg/d in both studies.

In one study tibolone was compared to oral CEE

In the other study tibolone was compared to transdermal 17 β -oestradiol.

Follow up was of 1 year in both studies.

One study also reported on vaginal dryness but was not included in this report as it doesn't meet our inclusion criteria (n < 40/study group).

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were inappropriate blinding, high attrition and poor reporting of study methods resulting in unclear selection bias and reporting bias. Only two small studies with low event rates and on hysterectomized women were included. As a consequence, evidence levels were downgraded for directness and imprecision.

There was no significant difference between tibolone and estrogens for vasomotor symptoms (occurrence or through scale) in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

6.15 Tibolone vs Estrogen/Progestagen Therapy (EPT) in post-menopausal women

Note: this table contains information on the prevention/risk of chronic conditions, see chapter 8

Tibolone vs EPT: short- and long-term effects			
Bibliography: Formoso 2016(144) (Short-term and long-term effects of tibolone in postmenopausal women)			
including Al-Azzawi 1999(165), Archer 2007(166), Baracat 2002(167), de Aloysio 1998(168), Doren 1999(169), Elfituri 2005(170), Hammar 1998(171), Hammar 2007(172), Hänggi 1997(173), Huber 2002(174), Kökçü 2000(175), Langer 2006(156), Mendoza 2002(176), Nappi 2006a(177), Nijland 2009(178), Osmanagaoglu 2006(133), Polisseni 2013(49), Roux 2002(179), Siseles 1995(180), Uygur 2005(181), Winkler 2000(182), Wu 2001(183), Ziaei 2010(162)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Vasomotor symptoms	N= 9 n= 1336	SMD (95 % CI): 0.17 (0.06 to 0.28) OR (95 % CI): 1.36 (1.11 to 1.66) SS in favour of EPT	⊕⊕⊕⊕ LOW Study quality: -1 Consistency: -1 Directness: Imprecision: 5 trials with high attrition bias, 1 trial with inappropriate blinding and selection bias, most of other studies unclear for selection bias and reporting bias, large heterogeneity.
Vaginal dryness and painful sexual intercourse	N= 7 n= 1098	SD (95 %CI): 0.02 (-0.12 to 0.17) NS	⊕⊕⊕⊕ LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: ok 5 trials with high attrition bias and 3 trials with inappropriate blinding, most of the studies with unclear reporting bias, CEE as comparator in most of the studies.
Unscheduled bleeding	N= 16 n= 6438	736/3205 vs 1533/3233 18% to 27% vs 47% OR (95 % CI): 0.32 (0.24 to 0.41) SS in favour of tibolone	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: -1 Directness: -1 Imprecision: ok 7 trials with high attrition bias and 4 trials with

			inappropriate blinding, most of the studies with unclear selection bias and reporting bias, CEE as comparator in most of the studies, high heterogeneity.
Endometrial hyperplasia	N= 5 n = 2846	0/1408 vs 3/1438 OR (95 % CI): 0.35 (0.05 to 2.21) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 3 trials with high attrition bias and 3 trials with inappropriate blinding, 3 studies with unclear selection bias and reporting bias, CEE as comparator in most of the studies, wide CI, low event rate.
Endometrial cancer	N=5 n= 3689	2/1826 vs 1/1863 OR (95 % CI): 1.47 (0.23 to 9.33) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 3 trials with high attrition bias 2 studies with unclear selection bias and reporting bias, CEE as comparator in most of the studies, wide CI, low event rate.
Breast cancer	N= 5 n= 4835	17/2351 vs 10/2484 OR (95 % CI): 1.69 (0.78 to 3.67) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 4 trials with high attrition bias 3 studies with unclear selection bias and reporting bias, CEE as comparator in most of the studies, wide CI, low event rate.
Venous thromboembolic events	N= 4 n= 4529	1/2251 vs 5/2278 OR (95 % CI): 0.44 (0.09 to 2.14) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 All trials with high attrition bias, 1 study with inappropriate blinding, 2 studies with unclear selection bias and reporting bias, CEE as comparator in most of the studies, wide CI, low event rate.

Cardiovascular events	N= 2 n= 3794	7/1884 vs 11/1910 OR (95 % CI): 0.63 (0.24 to 1.66) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 High attrition bias in 1 study and unclear selection bias and reporting bias in the other, CEE as comparator in all the studies, wide CI, low event rate.
Cerebrovascular events	N= 4 n= 4562	2/2265 vs 4/2297 OR (95 % CI): 0.76 (0.16 to 3.66) NS	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: -1 High attrition bias in 2 studies and unclear selection bias and reporting bias in 1 large trial, CEE as comparator in all the studies, wide CI, low event rate.
Mortality	N= 2 n= 970	1/485 vs 0/485 OR (95 % CI): (3.05 (0.12 to 75.2) NS	⊕⊕⊕⊕ LOW Study quality: ok Consistency: n.a. Directness: -1 Imprecision: -1 Unclear selection bias and reporting bias in 1 large trial, CEE as comparator in all the studies, wide CI, 1 assay with no event

The systematic review and meta-analysis by Formoso 2016 searched for RCTs that evaluated tibolone effectiveness and safety in peri and post-menopause.

All the RCTs that were found included post-menopausal women (surgical or spontaneous menopause) and in most of the studies, all or some participants had menopausal symptoms.

23 RCTs have compared tibolone to combined estrogen-progestogen therapy.

Different of tibolone were used but it was mainly 2.5mg/d.

10 studies compared tibolone with conjugated equine estrogen (0.625 mg/d) + medroxyprogesterone acetate (5mg/d or 2.5 mg/d), 1 study used sequential regimen.

7 studies compared tibolone with 17 β -oestradiol (1 mg/d or 2 mg/d) + norethisterone acetate (0.5 mg/d or 1 mg/d).

2 studies compared tibolone with 17 β -oestradiol (2 mg/d) sequentially combined with dydrogesterone (10 mg/d)

1 study compared tibolone with estradiol (2 mg/d) + oestrinol (1 mg/d) + norethindrone acetate (1 mg/d).

1 study compared tibolone with oestradiol valerate (2 mg/d) + dienogest (2 mg/d)
1 study compared tibolone with micronised oestradiol valerate (2 mg/d) + norethisterone 0.7 mg/d.
4 studies used transdermal administration as comparator:
1 used 17 β -oestradiol patch (50 micrograms/d) + sequential dydrogesterone orally 10 mg/d, 1 used
17 β -oestradiol patch (50 micrograms/d) + sequential oral norethisterone acetate (0.25 mg/d), 1 used
17 β -oestradiol patch (50 μ g/d) + oral micronised natural progesterone 200 mg twice a week, 1 used
transdermal patch of estradiol (50 microgr/d) + norethisterone acetate (140 microgr/d)
Follow up in available RCTs varies from 12 weeks to 3 years.

There are some methodological problems that limit our confidence in the estimate of the results.
Many of the relevant studies in these comparisons are subject to attrition bias. The drop out is very
large in several studies. As this could be informative (women with poorer responses or more
adverse events will be more likely to drop out), attrition could be fatal to the validity of a trial. Other
concerns are poor methodology reporting leading to uncertainty about selection bias and reporting
bias and presence of conflict of interest in nearly all the included studies.

For several outcomes, the level of confidence in the effect was also impacted by large imprecision
(low event rates).

Quality of the evidence was downgraded for lack of directness if CEE was predominantly used as
comparator as CEE are not available in BE and results are difficult to compare with other estrogen
(lack of direct comparisons).

In **post-menopausal** women **tibolone** resulted in **less improvement of vasomotor symptoms
(occurrence or through scale)** compared to **estrogen-progestogen therapy**.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no significant difference** between tibolone and **estrogen-progestogen therapy** for **vaginal
dryness and painful sexual intercourse** in post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **post-menopausal** women **tibolone** resulted in **less unscheduled vaginal bleeding** compared to
estrogen-progestogen therapy.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for
endometrial hyperplasia in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for
endometrial cancer in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **breast cancer** in post-menopausal women without history of breast cancer.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **venous thromboembolic events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **cardiovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **cerebrovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **mortality** in post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

7 Nonpharmacological therapy for the treatment of menopausal symptoms. Summary and conclusions from the literature review

7.1 Black cohosh versus placebo for the treatment of menopausal symptoms in peri- and post-menopausal women

Black cohosh vs placebo: menopausal symptoms			
Bibliography: Leach 2012(4) (Black cohosh (Cimicifuga spp.) for menopausal symptoms)			
including Amsterdam 2009(184), Frei-Kleiner 2005(185), Geller 2009(186), Jacobson 2001(187), Kronenberg 2009(188), Newton 2006(42), Osmer 2005(189), Pockaj 2006(190), Stoll 1987(191), Wuttke 2003(192)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Daily hot flush frequency	N= 3 n= 393	MD (95% CI): 0.07 (-0.43 to 0.56) NS	⊕⊕⊕⊖ LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: ok unclear selection bias in 2 trials, high attrition and reporting bias in 2 trials, 1 study (1/3 part.) on women with history of breast cancer.
Hot flush intensity	N= 3 n= 214	MD (95% CI): 0.12 (-0.06 to 0.30) NS	⊕⊕⊕⊖ LOW Study quality: -1 Consistency: ok Directness: -1 Imprecision: ok unclear selection bias in 3 trials, high attrition in 2 trials, high reporting bias in 2 trials, 1 study (1/2 part.) on women with history of breast cancer.
Daily frequency of night sweats	N= 1 n= 164	MD (95% CI): 0.27 (-0.16 to 0.70) p = 0.21 NS	⊕⊕⊕⊖ MODERATE Study quality:-0.5 Consistency: n.a. Directness: ok Imprecision: -0.5 High dropout, unclear reporting bias, 1 study, small n participants and wide CI.
Vulvovaginal symptoms	N= 4	/	Insufficient data
Menopausal symptom score	N=4 n=357	SMD (95%CI): -0.10 (-0.32 to 0.11) NS	⊕⊕⊕⊖ MODERATE Study quality: -1 Consistency: ok

			Directness: ok Imprecision: ok Unclear selection bias in 3 studies, high attrition bias in 2 studies, high reporting bias in 1 study, unclear reporting bias in 3 studies.
Adverse effects	N=7 n=822	<u>Number of recorded events:</u> 194/430 (0.45 events/person) vs 195/392 (0.50 events/person) <u>Number of women experiencing adverse events:</u> 53/173 vs 50/171 RR (95%CI): 1.04 (0.82 to 1.32) (N=2, n=344) NS	⊕⊕⊖⊖ LOW Study quality: -1 Consistency: n.a. Directness: ok Imprecision:-1 Lack of methodological details in most of the trials. Low recorded number of adverse events, only 2 trials reported on number of women having adverse events.

The systematic review and meta-analysis by Leach 2012 searched for RCTs that evaluated the effectiveness of black cohosh in peri and post-menopause.

10 studies on women with surgical and/or spontaneous menopause were included regardless of comorbidity comparing black cohosh to placebo.

One study only recruited women with anxiety symptoms and two studies recruited women with history of breast cancer. Any orally administered monopreparation of black cohosh was included. Different formulations (plant parts, extraction solvent), treatment durations (4 to 52 weeks) and doses were used (8 to 160 mg).

4 studies also evaluated vulvovaginal symptoms but authors were unable to pool results because heterogeneity in assessed outcomes. Individual results were not provided for vulvovaginal symptoms.

In the majority of included trials, there was a lack of methodological details. Much of the risk was attributed to the lack of detailed information on allocation concealment, randomization, handling of incomplete outcome data, reporting of outcomes and participant withdrawal. Differences between groups in the number or reasons for withdrawal were evident in several trials. Baseline differences between groups were observed in different studies.

For several outcomes, the level of confidence in the effect was also impacted by unexplained high level of heterogeneity and large imprecision. Quality of the evidence was downgraded for lack of directness if women with a history of breast cancer were relatively high in term of included population as results obtained on this population are not generalizable on all menopausal women.

There was **no significant difference** between black cohosh and placebo for **daily hot flush frequency** in peri- and post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no significant difference** between black cohosh and placebo for **hot flush intensity** in peri- and post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no significant difference** between black cohosh and placebo for **daily frequency of night sweats** in peri- and post-menopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no significant difference** between black cohosh and placebo in **menopausal symptom score** in peri- and post-menopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no significant difference** between black cohosh and placebo in number of **recorded adverse events and number of women experiencing adverse events** during peri- and post-menopause.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **insufficient data** to evaluate the effect of black cohosh versus placebo for **vulvovaginal symptoms**.

7.2 Black cohosh versus HRT for the treatment of menopausal symptoms in peri- and post-menopausal women

Black cohosh vs hormone therapy: menopausal symptoms			
Bibliography: Leach 2012(4) (Black cohosh (<i>Cimicifuga</i> spp.) for menopausal symptoms)			
including Bai 2007(193), Geller 2009(186), Lehmann-Willenbrock 1988(194), Nappi 2005(195), Newton 2006(42), Stoll 1987(191), Wuttke 2003(192)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Daily hot flush frequency	N= 2 n= N.A.	/	Insufficient data
Hot flush intensity	N= 2 n= N.A.	Not pooled <u>In Bai 2007:</u> n=238 MD (95% CI) : 0.07 (-0.10 to 0.24) NS	⊕⊕⊕⊕ VERY LOW Study quality:-1 Consistency: -1 Directness:-1 Imprecision: ok Unclear selection bias, high attrition bias, unclear reporting bias, tibolone as comparator (not general HT), not pooled with a second study due to heterogeneity.
Daily frequency of night sweats	N= 1 n= 112	MD (95% CI): 0.93 (0.47 to 1.39) P < 0.0001 SS in favour of HT	⊕⊕⊕⊕ LOW Study quality: -0.5 Consistency: ok Directness: -1 Imprecision: -0.5 High dropout, unclear reporting bias, 1 study, small n participants, comparison to CEE
Vulvovaginal symptoms	N= 2	/	Insufficient data
Menopausal symptom score	N=5 n= 468	SMD (95%CI): 0.32 (0.13 to 0.51) SS in favour of HT	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: -1 Directness: -1 Imprecision: Unclear selection bias in 1 study, unclear reporting bias in 5 studies, high attrition bias in 4 studies, inappropriate blinding in 1 study, most of the data with CEE as comparator, high heterogeneity.
Adverse effects	N=4 n=461	<u>Number of recorded events:</u>	⊕⊕⊕⊕ VERY LOW Study quality: -1 Consistency: n.a.

	202/253 (0.80 events/person) vs 304/208 (1.46 events/person)	Directness: -1 Imprecision:-1 Lack of methodological details in most of the trials. Low recorded number of adverse events, only 1 small trials reported on n of women having adverse events. Tibolone or CEE as comparator for most of the data.
	No Statistic	

The systematic review and meta-analysis by Leach 2012 searched for RCTs that evaluated the effectiveness of black cohosh in peri and post-menopause.

7 studies on women with surgical and/or spontaneous menopause were included regardless of comorbidity comparing black cohosh to hormone therapy.

Any orally administered monopreparation of black cohosh was included. Different formulations (plant parts, extraction solvent), treatment durations (4 to 52 weeks) and doses were used (8 to 160 mg).

One study compared black cohosh to tibolone 2.5 mg/d

3 studies compared black cohosh to oral CEE (0.625 mg/d) + oral medroxyprogesterone (2.5 mg/d).

1 study compared black cohosh to oral CEE (1.25 mg/).

1 study compared black cohosh to oral CEE (Oestrofeminal, 0.3 mg, 2caps/d).

1 study compared black cohosh to oral oestradiol + norethisterone acetate daily

1 study compared black cohosh to oral oestriol (1 mg/d).

1 study compared black cohosh to transdermal oestradiol (25 µg/week) + sequential dihydrogesterone 10 mg/d.

Most of the studies used combination of estrogen with progestogen.

Two studies reported daily flush frequency, 3 studies reported hot flush intensity and 2 studies also evaluated vulvovaginal symptoms but authors where unable to pooled results because heterogeneity in assessed outcomes. Individual results were not provided for vulvovaginal symptoms and only one study for hot flush intensity meet our inclusion criteria.

In the majority of included trials, there was a lack of methodological details. Much of the risk was attributed to the lack of detailed information on allocation concealment, randomization, handling of incomplete outcome data, reporting of outcomes and participant withdrawal. Differences between groups in the number or reasons for withdrawal were evident in several trials. Baseline differences between groups were observed in different studies.

For several outcomes, the level of confidence in the effect was also impacted by unexplained high level of heterogeneity and large imprecision.

Quality of the evidence was downgraded for lack of directness if CEE was predominantly used as comparator as CEE are not available in BE and results are difficult to compare with other estrogen (lack of direct comparisons).

There was no significant difference between black cohosh and hormone therapy for hot flush intensity in peri- and post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

In peri- and post-menopausal women, **hormone therapy resulted in greater improvement of daily frequency of night sweats** compared to black cohosh.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In peri- and post-menopausal women, **hormone therapy resulted in greater improvement of menopausal symptom score compared** to black cohosh.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

Number of recorded adverse events were 0.80 events/person for black cohosh compared to 1.46 events/person for hormone therapy

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **insufficient data** to evaluate the effect of black cohosh versus placebo for **daily hot flush frequency** and **vulvovaginal symptoms**.

8 Hormone therapy for the primary prevention of chronic conditions. Summary and conclusions from the literature review

8.1 Primary prevention of chronic conditions: estrogen only versus placebo.

8.1.1 Cancer

8.1.1.1 Breast cancer

Estrogen only versus placebo: breast cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial, EPAT Estrogen-only trial, ERA Estrogen-only and estrogen plus progestin trial, PEPI Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Invasive breast cancer Intervention follow-up	N=1 n=10739 7.2 years (median)	104 (0.28%) vs. 135 (0.35%); HR, 0.79 (95% CI, 0.61 to 1.02); p=0.07 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Invasive breast cancer Postintervention (after stopping study treatment)	N=1 n=7645 6.6 years (median) postintervention	HR, 0.80 (95% CI, 0.58 to 1.11); p=0.19 NS	
	N=1 n=7645 10.8 years (median) postintervention	18 (0.037% annualized) vs. 32 (0.065% annualized); HR, 0.57 (95% CI, 0.32 to 1.02); p=0.06 NS	
Invasive breast cancer Cumulative follow-up	N=1 n=9939 13.0 years (median)	168 (0.28% annualized) vs. 216 (0.35% annualized); HR, 0.79 (95% CI, 0.65 to 0.97); p=0.02 SS	
	N=1 n=9939 20.7 years (median)	238 (0.30%) vs. 296 (0.37%); HR, 0.78 (95% CI, 0.65 to 0.93); p=0.005 SS	
Breast cancer mortality Intervention follow-up	N=1 n=7645 7.2 years (median)	4 (0.010% annualized) vs. 9 (0.023%); HR, 0.45 (95% CI, 0.14 to 1.46); p=0.17 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1

Breast cancer mortality Cumulative follow-up	N=1 n=9939 17.7 years (median)	22 (0.025% annualized) vs. 41 (0.046% annualized); HR, 0.55 (95% CI, 0.33 to 0.92); p=0.02 SS
	N=1 n=9939 20.7 years (median)	30 (0.031%) vs. 46 (0.046%); HR, 0.60 (95% CI, 0.37 to 0.97); p=0.04 SS

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for the outcome breast cancer. Four RCT's (WHI, EPAT, ERA, EPEI) were found. The authors did not pool trial results, primarily because of heterogeneity in study duration and definitions of breast cancer incidence. Only results from the WHI trial are presented here because the three other trial had only a short duration (2 to 3 years) of follow-up and "any" (in contrast to "invasive") breast cancer was evaluated. Results at additional timepoints in the WHI trial than presented here and results for the three other trials can be found in [Appendix 13.1.1 \(full report\)](#). All conclusions presented here are based on the WHI trial.

Invasive breast cancer

There was **no difference** between conjugated equine estrogen (CEE) and placebo for the incidence of invasive breast cancer in generally healthy postmenopausal women with a prior hysterectomy aged 50-79 at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for the incidence of invasive breast cancer in generally healthy postmenopausal women in the **postintervention** phase (median follow-up of 6.6 years and 10.8 years).

CEE resulted in a **lower risk** of invasive breast cancer compared to placebo in generally healthy postmenopausal women after a median **cumulative (trial and postintervention phase) follow-up** of up to 20.7 years.

Breast cancer mortality

There was **no difference** between CEE and placebo for **breast cancer mortality** in postmenopausal women with a prior hysterectomy aged 50-79 at the end of the intervention phase (median follow-up 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

CEE resulted in a lower risk for **breast cancer mortality** compared to placebo in generally healthy postmenopausal women after a median cumulative follow-up of **17.7 years and 20.7 years**.

8.1.1.2 Colorectal cancer

Estrogen only versus placebo: colorectal cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial, Multiethnic Cohort Study)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Colorectal cancer Intervention follow-up	N=1 n=10739 7.2 years (median)	65 (1.22%) vs. 58 (1.07%); HR, 1.15 (95% CI, 0.81 to 1.64); p=0.44 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: -1 Directness: -1 Imprecision: ok
	N=1 n=NR NR Cohort study	Currently use estrogen only: 214 vs. 903 (2.3% calculated); HR, 0.77 (95% CI, 0.66 to 0.89) SS	
Colorectal cancer Cumulative follow- up	N=1 n=10739 13 years (median)	HR, 1.13 (95% CI, 0.85 to 1.51); p=0.39 NS	
	N=1 n=85734 16 years Cohort study	Ever used estrogen only: 547 (1.2% calculated) vs. 903 (2.3% calculated); HR, 0.85 (95% CI, 0.76 to 0.94) SS	
Colorectal cancer mortality Intervention follow-up	N=1 n=10739 7.2 years (median)	16 (0.041% annualized) vs. 17 (0.043%); HR, 0.98 (95% CI, 0.50 to 1.95); p=0.96 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Colorectal cancer mortality Cumulative follow- up	N=1 n=10739 17.7 years (median)	47 (0.054% annualized) vs. 40 (0.045%); HR, 1.21 (95% CI, 0.79 to 1.84); p=0.38 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for the outcome colorectal cancer. One RCT's (WHI) was found and the authors included a larger prospective cohort study.

There was **no difference** between CEE and placebo for the incidence of colorectal cancer in generally healthy postmenopausal women with a prior hysterectomy aged 50-79 at the end of the intervention phase (median follow-up 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

Gartlehner 2022 included a prospective cohort study "the multiethnic cohort study" in their review that analyzed as part of a larger study the association between the use of estrogen only and the incidence of colorectal cancer in 85734 postmenopausal women. The type of estrogen was not mentioned but the information was collected in 1999-2002 and 2003-2007. The multiethnic cohort study found that the current use or ever use of estrogen only was associated with a lower risk of colorectal cancer.

8.1.1.3 Cervical cancer

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year and large cohort studies that compared estrogen only to placebo in postmenopausal women for cervical cancer. No studies were found.

8.1.1.4 Endometrial cancer

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for endometrial cancer. Four trials (ERA, EPAT, PEPI, ULTRA) were found. There were no events of endometrial cancer in the trials. Gartlehner 2022 does not discuss the results because of the well-known risk of endometrial hyperplasia and cancer associated with unopposed estrogen use.

8.1.1.5 Ovarian cancer

Estrogen only versus placebo: ovarian cancer			
Bibliography: Gartlehner 2022(5) (Black Women's Health Study)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Ovarian cancer	N=1 n=7166 18 years	17 (0.7% calculated) vs. 61 (1.3% calculated) HR, 1.66 (95% CI, 0.90 to 3.07) NS	⊕⊕⊕⊕ VERY LOW Study quality: ok. Observational data Consistency: NA Directness: -1 Imprecision: ok

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for endometrial cancer. No RCT's were found. One prospective cohort study was identified: the Black Women's health study by Bethea 2017. The type of estrogen used was not specified.

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were a moderate risk of bias due to confounding and classification of interventions.

There was **no difference** between postmenopausal women who ever and never used estrogen for the **incidence of ovarian cancer** after a follow-up of 18 years.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

8.1.1.6 Lung cancer

Estrogen only versus placebo: lung cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Lung cancer	N=1 n=10739 7.2 years (median)	62 (0.16% annualized) vs. 61 (0.16% annualized); HR, 1.05 (95% CI, 0.74 to 1.49); p=0.79 NS	⊕⊕⊕⊕ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Intervention follow-up			
Lung cancer	N=1 n=9666 6.6 years (median) postintervention	47 (0.20% annualized) vs. 53 (0.22% annualized); HR, 0.90 (95% CI, 0.61 to 1.34); p=0.61 NS	
Postintervention (after stopping study treatment)			

lung cancer	N=1 n=10739	109 (0.18% annualized) vs. 114 (0.18% annualized);
Cumulative follow-up	13.0 years (median)	HR, 0.98 (95% CI, 0.75 to 1.27); p=0.87 NS
Lung cancer mortality	N=1 n=NR 7.9 years (mean)	34 (0.08% annualized) vs. 33 (0.08% annualized); HR, 1.07 (95% CI, 0.66 to 1.72); p=0.79 NS
Intervention and partial postintervention follow-up		

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for lung cancer. One trial was found: the WHI trial.

There was **no difference** between CEE and placebo for the **incidence of lung cancer** in generally healthy postmenopausal women at the end of intervention phase (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for the **incidence of lung cancer** in generally healthy postmenopausal women in the **postintervention** phase (median follow-up 6.6 years).

There was **no difference** between CEE and placebo for the **incidence of lung cancer** in generally healthy postmenopausal women after a median **cumulative** follow-up of 13.0 years.

8.1.1.7 Non-Hodgkin's Lymphoma

Estrogen only versus placebo: Non-Hodgkin's lymphoma			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Non-Hodgkin's lymphoma Intervention follow-up	N=1 n=10685 7.2 years (median)	HR, 0.89 (95% CI, 0.56 to 1.42) NS	⊕⊕⊖⊖ LOW Study quality: -1 Short study duration for rare cancer Consistency: NA Directness: -1 Imprecision: ok
Non-Hodgkin's lymphoma Cumulative follow-up	N=1 n=10685 12.9 years (median)	80 (0.117% annualized) vs. 80 (0.115% annualized); HR, 1.02 (95% CI, 0.74 to 1.39) NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for non-Hodgkin's lymphoma. One trial was found: the WHI trial.

There was **no difference** between CEE and placebo for the incidence of **Non-Hodgkin's lymphoma** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between CEE and placebo for the incidence of **Non-Hodgkin's lymphoma** in generally healthy postmenopausal women after a median **cumulative** follow-up of 12.9 years.

8.1.1.8 Total cancer mortality

Estrogen only versus placebo: total cancer mortality			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Total cancer mortality Intervention follow-up	N=1 n=10739 7.2 years (median)	126 (0.33% annualized) vs. 136 (0.34% annualized); HR, 0.96 (95% CI, 0.75 to 1.22); p=0.72) NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Non-Hodgkin's lymphoma Cumulative follow-up	N=1 n=10739 12.9 years (median)	424 (0.49% annualized) vs. 439 (0.49% annualized); HR, 0.99 (95% CI, 0.86 to 1.13); p=0.86 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for total mortality. One trial was found: the WHI trial.

There was **no difference** between CEE and placebo for **total mortality** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for **total mortality** in generally healthy postmenopausal women after a median **cumulative** follow-up of 12.9 years.

8.1.2 Cardiovascular disease

8.1.2.1 Coronary heart disease

Estrogen only versus placebo: coronary heart disease			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
coronary heart disease (CHD)	N=3 n=11310 2-7.2 years	203/5596 (3.6%) vs 219/5714 (4.0%) RR, 0.95 [95% CI, 0.79 to 1.14] NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Overall CHD (nonfatal myocardial infarction or coronary death) Intervention follow-up	N=1 n=10739 7.2 years (median)	CEE vs placebo 201 (annualized 0.53%) vs. 217 (annualized 0.56%); HR, 0.95 (95% CI, 0.79 to 1.16) NS	
Overall CHD (nonfatal myocardial infarction or coronary death) Postintervention	N=1 n=7645 3.9 years (median) postintervention	HR, 0.97 (95% CI, 0.75 to 1.25) NS	
Overall CHD (nonfatal myocardial infarction or coronary death)	N=1 n=10739 13.0 years (median)	363 (0.60% annualized) vs. 393 (0.63% annualized); HR, 0.94 (95% CI, 0.82 to 1.09); p=0.43 NS	
Cumulative follow-up	N=1 n=10739 19.4 years (median)	521 (9.8% calculated) vs. 550 (10.1%); HR, 0.97 (95% CI, 0.86 to 1.09); p=NR NS	
All cardiovascular events Intervention follow-up	N=1 n=10739 7.2 years	877 (2.51% annualized) vs. 813 (2.24%); HR, 1.11 (95% CI, 1.01 to 1.22); p=0.03 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for coronary heart disease.

Four RCT's (EPAT, PEPI, WHI, and ERA) were found that report on the risk of coronary heart disease (CHD). The authors performed a meta-analysis based on three RCT's which were similar enough to combine. The WHI study contributed 99% to the pooled estimate. The ERA study was not included because only women with an elevated cardiovascular risk were eligible for enrollment. Results for additional outcomes (myocardial infarction, heart failure, CHD mortality, etc.) from the WHI trial and results for additional timepoints for the outcomes presented here (WHI) can be found in [Appendix 13.2.1 \(full report\)](#).

There was **no difference** between conjugated equine estrogen (CEE) and placebo for **coronary heart disease (CHD)** in postmenopausal women with a hysterectomy after a median intervention follow-up of 2 to 7.2 years.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for **overall CHD** in postmenopausal women in the postintervention phase (median follow-up 3.9 years) up to 19.4 years.

There was **no difference** between CEE and placebo for **overall CHD** in postmenopausal women after a median **cumulative** follow-up up to 19.4 years.

CEE resulted in a **higher risk** of **“all cardiovascular events”** compared to placebo at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

8.1.2.2 Venous Thromboembolism

Estrogen only versus placebo: venous thromboembolism			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Venous thromboembolism Intervention follow-up	N=1 n=10739 7.2 years (median)	111 (2.1% calculated) vs. 86 (1.6%); HR, 1.32 (95% CI, 1.00 to 1.76); p=NR SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Venous thromboembolism Cumulative follow-up	N=1 n=9939 19.4 years (median)	270 (5.1% calculated) vs. 288 (5.3% calculated); HR, 0.97 (95% CI, 0.82 to 1.14); p=NR NS	
Deep vein thrombosis Intervention follow-up	N=1 n=10739 7.2 years (median)	85 (1.6%) vs. 59 (1.0%); HR, 1.48 (95% CI, 1.06 to 2.07); p=0.02 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Deep vein thrombosis Postintervention	N=1 n=7645 3.9 years postintervention	HR, 0.63 (95% CI, 0.41 to 0.98); p=0.003 SS	
Deep vein thrombosis Cumulative follow-up	N=1 n=9939 13.0 years	135 (0.22% annualized) vs. 133 (0.21%); HR, 1.05 (95% CI, 0.82 to 1.33); p=0.71 NS	
Pulmonary embolism Intervention follow-up	N=1 n=10739 7.2 years (median)	107 (0.17% annualized) vs. 96 (0.15%); HR, 1.15 (95% CI, 0.87 to 1.51); p=0.34 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Pulmonary embolism Cumulative follow-up	N=1 n=9939 13.0 years (median)	52 (0.14% annualized) vs. 39 (0.10%); HR, 1.35 (95% CI, 0.89 to 2.05); p=0.15 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for venous thromboembolism.

Three RCT's (WHI, EPAT, and ERA) were found that report on the risk of venous thromboembolism. The authors did not pool the trials because of heterogeneity in study duration and outcome

measures. Only results of the WHI trial are shown here given the few to none events in the other two trials.

Results for the WHI trial at additional timepoints for the outcomes presented here and results for the other two trials can be found in [Appendix 13.2.2 \(full report\)](#).

Venous thromboembolism

Conjugated equine estrogen (CEE) resulted in a **higher risk of venous thromboembolism** compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for **venous thromboembolism** in postmenopausal women after a median cumulative follow-up of 19.4 years.

Deep vein thrombosis

CEE resulted in a **higher risk of deep vein thrombosis** compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate

In the **postintervention** phase, CEE resulted in a **lower risk of deep vein thrombosis** compared to placebo in generally healthy postmenopausal women after a mean follow-up of 3.9 years.

There was **no difference** between CEE and placebo for **deep vein thrombosis** in postmenopausal women after a median **cumulative** follow-up of 13.0 years.

Pulmonary embolism

There was **no difference** between CEE and placebo for **pulmonary embolism** in postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between CEE and placebo for **pulmonary embolism** in postmenopausal women in the **postintervention** phase (median follow-up 3.9 years).

There was **no difference** between CEE and placebo for **pulmonary embolism** in postmenopausal women after a median **cumulative** follow-up of 13.0 years.

8.1.2.3 Stroke

Estrogen only versus placebo: stroke			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Stroke (Ischemic or hemorrhagic stroke) Intervention followup	N=1 n=10739 7.2 years (median)	169 (3.2% calculated) vs. 129 (2.4%); HR, 1.35 (95% CI, 1.07 to 1.70); p=0.01 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Stroke (Ischemic or hemorrhagic stroke) Postintervention	N=1 n=7645 3.9 years postintervention	66 (0.36% annualized) vs. 77 (0.41%); HR, 0.89 (95% CI, 0.64 to 1.24); p=NR NS	
Stroke (Ischemic or hemorrhagic stroke) Cumulative followup	N=1 n=10739 19.4 years (median)	399 (7.5% calculated) vs. 392 (7.2%); HR, 1.06 (95% CI, 0.92 to 1.22); p=NR NS	
Stroke mortality Intervention followup	N=1 n=10739 7.2 years (median)	23 (0.060%) vs. 24 (0.060%); HR, 1.00 (95% CI, 0.57 to 1.78); p=0.99 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Stroke mortality Cumulative followup	N=1 n=10739 17.7 years (median)	126 (0.14%) vs. 132 (0.15%); HR, 0.98 (95% CI, 0.77 to 1.26); p=0.89 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for the outcome stroke. Three RCTs (WHI, EPAT, ERA) were found. No meta-analysis was performed because of heterogeneity in study duration and outcome measures. Results for the WHI are shown, the other two RCT's had few to none events. For details see [Appendix 13.2.3 \(full report\)](#).

Stroke

CEE resulted in **a higher risk of stroke** compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate

In the **postintervention** phase, there was **no difference** between CEE and placebo for the outcome **stroke** in generally healthy postmenopausal women after a mean follow-up of 3.9 years.

There was **no difference** between CEE and placebo for the outcome **stroke** in generally healthy postmenopausal women after a **cumulative** follow-up of up to 19.4 years.

Stroke mortality

There was **no difference** between CEE and placebo for the outcome **stroke mortality** in postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between CEE and placebo for the outcome **stroke mortality** in postmenopausal women after a **cumulative** follow-up of 17.7 years.

8.1.2.4 Peripheral Arterial Disease

Estrogen only versus placebo: peripheral arterial disease			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Peripheral arterial disease	N=1 n=10739 7.2 years	82/5310 vs. 62/5429; HR, 1.35 (95% CI, 0.97 to 1.88)	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Intervention follow-up		NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for peripheral arterial disease. One trial was found: the WHI trial.

There was **no difference** between CEE and placebo for **peripheral arterial disease** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate

8.1.3 Cognition and dementia

8.1.3.1 Dementia and mild cognitive impairment incidence

Estrogen only versus placebo: dementia and mild cognitive impairment			
Bibliography: Gartlehner 2022(5) (WHIMS Estrogen-only trial; WHISCA Estrogen-only trial; WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Probable dementia Intervention follow-up	N=1 n=2947 5.2 years	28 (1.9%) vs. 19 (1.3%); cumulative HR, 1.49 (95% CI, 0.83 to 2.66); p=0.18 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=886 2.7 years	4 (0.9%) vs. 2 (0.4%); calculated RR, 2.08 (95% CI, 0.38 to 11.31); p=0.40 NS	
Mild cognitive impairment Intervention follow-up	N=1 n=2947 5.2 years	76 (5.2%) vs. 58 (3.9%); cumulative HR, 1.34 (95% CI, 0.95 to 1.89); NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=886 2.7 years	18 (4.1%) vs. 15 (3.3%); calculated RR, 1.25 (95% CI, 0.64 to 2.45); p=0.52 NS	
Probable dementia or Mild cognitive impairment Intervention follow-up	N=1 n=2947 5.2 years	93 (6.4%) vs. 69 (4.7%); cumulative HR, 1.38 (95% CI, 1.01 to 1.89); p=0.04 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Alzheimer's disease or other dementia mortality Intervention follow-up	N=1 n=10739 7.2 years (median)	5 (0.013% annualized) vs. 6 (0.015%); HR, 0.90 (95% CI, 0.27 to 2.95); p=0.86 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Alzheimer's disease or other dementia mortality Postintervention	N=1 n=NR 10.8 years postintervention	122 (0.25% annualized) vs. 169 (0.34%); HR, 0.73 (95% CI, 0.58 to 0.92); p=0.008 SS	

Alzheimer's disease or other dementia mortality	N=1 n=10739 17.7 years (median)	278 (0.46% annualized) vs. 253 (0.41%); 127 (0.15% annualized) vs. 175 (0.20%); HR, 0.74 (95% CI, 0.59 to 0.94); p=0.01 SS
Cumulative follow-up		

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for dementia and mild cognitive impairment.

Results for the outcomes probable dementia or mild cognitive impairment were obtained from the The Women's Health Initiative Memory Study (WHIMS) trial and the Women's Health Initiative Study of Cognitive Aging (WHISCA) trial. The WHIMS trial is a subset of the WHI trial limited to women ages 65 to 79 years at baseline who were free of probable dementia. The WHISCA trial, an ancillary study of the WHIMS trial, began 3 years after the start of the WHI and WHIMS trials and evaluated changes in more detailed, domain-specific cognitive functioning over time. Results for dementia-related mortality were obtained from the WHI trial.

Probable dementia

There was **no difference** between conjugated equine estrogen (CEE) and placebo for probable dementia in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Mild cognitive impairment

There was **no difference** between CEE and placebo for the outcome mild cognitive impairment in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Probable dementia or mild cognitive impairment

CEE resulted in a **higher risk** for "probable dementia or mild cognitive impairment" compared to placebo in postmenopausal women at the end of the intervention phase (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Dementia-related mortality

There was **no difference** between CEE and placebo for dementia-related mortality in postmenopausal women at the end of the intervention phase (median follow-up of 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In the postintervention phase, CEE resulted in a **lower risk** of dementia-related mortality compared to placebo in postmenopausal women after a median follow-up of 10.8 years.

CEE resulted in a **lower risk** of dementia-related mortality compared to placebo in postmenopausal women after a median **cumulative follow-up** of 17.7 years.

8.1.3.2 Global cognitive function

Estrogen versus placebo: global cognitive function			
Bibliography: Gartlehner 2022(5) (WHIMS Estrogen-only trial; WHISCA Estrogen-only trial; WHIMSY Estrogen-only trial; ULTRA Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Global cognitive functioning At the end of intervention	N=1 n=2947 5.4 years (mean)	Mean difference in change from baseline, -0.26 (95% CI, -0.52 to 0.00); p=0.04 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision:
	N=1 n=1213 3.6 years	Mean decrement -0.092 (SE, 0.039); p=0.02 SS	
Global cognitive functioning Postintervention (after stopping treatment)	N=1 n=1213 2.4 years (mean) postintervention	Mean decrement -0.081 (SE, 0.047); p=0.09 NS	
	N=1 n=1326 7.2 years postintervention	37.67 (SE, 0.26) vs. 37.28 (SE, 0.27); p=NR NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for global cognitive function.

Four RCTs (WHIMS, WHISCA, WHIMSY, ULTRA) measured global cognitive functioning using the Modified Mini-Mental State (3MSE) examination or the Telephone Interview for Cognitive Status-modified (TICS-m). Heterogeneity in timing precluded meta-analysis.

The ULTRA trial did not find a difference when determining if treatment effect differed depending on a participant's baseline global cognitive score. For details see [Appendix 13.3.2 \(full report\)](#).

CEE resulted in **larger cognitive deficits** compared to placebo in postmenopausal women **at the end of the intervention phase**.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the postintervention phase, there was no difference between CEE and placebo for global cognitive function in postmenopausal women.

8.1.3.3 Other Cognitive Measures

The AHRQ systematic review and meta-analysis by Gartlehner 2022 found four RCTs (WHISCA, WHIMSY, UTRA, ELITE-Cog) evaluating other measures of cognitive functioning (e.g., spatial ability, verbal knowledge, working memory, etc.). The results can be found in [Appendix 13.3.3 \(full report\)](#). Heterogeneity in outcome measures precluded meta-analysis. No differences were found for the majority of outcomes.

8.1.4 Fractures

Estrogen only versus placebo: Fractures			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial; ERA Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Fractures - Total Intervention follow-up	N=1 n=10739 7.2 years	544 (1.53% annualized) vs. 767 (2.14% annualized); HR, 0.72 (95% CI, 0.64 to 0.80); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=205 3.2 years	Calculated RR, 0.42 (95% CI, 0.17 to 1.04); p=0.06 NS	
Fractures - Total Postintervention (after stopping treatment)	N=1 n=9666 4.3 years (mean) postintervention	321 (3.11% annualized) vs. 378 (3.69% annualized); HR, 0.85 (95% CI, 0.73 to 0.98); p=0.03 SS	
Fractures – Hip Intervention follow-up	N=1 n=10739 7.2 years	48 (0.13% annualized) vs. 74 (0.19% annualized); HR, 0.67 (95% CI, 0.46 to 0.96); p=0.03 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Fractures – Hip Postintervention (after stopping treatment)	N=1 n=9666 3.9 years postintervention	66 (0.36% annualized) vs. 53 (0.28% annualized); HR, 1.27 (95% CI, 0.88 to 1.82); p=NR NS	
Fractures – Hip Cumulative follow- up	N=1 n=7645 19.4 years	208 (3.9% calculated) vs. 229 (4.2% calculated); HR, 0.92 (95% CI, 0.76 to 1.11); p=NR NS	
Fractures - Vertebral Intervention follow-up	N=1 n=205 3.2 years	44 (0.12% annualized) vs. 70 (0.18% annualized); HR, 0.64 (95% CI, 0.44 to 0.93); p=0.02 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for outcome fractures. Two RCT's (WHI, ERA) were found that report on the risk of fractures.

Results for the WHI study at additional timepoints than presented here can be found in [Appendix 13.4 \(full report\)](#).

Fractures

The WHI trial found a lower risk for fractures at the end of the intervention phase (median follow-up 7.2 years). The smaller ERA trial with a shorter study duration (3.2 years) found fewer fractures compared to placebo but the difference was not statistically significant.

Conjugated equine estrogen (CEE) resulted in a **lower risk** of fractures compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE resulted in a **lower risk** of fractures compared to placebo in postmenopausal women in the **postintervention** phase after a mean follow-up of 4.3 years.

Hip fractures

CEE resulted in a **lower risk** of hip fractures compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for hip fractures in postmenopausal women in the **postintervention** phase after a mean follow-up of **3.9 years**.

There was **no difference** between CEE and placebo for hip fractures in postmenopausal women after a mean **cumulative** follow-up of 19.4 years.

Vertebral fractures

CEE resulted in a **lower risk** of vertebral fractures compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

8.1.5 Diabetes

Estrogen only versus placebo: diabetes			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Diabetes Intervention follow-up	N=1 n=9917 7.2 years (median)	449 (1.34% annualized) vs. 527 (1.55% annualized); HR, 0.86 (95% CI, 0.76 to 0.98); p=0.02 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Diabetes is self-reported Consistency: NA Directness: -1 Imprecision: ok
Diabetes Postintervention (after stopping treatment)	N=1 n=NR 6.6 years (median) Postintervention	323 (1.64% annualized) vs. 306 (1.54% annualized); HR, 1.07 (95% CI, 0.92 to 1.25); p=0.39 NS	
Diabetes cumulative follow- up	N=1 n=9917 13.0 years (median)	772 (1.45% annualized) vs. 833 (1.55% annualized); HR, 0.94 (95% CI, 0.85 to 1.04); p=0.22 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for diabetes. The WHI was the only trial that reported on the incidence of diabetes among women not receiving treatment for diabetes at baseline. The incidence of diabetes was self-reported and defined as a new diagnosis of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin.

Conjugated equine estrogen (CEE) resulted in a **lower risk** for diabetes compared to placebo in generally healthy postmenopausal women with a prior hysterectomy aged 50-79 **at the end of the intervention phase** (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the postintervention phase, there was **no difference** between CEE and placebo for the incidence of diabetes in generally healthy postmenopausal women with a prior hysterectomy aged 50-79 after a median follow-up of 6.6 years.

8.1.6 Gallbladder disease

Estrogen only versus placebo: Gallbladder disease			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial; PEPI Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Global gallbladder disease Intervention follow-up	N=1 n=8376 7.1 years (mean)	461 (1.64% annualized) vs. 312 (1.06% annualized); HR, 1.55 (95% CI, 1.34 to 1.79); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok gallbladder disease is self- reported Consistency: NA Directness: -1 Imprecision: ok
Gallbladder disease Postintervention (after stopping treatment)	N=1 n=8376 6.6 years (median) Postintervention	57 (1.65% annualized) vs. 61 (1.66% annualized); HR, 0.98 (95% CI, 0.68 to 1.41); p=0.92 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for dementia and mild cognitive impairment. Two RCT's (WHI, PEPI) were found that report on the risk of gallbladder disease. The definition of gallbladder disease used in PEPI is unclear; for WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all gallbladder or biliary tract stone disease.

The smaller PEPI trial had very few events. Only results of the WHI trial are presented here. Results for additional outcomes (WHI trial) and results from the PEPI trial can be found in [Appendix 13.6 \(full report\)](#).

Conjugated equine estrogen (CEE) resulted in a **higher risk of gallbladder disease** compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for **gallbladder disease** in postmenopausal women after a median **postintervention follow-up of 6.6 years**.

8.1.7 Urinary incontinence

Estrogen only versus placebo: urinary incontinence			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial; ULTRA)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Weekly total urinary incontinence Intervention follow-up	N=1 n=6767 1 year	773 (22.6% annualized) vs. 499 (14.0% annualized); HR, 1.61 (95% CI, 1.46 to 1.79); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Urinary incontinence is self-reported Consistency: ok Smaller ULTRA trial: NS Directness: -1 Imprecision: ok
	N=1 n=239 2 years	39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7 to 2.2); p=0.74 NS	
Weekly total urinary incontinence Postintervention (after stopping study treatment)	N=1 n=5644 6.6 years (median) postintervention	HR, 1.24 (95% CI, 1.13 to 1.35); p<0.001 SS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for urinary incontinence. Two RCT's (WHI, ULTRA) were found. Results for the outcome “weekly total urinary incontinence” are shown. Both studies defined urinary incontinence as at least one episode weekly. There was a higher risk for urinary incontinence at year 1 in the WHI trial; the smaller ULTRA trial found no difference at 2 years. The WHI trial also evaluated various subtypes of urinary incontinence. Details can be found in [Appendix 13.7 \(full report\)](#).

Conjugated equine estrogen (CEE) resulted in a **higher risk of urinary incontinence** compared to placebo in postmenopausal women **after 1-year follow-up**.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE resulted in a **higher risk of urinary incontinence** compared to placebo in postmenopausal women **after a median postintervention follow-up of 6.6 years**.

8.1.8 Quality of life

Estrogen only versus placebo: quality of life			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Quality of life Intervention follow-up	N=1 n=10739	Physical functioning: NS Physical role: NS Bodily pain: NS General health: NS Vitality: NS Mental health: NS Social functioning: SS 85.8 vs. 86.9; p=0.01 Emotional role: SS 81.0 vs. 82.2; p=0.04	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for quality of life. The WHI trial was the only trial that reported on quality of life. Quality of life was assessed with the Short Form Health Survey (SF-36) form.

Postmenopausal women in the WHI trial had similar scores on all items of SF-36 except for emotional role and social functioning, for which women taking placebo had statistically significantly better scores than women taking estrogen-only therapy

Overall, there was **no difference** between CEE and placebo for quality of life in postmenopausal women at the end of the intervention phase (median follow-up 7.2 year).

GRADE: MODERATE LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

8.1.9 Asthma

Estrogen only versus control: Asthma			
Bibliography: Shah 2021(196)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Asthma	N=1 n=353173 17 years	Previous users vs non-users Adjusted HR 0.89 (95% CI : 0.84-0.95) SS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: -1 No consistent results with other studies not included in this report.
		Current users vs non-users Adjusted HR 0.80 (95% CI : 0.73-0.87) SS	Directness: -1 Type of HT not specified. Possibly mostly CEE? Imprecision: ok +1 for dose-response association between duration of HT use and onset of asthma

The AHRQ review from Garthlehner 2022 mentioned in their appendix of eligible observational studies two studies with outcome asthma. This is not further studied in the review without mentioning a reason for this. We included one of the studies here and excluded the other study in our report due to the studied population (women with asthma).

The large retrospective cohort study from Shah 2021 compared the use of hormone therapy with controls in women recruited from primary care practices. Details can be found in [Appendix 13.9 \(full report\)](#). The analysis was adjusted for confounders including age, smoking, Charlson Comorbidity Index score and BMI. No separate analysis was performed for route of HT administration due to inconsistent documentation.

The use of estrogen-only hormone therapy was associated with a **lower risk** of developing **asthma** compared to non-users in menopausal women after 17 years of follow-up.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

8.1.10 COPD

Estrogen only versus placebo: COPD			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
COPD incidence	No eligible studies		Insufficient data
COPD mortality Intervention follow-up	N=1 n=10739 7.2 years (median)	6 (0.016% annualized) vs. 8 (0.020% annualized); HR, 0.76 (95% CI, 0.26 to 2.20); p=0.62 NS	⊕⊕⊕⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
COPD mortality Postintervention (after stopping treatment)	N=1 n=NR 10.8 years (median) Postintervention	77 (0.16% annualized) vs. 71 (0.14% annualized); HR, 1.09 (95% CI, 0.79 to 1.51); p=0.60 NS	
COPD mortality cumulative follow- up	N=1 n=10739 17.7 years (median)	83 (0.095% annualized) vs. 79 (0.088% annualized); HR, 1.07 (95% CI, 0.78 to 1.45); p=0.68 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for outcome COPD. No eligible studies reported on COPD incidence. The WHI trial did provide information about COPD mortality.

There was **no difference** between conjugated equine estrogen (CEE) and placebo for **COPD mortality** in postmenopausal women with a prior hysterectomy aged 50-79 at the end of the intervention phase (median follow-up of 7.2 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between CEE and placebo for **COPD mortality** in postmenopausal women with a prior hysterectomy aged 50-79 in the **postintervention** phase (median follow-up of 10.8 years).

There was **no difference** between CEE and placebo for **COPD mortality** in postmenopausal women with a prior hysterectomy aged 50-79 after a median **cumulative** follow-up of 17.7 years.

8.1.11 All-cause mortality

Estrogen only versus placebo: all-cause mortality			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial; ELITE-Cog; ERA Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
All-cause mortality Intervention follow-up	N=3 n=11587 2 - 7.2 years	RR, 1.04 [95% CI, 0.89 to 1.21) NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
All-cause mortality Intervention follow-up	N=1 n=10739 7.2 years (median)	300 (5.6%) vs. 297 (5.5%); HR, 1.04 (95% CI, 0.89 to 1.22); p=NR NS	
All-cause mortality Postintervention (after stopping study treatment)	N=1 n=7645 3.9 years (mean)	277 (1.47% annualized) vs. 284 (1.48% annualized); HR, 1.00 (95% CI, 0.84 to 1.18); p=NR NS	
	N=1 n=7645 10.8 years (median)	1,204 (2.48% annualized) vs. 1,331 (2.69%); HR, 0.92 (95% CI, 0.85 to 0.99); p=0.03 NS	
All-cause mortality Cumulative follow- up	N=1 n=9939 10.7 years (mean)	577 (1.02% annualized) vs. 581 (1.00% annualized); HR, 1.02 (95% CI, 0.91 to 1.15); p=NR NS	
	N=1 n=9939 13.0 years (median)	704 (1.14% annualized) vs. 725 (1.14% annualized); HR, 0.99 (95% CI, 0.90 to 1.10); p=0.92 NS	
	N=1 n=9939 17.7 years (median)	1,505 (1.73% annualized) vs. 1,630 (1.83% annualized); HR, 0.94 (95% CI, 0.88 to 1.01); p=0.11 NS	
	N=1 n=9939 19.4 years (median)	1,899 (35.8% calculated) vs. 2,004 (36.9% calculated); HR, 0.97 (95% CI, 0.91 to 1.03); p=NR NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for all-cause mortality. Three RCT's (WHI, ELITE-Cog, ERA) were found that report on all-cause mortality. The treatment duration of these trials ranged from 2 to 7.2 years. A meta-analysis was performed for data at the end of the intervention. The WHI trial contributed 97% of the events. Results of the meta-analysis are included in the table together with data of the WHI trial in order to have long-term results.

There was **no difference** between conjugated equine estrogen (CEE) and placebo for **all-cause mortality** in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE and placebo for all-cause mortality in postmenopausal women after a median **postintervention** follow-up of 10.8 years and after a **cumulative** follow-up of up to 19.4 years.

8.2 Primary prevention of chronic conditions: estrogen plus progestin versus placebo.

8.2.1 Cancer

8.2.1.1 Breast cancer

Estrogen + Progestin vs placebo: breast cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial, EPHT Estrogen plus progestin trial, ERA Estrogen-only and estrogen plus progestin trial, PEPI Estrogen-only and estrogen plus progestin trial, HERS Estrogen plus progestin trial, WISDOM Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Invasive breast cancer Intervention follow-up	N=1 n=16608 5.6 years (median)	206 (0.43% annualized) vs. 155 (0.35% annualized); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Invasive breast cancer Postintervention (after stopping study treatment)	N=1 n=12788 2.4 years (median)	HR, 1.27 (95% CI, 0.91 to 1.78) NS	
	N=1 n=12788 8.2 years (median)	228 (0.43% annualized) vs. 168 (0.33% annualized); HR, 1.32 (95% CI, 1.08 vs. 1.61); p=0.007 SS	
Invasive breast cancer Cumulative follow-up	N=1 n=16608 19.4 years (median)	574 (6.7% calculated) vs. 432 (5.3% calculated); HR, 1.28 (95% CI, 1.13 to 1.45); p=NR SS	
Breast cancer mortality Intervention follow-up	N=1 n=16608 5.6 years (median)	5 (0.010% annualized) vs. 4 (0.009%); HR, 1.08 (95% CI, 0.29 to 4.03); p=0.91 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Breast cancer mortality Cumulative follow-up	N=1 n=16608 20.3 years (median)	71 (0.045%) vs. 53 (0.035%); HR, 1.35 (95% CI, 0.94 to 1.95); p=0.11 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for the outcome breast cancer.

Six RCT's were found to report on breast cancer incidence. The authors did not pool trial results, primarily because of heterogeneity in study duration and definitions of breast cancer incidence. Only two trials followed women for more than 4 years (WHI and HERS), and only the WHI reported on the risk of invasive breast cancer (vs. any breast cancer). Only results from the WHI trial are presented here. Results from the WHI trial at additional timepoints than presented here and results from the other three RCT's can be found in [Appendix 13.11.1 \(full report\)](#). Only the WHI reported on breast cancer mortality.

Invasive breast cancer

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in **higher risk** of invasive breast cancer compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the **postintervention** phase, there was **no difference** between CEE+MPA and placebo for invasive breast cancer after a median follow-up of 2.4 years and a **higher risk** of invasive breast cancer after a median follow-up of 8.2 years.

CEE+MPA resulted in **higher risk** of invasive breast cancer compared to placebo in generally healthy postmenopausal women after a **cumulative** follow-up of 19.4 years.

Breast cancer mortality

There was **no difference** between CEE+MPA and placebo for breast cancer mortality in postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between CEE+MPA and placebo for breast cancer mortality in postmenopausal women after a **cumulative** follow-up of 20.3 years.

8.2.1.2 Colorectal cancer

Estrogen + Progestin vs placebo: colorectal cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial, HERS Estrogen plus progestin trial, WISDOM Estrogen plus progestin trial, EMS Estrogen plus progestin trial, Multiethnic Cohort Study)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Colorectal cancer	N=1 n=16608 5.6 years (median)	50 (0.59%) vs. 75 (0.93%); HR, 0.62 (95% CI, 0.43 to 0.89); p=0.009 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Intervention follow-up	N=1 n=NR NR Cohort study	Currently use estrogen plus progestin: 214 vs. 903 (2.3% calculated); HR, 0.72 (95% CI, 0.62 to 0.84) SS	
Colorectal cancer	N=1 n=15747 8.2 years (median) postintervention	HR, 0.97 (95% CI, 0.70 to 1.33); p=0.83 NS	
Postintervention follow-up			
Colorectal cancer	N=1 n=16608 13.2 years (median)	HR, 0.80 (95% CI, 0.63 to 1.01); p=0.06 NS	
Cumulative followup	N=1 n=85734 16 years Cohort study	Ever used estrogen plus progestin: 405 vs. 903 (2.3% calculated); HR, 0.76 (95% CI, 0.68 to 0.86) SS	
Colorectal cancer mortality	N=1 n=16608 5.6 years (median)	11 (0.022% annualized) vs. 12 (0.026%); HR, 0.87 (95% CI, 0.38 to 1.98); p=0.74 NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Intervention followup			
Colorectal cancer mortality	N=1 n=16608 17.7 years (median)	53 (0.037% annualized) vs. 50 (0.037%); HR, 1.01 (95% CI, 0.69 to 1.49); p=0.96 NS	
Cumulative followup			

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestine to placebo in postmenopausal women for the outcome colorectal cancer. Four RCT's (WHI, EMS, HERS, WISDOM) were found. No meta-analysis was performed. Only results from the WHI trial are presented here because the three other trials had only a short duration and few to none cases of colorectal cancer. Results at additional timepoints in the WHI trial than presented here and results for the three other trials can be found in [Appendix 13.11.2 \(full report\)](#).

CEE+MPA resulted in a **lower risk** of invasive colorectal cancer compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for colorectal cancer mortality in generally healthy postmenopausal women with a prior hysterectomy aged 50-79 at the end of the intervention phase (median follow-up 5.6 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

Gartlehner 2022 included a prospective cohort study “the multiethnic cohort study” in their review that analyzed as part of a larger study the association between the use of estrogen plus progestin and the incidence of colorectal cancer in 85734 postmenopausal women. The type of estrogen was not mentioned but the information was collected in 1999-2002 and 2003-2007. The multiethnic cohort study found that the current use or ever use of estrogen plus progestin was associated with a **lower risk** of colorectal cancer.

8.2.1.3 Cervical cancer

Estrogen + Progestin vs placebo: cervical cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Cervical cancer	N=1 n=16608 5.6 years (median)	8 (0.09%) vs. 5 (0.06%); HR, 1.44 (95% CI, 0.47 to 4.42) NS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: NA Directness: -1 Imprecision: -1
Intervention follow-up			

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for cervical cancer. One trial was found: the WHI trial.

There was **no difference** between CEE+MPA and placebo for **the incidence of cervical cancer** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

8.2.1.4 Endometrial cancer

Estrogen + Progestin vs placebo: endometrial cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial, HERS Estrogen plus progestin trial, Danish Sex Hormone Register Study)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Endometrial cancer	N=1 n=16608 5.6 years (median)	27 (0.32%) vs. 30 (0.37%); HR, 0.83 (95% CI, 0.49 to 1.40); p=0.49 NS	⊕⊕⊖⊖ LOW Study quality: -1 Short study duration for a rare cancer
Intervention follow-up	N=1 n=2763 4.1 years (mean)	2 (0.14%) vs. 5 (0.36%); HR, 0.39 (95% CI, 0.08 to 2.02); p=0.26 NS	Consistency: ok Directness: -1 Imprecision: ok
Endometrial cancer	N=1 n=15747 8.2 years (median) postintervention	41 (0.08% annualized) vs. 65 (0.13% annualized); HR, 0.59 (95% CI, 0.40 to 0.88); p=0.008 SS	
Endometrial cancer	N=1 n=16608 13.2 years (median)	66 (0.06% annualized) vs. 95 (0.10% annualized); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.007	

Cumulative follow-up	SS	
	N=1	HR, 0.25 (95% CI, 0.05 to
	n=2763	1.18); p=0.08
	6.8 years (mean)	NS

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for cervical cancer. Two RCTs estimated the incidence of endometrial cancer: WHI and HERS. Overall, only 64 women experienced endometrial cancer in these studies. The authors also included a large retrospective Danish cohort study: Danish Sex Hormone Register Study.

There was **no difference** between CEE+MPA and placebo for **the incidence of endometrial cancer** in generally healthy postmenopausal women in the WHI and HERS study at the end of the intervention phase (WHI: median follow-up 5.6 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In the **postintervention** phase (median 8.2 years follow-up), CEE+MPA resulted in **lower risk of endometrial cancer** compared to placebo in the WHI study.

CEE+MPA resulted in a **lower risk of endometrial cancer** compared to placebo in the WHI study after a median **cumulative** follow-up of 13.2 years. There was no difference in risk in the HERS study.

A large, retrospective Danish cohort study based on more than 900,000 women between ages 50 and 79 years without hysterectomy found that compared with women who never used hormone therapy, women with current use of estrogen plus progestin had a **higher risk** for endometrial cancer. A stratification by treatment regimen, however, revealed that a continuous combined estrogen and progestin regimen (**which was also used in the WHI**) had **no increased risk**. By comparison, a cyclic combined regimen increased the risk to a statistically significant level, as did a long cyclic combined regimen. No difference in risks could be detected between oral and transdermal use.

8.2.1.5 Ovarian cancer

Estrogen + Progestin vs placebo: ovarian cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial, Black Women's Health Study)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Ovarian cancer Intervention follow-up	N=1 n=16608 5.6 years (median)	24 (0.28%) vs.16 (0.20%); HR, 1.41 (95% CI, 0.75 to 2.66); p=0.28 NS	⊕⊕⊖⊖ LOW Study quality: -1 Short study duration for a rare cancer Consistency: NA Directness: -1 Imprecision: ok
Ovarian cancer Postintervention	N=1 n=15747 8.2 years (median) Postintervention	HR, 1.24 (95% CI, 0.83 to 1.87); p=0.30 NS	
Ovarian cancer Cumulative follow-up	N=1 n=16608 13.2 years (median)	HR, 1.24 (95% CI, 0.83 to 1.87); p=0.30 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for ovarian cancer. One RCT was found: the WHI trial.

There was **no difference** between CEE+MPA and placebo for **the incidence of ovarian cancer** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between CEE+MPA and placebo for **the incidence of ovarian cancer** in generally healthy postmenopausal women in **postintervention** phase (median follow-up 8.2 years).

There was **no difference** between CEE+MPA and placebo for **the incidence of ovarian cancer** in generally healthy postmenopausal women after a median **cumulative** follow-up of 13.2 years.

Gartlehner 2022 identified one prospective cohort study with data on 6525 postmenopausal Black women who have taken estrogen plus progestin therapy or have never used hormone therapy. During 18 years of follow-up, there was **no difference** in the risk of ovarian cancer.

8.2.1.6 Lung cancer

Estrogen + Progestin vs placebo: lung cancer			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial, HERS Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Lung cancer Intervention follow-up	N=1 n=16608 5.6 years (median)	78 (0.92%) vs. 70 (0.86%); HR, 1.05 (95% CI, 0.76 to 1.45); p=0.78 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Lung Postintervention (after stopping study treatment)	N=1 n=15747 5.6 years (median) postintervention	120 (0.22% annualized) vs. 101 (0.19% annualized); HR, 1.13 (95% CI, 0.86 to 1.47); p=0.38 NS	
Lung cancer Cumulative follow-up	N=1 n=16608 14 years (median)	219 (0.19% annualized) vs. 184 (0.17% annualized); HR, 1.12 (95% CI, 0.92 to 1.37); p=0.24 NS	
Lung cancer mortality Cumulative follow-up	N=1 n=16608 14 years (median)	153 (0.13% annualized) vs. 132 (0.12% annualized); HR, 1.09 (95% CI, 0.87 to 1.38); p=0.45 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for cervical cancer. Two RCTs estimated the incidence of lung cancer: WHI and HERS. Only the WHI reported on lung cancer mortality.

Lung cancer

There was **no difference** between CEE+MPA and placebo for **the incidence of lung cancer** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for **the incidence of lung cancer** in generally healthy postmenopausal women in **postintervention** phase (median follow-up 8.2 years).

There was **no difference** between CEE+MPA and placebo for **the incidence of lung cancer** in generally healthy postmenopausal women after a **cumulative** follow-up up to 14 years.

Lung cancer mortality

There was **no difference** between CEE+MPA and placebo for **lung cancer mortality** in postmenopausal women after a median cumulative follow-up of 14 years.

8.2.1.7 Non-Hodgkin's Lymphoma

Estrogen + Progestin vs placebo: non-Hodgkin's lymphoma			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Non-Hodgkin's lymphoma Intervention follow-up	N=1 n=16544 5.6 years (median)	HR, 0.81 (95% CI, 0.51 to 1.29) NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Non-Hodgkin's lymphoma Cumulative follow-up	N=1 n=16544 13.5 years (median)	113 (0.099% annualized) vs. 110 (0.101% annualized); HR, 0.98 (95% CI, 0.76 to 1.28) NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for the outcome Non-Hodgkin's lymphoma. One trial was found: the WHI trial.

There was **no difference** between CEE+MPA and placebo for **the incidence of non-Hodgkin's lymphoma** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for **the incidence of non-Hodgkin's lymphoma** in generally healthy postmenopausal women after a median cumulative follow-up of 13.5 years.

8.2.1.8 Total cancer mortality

Estrogen + Progestin vs placebo: total cancer mortality			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Total cancer mortality Intervention follow-up	N=1 n=16608 5.6 years (median)	133 (0.27% annualized) vs. 111 (0.24% annualized); HR, 1.10 (95% CI, 0.86 to 1.42); p=0.44 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Total cancer mortality Postintervention	N=1 n=16608 12.5 years postintervention	573 (0.62% annualized) vs. 527 (0.59% annualized); HR, 1.05 (95% CI, 0.93 to 1.18); p=0.43 NS	
Total cancer mortality Cumulative follow-up	N=1 n=16608 17.7 years (median)	706 (0.50% annualized) vs. 638 (0.47% annualized); HR, 1.06 (95% CI, 0.95 to 1.18); p=0.31 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for the outcome total cancer mortality. One trial was found: the WHI trial.

There was **no difference** between CEE+MPA and placebo for **total cancer mortality** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for **total cancer mortality** in generally healthy postmenopausal women in the **postintervention** phase (median follow-up 12.5 years).

There was **no difference** between CEE+MPA and placebo for **total cancer mortality** in generally healthy postmenopausal women after a median **cumulative** follow-up of 17.7 years.

8.2.2 Cardiovascular disease

8.2.2.1 Coronary heart disease

Estrogen + Progestin versus placebo: coronary heart disease and all cardiovascular events			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial; PEPI Estrogen-only and estrogen plus progestin trial; EPHT Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
coronary heart disease (CHD) 2 to 5.6 years; mean 4 years	N=3 n=18085 4 years	2.8% vs 2.6% RR, 1.12 [95% CI, 0.94 to 1.33] NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Overall CHD (nonfatal myocardial infarction or coronary death) Intervention follow-up	N=1 n=16608 5.6 years (median)	196 (0.41% annualized) vs. 159 (0.35% annualized); HR, 1.18 (95% CI, 0.95 to 1.45) NS	
Overall CHD Postintervention	N=1 n=16608 2.4 years (median) postintervention	HR, 1.04 (95% CI, 0.89 to 1.21) NS	
Overall CHD Cumulative follow-up	N=1 n=16608 19.4 years (median)	710 (8.3% calculated) vs. 652 (8.0%); HR, 1.05 (95% CI, 0.95 to 1.17); p=NR NS	
All cardiovascular events Intervention follow-up	N=1 n=16608 5.6 years (median)	786 (1.7% annualized) vs. 663 (1.52%); HR, 1.13 (95% CI, 1.02 to 1.25); p=0.02 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
All cardiovascular events Cumulative follow-up	N=1 n=16608 13 years (median)	1,606 (1.7% annualized) vs. 1,446 (1.6% annualized); HR, 1.08 (95% CI, 1.00 to 1.15); p=0.05 SS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for the outcome coronary heart disease.

Six RCT's (EMS, EPHT, PEPI, WHI, WISDOM, and ERA) were found that report on the risk of coronary heart disease. The authors performed a meta-analysis based on three RCT's which were similar enough to combine. The WHI trial contributed 99% to the pooled estimate. The ERA trial was not included because only women with an elevated cardiovascular risk were eligible for enrollment. The EMS trial was not included because its definition of cardiovascular events also included deep vein thrombosis and cerebrovascular events. The WISDOM trial was not included because it had a follow-up time of only 1 year. Results for additional outcomes (myocardial infarction, heart failure, etc.) from the WHI trial and results for additional timepoints for the outcomes presented here (WHI) can be found in [Appendix 13.12.1 \(full report\)](#).

Coronary heart disease

There was **no difference** between conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) and placebo for coronary heart disease in generally healthy postmenopausal women after a mean intervention follow-up of 4 years.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for coronary heart disease in generally healthy postmenopausal women in the **postintervention** phase (median follow-up 2.4 years).

There was **no difference** between CEE+MPA and placebo for coronary heart disease in generally healthy postmenopausal women after a **cumulative** follow-up of up to 19.4 years.

All cardiovascular events

CEE+MPA resulted in a **higher risk** of "all cardiovascular events" compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE+MPA resulted in a **higher risk** of "all cardiovascular events" compared to placebo in generally healthy postmenopausal women after a **cumulative** follow-up of 13.0 years.

8.2.2.2 Venous Thromboembolism

Estrogen plus progestin versus placebo: venous thromboembolism			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial, HERS)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)

Venous thromboembolism	N=1 n=16608 5.6 years (median)	167 (1.96% calculated) vs. 76 (0.94%); HR, 2.06 (95% CI, 1.57 to 2.70) SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Intervention follow-up	N=1 n=2763 4.1 years (mean)	34 (2.5% calculated) vs. 13 (0.9% calculated); HR, 2.66 (95% CI, 1.41 to 5.04); p=0.003 SS	
Venous thromboembolism	N=1 n=16608 19.4 years (median)	416 (4.9% calculated) vs. 348 (4.3%); HR, 1.14 (95% CI, 0.99 to 1.31); p=NR NS	
Cumulative follow-up	N=1 n=2763 6.8 years (mean)	49 (4.2% calculated) vs. 24 (1.7% calculated); HR, 2.06 (95% CI, 1.26 to 3.36); p=NR SS	
Deep vein thrombosis	N=1 n=16608 5.6 years (median)	122 (1.4% calculated) vs. 61 (0.8%); HR, 1.87 (95% CI, 1.37 to 2.54); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Intervention follow-up	N=1 n=15730 2.4 years postintervention	HR, 1.07 (95% CI, 0.66 to 1.75) NS	
Deep vein thrombosis	N=1 n=15730 2.4 years postintervention	HR, 1.07 (95% CI, 0.66 to 1.75) NS	
Deep vein thrombosis	N=1 n=16608 13.2 years (median)	212 (0.21% annualized) vs. 162 (0.17%); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 SS	
Cumulative follow-up			
Pulmonary embolism	N=1 n=10739 5.6 years (median)	87 (1.0% calculated) vs. 41 (0.5%); HR, 1.98 (95% CI, 1.36 to 2.87); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Pulmonary embolism	N=1 n=15730 2.4 years (mean) postintervention	HR, 1.07 (95% CI, 0.62 to 1.86) NS	
Postintervention follow-up			
Pulmonary embolism	N=1 n=9939 13.0 years (median)	172 (0.17% annualized) vs. 128 (0.13%); HR, 1.26 (95% CI, 1.00 to 1.59); p=0.05 SS	
Cumulative follow-up			

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for venous thromboembolism.

Five RCT's (WHI, ERA, EMS, EPHT, and HERS) were found that report on the risk of venous thromboembolism. The authors did not pool the trials because of heterogeneity in study duration and outcome measures. Results of the WHI trial and HERS trial are shown here. Results of the three smaller trials, for which there were few to none events, are included [Appendix 13.12.2 \(full report\)](#).

Venous thromboembolism

CEE+MPA resulted in a **higher risk** of **venous thromboembolism** compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

At the end of the intervention phase, there was a higher risk of venous thromboembolism in both the WHI trial and the HERS trial. After a cumulative follow-up of 19.4 years, results in the WHI became borderline nonsignificant. In the HERS trial, the higher risk remained present after a mean cumulative follow-up of 6.8 years

Deep vein thrombosis

CEE+MPA resulted in a **higher risk** of deep vein thrombosis compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the **postintervention** phase, there was **no difference** between CEE+MPA and placebo for deep vein thrombosis in postmenopausal women after a mean follow-up of 2.4 years.

CEE+MPA resulted in a **higher risk** of deep vein thrombosis compared to placebo in generally healthy postmenopausal women after a median **cumulative** follow-up of 13.2 years.

Pulmonary embolism

CEE+MPA resulted in a **higher risk** of pulmonary embolism compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the **postintervention** phase, there was **no difference** between CEE+MPA and placebo pulmonary embolism in postmenopausal women after a mean follow-up of 2.4 years.

CEE+MPA resulted in a **higher risk** of pulmonary embolism compared to placebo in generally healthy postmenopausal women after a median **cumulative** follow-up of 13.2 years.

8.2.2.3 Stroke

Estrogen plus progestin versus placebo: stroke			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Stroke (Ischemic or hemorrhagic stroke) Intervention follow-up: Median 5.6 years	N=1 n=16608 5.6 years	159 (1.9% calculated) vs. 109 (1.3%); HR, 1.37 (95% CI, 1.07 to 1.76); p=0.01(197) SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: Directness: -1 Imprecision: ok
Stroke (Ischemic or hemorrhagic stroke) Postintervention	N=1 n=15730 3.9 years postintervention	217 (0.40% annualized) vs. 202 (0.39%); HR, 1.04 (95% CI, 0.86 to 1.26); p=0.67 NS	
Stroke (Ischemic or hemorrhagic stroke) Cumulative follow-up	N=1 n=16608 13.2 years (median)	376 (0.37% annualized) vs. 311 (0.32%); HR, 1.16 (95% CI, 1.00 to 1.35); p=0.06 NS	
	N=1 n=16608 19.4 years (median)	579 (6.8% calculated) vs. 492 (6.1%); HR, 1.13 (95% CI, 1.00 to 1.27); p=NR SS	
Stroke mortality Intervention follow-up	N=1 n=16608 5.6 years (median)	27 (0.055% annualized) vs. 16 (0.035%); HR, 1.58 (95% CI, 0.85 to 2.94); p=0.14 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Stroke mortality Cumulative follow-up	N=1 n=16608 12.5 years (median)	161 (0.17%) vs. 145 (0.16%); HR, 1.08 (95% CI, 0.86 to 1.35); p=0.52 NS	
	N=1 n=16608 17.7 years (median)	188 (0.13% annualized) vs. 161 (0.12%); HR, 1.12 (95% CI, 0.91 to 1.38); p=0.29 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for the outcome stroke.

Four RCT's (WHI, EMS, EPHT, and ERA) were found that report on the risk of stroke. The authors did not pool the trials because of heterogeneity in study duration and outcome measures. Results of the WHI trial are shown here. Results of the four smaller trials, for which there were few to none events and results for some additional outcomes are included in [Appendix 13.12.3 \(full report\)](#).

Stroke

CEE+MPA resulted in a **higher risk** of stroke compared to placebo in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In the **postintervention** phase, there was **no difference** between CEE+MPA and placebo for the outcome stroke in generally healthy postmenopausal women after a mean follow-up of 3.9 years.

There was **no difference** between CEE+MPA and placebo for the outcome stroke in generally healthy postmenopausal women after a median **cumulative** follow-up of 13.2 years. However, after a median **cumulative** follow-up of 19.4 years there was a **higher risk** of stroke compared to placebo.

Stroke mortality

There was **no difference** between CEE+MPA and placebo for the outcome stroke mortality in postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for the outcome stroke mortality in postmenopausal women after a median cumulative follow-up of 12.5 years and 17.7 years.

8.2.2.4 Peripheral Arterial Disease

Estrogen plus progestin versus placebo: peripheral arterial disease			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Peripheral arterial disease	N=1 n=16608 5.6 years (median)	48 vs. 50; HR, 0.89 (95% CI, 0.60 to 1.32); p=0.57	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Intervention follow-up		NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for peripheral arterial disease. One trial was found: the WHI trial. Peripheral arterial disease was defined as incident carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease.

There was **no difference** between CEE+MPA and placebo for **peripheral arterial disease** in generally healthy postmenopausal women at the end of the intervention phase (median follow-up 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

8.2.3 Cognition and dementia

8.2.3.1 Dementia and mild cognitive impairment incidence

Estrogen + Progestin versus placebo: dementia and mild cognitive impairment			
Bibliography: Gartlehner 2022(5) (WHIMS Estrogen plus progestin trial; WHISCA Estrogen plus progestin trial; WHI Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Probable dementia Intervention follow-up	N=1 n=4532 ~4 years	40 (1.8%) vs. 21 (0.9%); cumulative HR, 2.05 (95% CI, 1.21 to 3.48); p=0.01 SS	⊕⊕⊕⊖ LOW Study quality: ok Consistency: -1 Directness: -1 Imprecision: ok
	N=1 n=1416 1.4 years (in WISCA after 3 years in WHI)	5 (0.7%) vs. 6 (0.8%); calculated RR, 0.88 (95% CI, 0.27 to 2.86); p=0.83 NS	
Mild cognitive impairment Intervention follow-up	N=1 n=4532 ~4 years	56 (2.5%) vs. 55 (2.4%); cumulative HR, 1.07 (95% CI, 0.74 to 1.55); p=0.72 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=1416 1.4 years (in WISCA after 3 years in WHI)	6 (0.9%) vs. 13 (1.8%); calculated RR, 0.49 (95% CI, 0.19 to 1.27); p=0.14 NS	
Probable dementia or Mild cognitive impairment Intervention follow-up	N=1 n=2947 5.2 years	85 (3.8%) vs. 66 (2.9%); cumulative HR, 1.37 (95% CI, 0.99 to 1.89) NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Alzheimer's disease or other dementia mortality Intervention follow-up: Median 5.6 years	N=1 n=16608 5.6 years	CEE + MPA vs placebo 0 (0% annualized) vs. 0 (0%); HR not estimable	Insufficient data
Alzheimer's disease or other	N=1 n=15747 12.5 years	223 (0.24% annualized) vs. 233 (0.26%);	

dementia mortality		HR, 0.94 (95% CI, 0.78 to 1.13); p=0.52 NS
Postintervention follow-up: Median 12.5 years		
Alzheimer's disease or other dementia mortality	N=1 n=12788 17.7 years	223 (0.16% annualized) vs. 233 (0.17%); HR, 0.93 (95% CI, 0.77 to 1.11); p=0.42 NS
Cumulative follow-up: Median 17.7 years		

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for dementia and mild cognitive impairment.

Results for the outcomes probable dementia or mild cognitive impairment were obtained from the The Women's Health Initiative Memory Study (WHIMS) trial and the Women's Health Initiative Study of Cognitive Aging (WHISCA) trial. The WHIMS trial is a subset of the WHI trial limited to women ages 65 to 79 years at baseline who were free of probable dementia. The WHISCA trial, an ancillary study of the WHIMS trial, began 3 years after the start of the WHI and WHIMS trials and evaluated changes in more detailed, domain-specific cognitive functioning over time. Results for dementia-related mortality were obtained from the WHI trial.

Probable dementia

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **higher risk** of probable dementia compared to placebo in postmenopausal women at the end of the intervention phase.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

The WHIMS trial found a higher risk for probable dementia. The WHISCA trial found no difference compared with placebo but there were few events (5 vs 6) in the WHISCA study.

Mild cognitive impairment

There was **no difference** between CEE+MPA and placebo for the outcome mild cognitive impairment in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Probable dementia or mild cognitive impairment

There was **no difference** between CEE+MPA and placebo for "probable dementia or mild cognitive impairment" in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Dementia-related mortality

There were no cases of dementia-related mortality **at the end of the intervention phase** (median follow-up of 7.2 years).

There was **no difference** between CEE+MPA and placebo for dementia-related mortality in the postintervention phase (median follow-up: 12.5 years) or after a median cumulative follow-up of 17.7 years.

8.2.3.2 Global cognitive function

Estrogen + Progestin versus placebo: global cognitive function			
Bibliography: Gartlehner 2022(5) (WHIMS Estrogen plus progestin trial; HERS Estrogen plus progestin trial; WHISCA Estrogen plus progestin trial; WHIMSY Estrogen + progestin trial; KEEPS-Cog Estrogen plus progestin trial; KEEPS-MRI)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Global cognitive functioning Intervention follow-up	N=1 n=4344 5.4 years	Mean difference in change from baseline, -0.18 (95% CI, -0.37 to 0.00); p=0.055 NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=1328 4.2 years	93.1 (SD, 6.4) vs. 93.4 (SD, 6.4); difference, -0.4 (95% CI, -1.1 to 0.4); p=0.36 NS	
	N=1 n=1213 2 years (during WHISCA and after 3 years in WHI)	Mean decrement in global cognitive function -0.080 (SE, 0.034); p=0.02 SS	
	N=1 n=693 4 years	Oral estrogen: Beta estimate, 1.02×10^{-2} (95% CI, -4.45×10^{-3} to 2.48×10^{-2}); p=0.178 NS Transdermal estrogen: Beta estimate, -9.40×10^{-4} (95% CI, -1.57×10^{-2} to 1.38×10^{-2}); p=0.840	

	NS	
	N=1 n=101 4 years	NS
Global cognitive functioning	N=1 n=1326 7.2 years	38.08 (SE, 0.20) vs. 38.26 (SE, 0.21); p=NR NS
Postintervention (after stopping treatment)	postintervention	
	N=1 n=NR 4 years (after 3 years in WHI and 2 years in WHISCA)	-0.059 (SE, 0.032); p=0.06 NS

3MS scores or TICS-m scores.

3MS=Modified Mini-Mental State Examination; TICS=Telephone Interview for Cognitive Status

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen plus progestin to placebo in postmenopausal women for global cognitive function.

Three studies (HERS, KEEPS, and WHI) comprising six trials (HERS; KEEPS-Cog; KEEPS-MRI; WHIMS; WISCA; WHIMSY) measured global cognitive functioning using a short form of the Modified Mini-Mental State Examination (3MS)E or the Telephone Interview for Cognitive Status (TICS-m). The KEEPS-Cog trial and KEEPS-MRI trial are ancillary studies that recruited patients from the KEEPS trial. The WHIMS and WISCA trial were mentioned above. The WHIMSY trial is a subset of the WHI trial limited to women ages 50 to 55 years at enrollment. No meta-analysis was performed. The HERS trial had a treatment regimen similar to that used in the WHI studies.

There was **no difference** between CEE+MPA and placebo for global cognitive function in postmenopausal women **at the end of intervention phase**.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for global cognitive function in postmenopausal women **in the postintervention phase**.

8.2.3.3 Other Cognitive Measures

The AHRQ systematic review and meta-analysis by Gartlehner 2022 found four RCTs (EMS, HERS, WHISCA, WHIMSY) evaluating other measures of cognitive functioning (e.g., spatial ability, verbal knowledge, working memory, etc.). The results can be found in [Appendix 13.13.3 \(full report\)](#). Heterogeneity in outcome measures precluded meta-analysis. No differences were found for the majority of outcomes.

8.2.4 Fractures

Estrogen + Progestin versus placebo: Fractures			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial; HERS Estrogen plus progestin trial; ERA Estrogen-only and estrogen plus progestin trial; EPHT Estrogen plus progestin trial; EMS Estrogen plus progestin trial; ERA Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Fractures During or at the end of intervention period	N=5 n=20499 2-5.6 years	CEE + MPA vs placebo 8.7% vs 10.9%; RR, 0.79 (95% CI, 0.66 to 0.94) SS Heterogeneity: $T^2=0.01$, $I^2=34.24\%$, $H^2=1.52$	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Fractures Intervention follow-up	N=1 n=16608 5.6 years (mean)	741 (1.61% annualized) vs. 903 (2.12% annualized); HR, 0.76 (95% CI, 0.69 to 0.83); p<0.001 SS	
Fractures Postintervention (after stopping treatment)	N=1 n=16608 2.4 years postintervention	337 (1.95% annualized) vs. 346 (2.16% annualized); HR, 0.91 (95% CI, 0.78 to 1.06); p=0.06 NS	
Fractures - Hip Intervention follow-up	N=1 n=16608 5.6 years (mean)	53 (0.11% annualized) vs. 75 (0.17% annualized); HR, 0.67 (95% CI, 0.47 to 0.96); p=0.03 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok
Fractures – Hip Postintervention (after stopping treatment)	N=1 n=15730 2.4 years (mean) postintervention	54 (0.28% annualized) vs. 57 (0.31% annualized); HR, 0.92 (95% CI, 0.64 to 1.34); p=0.20 NS	
	N=1 n=15730 4.2 years (mean) postintervention	50 (0.24% annualized) vs. 56 (0.26% annualized); HR, 0.93 (95% CI, 0.63 to 1.36); p=0.70 NS	
Fractures – Hip	N=1 n=16608	232 (0.23% annualized) vs. 270 (0.28% annualized);	

Cumulative follow-up	13.2 years	HR, 0.81 (95% CI, 0.68 to 0.97); p=0.02 SS
	N=1 n=16608 19.4 years	394 (4.6% calculated) vs. 421 (5.2% calculated); HR, 0.90 (95% CI, 0.78 to 1.03); p=NR NS

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for dementia and mild cognitive impairment. Five RCT's (WHI, HERS, ERA, EPHT, EMS) were found that report on the risk of fractures. The authors performed a meta-analysis measuring total fractures during or at the end of intervention period. The trials spanned reporting periods from 2 through 5.6 years and the sample size varied widely. Results for the WHI study at additional timepoints and additional outcomes than presented here can be found in [Appendix 13.14 \(full report\)](#).

Intervention phase

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **lower risk of fractures** compared to placebo in postmenopausal women **at the end of the intervention phase**.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE + MPA resulted in a **lower risk of hip fractures** compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Postintervention phase (total fractures and hip fractures)

There was **no difference** between CEE+MPA and placebo for **total fractures** and **hip fractures** in postmenopausal women after a mean **postintervention follow-up of 2.4 years**.

Cumulative follow-up (Hip fractures)

CEE+MPA resulted in a **lower risk** of hip fractures compared to placebo in postmenopausal women after a **cumulative follow-up of 13.2 years**.

There was **no difference** between CEE+MPA and placebo for hip fractures in postmenopausal women after a mean **cumulative follow-up of 19.4 years**.

8.2.5 Diabetes

Estrogen plus progestin versus placebo: diabetes			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial, HERS Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Diabetes Intervention follow-up	N=1 n=15784 5.6 years (mean)	328 (0.72% annualized) vs. 373 (0.88% annualized); HR, 0.81 (95% CI, 0.70 to 0.94); p=0.005 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=2029 4.1 years (mean)	62 (6.2%) vs. 98 (9.5%); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.006 SS	
Diabetes Postintervention (after stopping treatment)	N=1 n=NR 8.2 years (median) Postintervention	603 (1.24% annualized) vs. 482 (1.04% annualized); HR, 1.19 (95% CI, 1.05 to 1.34); p=0.005 SS	
Diabetes cumulative follow- up	N=1 n=9917 13.2 years (median)	931 (0.99% annualized) vs. 855 (0.96% annualized); HR, 1.02 (95% CI, 0.93 to 1.12); p=0.66 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women diabetes. Two trials (WHI, HERS) provided information about the incidence of diabetes. In the WHI trial the incidence of diabetes was self-reported and defined as a new diagnosis of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin. In the HERS trial diabetes was defined as having a fasting glucose level of 6.9 mmol/L or greater (≥126 mg/dL), self-report of new diabetes or diabetes-related complications (diabetic neuropathy, diabetic retinopathy, diabetic foot ulcer, diabetic renal disease, or hypoglycemia if taking an antidiabetic medication), or initiation of hypoglycemic medication; this analysis was conducted post hoc and should be considered cautiously.

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **lower risk** for diabetes compared to placebo in generally healthy postmenopausal women during **the intervention phase** (mean follow-up: 4.1 to 7.2 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE+MPA resulted in a **lower risk** for diabetes compared to placebo in generally healthy postmenopausal women aged 50-79 in the **postintervention** phase after a mean follow-up of 8.2 year.

There was **no difference** between CEE+MPA and placebo for the incidence of diabetes in generally healthy postmenopausal women aged 50-79 after a median **cumulative** follow-up of 13.2 years.

8.2.6 Gallbladder disease

Estrogen + Progestin versus placebo: Gallbladder disease			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial; PEPI Estrogen-only and estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Global gallbladder disease Intervention follow-up	N=1 n=14203 5.6 years (mean)	528 (1.31% annualized) vs. 319 (0.84% annualized); HR, 1.57 (95% CI, 1.36 to 1.80); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok gallbladder disease is self- reported Consistency: NA Directness: -1 Imprecision: ok
Gallbladder disease Postintervention follow-up (after stopping treatment)	N=1 n=14203 8.2 years (median) Postintervention	213 (1.27% annualized) vs. 166 (1.01% annualized); HR, 1.24 (95% CI, 1.01 to 1.52); p=0.04 SS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for the incidence of gallbladder disease. Two RCT's (WHI, PEPI) were found that report on the risk of gallbladder disease. The definition of gallbladder disease used in PEPI is unclear; for WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all gallbladder or biliary tract stone disease.

The smaller PEPI trial had very few events. Only results of the WHI trial are presented here. Results for additional outcomes (WHI trial) and results from the PEPI trial can be found in [Appendix 13.16 \(full report\)](#).

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **higher risk of gallbladder disease** compared to placebo in postmenopausal women **at the end of the intervention phase** (median follow-up of 5.6 years).

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE+MPA resulted in a **higher risk of gallbladder disease** compared to placebo in postmenopausal women **in the postintervention phase** (median follow-up of 8.2 years).

8.2.7 Urinary incontinence

Estrogen plus progestin versus placebo: urinary incontinence			
Bibliography: Gartlehner 2022(5) (WHI Estrogen plus progestin trial; HERS Estrogen plus progestin trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Weekly total urinary incontinence Intervention follow-up	N=1 n=10073 1 year	1,021 (16.6% annualized) vs. 641 (11.1% annualized); HR, 1.49 (95% CI, 1.36 to 1.63); p<0.001 SS	⊕⊕⊕⊖ MODERATE Study quality: ok Urinary incontinence is self-reported Consistency: ok Directness: -1 Imprecision: ok
	N=1 n=1208 4.2 years	382 vs. 302; OR, 1.6 (95% CI, 1.3 to 1.9); p<0.001 SS	
Weekly total urinary incontinence Postintervention (after stopping study treatment)	N=1 n= 8.2 years (median) postintervention	1,221 calculated (23.5%) vs. 990 calculated (20.3%); HR, 1.16 (95% CI, 1.08 to 1.25); p<0.001 SS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for urinary incontinence. Two RCT's (WHI, HERS) were found. Both trials had a similar treatment regimen and defined urinary incontinence as at least one episode weekly. Results for the outcome “weekly total urinary incontinence” are shown. The WHI trial and HERS trial also evaluated various subtypes of urinary incontinence. Details can be found in [Appendix 13.17 \(full report\)](#).

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **higher risk of urinary incontinence** compared to placebo in postmenopausal women **after a follow-up of 1 to 4.2 years**.

GRADE: MODERATE LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

CEE+MPA resulted in a **higher risk of urinary incontinence** compared to placebo in postmenopausal women **after a median postintervention follow-up of 8.2 years**.

8.2.8 Quality of life

Estrogen plus progestin versus placebo: quality of life			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Quality of life Intervention follow-up	N=1 n=16608 5.6 year (mean)	Bodily pain: NS Vitality: NS Mental health: NS Social functioning: NS Emotional role: NS Physical functioning: SS 82.6 vs. 81.8; p<0.001 Physical role: SS 77.4 vs. 76.2; p=0.02 bodily pain: SS 77.6 vs. 75.6; p<0.001 General health: SS 76.6 vs. 76.1; p=0.02	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: NA Directness: -1 Imprecision: ok

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen plus progestin to placebo in postmenopausal women for quality of life. The WHI trial was the only trial that reported on quality of life. Quality of life was assessed with the Short Form Health Survey (SF-36) form.

There were no statistically significant differences between conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) and placebo on all items of the SF-36 except for physical functioning (p<0.001), physical role (p=0.02), bodily pain (p<0.001), and general health (p=0.02). Women on CEE+MPA had statistically significantly better scores for these items. However, these differences do not seem clinically significant.

Overall, there was **no difference** between CEE+MPA and placebo for quality of life in postmenopausal women at the end of the intervention phase (mean follow-up 5.6 year).

GRADE: MODERATE LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

8.2.9 Asthma

Estrogen plus progestin versus control: Asthma			
Bibliography: Shah 2021(196)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Asthma	N=1 n=353173 17 years	Previous users vs non-users Adjusted HR 0.82 (95% CI : 0.76-0.88) SS	⊕⊕⊖⊖ LOW Study quality: ok Consistency: -1 No consistent results with other studies not included in this report.
		Current users vs non-users Adjusted HR 0.78 (95% CI : 0.70-0.87) SS	Directness: -1 Type of HT not specified. Possibly mostly CEE? Imprecision: ok +1 for dose-response association between duration of HT use and onset of asthma

The AHRQ review from Garthlehner 2022 mentioned in their appendix of eligible observational studies two studies with outcome asthma. This is not further studied in the review without mentioning a reason for this. We included one of the studies here and excluded the other study in our report due to the studied population (women with asthma).

The large retrospective cohort study from Shah 2021 compared the use of hormone therapy with controls in women recruited from primary care practices. Details can be found in [Appendix 13.20 \(full report\)](#). The analysis was adjusted for confounders including age, smoking, Charlson Comorbidity Index score and BMI. No separate analysis was performed for route of HT administration due to inconsistent documentation.

The use of estrogen plus progestin was associated with a **lower risk** of developing **asthma** compared to non-users in menopausal women after 17 years of follow-up.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

8.2.10 COPD

Estrogen plus progestin versus placebo: COPD			
Bibliography: Gartlehner 2022(5) (WHI Estrogen-only trial)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
COPD incidence	No eligible studies		Insufficient data
COPD mortality Intervention follow-up	N=1 n=10739 5.6 years (median)	1 (0.002% annualized) vs. 8 (0.017% annualized); HR, 0.12 (95% CI, 0.01 to 0.93); p=0.01 SS	⊕⊕⊕⊕ VERY LOW Study quality: -2 Very few events Consistency: NA Directness: -1 Imprecision: ok
COPD mortality Postintervention (after stopping treatment)	N=1 n=NR 12.5 years (median) Postintervention	107 (0.12% annualized) vs. 92 (0.10% annualized); HR, 1.13 (95% CI, 0.85 to 1.49); p=0.41 NS	
COPD mortality cumulative follow- up	N=1 n=10739 17.7 years (median)	108 (0.076% annualized) vs. 100 (0.074% annualized); HR, 1.03 (95% CI, 0.79 to 1.36); p=0.81 NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥1 year that compared estrogen only to placebo in postmenopausal women for outcome COPD. No eligible studies reported on COPD incidence. The WHI trial did provide information about COPD mortality.

The WHI trial found a lower risk for COPD mortality in the intervention group at the end of the intervention phase. However, this finding needs to be viewed cautiously because only nine women had died of COPD by this time point. Furthermore, the reduction was no longer observed at later timepoints.

Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) resulted in a **lower risk** for COPD mortality compared to placebo in postmenopausal women aged 50-79 at the end of **the intervention phase** (median follow-up: 5.6 years).

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between CEE+MPA and placebo for **COPD mortality** in postmenopausal women aged 50-79 in the **postintervention** phase (median follow-up of 12.5 years).

There was **no difference** between CEE+MPA and placebo for **COPD mortality** in postmenopausal women aged 50-79 after a median **cumulative** follow-up of 17.7 years.

8.2.11 All-cause mortality

Estrogen plus progestin versus placebo: all-cause mortality			
Bibliography: Gartlehner 2022(5) (WHI, HERS, ERA)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
All-cause mortality Intervention follow-up	N=3 n=19580 3.2 - 5.6 years	RR, 1.01 [95% CI, 0.88 to 1.16] NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
All-cause mortality Intervention follow-up	N=1 n=16608 5.6 years (mean)	250 (2.9% calculated) vs. 239 (2.9% calculated); HR, 0.97 (95% CI, 0.81 to 1.16) NS	
All-cause mortality Postintervention (after stopping study treatment)	N=1 n=12788 2.4 years (mean)	233 (1.20% annualized) vs. 196 (1.06% annualized); HR, 1.15 (95% CI, 0.95 to 1.39); p=0.27 NS	
	N=1 n=12788 8.2 years (median)	761 (1.39% annualized) vs. 728 (1.39% annualized); HR, 1.01 (95% CI, 0.91 to 1.11); p=0.90 NS	
All-cause mortality Cumulative follow-up	N=1 n=16608 12.5 years (mean)	1,994 (2.15% annualized) vs. 1,872 (2.11% annualized); HR, 1.04 (95% CI, 0.97 to 1.10); p=0.28 NS	
	N=1 n=16608 13.2 years (median)	1,011 (0.98% annualized) vs. 966 (0.99% annualized); HR, 0.99 (95% CI, 0.91 to 1.08); p=0.87 NS	
	N=1 n=16608 17.7 years (median)	2,244 (1.58% annualized) vs. 2,110 (1.57% annualized); HR, 1.02 (95% CI, 0.96 to 1.08); p=0.51 NS	
	N=1 n=16608 19.4 years (median)	2,802 (32.9% calculated) vs. 2,638 (32.6% calculated); HR, 1.02 (95% CI, 0.97 to 1.08); p=NR NS	

The AHRQ systematic review and meta-analysis by Gartlehner 2022 searched for RCTs with a study duration of ≥ 1 year that compared estrogen only to placebo in postmenopausal women for all-cause mortality. Three RCT's (WHI, HERS, ERA) were found that report on all-cause mortality. The treatment duration of these trials ranged from 2 to 7.2 years. A meta-analysis was performed for data at the end of the intervention. The WHI trial contributed 64% of the events. Results of the meta-analysis are included in the table together with data of the WHI trial in order to have long-term results.

There was **no difference** between conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) and placebo for **all-cause mortality** in postmenopausal women **at the end of the intervention phase**.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between CEE+MPA and placebo for **all-cause mortality** in postmenopausal women after a median **postintervention** follow-up of 8.2 years and after a **cumulative** follow-up of up to 19.4 years.

8.3 Non-oral hormone therapy

8.3.1 Non-oral HT versus control: venous thromboembolism

Non-oral hormone therapy versus control: venous thromboembolism			
Bibliography: Rovinski 2018(198) including			
Scarabin 2003(199) ; Douketis 2005(200), ESTHER 2007(201), Daly 1996(202), Pérez Gutthann 1997(203), Renoux 2010(204), Roach 2013(205), Bergendal 2016(206), E3N 2010(207), MILLION 2012(208)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Venous thromboembolism	(Non-oral hormone therapy (estrogen-only AND combined estrogen and progestin therapies) versus control) N=9 n=821155	OR 0.97 [0.9-1.06] NS Heterogeneity: I ² 0%	⊕⊕⊕⊕ LOW Study quality: no RCTs Consistency: ok Directness: ok Imprecision: ok
Venous thromboembolism	(Non-oral hormone therapy (estrogen-only) versus control) N=6 n=745697	OR 0.95 [0.81-1.10] NS Heterogeneity: I ² 14%	⊕⊕⊕⊕ LOW Study quality: no RCTs Consistency: ok Directness: ok Imprecision: ok
Venous thromboembolism	(Non-oral hormone therapy (combined estrogen and progestin) versus control) N=5 n=712900	OR 0.92 [0.77-1.09] NS Heterogeneity: I ² 0%	⊕⊕⊕⊕ LOW Study quality: no RCTs Consistency: ok Directness: ok Imprecision: ok

The systematic review and meta-analysis by Rovinski 2018 searched for studies (RCTs+ cohort studies+ case control) that assessed venous thromboembolism (VTE) (pulmonary embolism and/or deep vein thrombosis) in postmenopausal women using oral or non-oral hormonal treatment (HT) and without previous VTE.

The authors found 10 observational studies and no RCTs comparing non-oral HT to control (non-HT therapy users).

All studies evaluated transdermal 17 β -estradiol as non-oral HT. Gel or patch was not analyzed separately.

There are some methodological problems that limit our confidence in the estimate of the results. The most important is that no RCTs were found resulting in a reduced confidence in the evidence.

Non-oral HT was not associated with a difference in risk of **venous thromboembolism** compared to control in *postmenopausal without previous VTE*.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

8.3.2 Non-oral HT vs oral HT: venous thromboembolism

Non-oral hormone therapy versus oral hormone therapy: venous thromboembolism			
Bibliography: Rovinski 2018(198) including Douketis 2005(200), ESTHER 2007(201), Daly 1996(202), Pérez Gutthann 1997(203), Renoux 2010(204), Roach 2013(205), Bergendal 2016(206), E3N 2010(207), Laliberte 2011(209), MILLION 2012(208), Dinger 2016(210), Simon 2016(211)			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Venous thromboembolism	N=12 n=394077 1.8-20.2 years	OR 1.66 [1.39–1.98] SS Increased risk with oral HT	⊕⊕⊕⊕ VERY LOW Study quality: no RCTs Consistency: -1 Heterogeneity: I ² 58% Directness: -1 predominant CEE use Imprecision: ok
Venous thromboembolism sensitivity analysis: restricted to studies including participants without risk factors for VTE, cancer, previous HT use, or use of other (oral) HT-containing co-medication or other medication (aspirin) that could possibly influence VTE risk.	N=7 n=90817	OR 1.88 [1.35–2.39] SS Increased risk with oral HT	

The systematic review and meta-analysis by Rovinski 2018(198) searched for studies (RCTs+ cohort studies+ case control) that assessed venous thromboembolism (VTE) (pulmonary embolism and/or deep vein thrombosis) in postmenopausal women using oral or non-oral hormonal treatment (HT). The authors found 12 studies. Only cohort studies and case-control studies were found for the comparison of non-oral HT to oral HT including only postmenopausal women who did not have diseases that could increase the risk of VTE events.

In different studies estrogens were used alone or in combination with progestogens. Different progestogen types were used as well. Several studies included women using either micronized estradiol, estradiol valerate or conjugated equine estrogen (CEE). One large study only included women using CEE. Separate analyses were not performed for patches or gel, and risk was not analyzed according to dose.

There are some methodological problems that limit our confidence in the estimate of the results. The most important is that no RCTs were found resulting in a reduced confidence in the evidence. Moderate heterogeneity in the analyses of oral vs. non-oral HT groups was found. Level of evidence was also downgraded for directness as most of the studies included in most part women using CEE and the largest study only used CEE as comparator reducing general applicability of these results. CEE is currently not used in Belgium or available on the Belgian market.

Oral HT resulted in a **higher risk of venous thromboembolism** compared to **non-oral HT** in *postmenopausal women who did not have diseases that could increase the risk of VTE events.*

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

8.4 Levonorgestrel-releasing intrauterine system vs control

Levonorgestrel-releasing intrauterine system vs control in peri-menopausal women: breast cancer

We searched for RCTs or large cohort studies evaluating long-term effects of the use of a levonorgestrel-releasing intrauterine system in peri- and postmenopausal women.

We found 1 retrospective cohort study, Siegelmann 2018(212), using data from an Israeli health insurance database to evaluate the risk of breast cancer.

Siegelmann 2018 evaluated the risk of breast cancer (breast cancer, ductal carcinoma in situ (DCIS) and invasive breast cancer) in perimenopausal patients (women aged 40-50 years) using a levonorgestrel-releasing intrauterine system (LNG-IUS) versus age-matched non-users of LNG-IUS. Women with a previous breast cancer diagnosis or a breast cancer diagnosis within 6 months of inclusion were excluded from the study.

In this observational study, age was used as a proxy for menopausal state. The reproductive state of the participants is therefore not confirmed and it is likely that a majority of the women in the LNG-IUS user group received LNG-IUS for contraception or for menorrhagia and not for the treatment of menopausal symptoms.

There is a risk of selection bias in this study, since the choice of contraceptive may have been informed by personal or family medical history relating to the outcome of breast cancer.

We rate these results to have a VERY LOW quality of evidence as it is observational data with a high risk of bias.

There was **no significant association** between LNG-IUS use and breast cancer, ductal carcinoma in situ, or invasive breast cancer, compared to non-use.

8.5 Tibolone vs placebo in post-menopausal women

See conclusion chapter 6.13 for tables

There was **no significant difference** between tibolone and placebo for **endometrial hyperplasia** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **endometrial cancer** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **breast cancer** in post-menopausal women without history of breast cancer.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **venous thromboembolic events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **cardiovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very.

There was **no significant difference** between tibolone and placebo for **cerebrovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and placebo for **mortality** in post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

8.6 Tibolone vs Estrogen/Progestagen Therapy (EPT) in post-menopausal women

See conclusion chapter 6.15 for tables

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **endometrial hyperplasia** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **endometrial cancer** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **breast cancer** in post-menopausal women without history of breast cancer.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **venous thromboembolic events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **cardiovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **cerebrovascular events** in post-menopausal women.

GRADE: VERY LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is very low.

There was **no significant difference** between tibolone and estrogen-progestogen therapy for **mortality** in post-menopausal women.

GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

9 Hormone therapy for the secondary prevention of cardiovascular disease. Summary and conclusions from the literature review

Oral hormone therapy versus placebo: secondary prevention of cardiovascular disease			
Boardman 2015(3)			
including (EAGAR 2006(213); ERA 2000(214, 215) ; ESPRIT 2002(216); HERS I 1998(217); (218); (219); (220); (221); (222); (223); (224); (225); (226); (227) ; WAVE 2002(228); Waters 2001(229); WEST 2001(230); (231); (232); WHISP 2006(233); WELL-HART 2003(234); EVTET 2000(235))			
Outcomes	N° of studies (n° of participants) Follow up	Results	Quality of the evidence (GRADE)
Death (all causes)	N=7 n=5445 2-7 years	241/2801 vs 223/2644 RR 1.04 [95%CI: 0.87–1.24] NS	⊕⊕⊕⊖ MODERATE Study quality: ok WHISP 2006 (n=100): high risk incomplete outcome data; unclear for blinding outcome data and outcome death not prespecified Consistency: ok Directness: -1 Imprecision: ok
Death (cardiovascular causes)	N=6 n=5259 2-4.1 years	118/2684 vs 115/2575 RR 1.00 [95%CI: 0.78–1.29] NS	⊕⊕⊕⊖ MODERATE Study quality: ok EAGAR 2006 (n=83): unclear for multiple sources of bias Consistency: ok Directness: -1 Imprecision: ok
Stroke	N=5 n=5172 2-4.1 years	187/2640 vs 164/2532 RR 1.09 [95%CI: 0.89–1.33] NS	⊕⊕⊕⊖ MODERATE Study quality: ok Consistency: ok Directness: -1 Imprecision: ok
Venous thromboembolism	N=6 n=4399 1.3-7 years	57/2251 vs 24/2148 RR 2.02 [95%CI: 1.13–3.26] SS	⊕⊕⊕⊖ MODERATE Study quality: ok -EVTET 2000 (n=140): unclear for allocation concealment, high risk for incomplete outcome data -WHISP 2006 (n=100): high risk incomplete outcome data; unclear for blinding outcome data and cardiovascular outcomes were not prespecified as outcomes Consistency: ok Directness: -1 Imprecision: ok
Pulmonary thromboembolism	N=3 n=3920	22/1964 vs 8/1956 RR 2.48 [95%CI: 0.92–6.70]	⊕⊕⊕⊖ MODERATE Study quality: ok

	1.3-4.1years	NS	-EVTET 2000 (n=140): unclear for allocation concealment, high risk for incomplete outcome data Consistency: ok Directness: -1 Imprecision: ok

The Cochrane review from Boardman 2015 searched for RCTs with a study duration ≥ 6 months comparing oral hormone therapy with either placebo or no treatment in postmenopausal women.

Ten studies were found that included women with established cardiovascular disease. The majority of the studies were done with conjugated equine estrogen (CEE). Boardman 2015 did not stratify between estrogen-only and combination hormone therapy, which is a limitation of the review. ERA 2000, WAVE 2002 and WELL-HART 2003 included women who had coronary artery stenosis evidenced by angiogram. HERS I 1998 and EAGAR 2006 both included women who had undergone a revascularisation procedure (coronary artery bypass graft or percutaneous coronary intervention), whilst ESPRIT 2002, WEST 2001 and WHISP 2006 included women who had had a previous acute coronary syndrome or a transient ischaemic attack (TIA). HALL 1998 included women previously hospitalised with angina, and EVTET 2000 included women who had suffered a thromboembolic event, pulmonary embolism or deep vein thrombosis.

There were methodological problems in some studies. For example, in the EAGAR 2006 trial there were unclarieties regarding selection bias, allocation concealment, and blinding.

Results for outcomes non-fatal myocardial infarction, angina, and revascularisation can be found in [Appendix 16 \(full report\)](#).

There was **no difference** between conjugated equine estrogen (CEE) and placebo for **all-cause mortality** in postmenopausal women at the end of the intervention phase.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between hormone therapy and placebo for the secondary prevention of **all-cause mortality** in postmenopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between hormone therapy and placebo for the secondary prevention of **cardiovascular mortality** in postmenopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between hormone therapy and placebo for the secondary prevention of **stroke** in postmenopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

Hormone therapy resulted in **more events** of **venous thromboembolism** compared to placebo in postmenopausal women with established cardiovascular disease.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between hormone therapy and placebo for the secondary prevention of **pulmonary thromboembolism** in postmenopausal women.

GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

10 Additional safety information from other sources

10.1 Estrogens

The data on estrogen-only hormone replacement (used in women after hysterectomy) are contradictory.(236)

10.1.1 Contraindications

- Pregnancy.
- Unexplained vaginal bleeding.
- Mammary carcinoma or other hormone-dependent tumours, or history thereof.
- Presence, history or high risk (e.g. family history) of arterial or venous thromboembolism.
- Hepatic insufficiency, acute liver disease.(236)

10.1.2 Adverse events

Whether adverse effects of natural and synthetic oestrogens differ, and whether the dosage route has an effect, is less clear. (237)

- Gastrointestinal disorders, weight gain, mastodynia, premenstrual syndrome, fluid retention, chloasma and rash, lower limb cramps.
- Changes in libido, headache, migraine, dizziness, mood disorders and depression.
- Endometrial hyperplasia
- Spotting, dysmenorrhoea, vaginal candidiasis.
- Glucose intolerance.(236)
- Changes in blood lipids(237), cholestatic jaundice.(236)
- Current use of HRT for the menopause is associated with an increased risk of venous thromboembolism and breast cancer. (237)
 - Deep vein thrombosis, probably less frequent with transdermal administration. Observational studies suggest a lower risk of deep vein thrombosis with estrogens administered transdermally, but randomised studies are needed to confirm this.(236)
 - Increased risk of endometrial cancer in women with a uterus(237), especially when no progestin is combined with the estrogen(236), regardless of the route of administration. (237)
 - Conflicting data concerning the increased risk of breast cancer with estrogen alone.(236)
- Although high doses of oestrogen have been associated with an increase in blood pressure, the use of menopausal hormone therapy in normotensive and hypertensive women has little effect on blood pressure or may be associated with a slight decrease. (237)
- Transdermal and vaginal administration:
 - Local irritation, allergic reactions.(236)
 - Possibility of serious hypersensitivity reactions in the event of continuous exposure.
 - Transdermal patches in which the estradiol is dissolved in the adhesive matrix may cause fewer skin reactions than those which release estradiol from an alcohol reservoir. (237)

- The use of vaginal estrogens has not been associated with any increased risk of cancer(238).

10.1.3 Interactions

- As oral oestrogens are likely to decrease the concentration of free thyroxine, it may be necessary to increase the dose of levothyroxine. Thyroid function should therefore be monitored when starting or stopping treatment with oral estrogens.(236)
- Estrogens are substrates of CYP3A4 and inhibitors of CYP1A2.(236)

Drugs that increase the hepatic metabolism of oestrogens and progestogens have been associated with failure of the combined oral contraceptive. Important examples include rifamycins and some antiepileptics. It is not unreasonable to assume that these drugs would also be associated with decreased efficacy of HRT, but there appears to be little information on this. (237)

- Although oral contraceptives alter the effects of many drugs, the lower doses of oestrogens used in HRT are considered less likely to induce interactions, although the possibility remains. (237)

10.1.4 Special precautions

- Before menopausal HRT is given the woman should undergo an appropriate medical examination and her medical history should be carefully evaluated. Regular examination is recommended during use. (237)
- Prolonged treatment with systemically administered estrogens as a single agent leads to endometrial hyperplasia and an increased risk of endometrial carcinoma. In order to reduce this risk, a progestin is systematically combined when the uterus is in place. The progestin must be taken for at least 12 consecutive days a month, but it can also be taken continuously at a lower dose. Progestin should not be combined with oestrogen in hysterectomised women.(236)
- HRT should be used with caution in women with antiphospholipid antibodies or predisposing factors to thromboembolism and in gallbladder disease, migraine, a history of breast nodules or fibrocystic disease, uterine fibroids, or a history of endometriosis. HRT should also be used with caution in women with diabetes because of the increased risk of heart disease. (237)
- Given the increased risk of venous thromboembolism, estrogen treatment should preferably be stopped one month before scheduled surgery or in the event of immobilisation.(236)
- HRT should be stopped immediately, and appropriate investigations and treatment carried out, if any of the following occur:
 - sudden severe chest pain, sudden breathlessness, or severe pain/swelling in calf of one leg (possibly indicative of thromboembolic complications)
 - unusual, severe, prolonged headache, sudden disturbances of vision or hearing or other perceptual disorders, collapse, marked numbness or weakness affecting one side of the body, or other signs or symptoms suggestive of cerebrovascular accident

- a first unexplained epileptic seizure
- hepatitis, jaundice, generalised itching, liver enlargement, severe upper abdominal pain
- significant rise in blood pressure (above 160 mmHg systolic or 95 mmHg diastolic) (237)
- Beware of accidental exposure of children to spray or gel. Cases of (reversible) breast development and precocious sexual development (precocious puberty in girls and gynaecomastia in boys) (237) have been reported in children who have been exposed to an estrogen-containing spray or gel, for example after coming into contact with the skin to which the spray or gel has been applied. If accidental contact has occurred, the exposed area should be rinsed as soon as possible with soap and water.(236)
- Oestrogens have been reported to interfere with some diagnostic tests such as those for thyroid function and glucose tolerance.
- Doses of oestrogen in HRT are insufficient to provide contraception. (237)

10.2 Estrogen-progestogen associations

See also “estrogens”.

Use of oestrogen without a progestogen results in endometrial hyperplasia and an increased risk of endometrial carcinoma. The addition of a progestogen for 10 to 14 days of a 28-day cycle reduces this risk but results in regular withdrawal bleeding towards the end of the progestogen. Use of continuous progestogen and oestrogen avoids withdrawal bleeding, but may result in irregular breakthrough bleeding, particularly in the early stages of therapy, or if used within 12 months of the last menstrual period. (237)

The combination with a progestogen reduces the risk of endometrial hyperplasia and carcinoma, but does not completely rule them out.(236)

10.2.1 Contraindications

- Hepatic impairment, acute liver disease.
- Estradiol + drospirenone: severe renal insufficiency.(236)
- Progesterone and the progestogens should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history of thrombophlebitis, thromboembolism, or cerebral haemorrhage, and should generally be avoided in hepatic impairment, especially if severe. Unless progestogens are being used as part of the management of breast or genital-tract carcinoma they should not be given to patients with these conditions. (237)

10.2.2 Adverse events

- Progestogens probably play a role in the slightly increased long-term risk of breast carcinoma associated with estrogen-progestin combinations.(236)

It remains unclear whether hormone replacement therapy (HRT) for the menopause increases the risk of breast cancer. Non-randomised studies on this subject generally show that both estrogen-progestin replacement therapy and estrogen-alone replacement therapy

are associated with an increased risk of breast cancer (although the increase in risk is less pronounced with estrogen-alone)(239).

Long-term HRT (oral or transdermal), especially when it lasts 5 years or more, leads to a slight increase in cases of invasive breast cancer. The risk increases with the duration of treatment. Although the risk decreases after treatment is stopped, it persists for more than 10 years after it is discontinued(240).

Short-term HRT (oral or transdermal) does not increase the risk of cancer(238).

- The results of randomised studies of primary and secondary cardiovascular prevention have generally shown an increased incidence of stroke and venous thromboembolism. As far as coronary pathology is concerned, the data seem reassuring.(236)
- Most of the data comes from retrospective studies and often no distinction is made between the different routes of administration and the different types (including high or low estrogen content).(236)
- Adverse effects vary depending on the dose and type of progestogen. For example, androgenic effects such as acne and hirsutism are more likely to occur with nortestosterone derivatives such as norethisterone and norgestrel. These derivatives may also be more likely to adversely affect serum lipids. Conversely, adverse effects on serum lipids appear less likely with gestodene and desogestrel, but these 2 drugs have been associated with a higher incidence of thromboembolism than norethisterone and norgestrel when used in combined oral contraceptives. (237)
- Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely. Alterations in the serum lipid profile may occur, and rarely alterations in liver-function tests and jaundice. (237)
- Reversible increase in blood pressure, dyslipidaemia, glucose intolerance.
- Disturbances of certain thyroid function tests and of the hypothalamic-pituitary-adrenal axis, without clinical consequences.(236)
- Cholestasis, jaundice, benign liver tumours. Rare: malignant hepatic tumours. (236)
- Breakthrough uterine bleeding is more common with oral progestogen-only contraceptives than when progestogens are used for menstrual irregularities or as part of menopausal HRT. (237)
- There is no evidence that the risk of thromboembolism is lower with natural progesterone than with synthetic progestins(241).
- Transdermal routes of administration: also local reactions.(236)

10.2.3 Interactions

- Progestogens are CYP3A4 substrates. CYP3A4 inducers may reduce the efficacy of estrogen-progestogen combinations (oral, transdermal and vaginal) and cause metrorrhagia (spotting).(236)
- Enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, and rifampicin may enhance the clearance of progesterone and the progestogens.
- Aminoglutethimide markedly reduces the plasma concentrations of medroxyprogesterone acetate and megestrol, possibly through a hepatic enzyme-inducing effect; an increase in progestogen dose is likely to be required.
- Progestogens may inhibit ciclosporin metabolism leading to increased plasma-ciclosporin concentrations and a risk of toxicity. (237)

10.2.4 Special precautions

- The recommendation not to prolong treatment any longer than is necessary to treat menopausal complaints remains valid for most women.(236)
- Progesterone and the progestogens should be used with caution in patients with hypertension, cardiac or renal impairment, asthma, epilepsy, and migraine, or other conditions which may be aggravated by fluid retention. Progestogens can decrease glucose tolerance and diabetic patients should be carefully monitored. They should also be used with care in persons with a history of depression. High doses should be used with caution in patients susceptible to thromboembolism.
- Since progesterone and other progestogens can influence diabetic control an adjustment in antidiabetic dosage could be required. (237)

10.3 Association of bazedoxifene + conjugated estrogen

10.3.1 Bazedoxifene

The addition of bazedoxifene to conjugated estrogens reduces the risk of estrogen-induced endometrial hyperplasia in women for whom progestins are not appropriate.(236)

10.3.1.1 Contraindications

- Venous thromboembolism.
- Severe renal insufficiency; hepatic insufficiency. (236)

10.3.1.2 Adverse events

- Hot flushes, flu-like symptoms, headache, gastrointestinal symptoms: frequent.
- Calf cramps, malleolar oedema.
- Venous thromboembolism and stroke; hypertension. (236)
- Somnolence
- Dry mouth.

- Increases in blood triglycerides and liver enzymes values may also occur commonly.
- As for raloxifene:
 - Raloxifene is associated with an increased risk of venous thromboembolic events including deep-vein thrombosis, pulmonary embolism, and retinal vein thrombosis, particularly during the first 4 months of treatment.
 - Rashes, thrombocytopenia, headache including migraine, and mild breast symptoms such as pain, enlargement, and tenderness have occurred very rarely. (237)

10.3.1.3 Special precautions

- Same as raloxifene:
 - Raloxifene should be avoided in women with active venous thromboembolism, or a history of thromboembolic disorders.
 - It should be stopped at least 72 hours before periods of prolonged immobilisation, such as post-surgical recovery.
 - Raloxifene should be used with caution in women with risk factors for venous thromboembolism including congestive heart failure or active malignancy, or risk factors for stroke such as transient ischaemic attack or atrial fibrillation.
 - It should be avoided in hepatic and severe renal impairment, and used with caution in moderate renal impairment
 - It should not be given to women with undiagnosed uterine bleeding. (237)

10.3.2 Conjugated estrogens

- Same as for oestrogens in general (237)

10.4 Tibolone

Tibolone is a synthetic 19-nor-steroid with progestogenic, estrogenic and androgenic properties.

Data on the long-term safety of tibolone are limited compared with those of estrogen-progestin combinations.. (236)

10.4.1 Contraindications

Estrogen-dependent tumours (endometrial carcinoma, breast carcinoma) (236) and untreated endometrial hyperplasia.

- Tibolone is contra-indicated in women with breast cancer or oestrogen-dependent tumours, cardiovascular or cerebrovascular disorders including arterial or venous thromboembolism, or a history of these conditions. (237)
- Unexplained vaginal bleeding.
- Liver failure, acute liver disease. (236)
- Tibolone should not be given to pregnant or breast-feeding women and is not intended for use in premenopausal women, except those being treated with a gonadorelin analogue. (237)

10.4.2 Adverse events

- Spotting(236) mainly during the first few months of treatment; unlike cyclical, but similar to continuous, combination HR, tibolone does not produce regular withdrawal bleeding. (237)
- Leucorrhoea, vaginal candidiasis(236), pruritus and vaginitis. (237)
- Headache, dizziness, gastrointestinal disorders, rash, weight gain, hypertrichosis(236), breast pain, oedema, visual disturbances, altered liver function, depression, and arthralgia or myalgia. (237)
- Thromboembolism.
- Increased risk of breast cancer (especially an increased risk of recurrence) and endometrial carcinoma. (236)

10.4.3 Interactions

- Reinforces the effect of vitamin K antagonists. (236)
- Compounds that induce liver enzymes, such as phenytoin, carbamazepine, and rifampicin, might theoretically enhance the metabolism of tibolone and thus reduce its activity. (237)

10.4.4 Special precautions

Care should be taken when giving tibolone to patients with uterine fibroids, endometriosis, liver disease, gallstones, disorders that may be exacerbated by fluid retention such as cardiac or renal dysfunction, hypertension, epilepsy, or migraine, or with a history of these conditions. It should also be given with caution to patients with dyslipidaemia or diabetes mellitus. Patients with risk factors

for thromboembolic disorders or oestrogen-dependent tumours, or a history of endometrial hyperplasia, should be closely monitored. Tibolone should be stopped if there are signs of thromboembolism, a significant increase in blood pressure, new onset of migraine-type headache, or if abnormal liver function tests or cholestatic jaundice occur. Consideration should be given to stopping tibolone 4 to 6 weeks before elective surgery when prolonged immobilisation after surgery is likely. (237)

10.5 Levonorgestrel IUD

10.5.1 Contraindications

- **Pregnancy.**
- **Gynaecological infections, abnormalities or tumours, unexplained vaginal bleeding.**
- **Breast cancer or history thereof; liver failure, liver tumors and acute liver disease.**(236)

10.5.2 Adverse events

- Vasovagal reaction during insertion.
- Local complications in the weeks following insertion, such as expulsion, infection and, rarely, perforation.
- Increased risk of ectopic pregnancy in case of IUD pregnancy.
- Marked reduction or cessation of menstrual periods (amenorrhea in up to 30% of users), irregular cycles, prolonged blood loss and spotting (especially during the first three cycles), ovarian cysts (sometimes symptomatic).
- Systemic hormonal effects (including depressive mood, headaches, acne, weight gain and mastodynia).(236)

10.5.3 Interactions

- The contraceptive efficacy of the levonorgestrel IUD is not altered by drug interactions.(236)

10.5.4 Special precautions

- Chlamydia and gonococcal screening should be performed in women at risk of sexually transmitted infection (STI), especially < 25 years, history of STI, multiple partners.
- Inform women about symptoms of infection or ectopic pregnancy.
- If ischemic cardiovascular disease develops while using a levonorgestrel IUD, it is best to remove it.
- Use of menstrual cups and tampons does not appear to be associated with an increased risk of expulsion.(236)

10.6 Vaginal Prasterone (DHEA)

Prasterone, or dehydroepiandrosterone (DHEA), is a natural steroid that is a precursor of the male sex hormone (testosterone) and, to a lesser extent, the female sex hormone (estradiol). (236)

10.6.1 Contraindications

- Prasterone has the same contraindications as the estrogens used in the menopause(242).
- Liver failure, acute liver disorders. (236)

10.6.2 Adverse events

- Data on the long-term safety of prasterone are limited. (236)
- The most frequent side effects are leucorrhoea, urinary tract infection, cervical dysplasia, weight loss or weight gain(242).
- Other less frequent side effects are acne, erythema, hypertrichosis, headache, hypertension (242).
- Given the levels of DHEA detectable in the blood, systemic androgenic and estrogenic effects (e.g. increased risk of breast and ovarian cancer, thromboembolic risk) cannot be ruled out (242).

10.6.3 Special precautions

- The benefit/risk ratio should be reassessed at least once every six months. (236)

10.7 Phytotherapy (*Cimicifuga racemosa*, black cohosh)

Dry extract of *Cimicifuga racemosa* (syn. Cohosh) is proposed for the treatment of menopausal complaints. Its mechanism of action is unknown. Given the limited evidence of efficacy and potential adverse effects, the risk/benefit ratio of this product is unfavourable. (236)

10.7.1 Contraindications

- Liver failure. (236)

10.7.2 Adverse events

- Hepatotoxicity, sometimes severe.
- Skin reactions. (236)
- It has been reported that *cimicifuga* may cause dizziness, vertigo, headache, vomiting, and gastrointestinal irritation when taken in large doses. (237)
- The European Medicines Agency (EMA) has reported a risk of serious liver damage, allergic reactions and gastrointestinal disorders(243).
- As of March 2006, the UK MHRA² had received 21 reports of hepatotoxicity associated with *cimicifuga* ingestion since 1998, which represented more than two-thirds of the total number of reports for any reaction related to *cimicifuga*. Likewise, there have been similar reports of hepatotoxicity in other countries including the USA, Germany, and Sweden.

Adverse liver reactions reported worldwide have included abnormal liver function tests, jaundice, hepatitis, and liver failure. In general, patients showed signs of recovery on stopping ingestion.

Some regulatory authorities consider that the available evidence supports a rare association between *cimicifuga* and risk of liver toxicity, even though the level of risk is difficult to determine. They have recommended that warnings regarding potential adverse liver reactions should be added to product information and consumers are advised to stop taking *cimicifuga* if they develop symptoms of liver damage; also, patients who have previously had liver or other serious health problems should consult their doctor before starting to take *cimicifuga*. (237)

10.7.3 Interactions

- Some authors have expressed concern that herbs such as dong quai (which has been used to relieve hot flushes after chemotherapy for breast cancer), *agnus castus*, *cimicifuga*, ginseng, and *lupulus* have shown significant oestrogenic activity in studies in animals and in vitro, and might interfere with competitive oestrogen receptor antagonists such as tamoxifen.(237)

11 Appendix. Evidence tables. Hormone therapy for the treatment of menopausal symptoms

11.1 Estrogen vs placebo for vasomotor symptoms, QoL, psychological well-being, depressive symptoms, urogenital atrophy, dyspareunia

Meta-analysis: SR Grant 2015 (AHRQ)(1)

Inclusion criteria:

Population: Women experiencing symptoms accompanying natural menopause (during perimenopausal or postmenopausal periods) or surgically induced menopause (during the postmenopausal period).; trials enrolling women with pre-existing conditions were excluded; primary care and community settings

Interventions:

Hormone therapies including estrogen therapy and estrogen/progestogen (or estrogen/androgen) therapy administered by oral, transdermal, nasal, or vaginal route; combined estrogen-progestogen and progesterone-only contraceptives; compounded menopausal hormone therapy, often referred to as “bioidentical hormones; **Nonhormone prescription therapies** including SSRI/SNRIs, eszopiclone, clonidine, methyldopa, and gabapentin; **Nonprescription therapies** including isoflavones, red clover, black cohosh, St. John’s wort, ginseng, flax seed, vitamin E, dong quai, and DHEA

Comparison: placebo or direct comparison between therapies

Outcomes: Vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, sexual function, quality of life

Study type: RCTs with 25 or more participants per arm and a followup of at least 12 weeks.

Search strategy: MEDLINE®, Embase®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine were searched up until January 2014.

Assessment of quality of included trials: yes, applying the criteria of the USPSTF; GRADE scoring of the body of evidence

Other methodological remarks: Network meta-analysis was performed; we reported only the direct comparisons

Remarks:

Author's conclusions: "Women experiencing symptoms of menopause can consider a number of potential treatments of varying efficacy. From a large body of evidence, there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. For other common symptoms—psychological, urogenital, and sleep disturbance—although estrogens are effective, some nonhormonal agents compare favorably. Estrogens are accompanied by potential long-term harms that require consideration. There is limited evidence on the potential consequences of long-term use of nonhormonal agents when those agents are used to treat menopausal symptoms."

Ref	Comparison	N/n	Outcomes	Result
SR Grant 2015 (AHRQ)(1) Design: SR + MA Search date: (January 2014)	Estrogen (high dose) vs placebo	N= 9 n= 1399 (Martin 1971, Campbell 1977, Baumgardner 1978, Good 1996, de Vrijer 1999, Studd 1999, Speroff 2003, Utian 2004, Speroff study 1 2006)	Vasomotor symptoms	SMD -0.50 (95%CI -0.61 to -0.39) SS in favour of estrogens Tau ² = 0

	Estrogen (standard dose) vs placebo	N= 39 n= 9316 (Martin 1971, Baumgardner 1978, Wiklund 1993, Derman 1995, Good 1996, Chung 1996, Bacchi-Modena 1997, Bech 1998, de Vrijer 1999, Studd 1999, Polo-Kantola 1999, Speroff (Study 1) 2000, Rovati 2000, Strickler 2000, Notelovitz 2000, von Holst 2000, Notelovitz 2000, Speroff (Study 2) 2000, Utian (CEE alone arms) 2001, Simon 2001, Utian (CEE/MPA arms) 2001, Rozenbaum 2002, von Holst 2002, Vestergaard 2003, Berlex (SIP) 2003, Yang 2004, Utian 2004, Newton 2006, Speroff (Study 1) 2006, Nielsen 2006, Endrikat 2007, Veerus 2008, Welton 2008, Utian 2009, Baksu 2009, Hassa 2010, Bachmann 2010, Liu 2012, Pinkerton 2013)	Vasomotor symptoms	SMD -0.64 (95%CI -0.74 to -0.53) SS in favour of estrogens Tau²= 0.0818

	Estrogen (low/ultralow dose) vs placebo	N= 53 n= 11694 (Baumgardner 1978, Coope 1981, Speroff (Study 1) 1996, Speroff (Study 2) 1996, Speroff (Study 3) 1996, Baerug 1998, Studd 1999, Cohen 1999, Rebar 2000, Speroff (Study 1) 2000, Rovati 2000, Notelovitz 2000, Notelovitz 2000, DeAloysio 2000, Speroff (Study 2) 2000, Utian (CEE alone arms) 2001, Utian (CEE/MPA arms) 2001, Rozenbaum 2002, Shulman (Study 1) 2002, Archer 2003, Gambacciani 2003, Gelfand 2003, Schurmann 2004, Crisafulli 2004, Utian 2004, Duramed (SIP) 2004, Bayer Healthcare (SIP) 2005, Novartis (SIP) 2005, Simon 2006, Nielsen 2006, Speroff (Study 2) 2006, Bachmann (d) 2007, Lee 2007, Panay 2007, Simon 2007, Bayer Healthcare (SIP) 2007, Buster (Study 1) 2008, Buster (Study 2) 2008, Buster (Study 3) 2008, Utian 2009, Haines 2009, Hedrick 2009, Gast 2009, Stevenson 2010, Bachmann 2010, Liu 2011, Lin 2011, Liu 2012, Archer 2012a, Archer 2012b, Polisseni 2013, Archer 2013, Pinkerton 2013)	Vasomotor symptoms	SMD -0.55 (95%CI -0.61 to -0.48) SS in favour of estrogens Tau ² = 0.0344

SR Grant 2015 (AHRQ)(1) Design: SR + MA Search date: ()	Estrogen (standard dose) vs placebo	N= 26 n= 31263 (Wiklund 1993, Derman 1995, Saletu 1995, Chung 1996, Bacchi-Modena 1997, Bech 1998, de Vrijer 1999, Studd 1999, Rovati 2000, Strickler 2000, von Holst 2000, Alexandersen 2000, Rigano 2001, Rozenbaum 2002, von Holst 2002, Jirapinyo 2003, Haines 2003, Hays 2003, Yang 2004, Brunner 2005, Welton 2008, Utian 2009, Baksu 2009, Hassa 2010, Bachmann 2010, Pinkerton 2013)	Quality of life	SMD 0.55 (95%CI 0.41 to 0.69) SS in favour of estrogen $\text{Tau}^2 = 0.0954$
	Estrogen (high dose) vs placebo	N= 5 n= 789 (Jensen 1983, de Vrijer 1999, Studd 1999, Soares 2001, Speroff 2003)	Quality of life	SMD 0.76 (95%CI 0.48 to 1.03) SS in favour of estrogen $\text{Tau}^2 = 0.0148$
	Estrogen (low/ultralow dose) vs placebo	N= 17 n= 3507 (Baerug 1998, Studd 1999, Rebar 2000, Rovati 2000, DeAloysio 2000, Alexandersen 2000, Rozenbaum 2002, Haines 2003, Gelfand 2003, Panay 2007, Simon 2007, Utian 2009, Stevenson 2010, Bachmann 2010, Polisseni 2013, Pinkerton 2013)	Quality of life	SMD 0.36 (95%CI 0.27 to 0.45) SS in favour of estrogen $\text{Tau}^2 = 0.0628$

	Estrogen vs placebo	N= 14 n= 3386 (Wiklund 1993, Derman 1995, Baerug 1998, Rozenbaum 2002, Speroff 2003, Haines 2003, Gelfand 2003, Yang 2004, Nielsen 2006, Simon 2007, Utian 2009, Bachmann 2010, Demetrio 2011, Pinkerton 2013)	Global psychological well-being	SMD -0.26 (95%CI -0.40 to -0.13) SS in favour of estrogen Tau² = 0.0395
	Estrogen vs placebo	N= 18 n= 3386 (Campbell 1977, Coope 1981, Wiklund 1993, Derman 1995, Saletu 1995, Bech 1998, Polo-Kantola 1999, Soares 2001, Speroff 2003, Gambacciani 2003, Rudolph 2004, Yang 2004, Onalan 2005, Pefanco 2007, Baksu 2009, Hassa 2010, Demetrio 2011, Polisseni 2013)	Depressive symptoms	SMD -0.36 (95%CI -0.53 to -0.20) SS in favour of estrogen Tau² = 0.0734
	Vaginal estrogens vs placebo	N= 12 n= 3419 (Foidart 1991, Eriksen 1992, Casper 1999, Speroff 2003, Simunic 2003, Parsons 2003, Bachmann 2008, Bachmann (Study 1) 2009, Freedman 2009, Bachmann (Study 2) 2009, Raghunandan 2010, Cano 2012)	Urogenital atrophy	SMD -0.64 (95%CI -1.03 to -0.26) SS in favour of vaginal estrogen Tau² = 0.1056

	nonvaginal estrogens (standard dose) vs placebo	N= 6 n= 3600 (Chung 1996, Bech 1998, von Holst 2000, Rozenbaum 2002, Vestergaard 2003, Welton 2008)	Urogenital atrophy	SMD -0.32 (95%CI -0.47 to -0.18) SS in favour of estrogen $\text{Tau}^2 = 0.0159$
	nonvaginal estrogens (low/ultralow dose) vs placebo	N= 8 n= 1541 (Rozenbaum 2002, Schurmann 2004, Lee 2007, Simon 2007, Simon (SIP) 2008, Haines 2009, Bachmann (d) 2009, Lin 2011)	Urogenital atrophy	SMD -0.41 (95%CI -0.53 to -0.30) SS in favour of estrogens $\text{Tau}^2 = 0.0016$
	Vaginal estrogens vs placebo	N= 10 n= 3205 (Eriksen 1992, Casper 1999, Speroff 2003, Simunic 2003, Parsons 2003, Dessole 2004, Bachmann (Study 1) 2009, Freedman 2009, Bachmann (Study 2) 2009, Cano 2012)	Pain during sex	SMD -0.54 (95%CI -0.73 to -0.34) SS in favour of vaginal estrogens $\text{Tau}^2 = 0.0726$

	oral estrogens vs placebo	N= 4 n= 1661 (Campbell 1977, Vestergaard 2003, Simon (SIP) 2008, Gast 2009)	Pain during sex	SMD -0.22 (95%CI -0.35 to -0.09) SS in favour of oral estrogens Tau ² = 0.0063
	all estrogens vs placebo	N= 14 n= 4866 (Campbell 1977, Eriksen 1992, Casper 1999, Vestergaard 2003, Speroff 2003, Simunic 2003, Parsons 2003, Dessole 2004, Simon (SIP) 2008, Bachmann (Study 1) 2009, Freedman 2009, Gast 2009, Bachmann (Study 2) 2009, Cano 2012)	Pain during sex	SMD -0.45 (95%CI -0.61 to -0.29) SS in favour of estrogens Tau ² = 0.0699

* Characteristics of included studies: see below

Ref + design	year	n (analyzed)	Population	Duration (weeks)	Comparison	Methodology Risk of bias overall score (as assessed by Grant et al. 2015) ** for details of study quality assessment: see table below
Martin 1971	1971	165	56% intact uterus	12	0.025 mg E + 1 mg P Oral mestranol + norethindrone Standard Vs 0.05 mg E + 1 mg P Oral mestranol + norethindrone High Vs PLA	Poor
Campbell 1977	1977	136		52	1.25 mg Oral conjugated equine estrogens high Vs PLA	Poor
Baumgardner 1978	1978	156	63% intact uterus	24	0.1 mg Oral quinestrol (low) vs 0.2 mg Oral quinestrol(high) vs 1.25 mg Oral conjugated estrogen (high) Vs PLA	Poor

Coope 1981	1981	55	Mean age: 48.3 65.5% intact uterus	26	0.3mg Oral piperazine estrone sulphate (ultralow) Vs PLA	Poor
Jensen 1983	1983	131	Mean age: 49.2 Age range: 44 to 54 Years since menopause: 1.9	104	4 mg E + 1 mg P Oral estradiol + estriol + norethisterone acetate (high) Vs PLA	Poor
Foidart 1991	1991	109	Mean age: 54.4 Age range: 32 to 66 52.3% intact uterus	26	1 mg VagPes estriol (low) vs PLA	Poor
Eriksen 1992	1992	154	Mean age: 58.4	12	0.025 mg VagTab estradiol (low) Vs PLA	Poor
Wiklund 1993	1993	223	Mean age: 52.6 100% intact uterus Years since menopause:3.1	12	0.05 mg Patch estradiol (standard) Vs PLA	Poor
Derman 1995	1995	82		16	2 mg E + 1 mg P Oral estradiol + norethindrone acetate (standard) vs PLA	Poor
Saletu 1995	1995	64	Mean age: 51.2 71.9% intact uterus	12	0.05 mg Patch estradiol (standard) Vs PLA	Poor
Chung 1996	1996	83	Mean age: 43.8 0% intact uterus	26	2mg Oral estradiol (standard) Vs PLA	Poor

			Years since menopause:0.6			
Good 1996	1996	273	Mean age: 50.9 43.6% intact uterus	12	0.05 mg Patch estradiol (standard) Vs PLA	Poor
Speroff (Study 1) 1996	1996	108	Mean age: 51.6 0% intact uterus	12	0.02 mg Patch estradiol (ultralow) Vs PLA	Poor
Speroff (Study 2) 1996	1996	111	0% intact uterus	12	0.02 mg Patch estradiol (ultralow) Vs pla	Poor
Speroff (Study 3) 1996	1996	106	0% intact uterus	12	0.04 mg Patch estradiol (low) Vs PLA	Poor
Bacchi-Modena 1997	1997	109	Mean age: 51.9 Age range: 39 to 61 100% intact uterus Years since menopause:2.7	12	0.05 mg Patch estradiol (standard) Vs PLA	Poor
Baerug 1998	1998	119	Mean age: 51.3 Age range: 45 to 61 Years since menopause: 2.5	12	1mg E + 0.25mg P Oral estradiol + norethisterone acetate (low) Vs 1mg E + 0.5mg P Oral estradiol + norethisterone acetate (low) Vs PLA	Poor
Bech 1998	1998	151		52	3 mg E + 1 mg P Oral estradiol + norethisterone acetate (standard)	Poor

					vs 2 mg E + 1 mg P Oral estradiol + norethisterone acetate (standard) Vs PLA	
Casper 1999	1999	67	Unknown% intact uterus, mixed	24	0.0075 mg VayRin estradiol (low) Vs PLA	Poor
Cohen 1999	1999	259	Mean age: 50.0 81.5% intact uterus	12	0.0375mg Patch estradiol (low) Vs PLA	Poor
de Vrijer 1999	1999	254	Mean age: 52.0 Age range: 40 to 64 65% intact uterus Years since menopause: 4.4	12	0.05 mg Patch estradiol (standard) Vs 0.10 mg Patch estradiol (high) Vs PLA	Poor
Polo-Kantola 1999	1999	62	Mean age: 56.4 Age range: 47 to 65 0% intact uterus	12	SknGel estradiol (standard) Vs PLA	Poor
Studd 1999	1999	355	Mean age: 52.2 Years since menopause: 2.5	12	0.1mg E + 5mg P NasSpr estradiol + medroxyprogesterone acetate (low) Vs 0.2mg E + 5mg P NasSpr estradiol + medroxyprogesterone acetate (low) vs 0.3mg E + 5mg P NasSpr estradiol + medroxyprogesterone acetate (standard)	Poor

					vs 0.4mg E + 5mg P NasSpr estradiol + medroxyprogesterone acetate (high) vs PLA	
Alexandersen 2000	2000	200	Mean age: 59.2 Years since menopause: 9.3	104	0.75mg E + 0.35mg P Oral piperazine estrone sulphate + norethisterone (low) Vs seq 1.5mg E + 0.7mg P Oral piperazine estrone sulphate + norethisterone (standard) Vs 2mg E + 1mg P Oral estradiol + norethisterone acetate (standard)	Poor
DeAloysis 2000	2000	156	Mean age: 53.3 94.9% intact uterus Years since menopause: 1.1	12	0.025 mg Patch estradiol (ultralow) Vs PLA	Poor
Notelovitz 2000	2000	a) 145 b) 333 c) 219	a) Mean age: 49.5 30% intact uterus Years since menopause: 5.9 b) Mean age: 51.1 100% intact uterus	A,b,c 12	a) 1 mg Oral estradiol (low) Vs 0.5 mg Oral estradiol (ultralow) Vs PLA	a) Poor b) Poor c) Poor

			Years since menopause: 2.9 c) Mean age: 53.3 100% intact uterus Years since menopause: 5.2		b) 0.25 mg Oral estradiol (ultralow) Vs 0.5 mg Oral estradiol (ultralow) Vs 1.0mg Oral estradiol (low) Vs 2.0 mg Oral estradiol (standard) Vs PLA c) 0.050mg + 0.140mg Patch estradiol+ estradiol/norethindrone acetate (standard) Vs 0.050mg E + 0.250mg P Patch estradiol+ estradiol/norethindrone acetate (standard) Vs 0.050mg E + 0.400mg P Patch estradiol+ estradiol/norethindrone acetate (standard) Vs PLA	
Rebar 2000	2000	204	Mean age: 51.2 67.6% intact uterus	104	0.3 mg Oral esterified estrogen (low) Vs PLA	Poor
Rovati 2000	2000	311	Mean age: 53.0	12	0.025 mg Patch estradiol (ultralow)	Fair

			71.1% intact uterus Years since menopause: 3.5		Vs 0.05 mg Patch estradiol (standard) Vs 0.05 mg Patch estradiol (standard) Vs PLA	
Speroff (Study 1) 2000	2000	219	Mean age: 51.6 100% intact uterus Years since menopause: 2.0	16	0.001 mg EE + 0.2 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (ultralow) Vs 0.0025 mg EE + 0.5 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (low) Vs 0.005 mg EE + 1 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (low) Vs 0.010 mg EE + 1 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (standard)	Poor
Speroff (Study 2) 2000	2000	266	Mean age: 51.0 100% intact uterus Years since menopause: 2.1	12	0.0025 mg EE + 0.5 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (low) vs	Poor

					0.005 mg EE + 1 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (low) Vs 0.010 mg EE + 1 mg NA Oral ethinyl estradiol (EE) + norethindrone acetate (NA) (standard) Vs PLA	
Strickler 2000	2000	201	Mean age: 54.7 Years since menopause: 4.5	52	0.625 mg Oral conjugated equine estrogens (standard) Vs PLA	Poor
von Holst 2000	2000	186	Mean age: 53.5 0% intact uterus	12	0.05 mg Patch estradiol (standard) Vs PLA	Fair
Rigano 2001	2001	362	100% intact uterus	16	0.05 mg Patch estradiol (standard) Vs PLA	Poor
Simon 2001	2001	120	Mean age: 48.6 Age range: 38 to 66	12	0.625 mg Oral synthetic conjugated estrogen-A (standard) Vs PLA	Fair
Soares 2001	2001	50	Mean age: 49.8	12	0.1 mg Patch estradiol (high) vs PLA	Poor

Utian (CEE alone arms) 2001	2001	117	Mean age: 52.0 100% intact uterus Years since menopause: 4.2	52	0.3mg Oral conjugated equine estrogen (ultralow) Vs 0.45mg Oral conjugated equine estrogen (low) Vs 0.625mg Oral conjugated equine estrogen (standard) Vs PLA	Poor
Utian (CEE/MPA arms) 2001	2001	152	Mean age: 52.5 100% intact uterus Years since menopause: 4.2	52	0.3mg Oral conjugated equine estrogen (ultralow) + 1.5 mg medroxyprogesterone acetate Vs 0.45mg Oral conjugated equine estrogen (low) + 1.5 mg medroxyprogesterone acetate Vs 0.45mg Oral conjugated equine estrogen (low) + 2.5 mg medroxyprogesterone	Poor

					acetate vs 0.625mg Oral conjugated equine estrogen (standard) + 2.5 mg medroxyprogesterone acetate Vs PLA	
Rozenbaum 2002	2002	165	Mean age: 52.4 77.6% intact uterus Years since menopause: 3.4	12	0.15 mg NasSpr estradiol (low) Vs 0.30 mg NasSpr estradiol (standard) Vs PLA	Poor
Shulman (Study 1) 2002	2002	293	Mean age: 52.0 Age range: 43 to 68 Unknown% intact uterus	12	0.045 mg E + 0.030 mg P Patch estradiol + levonorgestrel (low) Vs 0.045 mg E + 0.040 mg P Patch estradiol + levonorgestrel (low) Vs PLA	Fair
von Holst 2002	2002	172	Mean age: 53.3 100% intact uterus	12	0.05 mg E + 0.01 mg P Patch estradiol + levonorgestrel (standard)	Poor

					Vs PLA	
Berlex (SIP) 2003	2003	180		12	0.045 mg E + 0.03 mg P Patch Estradiol + Levonorgestrel (standard) Vs PLA	Poor
Archer 2003	2003	221	Mean age: 50.9 76.9% intact uterus Years since menopause: 10.2	12	0.75 mg SknGel estradiol (low) Vs 1.5 mg SknGel estradiol (low) Vs PLA	Poor
Gambacciani 2003	2003	50	Mean age: 54.3 Years since menopause: 4.6	12	1mg E + 0.5 mg P Oral estradiol + norethisterone (low) vs PLA	Poor
Gelfand 2003	2003	119	Mean age: 52.6 100% intact uterus Years since menopause: 2.7	12	1 mg E + 0.09 mg P Oral estradiol + norgestimate (low) Vs PLA	Fair
Haines 2003	2003	152	0% intact uterus	52	1 mg Oral estradiol (low) Vs 2 mg Oral estradiol (standard) Vs	Fair

					PLA	
Hays 2003	2003	16608	Mean age: 63.2 100% intact uterus	52	0.625mg E + 2.5mg P Oral conjugated equine estrogen + medroxyprogesterone acetate (standard) Vs PLA	Good
Jirapinyo 2003	2003	120	Mean age: 54.3 100% intact uterus	52	2 mg E + 1 mg P Oral estradiol + norethisterone acetate (standard) Vs PLA	Poor
Parsons 2003	2003	94	Mean age: 59.1 100% intact uterus Years since menopause: 9.3	13	0.625 mg VagCr m conjugated estrogen (standard) Vs PLA	Poor
Simunic 2003	2003	1612	Mean age: 58.8 100% intact uterus Years since menopause: 9.2	52	0.025mg VagTab estradiol (low) Vs PLA	Poor
Speroff 2003	2003	333	Mean age: 51.7 Age range: 29 to 85 81% intact uterus	13	0.05 mg VayRin estradiol + progestin (high) Vs 0.10 mg VayRin estradiol + progestin (high) Vs PLA	Fair

Vestergaard 2003	2003	1006	Mean age: 49.8 81% intact uterus Years since menopause: 0.7	260	2 mg E + 1 mg P Oral estradiol + norethisterone acetate (standard) Vs PLA	Poor
Crisafulli 2004	2004	90	Mean age: 51.7 100% intact uterus Years since menopause: 6.7	52	54mg Oral genistein Vs 1mg E + 0.5mg P Oral estradiol + norethisterone acetate (low) Vs PLA	Poor
Dessole 2004	2004	88	Mean age: 57.0 Years since menopause: 7.2	26	1mg VagOv u estriol (low) Vs PLA	Poor
Duramed (SIP) 2004	2004	104		12	0.45mg Oral synthetic conjugated estrogens (ow) Vs PLA	Poor
Rudolph 2004	2004	129	Mean age: 56.1 Unknown% intact uterus, mixed Years since menopause: 9.7	24	2mg E + 2mg P Oral estradiol valerate + dienogest (high) Vs PLA	Poor
Schurmann 2004	2004	225	Mean age: 53.6 100% intact uterus	16	1mg E + 1mg P Oral estradiol + drospirenone (low) Vs	Poor

					1mg E + 2mg P Oral estradiol + drospirenone (low) Vs 1mg E + 3mg P Oral estradiol + drospirenone (low) Vs pla	
Utian 2004	2004	281	Mean age: 51.1 Age range: 26 to 64 Unknown% intact uterus, mixed Years since menopause: 4.1	12	0.3mg Oral synthetic conjugated estrogen (ultralow) Vs 0.625mg Oral synthetic conjugated estrogen (standard) Vs 1.25mg Oral synthetic conjugated estrogen (high) Vs PLA	Poor
Yang 2004	2004	51	Mean age: 53.2 100% intact uterus	24	0.625mg E + 2.5mg P Oral conjugated estrogen + medroxyprogesterone acetate (standard) Vs PLA	Poor
Bayer Healthcare (SIP) 2005	2005	351			0.50 mg E + 0.25 mg P Oral estradiol + drospirenone (low) Vs	Poor

					PLA	
Brunner 2005	2005	10739	Mean age: 63.6 0% intact uterus	52	0.625 mg Oral conjugated equine estrogens (standard) Vs PLA	Poor
Novartis (SIP) 2005	2005	160		12	0.05 mg E + 0.14 mg P Patch estradiol + norethindrone acetate (low) Vs 0.05 mg E + 0.25 mg P Patch estradiol + norethindrone acetate (low) Vs PLA	Poor
Onalan 2005	2005	210	Mean age: 52.1 100% intact uterus Years since menopause: 4.4	52	0.625 mg E + 2.5 mg P Oral conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) (standard) Vs 0.625 mg E + 5.0 mg P Oral conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) (standard) Vs PLA (calcium)	Poor
Newton 2006	2006	351	Mean age: 52.2 89% intact uterus	52	EP comb 0.625 mg E + 2.5 mg P Oral conjugated equine estrogen + medroxyprogesterone (standard)	Good

					Vs Black cohosh Vs PLA	
Nielsen 2006	2006	335	Mean age: 52.7 94.3% intact uterus Years since menopause: 2.2	104	0.15 mg E + 200mg P NasSpr estradiol (S21400) + progesterone (low) Vs 0.30 mg E + 200 mg P NasSpr estradiol (S21400) + progesterone (standard) Vs PLA	Poor
Simon 2006	2006	200	Mean age: 51.9 50.5% intact uterus	12	2.5 mg/1g of cream SknCr m estradiol (low) Vs PLA	Poor
Speroff (Study 1) 2006	2006	289	Mean age: 53.4 Age range: 41 to 68 57% intact uterus	12	0.9 mg Oral estradiol acetate (standard) Vs 1.8 mg Oral estradiol acetate (high) Vs PLA	Good
Speroff (Study 2) 2006	2006	221	Mean age: 52.2 Age range: 36 to 80 41% intact uterus	12	0.45 mg Oral estradiol acetate (low) Vs	Fair

					PLA	
Bachmann (d) 2007	2007	425	Mean age: 52.7 Age range: 40 to 71 42.4% intact uterus Years since menopause: 9.1	12	0.014 mg Patch estradiol (ultralow) Vs 0.023 mg E + 0.0075 mg P Patch estradiol + levonorgestrel (ultralow) Vs PLA	Good
Bayer Healthcare (SIP) 2007	2007	165		12	0.025 mg Patch estradiol (ultralow) Vs PLA	Poor
Endrikat 2007	2007	324	Mean age: 56.2 Age range: 40 to 68 67% intact uterus Years since menopause: 4.6	12	1mg E + 2mg P Oral estradiol valerate + dienogest (standard) Vs PLA	Poor
Lee 2007	2007	72	Mean age: 52.0 Unknown% intact uterus, mixed	16	1mg E + 2 mg P Oral estradiol + drospirenone (low) Vs PLA	Poor
Panay 2007	2007	575	Mean age: 55.5 Age range: 44 to 65 100% intact uterus	24	0.5 mg E + 0.1 mg P Oral estradiol + norethisterone acetate (ultralow) Vs 0.5 mg E + 0.25 mg P Oral estradiol + norethisterone acetate (ultralow) Vs PLA	Poor

Pefanco 2007	2007	57	Mean age: 75.6 68.4 % intact uterus	156	0.25mg + 100mg P Oral estradiol + progesterone (ultralow) Vs PLA	Poor
Simon 2007	2007	484	Mean age: 54.4 Unknown% intact uterus, mixed Years since menopause: 8.7	12	0.52 mg SknGel estradiol (low) Vs 1.02 mg SknGel estradiol (low) Vs 1.56 mg SknGel estradio (low) Vs PLA	Poor
Bachmann 2008	2008	230	Mean age: 57.9 Age range: 46 to 79 52.6% intact uterus Years since menopause: 14.0	12	0.01mg VagTab estradiol (low) vs 0.025 mg VagTab estradiol (low) Vs PLA	Good
Buster (Study 1) 2008	2008	151	Mean age: 52.2 Age range: 38 to 69 61.7% intact uterus	12	4.59 mg SknSpr estradiol (low) Vs PLA	Poor
Buster (Study 2) 2008	2008	150	Mean age: 52.1 Age range: 37 to 76 61.7% intact uterus	12	3.06 mg SknSpr estradiol (low) Vs PLA	Poor
Buster (Study 3) 2008	2008	153	Mean age: 53.1 Age range: 36 to 71 61.7% intact uterus	12	1.53 mg SknSpr estradiol (low) Vs	Poor

					PLA	
Simon (SIP) 2008	2008	248	Mean age: 58.7 58.1% intact uterus Years since menopause: 13.0	12	0.3mg Oral synthetic conjugated estrogens (low) Vs PLA	Poor
Veerus 2008	2008	796		187	0.625 mg + 2.5 mg Oral combined estrogens + medroxyprogesterone acetate (standard) Vs PLA	Poor
Welton 2008	2008	2130	Unknown% intact uterus, mixed	52	0.625 E + 2.5/5.0 P Oral conjugated equine estrogen + medroxyprogesterone acetate (standard) Vs PLA	Good
Bachmann (d) 2009	2009	121	Mean age: 53.0 Age range: 40 to 68 44.6% intact uterus Years since menopause: 9.8	12	0.014 mg Patch estradiol (ultralow) Vs 0.023mg E + 0.0075mg P Patch estradiol + levonorgestrel (ultralow) Vs PLA	Poor
Bachmann (Study 1) 2009	2009	215	Mean age: 57.8 100% intact uterus Years since menopause: 9.2	12	0.3mg VagCr m conjugated estrogen (ultralow) Vs PLA	Poor

Bachmann (Study 2) 2009	2009	208	Mean age: 57.8 100% intact uterus Years since menopause: 5.3	12	0.3mg VagCr m conjugated estrogen (low) vs PLA	Poor
Baksu 2009	2009	132	Mean age: 50.1 0% intact uterus	52	0.625 mg Oral conjugated estrogen (standard) Vs 0.3 mg NasSpr estradiol hemihidrate (standard) Vs 1.5 mg SknGel estradiol hemihidrate (standard) Vs PLA	Poor
Freedman 2009	2009	275	Mean age: 59.9 62.6% intact uterus Years since menopause: 13.0	12	0.625mg Oral conjugated estrogen (standard) Vs 0.3mg NasSpr estradiol hemihidrate (standard) Vs 1.5mg SknGel estradiol hemihidrate (standard)	Poor

					Vs PLA	
Gast 2009	2009	285	Mean age: 54.5 Age range: 42 to 68 Years since menopause: 5.2	24	0.45 mg E + 1.5 mg MPA oral + 0.625 mg cream Oral conjugated estrogen + medroxyprogesterone acetate (low) vs PLA	Poor
Haines 2009	2009	160	Mean age: 52.4 62.5% intact uterus Years since menopause: 5.1	12	0.014 mg Patch estradiol (ultralow) Vs PLA	Poor
Hedrick 2009	2009	495	Mean age: 54.5 47% intact uterus	12	0.25mg SknGel estradiol (low) Vs 0.5mg SknGel estradiol (low) vs 1.0mg SknGel estradiol (low) Vs PLA	Poor
Utian 2009	2009	318	Mean age: 53.4 100% intact uterus Years since menopause: 4.5	12	0.45 E + 20 BZA Oral conjugated equine estrogens + bazedoxifene (low) Vs 0.625 E + 20 BZA Oral conjugated equine estrogen + bazedoxifene (standard)	Fair

					Vs PLA	
Bachmann 2010	2010	542	Mean age: 56.3 100% intact uterus Years since menopause: 7.4	12	0.45 E + 20 BZA Oral conjugated equine estrogen + bazedoxifene (low) Vs 0.625 E + 20 BZA Oral conjugated equine estrogen + bazedoxifene (standard) Vs PLA	Fair
Hassa 2010	2010	247	Mean age: 50.2 0% intact uterus	26	0.625 mg Oral conjugated equine estrogen (standard) Vs 0.56 mg Patch estradiol (standard) Vs PLA	Poor
Raghunandan 2010	2010	75	Mean age: 51.7 Unknown % intact uterus, mixed Years since menopause: 7.0	12	0.625 mg VagCr m conjugated equine estrogen (standard) Vs 0.625 mg E + 2% T VagCr m conjugated equine estrogen + testosterone (standard) Vs PLA	Poor

Stevenson 2010	2010	313	Mean age: 53.7 Age range: 45 to 66 100% intact uterus Years since menopause: 5.5	13	0.5 mg E + 2.5 mg D Oral estradiol and dydrogesterone (ultralow) Vs 1mg E + 5 mg D Oral estradiol and dydrogesterone (low) Vs PLA	Poor
Demetrio 2011	2011	66	Mean age: 50.4 Age range: 45 to 56 0% intact uterus Years since menopause: 3.7	24	0.625 mg Oral conjugated equine estrogen (standard) Vs PLA	Poor
Lin 2011	2011	244	Mean age: 52.0 100% intact uterus Years since menopause: 2.8	16	1mg E + 2 mg P Oral estradiol + drospirenone (low) Vs PLA	Poor
Liu 2011	2011	1029	Unknown% intact uterus, mixed	12	0.30 mg Oral esterified estrogen (low) Vs 0.30 mg E + 0.30 mg MT Oral esterified estrogen + methyltestosterone (low) Vs 0.30 mg E + 0.60 mg MT Oral esterified estrogen + methyltestosterone (low)	Poor

					Vs 0.45 mg EE Oral esterified estrogen (low) Vs 0.60 mg Oral methyltestosterone vs PLA	
Archer 2012	2012	a) 351 b) 344	Mean age: 53.7 65.4% intact uterus Years since menopause: 8.5	12	0.27 mg SknGel Estradiol (low) Vs 0.375 mg SknGel Estradiol (low) Vs PLA	a) Poor b) Fair
Cano 2012	2012	167	Mean age: 56.7 86.2% intact uterus Years since menopause: 9.9	12	0.05 VagGel estriol (ultralow) Vs PLA	Fair
Liu 2012	2012	157	Mean age: 54.1 Age range: 33 to 66 Unknown% intact uterus, mixed	12	0.3mg Oral synthetic conjugated estrogen-B (ultralow) Vs 0.625mg Oral synthetic conjugated estrogen-B (standard) Vs PLA	Poor
Archer 2013	2013	710	Mean age: 53.5 45.6% intact uterus Years since menopause: 9.4	12	0.5 E + 0.25 P Oral estradiol + drospirenone (ultralow) Vs	Fair

					0.5 E + 0.5 P Oral estradiol + drospirenone (ultralow) Vs 0.3mg Oral estradiol (ultralow) Vs PLA	
Pinkerton 2013	2013	410	Mean age: 53.5 100% intact uterus Years since menopause: 3.6	52	0.45 E + 20 BZA Oral conjugated equine estrogen + bazedoxifene (low) Vs 0.625 E + 20 BZA Oral conjugated equine estrogen + bazedoxifene (standard) Vs 0.45 E + 1.5 P Oral conjugated equine estrogen + medroxyprogesterone acetate (low) Vs PLA	Fair
Polisseni 2013	2013	88	Mean age: 53.1 100% intact uterus Years since menopause: 4.7	12	1mg E + 0.5 P Oral estradiol + NETA (low) Vs PLA	Poor

**

Details from the risk of bias assessment (as assessed by Grant et al. 2015)

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Overall: Overall Quality Assessment

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Martin 1971	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor
Campbell 1977	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Baumgardner 1978	Unc	Yes	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Poor
Coope 1981	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Jensen 1983	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Foidart 1991	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Eriksen 1992	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor

Wiklund 1993	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Derman 1995	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Saletu 1995	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	No	Poor
Good 1996	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Speroff (Study 1) 1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Poor
Chung 1996	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor
Speroff (Study 2) 1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Speroff (Study 3) 1996	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Poor
Bacchi - Modena 1997	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Baerug 1998	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Bech 1998	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
De Vrijer 1999	Unc	Unc	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Studd 1999	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Polo -Kantola 1999	Yes	Yes	Yes	Yes	No	Unc	Yes	Yes	No	Poor
Casper 1999	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Cohen 1999	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Rebar 2000	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Speroff (Study 1) 2000	Unc	Yes	Unc	Unc	No	Unc	Yes	Yes	No	Poor
Rovati 2000	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Notelovitz 2000	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Strickler 2000	Yes	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Notelovitz 2000	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
DeAloysio 2000	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor

Von Holst 2000	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Notelovitz 2000a	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Notelovitz 2000b	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Notelovitz 2000c	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Alexandersen 2000	Unc	No	Yes	No	Yes	Unc	Yes	Yes	Yes	Poor
Speroff (Study 2) 2000	Unc	Yes	Unc	Unc	No	Unc	Yes	Yes	Yes	Poor
Rigano 2001	No	Unc	Unc	Unc	Unc	Unc	Unc	Yes	Unc	Poor
Utian (CEE alone arms) 2001	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Utian (CEE/MPA arms) 2001	Yes	yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Simon 2001	Unc	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Soares 2001	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Rozenbaum 2002	Yes	Unc	Unc	Yes	No	Unc	Yes	Yes	Yes	Poor
Shulman (Study 1) 2002	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Fair
Von Holst 2002	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Berlex (SIP) 2003	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Archer 2003	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Vestergaard 2003	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Poor
Speroff 2003	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Fair

Jirapinyo 2003	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Haines 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Hays 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Gambacciani 2003	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Gelfand 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Simunic 2003	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Parsons 2003	Yes	No	Yes	Yes	No	No	Yes	Yes	Unc	Poor
Rudolph 2004	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Yang 2004	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Schurmann 2004	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Utian 2004	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Dessole 2004	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Duramed (SIP) 2004	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Crisafulli 2004	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Brunner 2005	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Onalan 2005	Yes	Yes	Unc	Yes	Yes	Unc	Yes	Yes	Unc	Poor
Bayer Healthcare (SIP) 2005	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Novartis (SIP) 2005	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Speroff (Study 1) 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Simon 2006	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Nielsen 2006	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Speroff (Study 2) 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Newton 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good

Bachmann (d) 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Endrikat 2007	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Lee 2007	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	No	Poor
Panay 2007	No	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Simon 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Pefanco 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Unc	Yes	Poor
Bayer Healthcare (SIP) 2007	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Buster (Study 1) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Veerus 2008	Unc	No	No	Unc	Unc	No	Yes	Yes	Yes	Poor
Bachmann 2008	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Good
Welton 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Buster (Study 2) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Buster (Study 3) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Simon (SIP) 2008	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Utian 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Haines 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Bachmann (d) 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Hedrick 2009	Unc	Yes	Unc	Yes	No	No	Yes	Yes	Yes	Poor
Baksu 2009	Yes	No	No	Unc	No	No	Yes	Yes	Unc	Poor
Bachmann (Study 1) 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Freedman 2009	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor

Gast 2009	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Bachmann (Study 2) 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Hassa 2010	Unc	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Stevenson 2010	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Bachmann 2010	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Raghunandan 2010	Unc	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Unc	Poor
Liu 2011	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Lin 2011	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Demetrio 2011	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Liu 2012	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Archer 2012a	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Archer 2012b	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Cano 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Polisseni 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Archer 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Pinkerton 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair

Estrogen vs control in perimenopausal women with depression

Estrogen vs control in postmenopausal women with depression

Meta-analysis: Zhang 2023(90)

Inclusion criteria:

Population: women older than 18 years and **with depression scores exceeding the normal range;**

Exclusion: major organic disease or psychiatric disorders other than major depressive disorder

Interventions: exogenous estrogen, including agonists of the estrogen receptor versus placebo

Outcomes: depressive mood scores (well-established assessment scales)

Study type: RCTs

Search strategy: Databases of PubMed (including MEDLINE), Embase, Web of Science, Google Scholar, Cochrane library, PsychINFO and CINAHL (EBSCO platform) were searched up until October 2022.

Assessment of quality of included trials: yes, using the revised cochrane risk-of-bias tool, version 2 (ROB 2.0)

Other methodological remarks:

Remarks: for this literature report, only the subanalyses for perimenopausal and postmenopausal women were reported.

Author's conclusions: "To sum up, exogenous estrogens were superior to the control group either alone or in combination with progesterone or antidepressants, but whether Tibolone can enhance the effect of antidepressants remains to be seen. Women in perimenopause are more sensitive to estrogen than those in other reproductive statuses, which might be because depression during this period is more associated with estrogen fluctuations, and exogenous estrogen supplementation can mitigate these drastic changes."

transdermal estradiol plus intermittent micronized progesterone (TE+IMP) versus placebo in the prevention of depressive symptom onset among perimenopausal and early postmenopausal women

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 172		Efficacy	RANDO:

Gordon 2018(89)	Mean age: 51 years	0.1 mg 17β-estradiol patch + oral micronized progesterone (200 mg/d for 12 days) every 2 to 3 months	incidence of clinically significant depressive symptoms (PO)	OR: 2.5 (95% CI 1.1 to 5.7) SS in favour of TE+IMP	Unclear “randomly assigned” ALLOCATION CONC: Inadequate; the active and placebo patches were not identical BLINDING : Participants: yes Personnel: unclear (described as “double blind” without further information) Assessors: unclear(described as “double blind” without further information) FOLLOW-UP: Lost-to follow-up: 1.7% Drop-out and Exclusions: 19.8% (placebo) and 26.7% (TE+IMP) • Described: yes; 7 nonserious adverse events placebo vs 14 nonserious adverse events TE+IMP • Balanced across groups: no ITT: Yes (no defined by authors)
Design:	Uterine status: not reported; women without a uterus but with at least one ovary retained were included in the study		(CES-D score of at least 16)	(Greater incidence of clinically significant depressive symptoms with placebo)	
RCT DB, PG		Reproductive stage:	Vs		
Duration of follow-up:	Early perimenopausal: 21% TE+IMP; 21% PLA	Placebo patch			
12 months	Late perimenopausal: 59% TE+IMP; 56% PLA	+ identical schedule of placebo pills	Safety		
			Adverse effects	“adverse effects were reported more commonly by participants assigned to TE+IMP”	
	Early postmenopausal: 20% TE-IMP; 23% PLA		Severe adverse effects	PLA: 2 cases of major depression TE+IMP: 1 case of acute vein thrombosis	
	<u>Inclusion</u> euthymic perimenopausal and early postmenopausal women from the community, aged 45 to 60 years		Spotting	64% vs 34%; P < .01 SS in favour of placebo More spotting with TE+IMP	
			Mild or moderate bleeding	80% vs 44%; P < .01 SS in favour of placebo More mild to moderate bleeding with TE+IMP	

	<u>Exclusion</u> current major depressive disorder or a trauma- or stressrelated disorder with severity greater than mild, a history of severe substance use within the past 10 years, a history of suicide attempts, bipolar or other psychotic disorders		Heavy bleeding	37% vs. 13%; P < .01) SS in favour of placebo More heavy bleeding with TE+IMP	SELECTIVE REPORTING: yes; limited quantitative reporting of primary outcome and adverse events
			Prolonged bleeding	15% vs 1%;P < .01 SS in favour of placebo More prolonged bleeding with TE+IMP	
					Sponsor: : This research was supported by National Institutes of Health grants

Remarks:

For women with an intact uterus, reproductive stage, assessed at enrollment, was defined as follows:

early perimenopause, defined as menstrual cycle length at least 7 days longer than usual; late perimenopause, defined as at least 2 skipped cycles and an interval of amenorrhea of at least 60 days but within 1 year of the last menstrual period; and early postmenopause, defined as an interval of amenorrhea between 1 and 2 years.

11.2 Estrogen vs placebo in perimenopausal women with depression

Ref	Comparison	N/n	Outcomes	Result
Zhang 2023(90) Design: SR + MA Search date: (october 2022)	Estrogen versus placebo	N= 5 n= 177 (Schmidt 2000, De Novaes Soares 2001, Morgan 2005, Kulkarni 2018, Schmidt 2021)	Depressive mood	Std. Mean Difference -1.18 (-1.16 to -0.75) SS in favour of estrogen $I^2 = 38\%$

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Risk of bias as assessed by Zhang 2023

De Novaes Soares 2001	50	Perimenopause; Menstrual cycle irregularity or amenorrhea for less than 12 months.	12 weeks	Transdermal estrogen patch of 17 β -estradiol 100mcg/d Vs PLA	RCT does not meet our inclusion criteria (sample size) Risk of bias overall assessed as: low risk
Kulkarni 2018	44	Perimenopause: Menstrual cycle irregularity or amenorrhea for less than 12 months.	12 weeks	Tibolone 2.5 mg/d + Antidepressants Vs Antidepressants +placebo	RCT does not meet our inclusion criteria (sample size) Risk of bias overall assessed as: low risk
Morgan 2005	17	Perimenopause: Menstrual cycle irregularity or amenorrhea for less than 12 months.	6 weeks	Conjugated estrogen 0.625 mg/d + Antidepressants Vs Antidepressants + Placebo	RCT does not meet our inclusion criteria (sample size, duration) Risk of bias overall assessed as: low risk
Schmidt 2000	31	Perimenopause: Menstrual cycle irregularity of at least 6 months' duration but with ≤ 1 year of amenorrhea.	24	Transdermal estrogen patch of 17 β -estradiol 200 mcg/d Vs Placebo	RCT does not meet our inclusion criteria (sample size) Risk of bias overall assessed as: some concerns (deviation from the intended intervention)
Schmidt 2021	35	Perimenopause: Menopausal transition as determined by standardized classification guidelines for female reproductive aging were proposed at	8	Transdermal estrogen patch of 17 β -estradiol 100 mcg/d Vs	RCT does not meet our inclusion criteria (sample size, duration) Risk of bias overall assessed as: low risk

		the Stages of Reproductive (STRAW) (equal to perimenopause).		placebo	

11.3 Estrogen vs placebo in postmenopausal women with depression

Ref	Comparison	N/n	Outcomes	Result
Zhang 2023(90) Design: SR + MA Search date: (october 2022)	Estrogen versus placebo	N= 5 n= 360 (Berlana 2003, Morrison 2004, Rudolph 2004, Rasgon 2007, Karsidag 2012)	Depressive mood	Std. Mean Difference -0.40 (-0.92 to 0.11) NS I ² = 78%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Risk of bias as assessed by Zhang 2023
Berlanga 2003	31	Post-menopause: Amenorrhea at least 12 months	8 weeks	Tibolone 2.5 mg/d + Antidepressants Vs Antidepressants +placebo	RCT does not meet our inclusion criteria (sample size, duration) Risk of bias overall assessed as: some concerns (randomization process)
Karsidag 2012	121	post-menopause: Amenorrhea at least 12 months	12 weeks	Estradiol 1mg/d and norethisterone acetate Vs Placebo	Risk of bias overall assessed as: high risk (deviation from the intended interventions)
Morrison 2004	57	Post-menopause: Amenorrhea at least 12 months	8 weeks	Transdermal estrogen patch of 17 β -estradiol 100 mcg/d Vs placebo	RCT does not meet our inclusion criteria (sample size, duration) Risk of bias overall assessed as: low risk
Rasgon 2007	22	Post-menopause: Amenorrhea at least 12 months	10 weeks	Antidepressants + Transdermal estrogen patch of 17 β -estradiol 100 μ g/d Vs Antidepressants + placebo	RCT does not meet our inclusion criteria (sample size, duration) Risk of bias overall assessed as: some concerns (randomization process, deviation from intended intervention, selection of the reported result)
Rudolph 2004	129	Post-menopause: Amenorrhea at least 12 months	24 weeks	Combination of estradiol valerate 2 mg/d and dienogest	Risk of bias overall assessed as: low risk

				Vs placebo	

11.4 Estrogen versus control for sexual function

Meta-analysis: Meziou 2023(113)

Inclusion criteria:

Population: perimenopausal and postmenopausal women.

Perimenopausal women were defined as women who had their last menstrual period (LMP) within the last 12 months before inclusion. Postmenopausal women were defined as women with menopause induced by a medical intervention or with natural menopause defined as 12 consecutive months of spontaneous amenorrhea.

Interventions: estrogen therapy, estrogen plus progestogen therapy, tibolone, and SERM

Control: placebo or no intervention

Outcomes: The primary outcome: sexual function composite score. Secondary outcomes: desire, arousal, lubrication, orgasm, pain, and sexual satisfaction. Only outcomes measured and scored by validated questionnaires were included.

Study type: RCTs

Search strategy: Cochrane Natri 2013 was used as a source document. Cochrane Natri searched **up until December 2012**. Meziou 2023 searched Cochrane Central Register of Controlled Trials, EMBASE, Medical Literature Analysis and Retrieval System Online, PsycINFO, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Literatura Latino-Americana e do Caribe em Ciências da Saúde, Database of Abstracts of Reviews of Effects, ClinicalTrials.gov, International Clinical Trials Registry Platform, Iranian Registry of Clinical Trials, Chinese Clinical Trial Registry, ISRCTN from **December 2012 to March 2022**.

Assessment of quality of included trials: yes, using ROB.2 tool by the Cochrane Collaboration

Other methodological remarks: the analysis was stratified by participant characteristics with regard to menopausal symptoms: the 'symptomatic or early post-menopausal' group and an 'unselected postmenopausal women' group.

Remarks:

Author's conclusions: “: Hormone therapy may slightly improve sexual functioning. This potential small benefit should be considered when discussing treatment options for other menopausal symptoms.”

Ref	Comparison	N/n	Outcomes	Result

Meziou 2023(113) Design: SR + MA Search date: (march 2022)	Estrogen versus control	N= 16 n= 2925 (Bumphenkiatikul 2020, Cruz 2015, Haines 2009, Hirschberg 2020, Lillemon 2022, Mac Bride 2014, MsFLASH VHT, MsFLASH VMS, REJOICE, Speroff 2003, Sun 2016, Verghese 2020, Wiklund 1993, Dayal 2005, Simon 2007, Strickler 2000)	Sexual function composite score	Std. Mean Difference 0.16 (0.02 to 0.29) SS in favour of estrogen therapy $I^2 = 59\%$

	Systemic estrogen therapy vs control	N= 6 n= 1095 (Haines 2009, MsFLASH VMS, Wiklund 1993, Dayal 2005, Simon 2007, Strickler 2000)	Sexual function composite score	Std. Mean Difference 0.21 (0.02 to 0.41) SS in favour of estrogen therapy $I^2 = 56\%$

	Vaginal estrogen therapy vs control	N= 10 n= 1830 (Bumphenkiatikul 2020, Cruz 2015, Hirschberg 2020, Lillemon 2022, Mac Bride 2014, MsFLASH VHT, REJOICE, Speroff 2003, Sun 2016, Verghese 2020,)	Sexual function composite score	Std. Mean Difference 0.12 (-0.07 to 0.31) NS $I^2 = 63\%$

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Risk of bias as assessed by Meziou 2023 Or by Nastri 2013*
Bumphenkiatikul 2020	67	Postmenopausal GSM and female sexual dysfunction	12 weeks	CE vaginal tablet 0.625 mg 1x/day for 3 weeks, then 2x/week for 9 weeks	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: low

				Vs placebo	MISSING OUTCOME DATE: some concerns MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS : some concerns
Cruz 2015	30	Postmenopausal GSM	20 weeks	E2 vaginal cream 1 mg 3x/week for 20 weeks Vs placebo	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: high MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Dayal 2005	10	Perimenopausal and postmenopausal	3 months	CEE 0.625 mg daily Vs placebo	* RANDOMISATION: Unclear risk (not described) ALLOCATION CONCEALMENT: Low risk BLINDING of participants and personnel: Unclear risk (not described) BLINDING of outcome assessment: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: High risk (difference in baseline values between intervention

					and control for sexual function and QoL)
Haines 2009	151	Perimenopausal and postmenopausal	12 weeks	TD patch delivering micro-dose E2 (0.014 mg/day) Vs placebo	* RANDOMISATION: Unclear risk (centrally provided computer-generated list) ALLOCATION CONCEALMENT: Unclear risk (not described) BLINDING of participants and personnel: low risk BLINDING of outcome assessment: Unclear risk (not described) INCOMPLETE OUTCOME DATA: high risk (only those who completed study were assessed) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Hirschberg 2020	61	Perimenopausal and postmenopausal Hormone receptor positive early breast cancer treated with aromatase inhibitors for at least 6 mo and severe to moderate vaginal dryness at baseline	12 weeks	E3 vaginal gel (1 g (=50 mg of E3) once daily for 3 wk, then 1 g (=50 mg of E3) twice weekly for 9 wk) Vs placebo	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: high MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Lillemon 2022	39	Postmenopausal	12 weeks	E2 vaginal ring (2mg) Vs placebo	RANDOMISATION: some concerns DEVIATION FROM INTENDED INTERVENTION: some concerns MISSING OUTCOME DATE: some concerns

					MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Mac Bride 2014	56	Postmenopausal GSM	12 weeks	E2 vaginal cream (0.5 g (=10 µg of E2) once daily for 2 wk, then twice weekly for 10 wk) Vs E3 vaginal cream (0.5 g (=10 µg of E3) once daily for 2 wk, then twice weekly for 10 wk) Vs placebo	RANDOMISATION: some concerns DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: some concerns MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: high OVERALL RISK OF BIAS: high
MsFLASH VHT	202	Postmenopausal GSM at baseline	12 weeks	E2 vaginal tablet (10 µg once daily for 2 wk, then twice weekly for 10 wk) Vs placebo	RANDOMISATION: low risk DEVIATION FROM INTENDED INTERVENTION: low risk MISSING OUTCOME DATE: high risk MEASUREMENT OF THE OUTCOME: low low risk SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high risk
MsFLASH VMS	243	Perimenopausal or recently menopausal	12 weeks	Oral 17β-E2 (0.5 daily for 8 weeks) Vs placebo	RANDOMISATION: low risk DEVIATION FROM INTENDED INTERVENTION: low risk MISSING OUTCOME DATE: low risk MEASUREMENT OF THE OUTCOME: low low risk SELECTION OF REPORTED RESULTS: low risk

					OVERALL RISK OF BIAS: low risk
REJOICE	764	Postmenopausal GSM with dyspareunia as MBS	12 weeks	17β-E2 vaginal soft-gel capsule (4 µg once daily for 2 wk, then twice a week for 10 wk)) Vs 17β-E2 vaginal soft-gel capsule (10 µg once daily for 2 wk, then twice a week for 10 wk) vs 17β-E2 vaginal soft-gel capsule (25 µg once daily for 2 wk, then twice a week for 10 wk) Vs placebo	RANDOMISATION: some concerns DEVIATION FROM INTENDED INTERVENTION: some concerns MISSING OUTCOME DATE: some concerns MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Simon 2007	279	Postmenopausal Surgical or natural menopause	12 weeks	estradiol gel 0.87 g/d vs estradiol gel 1.7 g/d vs estradiol gel 2.6 g/d	* RANDOMISATION: low risk ALLOCATION CONCEALMENT: unclear risk (study coordinators assigned treatment numbers) BLINDING of participants and personnel: low risk

				vs placebo	BLINDING of outcome assessment: low risk INCOMPLETE OUTCOME DATA: high risk (The assessment of sexual function is only reported for the higher doses - 1.7 g/ d and 2.6g/d. The intervention group of 2.6g/d has discontinued from further enrolment in the middle of the study because of safety issues. The results for sexual function for the lower dose group 'E2 gel 0.87 g/day' is omitted.) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Speroff 2003	230	Postmenopausal women With or without uterus	13 weeks	vaginal ring (estradiol 50 mcg/day) vs vaginal ring (estradiol 100 mcg/day) vs placebo	* RANDOMISATION: low risk ALLOCATION CONCEALMENT: unclear risk (not described) BLINDING of participants and personnel: low risk BLINDING of outcome assessment: unclear risk (not described) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Strickler 2000	189	Postmenopausal	12 months	CEE 0.625 mg/day Vs Raloxifene 60 mg/day Vs Raloxifene 150 mg/day	* RANDOMISATION: low risk ALLOCATION CONCEALMENT: unclear risk (not described) BLINDING of participants and personnel: low risk

				Vs placebo	BLINDING of outcome assessment: unclear risk (not described) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Sun 2016	186	Postmenopausal Women with severe uterine and anterior vaginal wall prolapse at baseline referred for transvaginal pelvic reconstructive surgery with mesh	12 months	Promestriene vaginal cream (0.5 g twice weekly for 6 wk) Vs No intervention	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: some concerns MISSING OUTCOME DATE: high MEASUREMENT OF THE OUTCOME: some concerns SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Vergheze 2020	100	Postmenopausal Women with pelvic organ prolapse at baseline having pelvic organ prolapse surgery without use of vaginal mesh	12 months	E2 vaginal pessaries (10 µg once daily for 2 wk, then twice weekly for 4 wk, then 6 wk with no treatment after surgery, then twice weekly for 20 wk) Vs No intervention	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: some concerns MISSING OUTCOME DATE: high MEASUREMENT OF THE OUTCOME: some concerns SELECTION OF REPORTED RESULTS: low OVERALL RISK OF BIAS: high
Wiklund 1993	223	Postmenopausal women with climacteric symptoms	12 weeks	TD estradiol (50mcg/24 hrs, changed twice a week) Vs	* RANDOMISATION: unclear risk (not described) ALLOCATION CONCEALMENT: unclear risk (not described)

				olacebo	BLINDING of participants and personnel: low risk BLINDING of outcome assessment: low risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: unclear risk (no conflict of interest disclosure)

11.5 Estrogen plus progestogen versus control for sexual function

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Meziou 2023(113) Design: SR + MA Search date: (march 2022)	Estrogen plus progestogen versus control	N= 7 n= 2432 (Davison 2013, KEEPS-Sexual, Nielsen 2006, Olmez 2017, Czarnecka 2000, Osmanagaoglu 2006, WISDOM)	Sexual function composite score	Std. Mean Difference 0.11 (-0.07 to 0.29) NS $I^2 = 65\%$

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Risk of bias as assessed by Meziou 2023 Or by Nastri 2013*
Czarnecka 2000	53	Postmenopausal women	12 weeks	17- β -estradiol and norethisterone acetate Vs No treatment	* RANDOMISATION: unclear risk (not described) ALLOCATION CONCEALMENT: unclear risk (not described) BLINDING of participants and personnel: high risk (open label) BLINDING of outcome assessment: unclear risk (not described) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS: high risk (differences between groups in baseline sexual function)
Davison 2013	23	Recently postmenopausal Healthy postmenopausal women	6 months	E2 and drospirenone oral tablet (1 mg of E2 and 2 mg of drospirenone once daily for 26 wk) Vs placebo	RANDOMISATION: low DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: some concerns MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: some concerns

KEEPS-Sexual	727	Perimenopausal or recently postmenopausal Symptomatic or asymptomatic menopausal women	48 months	CEE oral pill and progesterone oral capsule (0.45 mg of CEE daily and 200 mg of progesterone for 12 d a month) Vs 17β-E2 transdermal patch and progesterone oral capsule (50 µg E2 daily and 200 mg of progesterone for 12 d a month) Vs placebo	RANDOMISATION: some concerns DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: high MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Nielsen 2006	335	Perimenopausal or recently postmenopausal	2 years	intranasal spray estrogen 150mcg/day (women with intact uterus: + micronized progestogen for the last 14 days of each 28-day cycle) vs 300mcg/day (women with intact uterus: + micronized progestogen for the last 14 days of each 28-day cycle) vs placebo	* RANDOMISATION: low risk ALLOCATION CONCEALMENT: low risk BLINDING of participants and personnel: low risk BLINDING of outcome assessment: unclear risk (not described) INCOMPLETE OUTCOME DATA: high risk (only 268/335 women completed) SELECTIVE REPORTING: low risk OTHER BIAS: low risk
Olmez 2017	49	Postmenopausal Cervical cancer survivors with radiotherapy treatment at least 6 mo before enrollment in the trial	6 months	Tibolone (2.5 mg daily) Vs	RANDOMISATION: some concerns DEVIATION FROM INTENDED INTERVENTION: low MISSING OUTCOME DATE: high

				E2 and MPA (0.625 mg of E2 and 5 mg of MPA daily) Vs placebo	MEASUREMENT OF THE OUTCOME: low SELECTION OF REPORTED RESULTS: some concerns OVERALL RISK OF BIAS: high
Osmanagaoglu 2006	104	Postmenopausal women	6 months	Tibolone 2.5 mg Vs Estradiol valerate 2 mg + dienogest 2 mg Vs No intervention	* RANDOMISATION: unclear risk (not described) ALLOCATION CONCEALMENT: unclear risk (not described) BLINDING of participants and personnel: high risk (open label design although the authors claim to be single-blind) BLINDING of outcome assessment: unclear risk (not described) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: OTHER BIAS: high risk (interventions differed in baseline sexual function (tibolone higher score))
WISDOM	1157	Postmenopausal women	1 year	CEE 0.625 mg/day + MPA 2.5/5.0 mg/day Vs placebo	* RANDOMISATION: low risk ALLOCATION CONCEALMENT: low risk BLINDING of participants and personnel: low risk BLINDING of outcome assessment: low risk

					INCOMPLETE OUTCOME DATA: high risk (sexual function evaluated in 54% of participants) SELECTIVE REPORTING: low risk OTHER BIAS: low risk

11.6 Intravaginal DHEA vs placebo in postmenopausal women

Study details	n/Population	Comparison	Outcomes		Methodological
Labrie 2009(135)	n= 218 (n=109 for 0.5% dose vs placebo)	DHEA 0.25% vaginal ovule	Efficacy – as only the 6.5 mg (0.5%) dose is available in Belgium, only the results of this dose versus placebo will be reported		RANDO: unclear
ERC-210	Median age: 58 years	Vs	Change in severity score of most bothersome symptom* (PO)	Placebo: -0.6 ± 0.13 DHEA: -1.5 ± 0.14 P <0.0001 SS in favour of DHEA	ALLOCATION CONC: unclear
Design:	Uterine status: not reported	DHEA 0.5% vaginal ovule (n=56)	*self-reported most bothersome symptom among vaginal dryness, vaginal and/or vulvar itching, and vaginal pain associated with sexual activity		BLINDING : Participants: yes Personnel: yes Assessors: yes
RCT	Time since menopause: not reported	Vs			Drop-out and Exclusions: 2/118 • Described: no • Balanced across groups: yes
DB		DHEA 1.0% vaginal ovule	(severity score 0-3)		
PG	<u>Inclusion</u> Postmenopausal women 40-75 years of		Safety		ITT:

Duration of follow-up: 12 weeks	age with at least moderate to severe vaginal dryness, irritation/itching, or dyspareunia <u>Exclusion</u> Previous diagnosis of cancer, active or history of thromboembolic disease, significant metabolic, endocrine, gastrointestinal, liver or gallbladder disease, ...	Vs Placebo vaginal ovule (n=53)	Drug-related significant adverse event	None observed	No: ITT defined as treated participants with a baseline and at least one postbaseline efficacy assessment. SELECTIVE REPORTING: unclear; not clear whether subgroup analyses were predefined Sponsor: Endoceutics (Dr. Labrie is President and CEO of Endoceutics)

Study details	n/Population	Comparison	Outcomes	Methodological
Archer 2015(136)	n= 255	DHEA 0.25% vaginal ovule	Efficacy – as only the 6.5 mg (0.5%) dose is available in Belgium, only the results of this dose versus placebo will be reported	RANDO: adequate

ERC-231 Design: RCT DB PG Duration of follow-up: 12 weeks	(n=187 in the DHEA 0.5% v placebo group)	(n=86) vs	Severity of dyspareunia (PO)	Placebo: -1.71 ± 0.11 DHEA 0.5%: -1.36 ±0.12	ALLOCATION CONC: adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 13% • Described: yes • Balanced across groups: yes ITT: Modified ITT: ITT defined as all participants who have received at least one dose of study drug with baseline evaluation meeting the entry criteria. SELECTIVE REPORTING: yes; DHEA 0.25% results were not consistently reported Sponsor: EndoCeutics
	Mean age: 58.5 years		(severity score 0-3)	p 0.013 SS in favour of DHEA	
	Uterine status: 61% hysterectomy	DHEA 0.5% vaginal ovule (n=87)			
	Mean time since menopause: 14.5 y	Vs	Safety		
	<u>Inclusion</u> Postmenopausal, nonhysterectomized or hysterectomized women 40-75 years of age who self-identified pain at sexual activity as moderate to severe and as most bothersome vaginal atrophy symptom at baseline	Placebo vaginal ovule (n=80)	Participants with at least one adverse event	Placebo: 35 (43.8%) 0.50% DHEA: 46 (52.9%)	
	<u>Exclusion</u>				

	Previous diagnosis of cancer, active or history of thromboembolic disease, significant metabolic, endocrine, gastrointestinal, liver or gallbladder disease, ...				

Study details	n/Population	Comparison	Outcomes		Methodological
Labrie 2015(137), Labrie 2016(138) ERC-238	n= 558 (482 analyzed) Mean age: 59.5 years Uterine status:	DHEA 0.5% vaginal ovule Vs	Efficacy Severity of pain at sexual activity (dyspareunia) (PO) (severity score 0-3)	Placebo: -1.06 DHEA: -1.42 p 0.0002 SS in favour of DHEA	RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: yes

Design:	38% hysterectomy	Placebo vaginal ovule	Sexual function	Placebo: 6.28 ±0.68	Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 17% • Described: yes • Balanced across groups: yes ITT: No: ITT defined as all women who have received at least one dose of the study drug with a baseline evaluation meeting the study entry criteria (482 analyzed out of 558 randomized) SELECTIVE REPORTING: no Sponsor: EndoCeutics
RCT	Mean time since menopause: 13.9 y		(Change in Female Sexual Function Index total score)	DHEA: 8.85 ±0.45 p 0.0006 SS in favour of DHEA	
DB PG	<u>Inclusion</u> Postmenopausal, nonhysterectomized or hysterectomized women 40-80 years of age Who self-identified pain at sexual activity as moderate to severe and as most bothersome vaginal atrophy symptom at baseline		Safety		
Duration of follow-up: 12 weeks	<u>Exclusion</u> Previous diagnosis of cancer, active or history of thromboembolic disease, significant metabolic, endocrine,		Participants with at least one adverse event	Placebo: 77 (42.8%) DHEA: 179 (47.9%)	

	gastrointestinal, liver or gallbladder disease, ...				

11.7 Different routes of estrogen administration for the treatment of symptoms of menopause

Meta-analysis: SR Grant 2015 (AHRQ)(1)

Inclusion criteria:

Population: Women experiencing symptoms accompanying natural menopause (during perimenopausal or postmenopausal periods) or surgically induced menopause (during the postmenopausal period).; trials enrolling women with pre-existing conditions were excluded; primary care and community settings

Interventions:

Hormone therapies including estrogen therapy and estrogen/progestogen (or estrogen/androgen) therapy administered by oral, transdermal, nasal, or vaginal route; combined estrogen-progestogen and progesterone-only contraceptives; compounded menopausal hormone therapy, often referred to as “bioidentical hormones; **Nonhormone prescription therapies** including SSRI/SNRIs, eszopiclone, clonidine, methyldopa, and gabapentin; **Nonprescription therapies** including isoflavones, red clover, black cohosh, St. John’s wort, ginseng, flax seed, vitamin E, dong quai, and DHEA

Comparison: placebo or direct comparison between therapies

Outcomes: Vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, sexual function, quality of life

Study type: RCTs with 25 or more participants per arm and a followup of at least 12 weeks.

Search strategy: MEDLINE®, Embase®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine were searched up until January 2014.

Assessment of quality of included trials: yes, applying the criteria of the USPSTF; GRADE scoring of the body of evidence

Other methodological remarks: Network meta-analysis was performed; we reported only the direct comparisons

Ref	Comparison	N/n	Outcomes	Result
SR Grant 2015 (AHRQ)(1)	oral vs patch	N=4 Studd 1995 (n=204) Parsey 2000 (n=193) Good 1999 (n=312) Serrano 2006 (n=104)	Vasomotor symptoms	No meta-analysis NS in all RCTs
	oral CEE+ MPA versus estradiol + MPA patch	N= 1 n= 300 (Polvani 1991)	Quality of life	Std. Mean Difference -0.03 (-0.23 to 0.18) NS
	oral CEE+ MPA versus estradiol + MPA patch	N= 1 n= 104 (Serrano 2006)	Global psychological well-being	Std. Mean Difference -0.00 (-0.39 to 0.39) NS

	oral CEE+ MPA versus estradiol + MPA patch	N= 1 n= 104 (Serrano 2006)	Sexual function	Std. Mean Difference 0.35 (-0.04 to 0.74) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Risk of bias overall score (as assessed by Grant et al. 2015) ** for details of study quality assessment: see table below
Good 1999 (139)	312	Mean age 50.4y 45.8% intact uterus	12 weeks	0.625 mg Oral conjugated equine estrogen Premarin (Standard) vs 1.25 mg Oral conjugated equine estrogen Premarin (High) Vs 0.05 mg Patch estradiol Alora (Standard) vs	Poor

				0.1 mg Patch estradiol Alora (High)	
Parsey 2000 (140)	193	Mean age 52.0y 28.5% intact uterus	12 weeks	0.025mg Patch estradiol Climara (UltraLow) Vs 0.3mg Oral conjugated equine estrogen Premarin (UltraLow)	Poor
Polvani 1991(141)	373	100% intact uterus	26 weeks	0.625 mg E + 10 mg P Oral conjugated equine estrogens + medroxyprogesterone acetate (Standard) vs seq 0.05 mg E + 10 mg P Patch estradiol + medroxyprogesterone acetate (Standard)	Poor
Serrano 2006(142)	114	Mean age 52.2y 100% intact uterus Mean years since menopause 1.9	52 weeks	0.625 mg Oral conjugated estrogens + 10 mg medroxyprogesterone acetate (Standard) Vs seq 0.05 mg estradiol + 10 mg medroxyprogesterone acetate Patch (Standard)	Poor
Studd 1995(143)	204	Mean age 52y 99% intact uterus Mean years since menopause 4.4	12 weeks	0.625 mg conjugated estrogen + 20 mg dydrogesteron (Standard)	Poor

				vs seq 0.05 mg Patch estradiol + 20 mg dydrogesterone (Standard)	

**

Details from the risk of bias assessment (as assessed by Grant et al. 2015)

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Overall: Overall Quality Assessment

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Good 1999	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Parsey 2000	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor

Polvani 1991	Unc	No	No	No	Yes	Yes	Yes	Yes	No	Poor
Serrano 2006	Yes	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Studd 1995	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor

11.8 Tibolone versus placebo

Meta-analysis: Formoso 2016: Short-term and long-term effects of tibolone in postmenopausal women

Inclusion criteria:

- Randomised controlled trials (RCTs). We did not include quasirandomised and cross-over trials.
- Menopausal and perimenopausal women with or without vasomotor and/or genital symptoms, defined as women with surgical menopause or with spontaneous menopause, or women who had menstruated irregularly over the past 12 months.
- This review did not consider tibolone use versus no treatment.

Search strategy: We searched the CGF Specialised Register (formerly known as the Menstrual Disorders and Subfertility Group Specialised Register), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from inception until 15 October 2015.

We contacted individual researchers working in relevant fields (gynaecology, endocrinology) and the current manufacturer of tibolone (Merck Sharp & Dome) to check for additional relevant references and unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods.

Assessment of quality of included trials: yes

ITT analysis: yes

Other methodological remarks:

We used a random-effects model, except for vasomotor symptoms, vaginal dryness and sleep, for which we combined data from dichotomous and continuous outcomes in a fixed-effect model by converting all treatment effect estimates to standardised mean differences (SMDs). Pooled SMDs computed in this manner can be transformed and interpreted as odds ratios, at the cost of information related to symptom severity. Poor reporting standards required that we impute standard deviations for several studies reporting on menopausal symptoms to combine their results; we calculated all effect sizes and corresponding standard errors by using the metaphor package in R. If results for this outcome were available at several time points, we used results corresponding to the longest period of use.

Ref	Comparison	N/n	Outcomes	Result
Formoso 2016 Design: MA	Tibolone (all doses) vs Placebo	N= 7 n= 1657 (Landgren 2002, Hudita 2003, Swanson 2006, Benedek-	Vasomotor symptoms (occurrences or through scales, defined as any otherwise unexplained sensation of flushing/sweating experienced by the participant.)	SMD (95% CI): -0.99 (-1.10 to -0.89) SS in favour of tibolone I ² = 96%

October 2015		Jaszmann 1987, Bouchard 2012, Morais-Socorro 2012, Ziaei 2010,		
		N= 3 n= 3348 (Hudita 2003; Kenemans 2009; Ziaei 2010)	Vaginal dryness and painful sexual intercourse (SO)	SMD (95% CI): -0.66[-0.9,-0.43] SS in favour of tibolone $I^2=91\%$
		N= 9 n= 7814 (Berning 2000, Bouchard 2012, Hudita 2003, Kenemans 2009, Kroiss 2005, Langer 2006, Meeuwssen 2002, Wender 2004, Cummings 2008)	Unscheduled bleeding	617/3953 vs 242/3861 31% to 44% vs 18% OR (95 % CI): 2.79 (2.10 to 3.70) SS in favour of placebo $I^2 = 43\%$;
		N = 4 n = 4518 (Cummings 2008, Gallagher 2001, Kroiss	Endometrial hyperplasia	5/2485 vs 2/2033 OR (95% CI): 1..20 (0.23 to 6.25) NS $I^2 = 0\%$

		2005, Swanson 2006)		
		N= 9 n= 8504 (Bouchard 2012,] Cummings 2008, Gallagher 2001, Kenemans 2009, Kroiss 2005, Langer 2006, Swanson 2006, Vieira 2009, Wender 2004)	Endometrial cancer	16/4486 vs 5/4018 OR (95 % CI): 2.04 (0.79 to 5.24) NS $I^2 = 0\%$
		N= 4 n= 5500 (Cummings 2008, Langer 2006, Swanson 2006, Vieira 2009)	Breast cancer	11/2808 vs 23/2692 OR (95 % CI): 0.52 (0.221 to 1.25) NS $I^2 = 17\%$
		N= 5 n= 9176 (Cummings 2008, Gallagher 2001, Kenemans 2009, Langer 2006, Vieira 2009)	Venous thromboembolic events	12/5054 vs 12/ 4122 OR (95%CI): 0.85 (0.37 to 1.97) NS $I^2 = 0\%$

		N= 4 n= 8401 (Cummings 2008,, Jacobsen 2012, Kenemans 2009, Langer 2006)	Cardiovascular events	37/4202 vs 27/4199 OR (95 % CI): 1.38 (0.84 to 2.27) NS $I^2 = 0\%$
		N= 4 n= 7930 (Cummings 2008,, Jacobsen 2012, Kenemans 2009, Kubista 2007)	Cerebrovascular events	35/3967 vs 20/3963 OR (95 % CI): 1.74 (0.99 to 3.04) NS $I^2 = 0\%$
		N = 4 n = 8242 (Kenemans 2009, Langer 2006, Vieira 2009, Cummings 2008)	Mortality	98/4125 vs 93/4117 OR (95% CI): 1.06 (0.79 to 1.41) NS $I^2 = 0\%$

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Benedek-Jaszmán 1987 PG-RCT	60	Healthy postmenopausal women 44 to 61 years old, with hot flushes, who had undergone natural or surgical	1 year	Tibolone 2.5 mg/d Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided

		menopause and were experiencing hot flushes and associated symptoms		Placebo 1 tablet/d	BLINDING: - Participants/personnel: adequate Study authors state that the trial is double-blind and that identical-looking placebo tablets have been used - Assessors: unclear Outcomes evaluated through a questionnaire with insufficient information to judge whether outcome measurement could have been influenced FOLLOW-UP: high risk of attrition bias 17/60 participants dropped out. Unclear how many were randomised to each group SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: Unclear No information provided
Berning 2000 RCT	94	Healthy non-smoking women, 1 to 3 years following spontaneous menopause (mean 22 months), with body mass index < 27 kg/m ² , free of diseases or medication known to influence calcium metabolism or to contraindicate the trial medication. Mean age: 53 years	2 years	Tibolone 2.5 mg/d Vs Tibolone 1.25 mg/d Vs Placebo	ALLOCATION CONC: unclear Method not specified RANDOMIZATION: unclear Unclear what "random medication number" means BLINDING: - Participants/personnel: adequate Although study authors do not state whether trial is double-blind or single-

					blind, they used identical looking interventions and a placebo control - Assessors: adequate Not specified, evaluation is likely to be "objective" FOLLOW-UP: adequate Bleeding: all randomised participants assessed SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Financed by the drug manufacturer. Study authors have conflicts of interest
Bouchard 2012 RCT	485	Postmenopausal women 40 to 65 years of age, seeking treatment for hot flushes, who had completed their last natural menstrual period 12 months before screening (or had a follicle-stimulating hormone (FSH) level 40 mIU/mL). Women had intact uterus, BMI < 34 and minimum of 7 moderate and severe hot flushes per day, or 50 moderate and severe hot flushes per week, recorded for 7 consecutive days during screening. Mean age: 53.6 years	1 year	Tibolone 2.5 mg/d Vs Placebo Vs Desvenlafaxine 100 mg/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: unclear Study authors do not provide information on blinding methods - Assessors: unclear No information provided FOLLOW-UP: unclear risk of attrition bias 2 participants in each of tibolone and placebo groups not assessed for taking study medications for less than 5 days SELECTIVE REPORTING: unclear

					Study protocol not available Conflict of interest: high risk Study sponsored by Wyeth; 4 study authors are former Wyeth or current Pfizer employees
Cumming 2008 RCT	4538	women between 60 and 85 years of age (mean 68) who had bone mineral density T score ≤ -2.5 at the hip or lumbar spine or T score ≤ -2.0 with radiological evidence of vertebral fracture	34 months (median, trial was stopped because increased risk of stroke was identified	Tibolone 1.25 mg/d Vs Placebo All participants received 2 to 4 tablets of calcium + vit D daily	ALLOCATION CONC: adequate Centralised interactive voice response system RANDOMIZATION: adequate Use of an interactive voice response system should keep risk of selection bias very low BLINDING: - Participants/personnel: adequate Placebo-controlled and identical looking interventions - Assessors: adequate Not specified, evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias 32 of 4538 participants not evaluated for not receiving any dose of the interventions under study SELECTIVE REPORTING: low risk Study reported data on outcomes as indicated in the protocol I+ additional data Conflict of interest: high risk

					Financed by the drug manufacturer. Study authors have conflicts of interest
Gallagher 2001	770	Healthy postmenopausal Caucasian or Asian women, mean duration of menopause 2.5 years, without osteoporosis (BMD of lumbar vertebrae within 2 standard deviations of age-matched mean). Mean age: 52.4 years	2 years	Tibolone 0.3 mg/d Vs Tibolone 0.625 mg/d Vs Tibolone 1.25 mg/d Vs Tibolone 2.5 mg/d Vs Placebo All groups also received 500 mg/d of calcium	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No details given on random sequence generation BLINDING: - Participants/personnel: adequate Identical appearing tibolone and placebo tablets - Assessors: adequate Not specified, their evaluation is likely to be "objective" FOLLOW-UP: high risk of attrition bias 85% of randomised participants analysed SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Financed by drug manufacturer, no declaration of conflicts of interest
Hudita 2003 RCT	162	Healthy, non-obese, postmenopausal women (with evidence of m 12 months of amenorrhoea with levels of FSH > 30 mIU/mL and of 17Y-oestradiol < 50 pg/mL), between 40 and 65 years of age (mean age 55), with an intact uterus.	24 weeks	Tibolone 2.5 mg/d Vs Tibolone 1.25 mg/d Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No details given on random sequence generation BLINDING:

				Placebo	- Participants/personnel: unclear Defined as "double-blind" but no other specific information provided - Assessors: unclear No information provided about assessment of vaginal bleeding; unclear if trial is truly "double-blind" FOLLOW-UP: high risk of attrition bias 42/162 participants not analysed because of adverse events, loss to follow-up, lack of efficacy, etc SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk Not reported
Jacobsen 2012 DD-RCT	318	Community-living women > 70 years of age	2 years	Tibolone 1.25 mg/d Vs Placebo Vs Raloxifene 60 mg/d (not considered in the meta-analysis)	ALLOCATION CONC: unclear No information provided RANDOMIZATION: adequate Block randomisation with computer-generated list of random numbers BLINDING: - Participants/personnel: adequate Double dummy blinded participants - Assessors: unclear No information provided FOLLOW-UP: high risk of attrition bias

					Substantial losses to follow-up (already > 20% at 3 months) SELECTIVE REPORTING: low risk Study reported data on outcomes as indicated in the protocol. Additional data on cardiovascular and cerebrovascular events available in the study publication and included in this review Conflict of interest: low risk Sponsored by the Dutch Organization for Health Research and Development. Study authors declare that they have no conflicts of interest
Kenemans 2009 Non inferiority RCT	3148	Postmenopausal women with vasomotor symptoms, in menopause for more than 12 months, who were surgically treated for breast cancer (T1-3, N0-2, M0) within the previous 5 years; excluded women with endometrial abnormalities at transvaginal ultrasonography. Mean time since menopause 6.2 years. Mean age 52.7 years. At study entry, 67% of participants were using tamoxifen	2.75 years	Tibolone 2.5 mg/d Vs Placebo Women who did not have adequate relief of their vasomotor symptoms were allowed to use concomitant non-hormonal medication, such as soy products, clonidine and antidepressants	ALLOCATION CONC: adequate Centralised interactive voice response system RANDOMIZATION: adequate Randomisation was done by use of a centralised interactive voice response system, stratified by centre, with a block size of 4 BLINDING: - Participants/personnel: adequate Double-blind fashion - Assessors: adequate Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"

					FOLLOW-UP: low risk of attrition bias 98% of randomised participants were analysed; reasons given for withdrawals/dropouts SELECTIVE REPORTING: low risk Data on all outcomes indicated in the protocol were eventually available in the study publication Conflict of interest: high risk Financed by the drug producer. Some study authors with conflicts of interest
Kroiss 2015 RCT	70	Postmenopausal women (hospital outpatients; < 75 years old; body mass index 18 to 30 kg/m²) with newly diagnosed and histologically confirmed invasive or non-invasive early-stage breast cancer (< stage IIb), for which they were to receive surgical treatment (conservation therapy or modified radical mastectomy) followed by tamoxifen (20 mg/d). The women were required to have had their last natural menstrual period > 1 year before diagnosis of breast cancer (mean time since menopause 107 months) and to have a serum oestradiol concentration < 30 pg/mL. Mean age 58 years	1 year	Tibolone 2.5 mg Vs Placebo	ALLOCATION CONC: adequate Automated random assignment using ADLS system RANDOMIZATION: adequate Automated random assignment using ADLS system BLINDING: - Participants/personnel: adequate Placebo-controlled, double-blind (identical medication) - Assessors: adequate Not specified, evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias 3/35 participants in the placebo group did not receive study treatment

					SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Two study authors were employees of the drug manufacturer
Kubista 2007 RCT	102	Postmenopausal women with initially stage I or II, oestrogen receptor-positive (ER+), previously untreated, core-biopsy proven, invasive breast cancer without evidence of metastatic spread; any endocrine or enzyme modulator therapy was stopped m 3 months before randomisation. Mean age 65 years. Mean time since menopause 17 years	14 days	Tibolone 2.5 mg Vs Placebo	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: adequate Placebo-controlled and defined as "double-blind" (1 pill administered per day) - Assessors: adequate Not specified, evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias Stroke evaluated referring to the "all subject treated group" SELECTIVE REPORTING: low risk Some of the outcomes indicated in the protocol were assessed and reported in the study publication. Those not reported were of no interest for the review. Conflict of interest: high risk

					Financed by the drug manufacturer. Two study authors were employees of the drug manufacturer
Landgren 2002 RCT	775	Women with a uterus between 40 and 60 years (mean 52 years), with absence of spontaneous vaginal bleeding for more than 10 months and presence of menopausal symptoms (more than 1 moderate to severe hot flush per day). Body weight had to be between 80% and 130% of ideal body weight. Mean time since menopause 35 months	12 weeks	Tibolone 5 mg/d Vs Tibolone 2.5 mg/d Vs Tibolone 1.25 mg/d Vs Tibolone 0.625 mg/d Vs Placebo	ALLOCATION CONC: unclear Not specified RANDOMIZATION: unclear Not explained BLINDING: - Participants/personnel: adequate Placebo-controlled, double-blind (use of identical tablets) - Assessors: adequate Not specified, evaluation is likely to be "objective" FOLLOW-UP: unclear risk of attrition bias 30 of 770 participants who started treatment were not evaluable (reasons not specified) SELECTIVE REPORTING: unclear risk Study protocol not available. Conflict of interest: high risk 3 out of 4 study authors were employees of the drug producer
Langer 2006 RCT	866	Healthy postmenopausal women (45 to 79 years of age with a body mass index > 19 and < 32 kg/m ²) who had been amenorrhoeic for more than 1 year (mean time since menopause 11 years), with or without intact uterus. If the date of final menstruation was unclear, the woman was to have used	3 years	Tibolone 2.5mg/d Vs 0.625 mg continuous combined conjugated equine oestrogen and 2.5	ALLOCATION CONC: unclear "code numbers were assigned to subjects in the order of their randomisation in the trial, that is, the first subject received the first number (the lowest), the second subject received the next number in

		hormone therapy (HT) for > 2 years and had to be > 53 years old or fulfil the US Food and Drug Administration (FDA) criteria for menopause (serum oestradiol n 20pg/mL [or 73 pmol/L] and follicle-stimulating hormone m 40 mIU/mL). Mean age 59 years		mg medroxyprogesterone acetate (CEE/MPA) Vs Placebo	sequence, and so on". This specification made the allocation concealment issue unclear, but in a private communication, the main study author assured that such process was concealed to investigators but provided no further details RANDOMIZATION: low In a private communication, the main study author assured that study treatments were allocated through random codes generated by a central co-ordinating group BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: unclear risk of attrition bias Number of women not completing the trial and with no assessment of outcomes of interest is unclear SELECTIVE REPORTING: low risk Study reported data on outcomes as indicated in the protocol. Conflict of interest: high risk Financed by the drug manufacturer. One study author was an employee of the drug manufacturer

Meeuwssen 2002 RCT	85	Healthy postmenopausal women, who were > 1 year and at maximum 15 years after natural menopause. Mean age 54.2 years	1 year	Tibolone 2.5mg/d Vs Placebo	ALLOCATION CONC: unclear Not specified RANDOMIZATION: unclear Not explained BLINDING: - Participants/personnel: adequate Tablets of identical appearance - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias Reasons given for withdrawals (4 women) SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Drug manufacturer was involved in the trial (random sequence generation was performed by the drug manufacturer)
Morais-Socorro 2012 RCT	65	Women between 40 and 55 years of age, with menstrual irregularity during the previous 6 months but fewer than 12 months of amenorrhoea, presence of a uterus without anomalies in an initial vaginal ultrasonography evaluation and an endometrial thickness measurement n 10 mm; Kupperman Menopausal Index (KMI) score m 14 points.	12 weeks	Tibolone 2.5 mg/d Vs placebo	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: unclear Study authors do not provide information on blinding methods - Assessors: unclear

		Mean age 48.5 years			No information provided FOLLOW-UP: high risk of attrition bias 10% and 14% dropout in tibolone and placebo arms, respectively SELECTIVE REPORTING: low risk Some of the outcomes indicated in the protocol (Kupperman Index, Greene scale) were assessed and reported in the study publication. Those not reported were of no interest for this review. Conflict of interest: low risk Supported by grant from the CNPq
Swanson 2006 RCT	396	Healthy postmenopausal women (m 40 years of age; mean age 52 years) who had been amenorrhoeic > 6 months (women with a uterus only) and who were experiencing a minimum of 7 moderate to severe hot flashes per day (or 60 per week). Mean time since menopause 84 months	12 weeks	Tibolone 2.5 mg/d Vs Tibolone 1.25 mg/d Vs Placebo	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: low Defined as "double-blind"; 3 daily interventions were compared - Assessors: unclear Methods for (and blinding when) diagnosing heart failure not specified FOLLOW-UP: low risk of attrition bias 5/396 excluded for not receiving any study treatment

					SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Financed by the drug manufacturer. Two study authors were employees of drug manufacturer
Vieira 2009 RCT	30	Postmenopausal women with systemic lupus erythematosus, between 30 and 65 years of age (mean age 51.7 years), who had not menstruated for over a year (mean 7.1 years); had follicle-stimulating hormone (FSH) levels > 20 mIU/mL in 2 (chemiluminescence) tests performed 30 days apart; had not used any HRT for > 6 months; and had presented with symptoms of hypoestrogenism (night sweats, hot flashes or symptoms of urogenital atrophy) at inclusion.	1 year	Tibolone 2.5 mg/d Vs Placebo	ALLOCATION CONC: unclear No information provided RANDOMIZATION: low Software programme was used to randomise participants into 2 groups BLINDING: - Participants/personnel: low Double-dummy - Assessors: unclear Evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias 3/30 excluded owing to SLE reactivation SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: unclear risk Not reported
Wender 2004 RCT	40	Healthy postmenopausal women Mean age 55 years	1 year	Tibolone 2.5 mg/d Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided

		Mean time since natural menopause 5 to 7.7 years Mean BMI 26 kg/m2		Placebo	BLINDING: - Participants/personnel: low “the tibolone and the placebo tablets and bottles looked identical; the bottles were identified with numbers from 1 to 40. The correspondence between the numbers and the group to which the participant belonged was not disclosed until the end of the study” - Assessors: low “all ultrasonographic exams were performed at the Hospital’s Gynecology and Obstetrics Service by the same operator, who was blinded to information concerning participant groups. [...] “ The material was analysed twice by 2 pathologists who were also blinded to participant information” FOLLOW-UP: low risk of attrition bias Reasons for withdrawal given: 3 participants/group withdrew from the study SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: unclear risk No details given

Ziaei 2010 RTC	150	Healthy postmenopausal women (mean age at menopause: 49 years), 45 to 60 years of age (mean age 52 years), whose last menstrual period was more than a year ago with plasma 17β -oestradiol < 35 pg/mL	6 months	Tibolone 2.5 mg plus a Cal + vit D tablet (500 mg/200 IU) Vs 0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) plus 1 Cal+D tablet (500 mg/200 IU) An arm with 50 women who received only 1 Cal + D tablet (500 mg + 200 IU) was not considered	ALLOCATION CONC: unclear No information provided RANDOMIZATION: low Computer-generated list of random numbers BLINDING: - Participants/personnel: high Not specified whether blind/double-blind trial. All women received Ca + vit D but 1 control group did not receive active treatments; no dummy placebo mentioned - Assessors: high Only blood samples stated to have been assessed in blinded fashion FOLLOW-UP: unclear risk of attrition bias 5/150 lost to follow-up for bleeding outcomes; 20/150 (13%) for vasomotor symptoms SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: low risk Publicly financed

Remarks:

-In most of the RCTs, all or some participants had menopausal symptoms. A few studies did not clearly specify whether women were symptomatic, or whether investigators had other reasons to test the effectiveness of tibolone. For vasomotor symptoms, authors have included studies that measured hot flushes (with or without night sweats), provided that they measured hot flushes as an outcome of efficacy in populations including symptomatic women.

- Most of the included RCTs studied women in natural menopause only, although a few studies also included women without a uterus. In these cases, investigators evaluated endometrial outcomes (bleeding, hyperplasia, cancer) only in women with an intact uterus.
 - The mean age of women in most of the selected studies was between 52 and 55 years. Concerning cardiovascular events, the four RCTs assessing this outcome involved women of very different age groups (mean from 53 years to 74 years) and having very different mean time since menopause (1.5 to 17 years).
 - Three RCTs (Kenemans 2009; Kroiss 2005; Kubista 2007) specifically studied individuals with breast cancer and were included in the MA.
 - Two of the largest RCTs, which strongly influenced results on several outcomes, included very specific populations:
 - patients with breast cancer (Kenemans 2009) n=3148
 - and those with osteoporosis (Cumming 2008) n=4538
- Findings of these studies are of limited applicability to women taking tibolone for menopausal symptoms.
- For cerebrovascular events, for which the estimate is at the limit of statistical significance, result may be incomplete as the RCT that provided most of the data was stopped prematurely for increased risk of stroke with 1.25 mg/d of tibolone and has selected osteoporotic women aged 60 to 85 years.
 - Different doses of oral tibolone were used, usually 2.5 mg daily, range 0.625 mg to 5 mg daily. Unless otherwise stated, doses were daily.
 - 2 studies have also reported on the impact of tibolone on breast cancer in women with breast cancer. As this population was excluded from our search criteria we haven't mentioned these results in the present document.
 - Follow up in available RCTs varies from 12 weeks to 3 years.

Author's conclusions:

- Moderate-quality evidence suggests that tibolone is more effective than placebo and is less effective than combined hormone therapy (HT) in treating vasomotor symptoms. Tibolone is associated with a higher rate of unscheduled bleeding than placebo but a lower rate than combined HT.
- We found no evidence that tibolone increases the risk of serious adverse events for women taking it over a short term to treat vasomotor symptoms, provided they have had no history of breast cancer, but data are scarce and more evidence is required.
- Evidence indicates that tibolone is associated with increased risk of serious adverse events when used in other contexts. Compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke in women over 60 years of age.
- Data on endometrial cancer are inconclusive.
- No evidence has revealed a difference between tibolone and HT with respect to long-term adverse events.

Tibolone provides a clear advantage in terms of less vaginal bleeding, but available data from RCTs on its long-term safety compared with other hormonal therapies are insufficient. Much of the evidence was of low or very low quality. Limitations included high risk of bias and imprecision. Most studies were financed by drug manufacturers or failed to disclose their funding source.

11.9 Tibolone versus estrogens

Meta-analysis: Formoso 2016: Short-term and long-term effects of tibolone in postmenopausal women

Inclusion criteria:

- Randomised controlled trials (RCTs). We did not include quasirandomised and cross-over trials.
- Menopausal and perimenopausal women with or without vasomotor and/or genital symptoms, defined as women with surgical menopause or with spontaneous menopause, or women who had menstruated irregularly over the past 12 months.
- This review did not consider tibolone use versus no treatment.

Search strategy: We searched the CGF Specialised Register (formerly known as the Menstrual Disorders and Subfertility Group Specialised Register), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from inception until 15 October 2015.

We contacted individual researchers working in relevant fields (gynaecology, endocrinology) and the current manufacturer of tibolone (Merck Sharp & Dome) to check for additional relevant references and unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods.

Assessment of quality of included trials: yes

ITT analysis: yes

Other methodological remarks:

We used a random-effects model, except for vasomotor symptoms, vaginal dryness and sleep, for which we combined data from dichotomous and continuous outcomes in a fixed-effect model by converting all treatment effect estimates to standardised mean differences (SMDs). Pooled SMDs computed in this manner can be transformed and interpreted as odds ratios, at the cost of information related to symptom severity. Poor reporting standards required that we impute standard deviations for several studies reporting on menopausal symptoms to combine their results; we calculated all effect sizes and corresponding standard errors by using the metaphor package in R. If results for this outcome were available at several time points, we used results corresponding to the longest period of use.

Ref	Comparison	N/n	Outcomes	Result
Formoso 2016 Design: MA October 2015	Tibolone (all doses) vs Estrogens	N= 2 n= 108 (Gupta 2013; Mendoza 2000)	Vasomotor symptoms (occurrences or through scales, defined as any otherwise unexplained sensation of flushing/sweating experienced by the participant.)	6/54 vs 5/54 OR (95 % CI): 1.23 (0.35 to 4.34) NS I ² = 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Gupta 2013 RCT	100	Asymptomatic patients (no menopausal symptoms) with surgical menopause 3 days earlier (total abdominal hysterectomy with bilateral salpingo-oophorectomy)	1 year	Tibolone 2.5 mg/d Vs CEE 0.625 mg Vs DHEA 25 mg/d (all administered orally) Vs No treatment.	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: inadequate presumably an open trial - includes a "no treatment" arm Assessors: unclear No information provided FOLLOW-UP: high risk of attrition bias Study authors acknowledged losses to follow-up, but total number of lost participants is unclear SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk No information provided
Mendoza 2000 PG-RCT	76	Hysterectomised women < 50 years old. Excluded if had had any previous malignant gynaecological process, oestrogen-producing tumour, endocrinological or metabolic problems, cardiovascular disease, uncontrolled	1 year	Tibolone 2.5 mg per day (n = 38) Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: adequate

		hypertension, active hepatic disease, serious skin illness, intestinal sickness or chronic obstructive respiratory disease. Patients with psychiatric problems or receiving anxiolytic or antidepressive drugs were also excluded Unclear whether all women were symptomatic		Transdermic 17Y-oestradiol 50 micrograms per day (n = 38)	Table of random numbers with simple blind randomisation BLINDING: - Participants/personnel: inadequate No mention of blinding - Assessors: inadequate Unlikely FOLLOW-UP: high risk of attrition bias 14/76 participants interrupted or changed therapy, or were lost to follow-up; 6/76 did not start therapy SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk No information provided

Remarks:

Estrogen used as comparator was either oral CEE or transdermal 17Y-oestradiol.

Population included in both studies undergone surgical menopause.

For vaginal dryness only one study was found. This one was not included in the present report as it does not meet our inclusion criteria (n< 40/study group).

-Follow up was 1 year in both RCTs.

Author's conclusions:

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11.10 Tibolone vs EPT

Ref	Comparison	N/n	Outcomes	Result
Formoso 2016 Design: MA October 2015	Tibolone (all doses) vs combined HT	N= 9 n= 1336 (Elfituri 2005, Hammar 1998, Hammar 2007, Kökçü 2000, Mendoza 2002, Nappi 2006a, Polisseni 2013, Wu 2001, Ziaei 2010)	Vasomotor symptoms (occurrences or through scales, defined as any otherwise unexplained sensation of flushing/sweating experienced by the participant.)	SMD (95 % CI): 0.17 (0.06 to 0.28) OR (95 % CI): 1.36 (1.11 to 1.66) SS in favour of EPT I ² = 67%
		N= 7 n= 1098 (Hammar 1998, Huber 2002, Kökçü 2000, Nappi 2006a, Osmanagaoglu 2006, Uygur 2005, Ziaei 2010)	Vaginal dryness and painful sexual intercourse (SO)	SD (95 %CI): 0.02 (-0.12 to 0.17) NS I ² = 0%
		N= 16 n= 6438 (Al-Azzawi, Archer 2007, Doren 1999, Elfituri 2005, Hammar 1998, Hammar 2007, Huber 2002,	Unscheduled bleeding	736/3205 vs 1533/3233 18% to 27% vs 47% OR (95 % CI): 0.32 (0.24 to 0.41) SS in favour of tibolone I ² =72%

		Kökçü 2000, Langer 2006, Mendoza 2002, Nappi 2006a, Nijland 2009, Roux 2002, Winkler 2000, Wu 2001, Ziaei 2010)		
		N= 5 n= 2846 (Archer 2007, Baracat 2002, de Aloysio 1998, Hänggi 1997, Siseles 1995)	Endometrial hyperplasia	0/1408 vs 3/1438 OR (95 % CI): 0.35 (0.05 to 2.21) NS $I^2=0\%$
		N= 5 n= 3689 (Archer 2007, Elfituri 2005, Hammar 1998, Hänggi 1997, Langer 2006)	Endometrial cancer	2/1826 vs 1/1863 OR (95 % CI): 1.47 (0.23 to 9.33) NS $I^2=0\%$
		N= 5 n= 4835 (Archer 2007, Hammar 2007, Hammar 1998, Hänggi 1997, Langer 2006)	Breast cancer	17/2351 vs 10/2484 OR (95 % CI): 1.69 (0.78 to 3.67) NS $I^2=0\%$

		N= 4 n= 4529 (Al-Azzawi 1999, Archer 2007, Hammar 2007, Huber 2002)	Venous thromboembolic events	1/2251 vs 5/2278 OR (95 % CI): 0.44 (0.09 to 2.14) NS I ² =0%
		N= 2 n= 3794 (Archer 2007, Langer 2006)	Cardiovascular events	7/1884 vs 11/1910 OR (95 % CI): 0.63 (0.24 to 1.66) NS I ² =0%
		N= 4 n= 4562 (Archer 2007, Hammar 2007, Huber 2002, Nijland 2009)	Cerebrovascular events	2/2265 vs 4/2297 OR (95 % CI): 0.76 (0.16 to 3.66) NS I ² =0%
		N= 2 n= 970 (Langer 2006, Nijland 2009)	Mortality	1/485 vs 0/485 OR (95 % CI): (3.05 (0.12 to 75.2) NS I ² : not applicable (1 assay with no event)

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Al-Azzawi 1999 Open label RCT	235	Healthy women with intact uteri, m 12 months postmenopausal (mean 61 months), with serum FSH exceeding 20 IU/L. None of the women enrolled in	1 year	Tibolone 2.5 mg/d Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: adequate Computer generated

		the study had received hormone therapy during the 3 months before enrolment. Mean age: 54 years		Micronised oestradiol valerate 2 mg/d + norethisterone 0.7 mg/d	BLINDING: - Participants/personnel: inadequate Open label - Assessors: adequate Evaluation likely to be "objective". Open design may affect evaluation of climacteric symptoms, but these were not taken into consideration (score)" FOLLOW-UP: high risk of attrition bias Number of participants analysed was variable for different outcomes and throughout the study, depending on the number of completed diaries. Cumulative 12-month incidence of vaginal bleeding not available SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Financed by the drug manufacturer. Study authors have conflicts of interest
Archer 2007 RCT	3240	Postmenopausal healthy women, with an intact uterus and with a screening biopsy classified as atrophic or inactive endometrium and a double-layer endometrial thickness $\leq$ 6 mm as assessed by transvaginal ultrasonography (TVUS).	2 years	Tibolone 2.5 mg/d Vs Tibolone 1.25 mg/d Vs	ALLOCATION CONC: adequate Interactive voice response system RANDOMIZATION: adequate use of an interactive voice response system should keep risk of selection bias very low BLINDING:

		Mean time since menopause: 4.5 years. Mean age: 54.4 years		Continuous combined conjugated equine oestrogen 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d	- Participants/personnel: adequate Double-dummy method - Assessors: adequate Evaluation likely to be "objective". FOLLOW-UP: high risk of attrition bias No information on withdrawals/dropouts SELECTIVE REPORTING: adequate No information on withdrawals/dropouts Conflict of interest: high risk Financed by the drug manufacturer; some study authors are employees of the drug manufacturer
Baracat 2002 Open label RCT	85	Generally healthy postmenopausal women, with an intact uterus, in menopause form 4 years, absence of endometrial hyperplasia Mean age 52 years	13 cycles of 28 days	Tibolone 2.5 mg/d Vs CEE/MPA 0.625 mg/5.0 mg/d	ALLOCATION CONC: adequate respective code (treatment group) RANDOMIZATION: adequate balanced blocks of ten subjects using the table of aleatory numbers BLINDING: - Participants/personnel: inadequate Open label - Assessors: inadequate Open label FOLLOW-UP: low risk of attrition bias similar rates of discontinuation, reasons given

					SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Sponsored by manufacturer of CEE/MPA
de Aloysio 1998 RCT	50	13 to 30 months since menopause (mean 20 months); 1 to 4 submucous or intramural asymptomatic uterine leiomyomas (with longest diameter ranging from 3 to 8 cm); body mass index (BMI) < 28; without blood coagulation disease; without endometrial pathology. Mean age: 51 years	12 cycles of 28 days	Tibolone 2.5 mg/d Vs Conjugated equine oestrogens (CEE), 0.625 mg/d plus medroxyprogesterone acetate (MPA), 5 mg/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: unclear No information provided - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: unclear risk of attrition bias 3 participants excluded from analysis for non-compliance SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk Conflicts of interest not stated
Doren 1999 DB-RCT	98	Healthy postmenopausal women, with intact uterus (mean age 56 years), mean BMI 25 kg/m ² Mean time since menopause 6 years	1 year	Tibolone 2.5 mg/d Vs 17beta-oestradiol + NETA (2 + 1 mg/d)	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: unclear No information provided on personnel - Assessors: adequate

					Participants recorded bleeding episodes in a diary FOLLOW-UP: low risk of attrition bias reasons for withdrawal explained SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Describe: study sponsored by manufacturer of tibolone; employer among study authors
Elfituri 2005 RCT	100	Healthy Libyan women with a uterus, with natural or surgical menopause, with menopausal symptoms. All had received no previous oestrogen and/or progestogen in preceding 12 months. 1 to 9 years since menopause (mean 2 years). Mean age 44.3 years	1 year	Tibolone 2.5 mg/d Vs 17beta-oestradiol 2 mg sequentially combined with dydrogesterone 10 mg	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: unclear - Assessors: adequate No information provided Evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias reasons for withdrawal explained (2 women) SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk Not reported
Hammar 1998 RCT	437	Women with menopausal symptoms, in good physical and mental health, m 1 year since last menstrual bleeding,	48 weeks	Tibolone 2.5 mg/d Vs	ALLOCATION CONC: adequate Opaque sealed envelopes RANDOMIZATION: unclear No information provided

		menopausal symptoms, intact uterus, body mass index (BMI) < 30 kg/m ² . Mean age 55 years		17 β -Oestradiol 2 mg plus norethisterone acetate 1 mg (E2/NETA)	BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias 14/437 participants not assessed for lack of post-baseline assessment SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Financed by drug manufacturer. Study authors have conflicts of interest.
Hammar 2007 RCT	572	postmenopausal healthy women with an intact uterus, with or without vasomotor symptoms. Mean age 55 years. Time since menopause 5 years. Mean number of hot flashes at baseline 5.8	48 weeks	Tibolone 2.5 mg/d Vs 17-beta-oestradiol 1 mg + norethisterone acetate 0.5 mg/d	ALLOCATION CONC: adequate Automatic interactive voice response system RANDOMIZATION: adequate Restricted block-wise randomisation BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Investigators, study site personnel and participants remained blinded FOLLOW-UP: high risk of attrition bias

					87% of randomised participants analysed but reasons for withdrawals/ dropouts not given SELECTIVE REPORTING: low risk indicated in the protocol Conflict of interest: high risk Financed by the drug producer. One study author was an employee of the drug producer
Hänggi 1997 RCT	140	Healthy early postmenopausal women between 45 and 55 years of age (mean age 52) with an amenorrhoeic interval >12 months or serum FSH > 30 IU/L. In addition, women > 55 years of age were included if they had a menopausal age < 5 years	2 years	Tibolone 2.5 mg/d Vs Micronised 17 β-oestradiol, orally 2 mg/d continuously plus sequential dydrogesterone orally 10 mg/d for 14 days every 4 weeks Vs 17β-oestradiol patch releasing 50 micrograms/d continuously plus sequential dydrogesterone orally 10 mg/d for 14 days every 4 weeks	ALLOCATION CONC: unclear Not specified RANDOMIZATION: adequate Computer-generated list BLINDING: - Participants/personnel: inadequate Open trial because women in 1 study arm were treated with an oestrogen patch - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: high risk of attrition bias 55/105 (after 12 months) and 46/105 (after 24 months) participants were evaluated through endometrial biopsy. Reasons why remaining women were not assessed were not specified SELECTIVE REPORTING: unclear risk

					Study protocol not available Conflict of interest: high risk Sponsored by the drug manufacturer. Study authors' conflicts of interest not reported
Huber 2002 RCT	502	Postmenopausal women, with last menstrual period m 12 months previously, younger than 65 years of age (mean age 55). If the date of natural menopause could not be established because of hormonal treatment, participants had to be m 53 years of age and must have been receiving hormonal therapy for > 2 years; if applicable, hormone therapy had to end with a progestogen phase. All participants were required to have an intact uterus and a body mass index (BMI) of 18 to 29 kg/m	1 year	Tibolone 2.5 mg/d Vs Conjugated equine oestrogens 0.625 mg continuously combined with medroxyprogesterone acetate 5 mg (CEE-MPA)/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Self-evaluation by blind patients, their evaluation is likely to be "objective" FOLLOW-UP: high risk of attrition bias Several participants (about 80, depending on different outcomes) were excluded from final analyses for adverse events and insufficient compliance/efficacy SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: high risk Financed by the drug producer. One study author was the employee of a drug producer
Kökçü 2000 RCT	50	Women in spontaneous menopause > 1 year (mean 25 months), still sexually active with a partner with no sexual problems, did not have any	1 year	Tibolone 2.5 mg/d Vs	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided

		gynaecological surgery and had no absolute contraindication for HRT. Mean age 52 years		Conjugated oestrogens (CEE) 0.625 mg/d plus medroxyprogesterone acetate (MPA) 2.5 mg/d	BLINDING: - Participants/personnel: unclear Study authors did not specify whether study drugs were identical looking. - Assessors: unclear Not specified (and not clear whether the women were blind) FOLLOW-UP: high risk of attrition bias 6/50 women were not evaluated for not attending visits SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk No information
Langer 2006 RCT	866	Healthy postmenopausal women (45 to 79 years of age with a body mass index > 19 and < 32 kg/m²) who had been amenorrhoeic for more than 1 year (mean time since menopause 11 years), with or without intact uterus. If the date of final menstruation was unclear, the woman was to have used hormone therapy (HT) for > 2 years and had to be > 53 years old or fulfil the US Food and Drug Administration (FDA) criteria for menopause (serum oestradiol < 20pg/mL [or 73 pmol/L] and follicle-stimulating hormone < 40 mIU/mL).	3 years	Tibolone 2.5mg/d Vs 0.625 mg continuous combined conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) Vs Placebo	ALLOCATION CONC: unclear "code numbers were assigned to subjects in the order of their randomisation in the trial, that is, the first subject received the first number (the lowest), the second subject received the next number in sequence, and so on". This specification made the allocation concealment issue unclear, but in a private communication, the main study author assured that such process was concealed to investigators but provided no further details

		Mean age 59 years			RANDOMIZATION: low In a private communication, the main study author assured that study treatments were allocated through random codes generated by a central co-ordinating group BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Evaluation is likely to be "objective" FOLLOW-UP: unclear risk of attrition bias Number of women not completing the trial and with no assessment of outcomes of interest is unclear SELECTIVE REPORTING: low risk Study reported data on outcomes as indicated in the protocol. Conflict of interest: high risk Financed by the drug manufacturer. One study author was an employee of the drug manufacturer
Mendoza 2002 RCT	165	Women with intact uterus younger than 60 years (mean 50 years), who had been amenorrhoeic for 1 to 5 years (mean 22.3 months). Women who had had a hysterectomy or had received hormone treatment in the 3 months before the trial were excluded, as were those with a history of a malignant gynaecological process,	1 year	Tibolone 2.5 mg/d Vs Cyclical combined regimen of transdermal oestrogen and progestogen: transdermal patch of 17β-oestradiol 50 μg/d during 14	ALLOCATION CONC: unclear No information provided RANDOMIZATION: adequate table of random numbers BLINDING: - Participants/personnel: unclear Defined as "simple-blind" - Assessors: adequate

		oestrogen-producing tumour or obesity (body mass index > 32)		days and transdermal patch of 17Y-oestradiol 50 µg/d plus 0.25 mg/d of norethisterone acetate during the following 14 days Vs Intermittent progesterone regimen: transdermal 17Y-oestradiol 50 µg/d and oral micronised natural progesterone 200 mg twice a week	Evaluation is likely to be "objective" FOLLOW-UP: high risk of attrition bias 32/165 women did not start HRT, no reasons given SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: unclear risk Not reported
Nappi 2006a RCT	40	Women with menopausal symptoms and primary headache (migraine without aura [MwA] and ETTH) of premenopausal onset (history m 10 years), spontaneous menopausal status m 12 months (mean 18 months) with follicle-stimulating hormone levels > 30 IU/L, age between 51 and 55 years (mean age 53 years), body mass index > 19 and < 30 kg/m² Women had been using symptomatic medications and headache drug prophylaxis > 3 months before entering the study	6 months	Tibolone 2.5 mg/d Vs 1 mg 17β-oestradiol + 0.5 mg norethisterone acetate	ALLOCATION CONC: unclear No information provided RANDOMIZATION: adequate Computer-generated list of numbers BLINDING: - Participants/personnel: unclear No information - Assessors: unclear Evaluated by a blind study author, although it is not clear whether this referred to the database level or to the clinical assessment of outcomes, which was not likely to be conducted in a blind fashion

					FOLLOW-UP: low risk of attrition bias Study authors state that all women completed the study following appropriate Evaluation SELECTIVE REPORTING: unclear Study protocol not available Conflict of interest: low risk Supported by a grant from the Italian Ministry of Health.
Nijland 2009 RCT	403	Healthy women who had undergone natural menopause, with an intact uterus and with female sexual dysfunction associated with sexuality-related personal distress. Mean age 55.8 years	24 weeks	Tibolone 2.5 mg/d Vs Estradiol (50 microgr) + norethisterone acetate (140 microgr) in the form of a transdermal patch	ALLOCATION CONC: adequate Computerised automatic interactive voice response system RANDOMIZATION: adequate Computerised automatic interactive voice response system BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Assessors blinded FOLLOW-UP: unclear risk of attrition bias 6% to 10% were not analysed for unspecified protocol violations SELECTIVE REPORTING: low risk Some outcomes indicated in the protocol (vaginal bleeding and spotting rate)

					were assessed and reported in the study publication. Those not reported were of no interest for this review. Conflict of interest: high risk Study sponsored by the drug manufacturer, and some study authors were employees of the drug firm.
Osmanagaoglu 2006 RCT	165	Naturally postmenopausal women; absence of menstruation > 1 year; FSH m 30 IU/L; not undergone any gynaecological operation; no absolute contraindication for HT. Mean age 50 years	6 months	Tibolone 2.5 mg/d Vs Oestradiol valerate 2 mg_plus dienogest 2 mg/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear Not specified BLINDING: - Participants/personnel: inadequate single-blind (participant), but in some cases, women were given doctor samples from drug companies - Assessors: inadequate self-administered questionnaire, but it is unclear whether participating women were blind FOLLOW-UP: low risk of attrition bias 7/165_participants without follow-up data SELECTIVE REPORTING: unclear risk Study protocol not available conflict of interest: low risk Authors did not receive external funding and that they do not have conflicts of interest
Polisseni 2013	174	Postmenopausal women between 45 and 60 years of age with moderate or	12 weeks	Tibolone 2.5 mg/d	ALLOCATION CONC: unclear No information provided

RCT		pronounced vasomotor symptoms and a Blatt–Kupperman menopausal index (BKMI) m 20 points, with no treatment for menopausal symptoms in the past 6 months		Vs 1 mg oestradiol + 0.5 mg norethindrone acetate Vs 50 mg calcium carbonate and 200 UI vitamin D3	RANDOMIZATION: adequate Computer-generated list of random numbers BLINDING: - Participants/personnel: adequate all capsules appeared identical - Assessors: unclear No information provided FOLLOW-UP: high risk of attrition bias 47 participants lost to follow-up (with differential attrition among groups); probably no ITT SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: low risk Study authors declare that they have no conflicts of interest
Roux 2002 RCT	225	Healthy women with physiological menopause (time since menopause 3.9 years, mean age 53.3 years)	24 months	Tibolone 1.25 mg/d Vs Tibolone 2.5 mg/d Vs Estradiol 2 mg/d + norethindrone acetate 1 mg/d	ALLOCATION CONC: unclear Not clear if centralised randomisation RANDOMIZATION: adequate Block randomisation (block size of 6) BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate Self-reported outcome

					FOLLOW-UP: low risk of attrition bias ITT: Bleeding was evaluated for all randomised women SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Study sponsored by drug manufacturer
Siseles 1995 Open label RCT	30	Postmenopausal women > 1 year postmenopausal and reporting hot flushes and other menopausal symptoms (but otherwise healthy). Age range 48 to 62 years	6 cycles of 28 days	Tibolone 2.5 mg/d Vs Conjugated oestrogens 0.625 mg/d continuously, medroxyprogesterone 5 mg/d sequentially for 12 days of each 28-day cycle	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: inadequate Open label - Assessors: adequate evaluation is likely to be "objective" FOLLOW-UP: high risk of attrition bias 6/30 patients excluded from final analyses SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Financed by drug manufacturer. Study authors' conflicts of interest not stated
Uygur 2005	80	Postmenopausal women (56 years old), married, with spontaneous	6 months	Tibolone 2.5 mg/d (n = 40)	ALLOCATION CONC: unclear No information provided

PG-RCT		menopausal status m 1 year with follicle-stimulating hormone level > 30 mIU/L and no contraindication to use of HRT, without chronic disease. Participants were not selected on the basis of sexual function or dysfunction		Vs 0.625 mg continuous conjugated equine oestrogen and 5 mg medroxyprogesterone acetate (CEE/MPA)/d	RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: inadequate not double blind - Assessors: inadequate No blinding, with outcomes evaluated through a questionnaire FOLLOW-UP: high risk of attrition bias 8/80 dropped out (2 from tibolone group because of bleeding, 6 from CEE/MPA group - 1 for mastalgia, 1 for menorrhagia, 2 for weight gain, 2 for loss to follow-up) SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: unclear risk No information provided
Winkler 2000 RCT	62	Healthy postmenopausal women, between 45 and 70 years of age (mean age 54 years), spontaneous menopause with last menstrual period m 36 months before enrolment or artificial menopause (hysterectomy and/or oophorectomy) with FSH level > 30 IU/L Mean time since menopause 8.5 years	24 weeks	Tibolone 2.5 mg/d Vs Oestradiol 2 mg/d + oestriol 1 mg/d + norethindrone acetate 1 mg/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: unclear No information provided BLINDING: - Participants/personnel: adequate Double dummy - Assessors: adequate evaluation is likely to be "objective" FOLLOW-UP: low risk of attrition bias

					All women with a uterus were evaluated for vaginal bleeding/spotting SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Financed by the drug producer. One study author was an employee of the drug producer
Wu 2001 RCT	48	Healthy postmenopausal women (52 years old), postmenopausal for 12 to 36 months (confirmation by FSH > 40 mIU/mL and oestradiol < 20 pg/mL), with m 1 climacteric symptom according to the Greene Climateric Scale	3 months	Tibolone 2.5 mg/d vs 0.625 mg conjugated equine oestrogen and 5 mg medroxyprogesterone acetate (CEE/MPA)/d	ALLOCATION CONC: unclear No information provided RANDOMIZATION: inadequate selected pairs of 2 women were allocated to treatment groups BLINDING: - Participants/personnel: inadequate Open label - Assessors: Inadequate Open label FOLLOW-UP: high risk of attrition bias 12/48 dropped out, but reasons given SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: high risk Study sponsored by the manufacturer. Study authors declare that they have no conflicts of interest

Ziaei 2010 RTC	150	Healthy postmenopausal women (mean age at menopause: 49 years), 45 to 60 years of age (mean age 52 years), whose last menstrual period was more than a year ago with plasma 17Y-oestradiol < 35 pg/mL	6 months	Tibolone 2.5 mg plus a Cal + vit D tablet (500 mg/200 IU) Vs 0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) plus 1 Cal+D tablet (500 mg/200 IU) An arm with 50 women who received only 1 Cal + D tablet (500 mg + 200 IU) was not considered	ALLOCATION CONC: unclear No information provided RANDOMIZATION: low Computer-generated list of random numbers BLINDING: - Participants/personnel: high Not specified whether blind/double-blind trial. All women received Ca + vit D but 1 control group did not receive active treatments; no dummy placebo mentioned - Assessors: high Only blood samples stated to have been assessed in blinded fashion FOLLOW-UP: unclear risk of attrition bias 5/150 lost to follow-up for bleeding outcomes; 20/150 (13%) for vasomotor symptoms SELECTIVE REPORTING: unclear risk Study protocol not available Conflict of interest: low risk Publicly financed

Remarks:

-In most of the RCTs, all or some participants had menopausal symptoms. A few studies did not clearly specify whether women were symptomatic, or whether investigators had other reasons to test the effectiveness of tibolone. For vasomotor symptoms, authors have included studies that measured hot flushes (with or without night sweats), provided that they measured hot flushes as an outcome of efficacy in populations including symptomatic women.

-Most of the included RCTs studied women in natural menopause only, although a few studies also included women without a uterus. In these cases, investigators evaluated endometrial outcomes (bleeding, hyperplasia, cancer) only in women with an intact uterus.

-Different doses of oral tibolone were used, usually 2.5 mg daily. Unless otherwise stated, doses were daily and progesterone was continuous.

Different comparators were used in the studies, 10 of which used CEE. Different doses of estrogens and/or progestogens, different forms and different regimen were also used.

Tibolone was compared with

- conjugated equine estrogen 0.625 mg/d plus medroxyprogesterone acetate 5mg/d or 2.5 mg/d (used in 10 studies (1 used sequential regimen)),
- oestradiol valerate 2 mg plus dienogest 2 mg/d
- micronised oestradiol valerate 2 mg/d + norethisterone 0.7 mg/d,
- estradiol 2 mg/d + oestril 1 mg/d + norethindrone acetate 1 mg/d
- estradiol 2 mg/d + oestril 1 mg/d + norethindrone acetate 1 mg/d
- 17β -oestradiol 2 mg ou 1 mg plus norethisterone acetate 1 mg ou 0.5 mg (7 studies),
- 17β -oestradiol 2 mg sequentially combined with dydrogesterone 10 mg (2 studies),
- 17β -oestradiol patch releasing 50 micrograms/d continuously plus sequential dydrogesterone orally 10 mg/d
- 17β -oestradiol patch releasing 50 micrograms/d continuously plus sequential 0.25 mg/d norethisterone acetate
- transdermal 17β -oestradiol 50 µg/d and oral micronised natural progesterone 200 mg twice a week
- transdermal patch of estradiol (50 microgr) + norethisterone acetate (140 microgr)

-Follow up in available RCTs varies from 12 weeks to 3 years.

Author's conclusions:

- Moderate-quality evidence suggests that tibolone is more effective than placebo and is less effective than combined hormone therapy (HT) in treating vasomotor symptoms. Tibolone is associated with a higher rate of unscheduled bleeding than placebo but a lower rate than combined HT.
- No clinically relevant differences are apparent between tibolone and combined HT in relation to vaginal dryness outcomes.
- No evidence has revealed a difference between tibolone and HT with respect to long-term adverse events.

Tibolone provides a clear advantage in terms of less vaginal bleeding, but available data from RCTs on its long-term safety compared with other hormonal therapies are insufficient. Much of the evidence was of low or very low quality. Limitations included high risk of bias and imprecision. Most studies were financed by drug manufacturers or failed to disclose their funding source.

12 Appendix. Evidence tables. Nonpharmacological therapy for the treatment of menopausal symptoms

12.1 Black cohosh versus placebo

Meta-analysis: Leach 2012: Black cohosh (*Cimicifuga* spp.) for menopausal symptoms

Inclusion criteria:

- any published or unpublished randomized controlled trials (RCTs) that had evaluated the effectiveness of black cohosh in menopause, without restriction on language or trial duration. Other research designs, such as observational studies and case studies, were excluded.
- women 18 years of age or older with surgical or spontaneous menopause, experiencing climacteric symptoms in the perimenopausal or postmenopausal period and recruited from any setting. Perimenopausal women were defined as women with spontaneous menopause who have experienced irregular menstruation within the previous 12 months. Postmenopausal women were defined as women with surgical or spontaneous menopause and amenorrhoea for more than 12 months.
- all women, regardless of any prior or existing morbidity
- any orally administered monopreparation of black cohosh of any dose, form and duration. Combination preparations of black cohosh were excluded.

Search strategy: The authors searched the following electronic sources from inception to March 2012 for the identification of trials: AARP Ageline; Allied & Complementary Medicine (AMED); Australasian Medical Index (AMI); BioMed Central gateway; CAM on PubMed; CINAHL; Cochrane Central Register of Controlled Trials

(CENTRAL) (The Cochrane library); Cochrane Menstrual Disorders and Subfertility group Trials Register; EMBASE; Health Source Nursing/Academic edition; International Pharmaceutical Abstracts; MEDLINE; Natural medicines comprehensive database; PsycINFO; Turning Research Into Practice (TRIP) database. The authors also searched databases of ongoing trials (www.controlled-trials.com/ and www.clinicaltrialsregister.eu/). Additional studies were sought by searching the reference lists.

Content experts and manufacturers of black cohosh extracts were contacted in order to obtain additional references, as well as details of unpublished trials and ongoing trials. The grey literature was also searched for unpublished studies.

Assessment of quality of included trials: yes

ITT analysis: yes

Other methodological remarks: data (final value scores only) were pooled in a meta-analysis with Review Manager (RevMan) 5 software, using a fixed-effect model

Ref	Comparison	N/n	Outcomes	Result
Leach 2012 Design: MA March 2012 (month-year)	Black cohosh vs placebo	N= 3 n= 393 (Frei-Kleiner 2005, Newton 2006, Pockaj 2006)	Daily hot flush frequency	MD (95% CI): 0.07 (-0.43 to 0.56) NS $I^2 = 47\%$
		N= 3 n= 214 (Geller 2009, Kronenberg 2009, Pockaj 2006)	Hot flush intensity	MD (95% CI): 0.12 (-0.06 to 0.30) NS $I^2 = 42\%$
		N= 1 n= 164 (Newton 2006)	Daily frequency of night sweats	MD (95% CI): 0.27 (-0.16 to 0.70) P = 0.21 NS $I^2 = \text{N.A.}$
		N= 4 n= N.A. (Geller 2009; Newton 2006; Stoll 1987; Wuttke 2003).	Frequency or intensity of vulvovaginal symptoms	Not pooled due to heterogeneity in assessed outcomes Insufficient data
		N= 4 n= 357 (Frei-Kleiner 2005, Geller 2009, Amsterdam 2009, Newton 2006)	Menopausal symptom score	SMD (95%CI): -0.10 (-0.32 to 0.11) NS $I^2 = 21\%$

		N= 7 n= 822 (Amsterdam 2009; Frei-Kleiner 2005; Jacobson 2001; Kronenberg 2009; Newton 2006; Osmers 2005; Wuttke 2003).	Adverse effects	<u>Number of recorded events:</u> 194/430 (0.45 events/person) vs 195/392 (0.50 events/person) <u>Number of women experiencing adverse events:</u> 53/173 vs 50/171 RR (95%CI): 1.04 (0.82 to 1.32) (N=2, n=344 women) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Amsterdam 2009 R, DB, placebo-controlled, PG	n = 28	<u>Inclusion:</u> Female, aged ≥ 40 years, postmenopausal for ≥ 12 months or perimenopausal (amenorrhoea lasting 2 to 11 months in the preceding year). Onset of anxiety symptoms occurred within 3 years of onset of menopause or perimenopause or < 5 years after cessation of menstruation. Women with prior hysterectomy and uncertain menopausal status required a serum FSH ≥ 40 mIU/mL <u>Exclusion:</u> major depressive disorder, bipolar disorder, panic disorder, phobic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, substance-induced anxiety disorder,	12 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> 32 to 128 mg (32 mg, standardised to 5.6% triterpene glycosides), 1 to 4 capsules daily Vs Control: oral rice flour, 1 to 4 capsules daily 2 capsules daily for 2 weeks. Dose was increased to 4 capsules daily by study week 4 in women with $\leq$	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: Adequate “Randomisation was performed using blocked randomisation with varying block sizes” BLINDING : unclear Participants/personnel/assessors All study subjects and outcome raters were blinded as to treatment condition, and all results were analysed under blinded conditions...”; though there was no assurance that interventions

	schizophrenia, dementia, substance abuse or dependence disorder within the past 3 months; unstable medical condition, hepatic or renal disease, malignancy, serumthyrotropin level ≥ 5 μU/mL, abnormal breast examination or mammogram result, history of endometrial hyperplasia or endometrial cancer, rapidly growing uterine leiomyomata, undiagnosed abnormal uterine bleeding, abnormal gynaecological examination result precluding use of black cohosh, known sensitivity to black cohosh; and concurrent use of prescribed anxiolytics, antidepressants, mood stabilisers, sedatives, complementary medicines (e.g. St. John's Wort), oral oestrogen, oestrogen cream, and phyto-oestrogen preparations Black cohosh n= 15 Placebo n= 13 Mean age (black cohosh = 56.7 ± 6.5 years, placebo = 50.8 ± 3.2 years). Duration of menopause not stated Co-morbidities not stated Climateric disorders not stated		50% reduction in total Hamilton Anxiety Rating Scale Score	matched in appearance, taste or odour FOLLOW-UP: 25% drop out ITT: probably yes "Intention-to-treat" (which assumed that those who withdrew were non-responders) SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: Unclear risk Baseline differences in age and duration of illness were evident

Frei-Kleiner 2005 R, DB, placebo-controlled, PG	129	<u>Inclusion:</u> female, early or perimenopause with climacteric disorders, aged between 45 and 60 years, ≥ 3 hot flushes daily (corresponding to ≥ 42 hot flushes during the run-in period), ≥ 1 functioning ovary, normal gynaecological examination <u>Exclusion:</u> history of breast or endometrial carcinoma, medication affecting menopausal complaints, hormone replacement therapy within the last month, alcohol abuse, drug abuse, serious conditions interfering with study objectives Black cohosh n = 84 Placebo n = 45 Mean age (black cohosh = 52.5 ± 3.7 years, placebo = 52.2 ± 3.5 years). Duration of amenorrhoea (black cohosh = 38.7 ± 50.5 months, placebo = 37.3 ± 51.4 months) Co-morbidities not stated	12 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> (6.5 mg dry extract or 42 mg crude drug), 1 capsule daily Vs Oral placebo (excipients only), 1 capsule daily	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear “patients were randomized in the ratio of 2:1” (method not described) BLINDING : adequate “double-blind”; “one group received capsules of <i>Cimicifuga racemosa</i> extract... and the other group identically appearing placebo capsules” FOLLOW-UP: 20% drop out ITT: yes but probably high risk of attrition bias Used the expression ITT, but “five patients were excluded from the intention-to-treat population because of serious protocol violations or a posteriori detected exclusion criteria” 15 women discontinued the study; however, the number and reasons for withdrawal were not given for each group separately SELECTIVE REPORTING: inadequate no study protocol was published or lodged, there was limited discussion of many secondary outcome measures OTHER: Unclear risk

					Baseline differences in menopausal status and level of FSH were observed
Geller 2009 R, DB, placebo-controlled, PG	89	<u>Inclusion:</u> female, perimenopausal or postmenopausal with intact uterus, experiencing ≥ 35 vasomotor symptoms (hot flushes and night sweats) per week, amenorrhoea > 6 months and < 10 years' duration, FSH > 40 mIU/mL, HT not contraindicated <u>Exclusion:</u> hysterectomy, abnormal vaginal bleeding of undetermined aetiology, abnormal transvaginal ultrasound (> 7 mm thickness), abnormal endometrial biopsy or mammogram, diabetes, positive pregnancy test, breastfeeding, history of endometrial hyperplasia/neoplasia, breast cancer or cancer of the reproductive tract, history of myocardial infarction, stroke, severe varicose veins, sickle cell anaemia, deep vein thrombosis, thrombophlebitis or thromboembolic disorder, untreated or uncontrolled hypertension (systolic blood pressure > 165 mmHg or diastolic blood pressure > 95 mmHg), history of severe recurrent depression, severe psychiatric disturbance, alcohol abuse or drug abuse, concurrent use of medication containing oestrogen,	52 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> below-ground parts (64 mg, standardised to 5.68% triterpene glycosides) 2 capsules daily; Vs Oral CEO (0.625 mg) 1 capsule daily and oral MDP (2.5 mg) 1 capsule daily Vs Oral placebo (not described) 2 capsules daily 1-month washout period for women using transdermal hormone preparations or oral botanical supplements, and 2-month washout period for women using oral HT	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: adequate "a random, computer-generated code assigned two women in each cluster to each of the four treatment arms. There were 11 clusters with eight women in each cluster" BLINDING : adequate "Double blinded"; "the study capsules were identical in appearance, and there was no detectable odor for any of the preparations" FOLLOW-UP: 10.1% drop out ITT: yes but probably high risk of attrition bias "intention-to-treat" was quoted, but the analysis consisted only of "randomized women who had been in the study for at least 3 months" 9 women withdrew from the study – the number and reasons for withdrawal differed between groups SELECTIVE REPORTING: unclear No study protocol was published or lodged.

		progestin, SERM, St.John'sWort, biphosphonates or dietary phyto-oestrogens, history of migraine associated with hormone use, smoker, vegan diet, participation in another clinical trial within 30 days of enrolment, Black cohosh n = 22, Red clover n = 22 CEO/MPA n = 23 Placebo n = 22 Mean age (black cohosh = 54.4 ± 3.9 years, red clover = 52.4 ± 4.6 years, CEO/MPA = 53.3 ± 4.0 years, placebo = 52.0 ± 4.2 years). Duration of amenorrhoea (black cohosh = 3.4 ± 2.6 years, red clover = 4.1 ± 2.8 years, CEO/MPA = 3.6 ± 2.9 years, placebo = 2.8 ± 2.9 years) Co-morbidities not stated			OTHER: Unclear risk Baseline differences in race and BMI were evident, although all analyses controlled for these variables.
Jacobson 2001 R, DB, placebo-controlled, PG	85	<u>Inclusion:</u> female, aged > 18 years, previously treated for breast cancer at the Columbia-Presbyterian Medical Centre or 1 of its affiliates, experienced hot flushes daily, had completed primary therapy (including chemotherapy and radiotherapy) for breast cancer at least 2 months prior to study enrolment	60 days	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, 10 mg) 2 capsules daily with meals Vs Oral placebo (not described) 2 capsules daily with meals	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: adequate "We used one randomization list developed using the RanCode Plus program... Study participants [had] 50%probability of assignment to either group"

		<u>Exclusion:</u> using hormone replacement therapy for hot flushes, pregnant, history of major psychiatric illness, known to have recurrent or metastatic breast cancer Black cohosh n = 42, Placebo n = 43 Mean age (black cohosh = 52% were aged between 50 to 59 years, placebo = 51% were aged between 50 to 59 years). Duration of menopause not stated Co-morbidities: history of breast cancer			BLINDING : unclear “double-masked”, though there was no mention of who was blinded, or any assurance that interventions matched in appearance, taste or odour FOLLOW-UP: 18.8 % drop out ITT: yes “Intention-to-treat”; “missing data were handled by including all available data in the primary analyses” Number and reasons for withdrawal were similar between groups SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: Unclear risk Baseline differences in age, race, years of education, employment status and marital status were observed

Kronenberg 2009 R, DB, placebo-controlled, PG	74	<u>Inclusion:</u> female, postmenopausal, aged between 45 and 70 years, resident of New York Metro area, BMI < 33 kg/m², amenorrhoea ≥ 12 months, serum oestradiol < 30 pg/mL, ≥ 5 hot flushes per day <u>Exclusion:</u> hormone replacement therapy within the past 60 days, abnormal mammogram or transvaginal ultrasound Black cohosh n = 37 Placebo n = 37 Mean age (black cohosh = 55.12 ± 4.08 years, placebo = 54.18 ± 3.58 years). Duration of menopause not stated Co-morbidities not stated	52 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> rhizome (CimiPure, 40 mg, standardised to 2.5% triterpene glycosides) 1 capsule, twice daily Vs Oral placebo (dosage and formulation not described)	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method not described BLINDING : unclear therewas no mention of who was blinded, or any assurance that interventions matched in appearance, taste or odour FOLLOW-UP: 12 % drop out ITT: yes “All [women] were included in the Intention-to-treat analysis” 9 women withdrew from the study SELECTIVE REPORTING: inappropriate No study protocol was published or lodged. Data were reported for the primary outcomes, but not for all secondary outcomes OTHER: low risk
Newton 2006 R, DB, placebo-controlled, PG,	351	<u>Inclusion:</u> female, late menopausal transition (≥ 1 skipped menses in the last 12 months) or postmenopausal (no bleeding in the last 12 months) or FSH > 20 IU/mL (if participant had undergone hysterectomy without bilateral oophorectomy), aged between 45 and 55 years, and ≥ 2 vasomotor symptoms daily over the	52 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> rhizome and root (CimiPure, 80mg, standardised to 2.5% triterpene glycosides) 2 capsules daily; Vs	ALLOCATION CONC: adequate “the study nurse determined the appropriate stratum, assigned the participant the next study number in that stratum without knowledge of group assignment, and distributed study medications” RANDOMIZATION: adequate “participants were randomly assigned

		past 2 weeks (with ≥ 6 moderate to severe symptoms), negative mammogram in the last 2 years, normal thyroid stimulating hormone level <u>Exclusion:</u> contraindications to HT, use of HT or oral contraceptives within the last 3 months, use of herbal medicines for menopausal symptoms within the last month, allergy to soy, bilateral oophorectomy, history of breast cancer, non-adherence ($< 80\%$ of capsules administered) during the run-in period Black cohosh n = 80 Multibotanical n = 76 Multi-botanical plus dietary soy n = 79 CEO and MPA n = 32 Placebo n = 84 Mean age (black cohosh = 52.0 ± 2.2 years, multibotanical = 52.2 ± 2.5 years, multi-botanical plus dietary soy = 52.5 ± 2.5 years, CEO and MPA = 52.3 ± 2.6 years, placebo = 52.0 ± 2.5 years). Duration of menopause not stated Co-morbidities not stated		Oral CEO (0.625 mg) 1 tablet daily, with (for women with a uterus) or without (for women without a uterus) MDP (2.5 mg) 1 tablet daily Vs Oral placebo (dose and constitution is not described) Vs Mutibotanical vs Multibotanical plus soy	by using SAS software, stratified by previous HT and hysterectomy; block sizes within strata ranged from 5 to 25" BLINDING: adequate "double-blind"; "to facilitate blinding, medications and lactose placebo were encapsulated to provide 2 white and 2 blue capsules to each woman" FOLLOW-UP: 12.8% drop out ITT: yes 1 "mixed-model analysis allowed us to use a true intention-to-treat approach" Numbers of withdrawals were similar between groups, though reasons for withdrawal differed. 16 women were unblinded; however, numbers were not given for each group separately SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: unclear risk Baseline differences in BMI were observed
Osmers 2005 R, placebo-controlled, DB, PG	304	<u>Inclusion:</u> female, postmenopausal (≥ 12 months since last regular menstruation)	12 weeks	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, equivalent to	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear

		or ≥ 6 months since last regular menstruation plus FSH ≥ 50 U/L), ≥ 45 years of age, MRS ≥ 0.4 in at least 3 items <u>Exclusion:</u> BMI > 35 kg/m², cancer, drug abuse, diseases interfering with the assessment of climacteric symptoms, participation in another clinical trial within the last 180 days Black cohosh n = 153 Placebo n = 151 Mean age (black cohosh = 54.0 ± 6.0 years, placebo = 55.0 ± 6.0 years). Median duration of climacteric complaints (black cohosh = 4.4 years, placebo = 5.1 years) Co-morbidities not stated		2.5 mg extract or 20 mg root stock) 1 tablet, twice a day Vs Oral placebo (excipients only) 1 tablet, twice a day 1-week washout period for those taking non-hormonal climacteric drugs, supplements, antiepileptics, psycholeptics or psychoanaleptics. 4-week washout period for those taking hormone replacement therapy	“each patient was randomly assigned to receive one blinded Remifemin tablet or matching placebo...medication was prenumbered using a 1:1 - randomization block size of 4” (method of sequence generation not described) BLINDING: unclear “double-blind”, though there was no mention of who was blinded, or any assurance that interventions matched in appearance, taste or odour FOLLOW-UP: 11.8% drop out ITT: yes Number and reasons for withdrawal were similar between groups SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: low risk
Pockaj 2006 R, placebo-controlled, DB, CO	131	<u>Inclusion:</u> female, history of breast cancer or a perceived increased risk of breast cancer or did not wish to take oestrogen owing to the increased risk of breast cancer, ≥ 14 hot flushes per week for a period of at least 1 month for which therapeutic intervention was desired	8 weeks 4 weeks' active treatment and 4 weeks' placebo treatment	Oral extract of <i>Cimicifuga racemosa</i> rhizome (20 mg, standardised to 5% triterpene glycosides) 1 tablet, twice a day Vs	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method of sequence generation not described BLINDING: adequate “all treatments were doubleblinded”;

	<u>Exclusion:</u> malignant disease, concomitant use of anti-neoplastic chemotherapy, androgens, oestrogens, oral herbal therapies, therapeutic herbal teas or tinctures, any prior use of black cohosh, use of antidepressants within the last 2 weeks (or planned use in the next 9 weeks), and current or planned use of other agents for treating hot flushes. Concomitant use of tamoxifen, raloxifene, aromatase inhibitors, vitamin E or soy were permitted if the participant had been on therapy for at least 1 month and were not anticipating a change in therapy/dosage during the study Black cohosh n = 66 Placebo n = 65 Mean age (black cohosh = 56.0 ± 8.3 years, placebo = 56.7 ± 8.9 years). Duration of menopause not stated Co-morbidities: history of breast cancer (black cohosh = 59%, placebo = 69%) Co-medications: tamoxifen (black cohosh = 40%, placebo = 48%), raloxifene (black		Oral placebo (dosage and constitution not described) 1 tablet, twice a day	“participants received...black cohosh or an identical appearing placebo” FOLLOW-UP: 24.4% drop out ITT: not mentioned, probably high risk of attrition bias 16 women failed to provide hot flush data after baseline; however, the number and reasons for refusal were not given for each group separately SELECTIVE REPORTING: inappropriate Excluding adverse events, data were reported for most primary and secondary outcomes, although no study protocol was published or lodged OTHER: low risk

		cohosh = 2%, placebo = 0%), aromatase inhibitor (black cohosh = 12%, placebo = 10%), not receiving HT (black cohosh = 40%, placebo = 33%)			
Stoll 1987 R, DB, placebo-controlled	80	<u>Inclusion:</u> female, aged 46 to 58 years, ≥ 3 hot flushes a day, ≥ 1 other climacteric symptom <u>Exclusion:</u> contraindications to HT, use of antihypertensive drugs, use of exogenous sexual hormones in the last 4 weeks, metabolic menopausal syndrome in the form of osteoporosis, menopause secondary to ovariectomy or radiation castration Black cohosh n = 30, CEO n = 30, Placebo n = 20 Mean age (black cohosh = 51.3 ± 3.1 years, CEO = 50.3 ± 2.8 years, placebo = 49.8 ± 3.1 years). Duration of menopause not stated Co-morbidities: hysterectomy, uterine or vaginal prolapse, mycosis, biliary troubles, hypotension and varicosis were reported in 33 women (black cohosh = 11, CEO = 13, placebo = 9)	12 weeks	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, 2 mg) 2 tablets twice a day Vs Oral CEO (0.625 mg, plus 3 oral placebo tablets) daily for 21 days, then oral placebo (not described) 2 tablets, twice a day Vs Oral placebo (not described) 2 tablets, twice a day	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method of sequence generation not described BLINDING: adequate “double blind”; interventions were identical in taste and appearance” FOLLOW-UP: 20% drop out ITT: not mentioned, probably high risk of attrition bias The number and reasons for withdrawal differed between groups SELECTIVE REPORTING: unclear no study protocol was published or lodged OTHER: unclear risk Baseline differences in mean parturition rate were observed

Wuttke 2003 R, DB, placebo-controlled, PG	97	Inclusion: female, postmenopausal, aged 40 to 60 years, BMI $\leq$ 30 kg/m², last menstrual bleed $\geq$ 6 months ago, 17β-oestradiol $\leq$ 40 pg/mL and FSH $\geq$ 25 mIU/mL, $\geq$ 3 hot flushes a day during the run-in period, MRS (MRS, sum of items 1 to 6) $\geq$ 1.7 at visits 1 and 2, MRS item 1 $\geq$ 0.3 at visits 1 and 2 Exclusion: signs of ovulatory or anovulatory cycles during the run-in period, hysterectomy, non-response to pretreatment with oestrogens, contraindications to HT unresolved genital bleeding, suspicion or existence of an oestrogen-dependent breast or endometrial carcinoma, endometrial thickness $>$ 5 mm, endometriosis, past or present thromboembolism, phlebitis, acute or chronic hepatic lesion, metabolic disorders of bile pigments, diabetes mellitus, sickle cell anaemia, clinically relevant hypertriglyceridaemia or hypercholesterolaemia, history of myocardial infarction, genital neoplasms, known sensitivity to investigational drugs or ingredients, concomitant treatment with oestrogenic substances, psychotropics, antidepressants, hypnotics or sedatives, alcohol or drug	12 weeks	Oral dried/ethanolic extract of <i>Cimicifuga racemosa</i> rhizome (Klimadynon or Menofem, 20 mg) 2 capsules daily Vs Oral CEO (Oestrofemal, 0.3 mg) 2 capsules daily Vs Oral placebo (constitution not described) 2 capsules daily	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method of sequence generation not described BLINDING: adequate "double blind"; interventions were identical in taste and appearance" FOLLOW-UP: 2.1% drop out, 34% violated the study protocol ITT: no "The remaining...women were included in the per-protocol (PP) analysis" SELECTIVE REPORTING: inappropriate Data is reported for the primary outcome, and for most secondary outcomes (excluding hot flushes, vaginal bleeding and sleep disturbances). No study protocol was published or lodged OTHER: unclear risk Baseline differences in MRS scores and oestradiol and FSH levels were observed Intervention may be a combination formula, although this is not clear. This study reported change-from-

		abuse, poor general condition Black cohosh = 20 CEO n = 22 Placebo n = 20 Mean age (black cohosh = 52.25 ± 3.19 , CEO = 52.32 ± 3.03 , placebo = 54.05 ± 4.36). Mean duration of menopause not stated Co-morbidities not stated			baseline scores; final value scores were not provided on request.

Remarks:

Population:

- The mean age of women in the trials ranged from 50.5 to 56.4 years.
- According to author's definition, all studies included perimenopausal and postmenopausal women, except Kronenberg 2009 and Wuttke 2003, which recruited postmenopausal women only.
- Pokaj 2006 and Jacobson 2001 only included women with a history of breast cancer and Amsterdam 2009 only includes women with anxiety symptoms.
- The mean body mass index (BMI) of women exceeded 25.0 kg/m² in Geller 2009; Kronenberg 2009; Newton 2006, Osmer 2005.

Preparation of *Cimicifuga racemosa*:

- All studies used oral monoprparations of *Cimicifuga racemosa*, extracts were ethanolic, isopropanolic, or not defined solvent. Different formulations and/or of part (root/rhizome) of *C. racemosa* part were also used. Some studies but not all used *C. racemosa* extract standardised to 2.5% to 5.68% triterpene glycosides (mean 3.96%).
- The daily dose of *C. racemosa* extract varied between 8 and 160 mg.

-The range of intervention periods greatly varied between studies from 4 to 52 weeks

-Daily hot flushes frequency is reported in this document. Two studies (Geller 2009, Kronenberg 2009) also reported weekly hot flush frequency. However these were unsuitable for pooling owing to high heterogeneity between them ($I^2 = 91\%$), for which there was no clear explanation. Individual studies do not correspond to our inclusion criteria ($n < 40$ /study group) and are therefore not reported in the present document.

-Different menopausal symptom scores were used in the different study but were nevertheless pooled (KI, GCS, MRS, Wiklund Menopause Symptom Score). Two trials (Frei-Kleiner 2005; Geller 2009) each reported results for two scales. Authors stated that for the MA, only results for one scale were used. The overall effect changed little regardless of the scale selected for inclusion (four possible combinations).

-There were insufficient data to pool results for health-related quality of life, sexuality, vulvovaginal symptoms (Trials assessed vaginal dryness, vaginal bleeding or vaginal pruritus-Individual data were not reported).

Author's conclusions:

- This review is unable to draw any conclusions about the effect of orally administered monopreparations of black cohosh (*C. racemosa*; at doses ranging from 8 to 160 mg daily, for periods varying between four and 52 weeks) on the frequency and intensity of vasomotor symptoms, or global changes in menopausal symptom scores.
- The effect of black cohosh on vulvovaginal atrophic symptoms, HRQoL, sexuality and bone health is inconclusive also.
- No evidence was found that black cohosh was associated with more risk of harm than placebo, but there was insufficient good evidence to reach a firm conclusion on safety.

There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. The uncertain quality of identified trials highlights the need for improved reporting of study methods, particularly with regards to allocation concealment and the handling of incomplete outcome data.

12.2 Black cohosh versus hormone therapy

Meta-analysis: Leach 2012: Black cohosh (*Cimicifuga* spp.) for menopausal symptoms

Inclusion criteria:

- any published or unpublished randomized controlled trials (RCTs) that had evaluated the effectiveness of black cohosh in menopause, without restriction on language or trial duration. Other research designs, such as observational studies and case studies, were excluded.
- women 18 years of age or older with surgical or spontaneous menopause, experiencing climacteric symptoms in the perimenopausal or postmenopausal period and recruited from any setting. Perimenopausal women were defined as women with spontaneous menopause who have experienced irregular menstruation within the previous 12 months. Postmenopausal women were defined as women with surgical or spontaneous menopause and amenorrhoea for more than 12 months
- all women, regardless of any prior or existing morbidity
- any orally administered monopreparation of black cohosh of any dose, form and duration. Combination preparations of black cohosh were excluded.

Search strategy: The authors searched the following electronic sources from inception to March 2012 for the identification of trials: AARP Ageline; Allied & Complementary Medicine (AMED); Australasian Medical Index (AMI); BioMed Central gateway; CAM on PubMed; CINAHL; Cochrane Central Register of Controlled Trials

(CENTRAL) (The Cochrane library); Cochrane Menstrual Disorders and Subfertility group Trials Register; EMBASE; Health Source Nursing/Academic edition; International Pharmaceutical Abstracts; MEDLINE; Natural medicines comprehensive database; PsycINFO; Turning Research Into Practice (TRIP) database. The authors also searched databases of ongoing trials (www.controlled-trials.com/ and www.clinicaltrialsregister.eu/). Additional studies were sought by searching the reference lists.

Content experts and manufacturers of black cohosh extracts were contacted in order to obtain additional references, as well as details of unpublished trials and ongoing trials. The grey literature was also searched for unpublished studies.

Assessment of quality of included trials: yes

ITT analysis: yes

Other methodological remarks: data (final value scores only) were pooled in a meta-analysis with Review Manager (RevMan) 5 software, using a fixed-effect model

Ref	Comparison	N/n	Outcomes	Result
Leach 2012	Black cohosh Vs Hormone therapy	N= 2 n= N.A. (Nappi 2005; Newton 2006)	Daily hot flush frequency	Not pooled due to heterogeneity between studies
Design: MA				Insufficient data
March 2012		N= 2	Hot flush intensity	Not pooled due to heterogeneity between studies

(month-year)		n= N.A. (Bai 2007; Geller 2009)		Geller 2009: Did not meet our inclusion criteria (< n=40/study group) <u>Bai 2007:</u> n=238 MD (95% CI) : 0.07 (-0.10 to 0.24) NS NS
		N= 1 n= 112 (Newton 2006)	Daily frequency of night sweats	MD (95% CI): 0.93 (0.47 to 1.39) P < 0.0001 SS in favour of HT I ² = N.A.
		N= 2 n= N.A. (Stoll 1987; Wuttke 2003).	Frequency or intensity of vulvovaginal symptoms	Not pooled due to heterogeneity in assessed outcomes Insufficient data
		N= 5 n= 468 (Bai 2007; Geller2009; Lehmann-Willenbrock 1988, Nappi 2005, Newton 2006)	Menopausal symptom score	SMD (95%CI): 0.32 (0.13 to 0.51) SS in favour of HT I ² = 69%
		N= 4 n= 461 (Bai 2007; Nappi 2005; Newton 2006; Wuttke 2003).	Adverse effects	<u>Number of recorded events:</u> 202/253 (0.80 events/person) vs 304/208 (1.46 events/person) Statistic not provided <u>Number of women reporting adverse events</u>

				N=1, does not correspond to our inclusion criteria (< n=40/study group)

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Bai 2007 R, DB, active controlled, DD, PG	244	<u>Inclusion:</u> female, aged between 40 and 60 years, history of menopausal complaints for at least 4 weeks, spontaneous amenorrhoeic interval ≥ 5 months since last regular menstruation, baseline E2 ≤ 30 pg/mL if amenorrhoeic < 12 months, KI ≥ 15 <u>Exclusion:</u> HT within the last 4 weeks, psychoactive drugs, BMI > 28 kg/m ² , endometrial thickness ≥ 5 mm if amenorrhoea ≥ 12 months or ≥ 15 mm if < 12 months, irregular gynaecological bleeding within the last 4 weeks, hysterectomy, amenorrhoea > 8 years, abnormal cervical smear examination, contraindication of tibolone, cancer, severe or current disease that could interfere with climacteric manifestations or treatment, drug abuse, alcohol addiction, participation in a Phase I or II trial in the last 180 days or a	12 weeks	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, equivalent to 2.5 mg dry extract or 20 mg <i>C. racemosa</i> root) 2 tablet twice a day, and 2 tibolone-matching placebo tablet daily Vs Oral tibolone 2.5 mg tablet daily, and 2 <i>C. racemosa</i> -matching placebo tablets daily	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear All eligible subjects were randomly allocated to the two treatment groups" (method not described) BLINDING: adequate "double-blind"; "double dummy"; "patients received two Remifemin® tablets (1-0-1) and one tibolone-matching placebo...the tibolone group applied two Remifemin®-matching placebos and one tibolone tablet" FOLLOW-UP: 10.7% dropped out ITT: not mentioned, probably high risk of attrition bias the term 'full analysis set' was used; however, "six subjects were excluded from the full analysis set... for discontinuing the trial for any reason". A similar proportion of

		Phase III or IV trial within the last 90 days, and any drug, food, traditional Chinese medicine or nutritional supplement used for climacteric symptoms Black cohosh n = 122 Tibolone n = 122 Mean age (black cohosh = 51.8 ± 3.7 years, tibolone = 51.5 ± 3.5 years). Duration of amenorrhoea (black cohosh = 32.2 ± 24.6 months, tibolone = 35.4 ± 25.3 months) Co-morbidities not stated			women withdrew from each group, though the reasons differed. SELECTIVE REPORTING: unclear no study protocol was published or lodged OTHER: low risk of bias
Geller 2009 R, DB, placebo-controlled, PG	89	<u>Inclusion:</u> female, perimenopausal or postmenopausal with intact uterus, experiencing ≥ 35 vasomotor symptoms (hot flushes and night sweats) per week, amenorrhoea > 6 months and < 10 years' duration, FSH > 40 mIU/mL, HT not contraindicated <u>Exclusion:</u> hysterectomy, abnormal vaginal bleeding of undetermined aetiology, abnormal transvaginal ultrasound (> 7 mm thickness), abnormal endometrial biopsy or mammogram, diabetes, positive pregnancy test, breastfeeding, history of endometrial	52 weeks	Oral ethanolic extract of <i>Cimicifuga racemosa</i> below-ground parts (64 mg, standardised to 5.68% triterpene glycosides) 2 capsules daily; Vs Oral CEO (0.625 mg) 1 capsule daily and oral MDP (2.5 mg) 1 capsule daily Vs	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: adequate “a random, computer-generated code assigned two women in each cluster to each of the four treatment arms. There were 11 clusters with eight women in each cluster” BLINDING : adequate “Double blinded”; “the study capsules were identical in appearance, and there was no detectable odor for any of the preparations”

	hyperplasia/neoplasia, breast cancer or cancer of the reproductive tract, history of myocardial infarction, stroke, severe varicose veins, sickle cell anaemia, deep vein thrombosis, thrombophlebitis or thromboembolic disorder, untreated or uncontrolled hypertension (systolic blood pressure > 165 mmHg or diastolic blood pressure > 95 mmHg), history of severe recurrent depression, severe psychiatric disturbance, alcohol abuse or drug abuse, concurrent use of medication containing oestrogen, progestin, SERM, St.John'sWort, biphosphonates or dietary phyto-oestrogens, history of migraine associated with hormone use, smoker, vegan diet, participation in another clinical trial within 30 days of enrolment, Black cohosh n = 22, Red clover n = 22 CEO/MPA n = 23 Placebo n = 22 Mean age (black cohosh = 54.4 ± 3.9 years, red clover = 52.4 ± 4.6 years, CEO/MPA = 53.3 ± 4.0 years, placebo = 52.0 ± 4.2 years).		Oral placebo (not described) 2 capsules daily 1-month washout period for women using transdermal hormone preparations or oral botanical supplements, and 2-month washout period for women using oral HT	FOLLOW-UP: 10.1% drop out ITT: yes but probably high risk of attrition bias "intention-to-treat" was quoted, but the analysis consisted only of "randomized women who had been in the study for at least 3 months" 9 women withdrew from the study – the number and reasons for withdrawal differed between groups SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: Unclear risk Baseline differences in race and BMI were evident, although all analyses controlled for these variables

		Duration of amenorrhoea (black cohosh = 3.4 ± 2.6 years, red clover = 4.1 ± 2.8 years, CEO/MPA = 3.6 ± 2.9 years, placebo = 2.8 ± 2.9 years) Co-morbidities not stated			
Lehmann-Willenbrock 1988 R	60	<u>Inclusion:</u> female, hysterectomised, aged under 40 years, has at least 1 intact ovary, complaining of climacteric symptoms <u>Exclusion:</u> type I diabetes mellitus, chronic hepatitis, deep vein thrombosis, breast cancer, contraindication to HT Oestriol n = 15 Conjugated-oestrogen n = 15 Oestradiol/norethisterone n = 15 Black cohosh n = 15 Menage not stated. Duration of menopause not stated Co-morbidities not stated Climacteric symptoms?	Not stated	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, 2 mg) 2 tablets, twice daily Vs Oral oestriol (Ovestin, 1 mg) 1 tablet daily Vs Oral conjugated oestrogen (Presomen, 1.25 mg) 1 tablet daily Vs Oral oestradiol/norethisterone acetate (Trisequens) 1 tablet, daily	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method not described BLINDING : unclear There is no mention of blinding FOLLOW-UP: 8.3% drop out ITT: not mentioned, probably high risk of attrition bias 5 women withdrew from the study; however, the number and reasons for withdrawal were not given for each group separately SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: Unclear risk Participant characteristics at baseline were not reported
Nappi 2005 R, PG	64	<u>Inclusion:</u> spontaneous menopause of at least 6 months' duration, FSH > 30 mIU/L, presence of at least 5 hot flushes daily, endometrial thickness < 5 mm	12 weeks	Oral isopropanolic extract of <i>Cimicifuga racemosa</i> (Remifemin, 40 mg) 1 tablet daily	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: adequate "patients were randomly allocated"

		<u>Exclusion:</u> previous HT, contraindications to HT Black cohosh n = 32, Oestradiol n = 32 Mean age (black cohosh = 50.5 ± 2.1 years, oestradiol = 50.9 ± 1.8 years). Duration of menopause (black cohosh = 9.0 ± 2.9 months, oestradiol = 9.1 ± 3.0 months) Co-morbidities: not stated		Vs Transdermal oestradiol (Estraderm, 25 µg) every 7 days, plus dihydrogesterone (Dufaston, 10 mg) 1 tablet daily for the last 12 days of the 3-month oestradiol treatment	on the basis of a computer-generated number list” BLINDING : inadequate Women were not blinded to treatment as the 2 interventions used different routes of administration and different dosage regimens. It is not clear if observers were blinded to treatment FOLLOW-UP: 1.6% drop out ITT: not mentioned, probably high risk of attrition bias 1 woman withdrew from the intervention group owing to nausea. A similar number of women in each group “refused to provide a blood sample at follow-up” SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: low risk
Newton 2006 R, DB, placebo-controlled, PG,	351	<u>Inclusion:</u> female, late menopausal transition (≥ 1 skipped menses in the last 12 months) or postmenopausal (no bleeding in the last 12 months) or FSH > 20 IU/mL (if participant had undergone hysterectomy without bilateral oophorectomy), aged between 45 and 55 years, and ≥ 2	52 weeks	oral ethanolic extract of <i>Cimicifuga racemosa</i> rhizome and root (CimiPure, 80mg, standardised to 2.5% triterpene glycosides) 2 capsules daily; Vs	ALLOCATION CONC: adequate “the study nurse determined the appropriate stratum, assigned the participant the next study number in that stratum without knowledge of group assignment, and distributed study medications” RANDOMIZATION: adequate “participants were randomly assigned

		vasomotor symptoms daily over the past 2 weeks (with ≥ 6 moderate to severe symptoms), negative mammogram in the last 2 years, normal thyroid stimulating hormone level <u>Exclusion:</u> contraindications to HT, use of HT or oral contraceptives within the last 3 months, use of herbal medicines for menopausal symptoms within the last month, allergy to soy, bilateral oophorectomy, history of breast cancer, non-adherence ($< 80\%$ of capsules administered) during the run-in period Black cohosh n = 80 Multibotanical n = 76 Multi-botanical plus dietary soy n = 79 CEO and MPA n = 32 Placebo n = 84 Mean age (black cohosh = 52.0 ± 2.2 years, multibotanical = 52.2 ± 2.5 years, multi-botanical plus dietary soy = 52.5 ± 2.5 years, CEO and MPA = 52.3 ± 2.6 years, placebo = 52.0 ± 2.5 years). Duration of menopause not stated Co-morbidities not stated		Oral CEO (0.625 mg) 1 tablet daily, with (for women with a uterus) or without (for women without a uterus) MDP (2.5 mg) 1 tablet daily Vs Oral placebo (dose and constitution is not described) Vs Multibotanical Vs Multibotanical + soy	by using SAS software, stratified by previous HT and hysterectomy; block sizes within strata ranged from 5 to 25" BLINDING: adequate "double-blind"; "to facilitate blinding, medications and lactose placebo were encapsulated to provide 2 white and 2 blue capsules to each woman" FOLLOW-UP: 12.8% drop out ITT: yes 1 "mixed-model analysis allowed us to use a true intention-to-treat approach" Numbers of withdrawals were similar between groups, though reasons for withdrawal differed. 16 women were unblinded; however, numbers were not given for each group separately SELECTIVE REPORTING: unclear No study protocol was published or lodged. OTHER: unclear risk Baseline differences in BMI were observed
Stoll 1987	80	<u>Inclusion:</u> female, aged 46 to 58 years, ≥ 3 hot flushes a day, ≥ 1 other climacteric	12 weeks	Oral isopropanolic extract of <i>Cimicifuga racemosa</i>	ALLOCATION CONC: unclear Method of allocation concealment not described

R, DB, placebo-controlled		symptom <u>Exclusion:</u> contraindications to HT, use of antihypertensive drugs, use of exogenous sexual hormones in the last 4 weeks, metabolic menopausal syndrome in the form of osteoporosis, menopause secondary to ovariectomy or radiation castration Black cohosh n = 30, CEO n = 30, Placebo n = 20 Mean age (black cohosh = 51.3 ± 3.1 years, CEO = 50.3 ± 2.8 years, placebo = 49.8 ± 3.1 years). Duration of menopause not stated Co-morbidities: hysterectomy, uterine or vaginal prolapse, mycosis, biliary troubles, hypotension and varicosis were reported in 33 women (black cohosh = 11, CEO = 13, placebo = 9)		(Remifemin, 2 mg) 2 tablets twice a day Vs Oral CEO (0.625 mg, plus 3 oral placebo tablets) daily for 21 days, then oral placebo (not described) 2 tablets, twice a day vs oral placebo (not described) 2 tablets, twice a day	RANDOMIZATION: unclear method of sequence generation not described BLINDING: adequate “double blind”; interventions were identical in taste and appearance” FOLLOW-UP: 20% drop out ITT: not mentioned, probably high risk of attrition bias The number and reasons for withdrawal differed between groups SELECTIVE REPORTING: unclear no study protocol was published or lodged OTHER: unclear risk Baseline differences in mean parturition rate were observed
Wuttke 2003 R, DB, placebo-controlled, PG	97	<u>Inclusion:</u> female, postmenopausal, aged 40 to 60 years, BMI ≤ 30 kg/m², last menstrual bleed ≥ 6 months ago, 17β-oestradiol ≤ 40 pg/mL and FSH ≥ 25 mIU/mL, ≥ 3 hot flushes a day during the run-in period, MRS (MRS, sum of	12 weeks	Oral dried/ethanolic extract of <i>Cimicifuga racemosa</i> rhizome (Klimadynon or Menofem, 20 mg) 2 capsules daily Vs	ALLOCATION CONC: unclear Method of allocation concealment not described RANDOMIZATION: unclear method of sequence generation not described BLINDING: adequate

	items 1 to 6) ≥ 1.7 at visits 1 and 2, MRS item 1 ≥ 0.3 at visits 1 and 2 <u>Exclusion:</u> signs of ovulatory or anovulatory cycles during the run-in period, hysterectomy, non-response to pretreatment with oestrogens, contraindications to HT unresolved genital bleeding, suspicion or existence of an oestrogen-dependent breast or endometrial carcinoma, endometrial thickness > 5 mm, endometriosis, past or present thromboembolism, phlebitis, acute or chronic hepatic lesion, metabolic disorders of bile pigments, diabetes mellitus, sickle cell anaemia, clinically relevant hypertriglyceridaemia or hypercholesterolaemia, history of myocardial infarction, genital neoplasms, known sensitivity to investigational drugs or ingredients, concomitant treatment with oestrogenic substances, psychotropics, antidepressants, hypnotics or sedatives, alcohol or drug abuse, poor general condition Black cohosh = 20 CEO n = 22 Placebo n = 20 Mean age (black cohosh = 52.25 ± 3.19, CEO = 52.32 ± 3).	Oral CEO (Oestrofeminal, 0.3 mg) 2 capsules daily Vs Oral placebo (constitution not described) 2 capsules daily	“double blind”; interventions were identical in taste and appearance” FOLLOW-UP: 2.1% drop out, 34% violated the study protocol ITT: no “The remaining...women were included in the per-protocol (PP) analysis” SELECTIVE REPORTING: inappropriate Data is reported for the primary outcome, and for most secondary outcomes (excluding hot flushes, vaginal bleeding and sleep disturbances). No study protocol was published or lodged OTHER: unclear risk Baseline differences in MRS scores and oestradiol and FSH levels were observed Intervention may be a combination formula, although this is not clear. This study reported change-from-baseline scores; final value scores were not provided on request.

		03, placebo = 54.05 ± 4.36).			
		Mean duration of menopause not stated			
		Co-morbidities not stated			

Remarks:

Population:

- The mean age of women in the trials ranged from 50.5 to 56.4 years.
- According to author's definition, all studies included perimenopausal and/or postmenopausal women, except Kronenberg 2009 and Wuttke 2003, which recruited postmenopausal women only.
- The mean body mass index (BMI) of women exceeded 25.0 kg/m² in Geller 2009; Kronenberg 2009; Newton 2006, Osmer 2005.

Preparation of *Cimicifuga racemosa*:

- All studies used oral monoprparations of *Cimicifuga racemosa*, extracts were ethanolic, isopropanolic, or not defined solvent. Different formulations and/or parts (root/rhizome) of *C. racemosa* were also used. Some studies but not all used *C. racemosa* extract standardised to 2.5% to 5.68% triterpene glycosides (mean 3.96%).
- The daily dose of *C. racemosa* extract varied between 8 and 160 mg.

-HT used as comparator differed between studies. Most of the studies used combination of estrogen with progestogen. One study used tibolone 2.5mg/d (Bai 2007). One study used transdermal formulation plus sequential progestogen (Transdermal oestradiol (25 µg/week + dihydrogesterone 10 mg/d 12 days, Nappi 2005). Oral CEE (0.625 mg/d) + oral MDP (2.5 mg/d) was used in 3 studies. Oral CEE (1.25 mg/) was used in 1 study. Oral CEE (Oestrofeminal, 0.3 mg, 2caps/d) was used in one study. Oral oestriol (1 mg/d) was used in 1 study. Oral oestradiol + norethisterone acetate daily was used in one study

-The range of intervention periods greatly varied between studies from 4 to 52 weeks.

-Different menopausal symptom scores were used in the different study but were nevertheless pooled (KI, GCS, MRS, Wiklund Menopause Symptom Score). Note that one trial (Geller 2009) reported results for two scales. For this analysis, results for only one scale were used at a time; when GCS scores were used instead of KI scores, the overall effect was marginally reduced but still statistically significant in favour of HT (not individually reported-does not meet our inclusion criteria).

-Two studies reported daily flush frequency, however these trials were not pooled owing to high heterogeneity between the two trials measuring hot flushes per day, for which there was no clear explanation. One study also reported weekly flush frequency. None of these studies meet our inclusion criteria (n< 40/study group) and they were therefore not reported.

-There were insufficient data to pool results for health-related quality of life, sexuality, vulvovaginal symptoms (Trials assessed vaginal dryness, vaginal bleeding or vaginal pruritus--Individual data were not reported).

Author's conclusions:

- This review is unable to draw any conclusions about the effect of orally administered monopreparations of black cohosh (*C. racemosa*; at doses ranging from 8 to 160 mg daily, for periods varying between four and 52 weeks) on the frequency and intensity of vasomotor symptoms, or global changes in menopausal symptom scores.
- The effect of black cohosh on vulvovaginal atrophic symptoms, HRQoL, sexuality and bone health is inconclusive also.
- No evidence was found that black cohosh was associated with more risk of harm than placebo, but there was insufficient good evidence to reach a firm conclusion on safety.

There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. The uncertain quality of identified trials highlights the need for improved reporting of study methods, particularly with regards to allocation concealment and the handling of incomplete outcome data.

13 Appendix. Evidence tables. Hormone therapy versus placebo: primary prevention of chronic conditions

13.1 Estrogen only versus placebo: Cancer

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

“For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization’s International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.”

Assessment of quality of included trials: yes

ITT analysis: yes for most

Other methodological remarks:

13.1.1 Breast cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N= 1 n= 10739 Postintervention extension followup: n=7645 Cumulative followup (intervention plus postintervention extension phases): n=9939	<u>Invasive breast cancer</u>	
			Intervention followup: Median 7.2 years	CEE vs placebo 104 (0.28%) vs. 135 (0.35%); HR, 0.79 (95% CI, 0.61 to 1.02); p=0.07 NS
			Postintervention followup: Median 6.6 years (197)	HR, 0.80 (95% CI, 0.58 to 1.11); p=0.19 NS
			Postintervention followup: Median 10.8 years (255)	18 (0.037% annualized) vs. 32 (0.065% annualized); HR, 0.57 (95% CI, 0.32 to 1.02); p=0.06 NS

		WHI Estrogen-only trial (Anderson, 2004(244); Anderson, 2012(245); LaCroix, 2011;(246) Prentice, 2009; (247) Manson, 2013;(197) Chlebowski, 2015; (248) Manson, 2019; (249) Chlebowski, 2016; (250) Chlebowski, 2020; (251) Chlebowski, 2017; (252) Prentice, 2019; (253) Prentice, 2020; (254) Manson, 2017 (255))	Cumulative followup: Median 13.0 years	168 (0.28% annualized) vs. 216 (0.35% annualized); HR, 0.79 (95% CI, 0.65 to 0.97); p=0.02 (197) SS
			Cumulative followup: Median 18.0 years (254)	231 (0.30% annualized) vs. 291 (0.38% annualized); no HR reported; p=NR
			Cumulative followup: Median 19.4 years (253)	231 (4.4% calculated) vs. 291 (5.4% calculated); HR, 0.80 (95% CI, 0.68 to 0.95); p=NR SS
			Cumulative followup: Median 20.7 years (251) It was 20.7 years for participants who consented to extended followup beyond September 30, 2010 (i.e., extension II), but 16.2 years overall when including patients who did not consent to participate in extension II. These data reflect both those who consented and did not consent to extended followup.	238 (0.30%) vs. 296 (0.37%); HR, 0.78 (95% CI, 0.65 to 0.93); p=0.005 SS
			Breast cancer mortality	
			Intervention followup: Median 7.2 years	4 (0.010% annualized) vs. 9 (0.023%); HR, 0.45 (95% CI, 0.14 to 1.46); p=0.17 NS
			Cumulative followup: Median 17.7 years (255)	22 (0.025% annualized) vs. 41 (0.046% annualized); HR, 0.55 (95% CI, 0.33 to 0.92); p=0.02 SS
			Cumulative followup: Median 20.7 years (251)	30 (0.031%) vs. 46 (0.046%); HR, 0.60 (95% CI, 0.37 to 0.97); p=0.04 SS

		N= 1 n= 222 EPAT Estrogen-only trial Hodis, 2001 (256)	Breast cancer (not defined) Intervention followup: Mean 2 years	Micronized 17 β -estradiol vs placebo 0 (0%) vs. 1 (1%)
		N= 1 n= 309 ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000 (215)	Breast cancer (not defined) Intervention followup: Mean 3.2 years	1 (CEE) vs. 0 (CEE + MPA) vs. 0 (placebo); p=0.35
		N= 1 n= 701 PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995 (257)	Breast cancer (not defined) Intervention followup: Mean 3 years	1 (estrogen) vs. 2 (estrogen plus progestin) vs. 4 (estrogen plus micronized progestin) vs. 1 (placebo); p=0.29

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks: The authors did not pool trial results, primarily because of heterogeneity in study duration and definitions of breast cancer incidence.

13.1.2 Colorectal cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT + cohort study Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=10739 Postintervention followup: n=9666 Postintervention extension followup: n=9786	Colorectal cancer	
			Intervention followup: Median 7.2 years	65 (1.22%) vs. 58 (1.07%); HR, 1.15 (95% CI, 0.81 to 1.64); p=0.44(197) NS
			Postintervention only followup: Median 6.6 years (197)	HR, 1.10 (95% CI, 0.68 to 1.78); p=0.69 NS
			Cumulative followup: Median 13.0 years (197)	HR, 1.13 (95% CI, 0.85 to 1.51); p=0.39 NS
		WHI Estrogen-only trial Anderson, 2004;(244) Ritenbaugh, 2008;(258) Prentice, 2009;(247) LaCroix, 2011;(246) Manson, 2013;(197) Manson, 2019;(249) Chlebowski, 2017;(252) Prentice, 2020;(254) Manson, 2017;(255) Prentice, 2020(254) RCT	Colorectal cancer mortality	
			Intervention followup: Median 7.2 years	16 (0.041% annualized) vs. 17 (0.043%); HR, 0.98 (95% CI, 0.50 to 1.95); p=0.96 NS
			Cumulative followup: Median 10.8 years(255)	31 (0.064% annualized) vs. 23 (0.046%); HR, 1.36 (95% CI, 0.79 to 2.34); p=0.26 NS
			Cumulative followup: Median 17.7 years	47 (0.054% annualized) vs. 40 (0.045%); HR, 1.21 (95% CI, 0.79 to 1.84); p=0.38 NS
			Other colorectal cancer outcomes(258)	Invasive colorectal cancer HR, 1.12 (95% CI, 0.77 to 1.63); p=0.55 NS
			Intervention followup: Median 7.2 years	Invasive colon cancer HR, 1.26 (95% CI, 0.84 to 1.88); p=0.26 NS
			The mean followup for some of these analyses (Ritenbaugh, 2008(258) and Prentice,	Invasive rectal cancer HR, 0.53 (95% CI, 0.18 to 1.56); p=0.25

			2009(247)) was 7.1 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson (2013).(197)	NS
		N=1 n=85734 Multiethnic Cohort Study Park, 2016(259) Cohort study	Colorectal cancer	<u>Followup: 16 years</u> Ever used estrogen only: 547 (1.2% calculated) vs. 903 (2.3% calculated); HR, 0.85 (95% CI, 0.76 to 0.94) SS Currently use estrogen only: 214 vs. 903 (2.3% calculated); HR, 0.77 (95% CI, 0.66 to 0.89) SS

* Characteristics of included studies: see below

Remarks:/

13.1.3 Cervical cancer

No studies were found

13.1.4 Endometrial cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT	Estrogen vs placebo	N=1 n=222 EPAT Estrogen- only trial	Endometrial cancer Intervention followup: Mean 2 years	0 (0.0%) vs. 0 (0.0%)

Search date: (Jun-2022)		Hodis 2001(256)		
		N=1 n=205 ERA Estrogen only and estrogen plus progestin trial Herrington, 2000(215)	Endometrial cancer Intervention followup: Mean 3.2 years	0 (0.0%) vs. 0 (0.0%)
		N=1 n=349 PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995(257)	Endometrial cancer Intervention followup: Mean 3 years	0 (estrogen plus progestin) vs. 0 (estrogen plus micronized progestin) vs. 0 (placebo)
		N=1 n=417 ULTRA Estrogen-only trial Johnson et al, 2005(260)	Endometrial cancer Intervention followup: Mean 2 years	0 (0.0%) vs. 0 (0.0%); difference, 0.0 (95% CI, -4.2 to 3.1); p=1.000 NS

* Characteristics of included studies: see below

Remarks: The authors do not discuss the results because of the well-known risk of endometrial hyperplasia and cancer associated with unopposed estrogen use.

13.1.5 Ovarian cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT + cohort study Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=7166 Black Women's Health Study Bethea, 2017(261) <u>Prospective cohort study</u>	Ovarian cancer Follow-up 18 years	17 (0.7% calculated) vs. 61 (1.3% calculated) HR, 1.66 (95% CI, 0.90 to 3.07) NS

* Characteristics of included studies: see below

Remarks: No eligible RCTs reported on incidence of ovarian cancer.

13.1.6 Lung cancer

Ref	Comparison	N/n	Outcomes	Result
	Estrogen		Lung cancer	

Gartlehner 2022 Design: RCT Search date: (Jun-2022)	vs placebo	N=1 n=10739 Postintervention followup: n=9666 Postintervention extension followup: n=9786 WHI Estrogen-only trial Chlebowski, 2010;(262) Manson, 2013(197) RCT	Intervention followup: Median 7.2 years (197)	CEE vs placebo 62 (0.16% annualized) vs. 61 (0.16% annualized); HR, 1.05 (95% CI, 0.74 to 1.49); p=0.79 NS
			Intervention and partial postintervention followup: Mean 7.9 years(262) (Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson(197); this would mean these results are for trial and posttrial phases combined together.)	Lung cancer 61 (0.15% annualized) vs. 54 (0.13% annualized); HR, 1.17 (95% CI, 0.81 to 1.69); p=0.39 NS NSCLC 51 (0.12% annualized) vs. 48 (0.11% annualized); HR, 1.10 (95% CI, 0.74 to 1.64); p=0.62 NS SCLC 9 (0.02% annualized) vs. 6 (0.01% annualized); HR, 1.57 (95% CI, 0.56 to 4.41); p=0.39 NS
			Postintervention followup: Median 6.6 years (197)	47 (0.20% annualized) vs. 53 (0.22% annualized); HR, 0.90 (95% CI, 0.61 to 1.34); p=0.61 NS
			Cumulative followup: Median 13.0 years (197)	109 (0.18% annualized) vs. 114 (0.18% annualized); HR, 0.98 (95% CI, 0.75 to 1.27); p=0.87 NS
			Mortality Intervention and partial postintervention followup: Mean 7.9 years(262) (Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson(197);	Mortality from lung cancer 34 (0.08% annualized) vs. 33 (0.08% annualized); HR, 1.07 (95% CI, 0.66 to 1.72); p=0.79 NS Mortality from NSCLC 25 (0.06% annualized) vs. 29 (0.07% annualized); HR, 0.89 (95% CI, 0.52 to 1.52); p=0.67

			this would mean these results are for trial and posttrial phases combined together.)	NS Mortality from SCLC 8 (0.02% annualized) vs. 4 (0.01% annualized); HR, 2.11 (95% CI, 0.62 to 7.01); p=0.22 NS

* Characteristics of included studies: see below

Remarks:/

13.1.7 Non-Hodgkin's Lymphoma

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen vs placebo	N=1 n=10685 WHI Estrogen-only trial Kato 2016(263) RCT	Incidence of non-Hodgkin's lymphoma	
			Intervention followup: Median 7.2 years	HR, 0.89 (95% CI, 0.56 to 1.42) NS
			Cumulative followup: Median 12.9 years	80 (0.117% annualized) vs. 80 (0.115% annualized); HR, 1.02 (95% CI, 0.74 to 1.39) NS

* Characteristics of included studies: see below

Remarks:/

13.1.8 Total cancer mortality

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1	Total cancer mortality	
		n=10739	Intervention followup: Median 7.2 years (255)	126 (0.33% annualized) vs. 136 (0.34% annualized); HR, 0.96 (95% CI, 0.75 to 1.22); p=0.72 NS
		Postintervention extension followup: n=10139	Postintervention followup: Median 10.8 years (255)	298 (0.61% annualized) vs. 303 (0.61% annualized); HR, 1.00 (95% CI, 0.85 to 1.17); p=1.00 NS
		Cumulative followup (intervention plus postintervention extension phases): n=10739	Cumulative followup: Median 13.0 years(197)	260 (0.42% annualized) vs. 278 (0.44% annualized); HR, 0.95 (95% CI, 0.81 to 1.13); p=0.58 NS
		Cumulative followup (intervention plus postintervention extension phases): n=10739 WHI Estrogen-only trial Manson 2013(197) ; Manson 2019(249); Manson, 2017(255) RCT	Cumulative followup: Median 17.7 years(255)	424 (0.49% annualized) vs. 439 (0.49% annualized); HR, 0.99 (95% CI, 0.86 to 1.13); p=0.86 NS

* Characteristics of included studies: see below

Remarks:/

13.1.9 Author's conclusions

Summary of review findings

Results of our review indicate some benefits of hormone therapy regarding the prevention of chronic conditions ([KQ 1](#)). For women using estrogen only, risk of diabetes (134 fewer cases per 10,000 women over 7.1 years) and risk of fractures (388 fewer cases per 10,000 women over 7.2 years) were statistically significantly reduced compared with women taking placebo. The risk for invasive breast cancer was numerically reduced in women using estrogen only, but the difference compared with placebo did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]). Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years), diabetes (78 fewer cases per 10,000 women over 5.6 years), and fractures (230 fewer cases per 10,000 women over 2 to 5.6 years) compared with women in the placebo groups. Benefits of hormone therapy for colorectal cancer attenuated with extended followup and were no longer statistically significant.

Our review also documented several important harms of hormone therapy ([KQ 2](#)). Women taking estrogen-only therapy had a statistically significant increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.2 years), urinary incontinence (885 more cases per 10,000 women over 1.0 year), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years) compared with women in the placebo groups.

Likewise, for women taking estrogen plus progestin therapy, risks of invasive breast cancer (51 more cases per 10,000 women over 5.6 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (260 more cases per 10,000 women over 5.6 years), stroke (52 more cases per 10,000 women over 5.6 years), urinary incontinence (562 more cases per 10,000 women over 1 year), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years) were statistically significantly increased compared with women taking placebo. A Danish retrospective cohort study also reported an increased risk for endometrial cancer (RR, 1.71 [1.58 to 1.86] over 9.8 years).

Based on high- or moderate-strength evidence, the risks for coronary heart disease and all-cause mortality were similar between estrogen-only hormone therapy and placebo. Likewise, high- or moderate-strength evidence indicates similar risks for lung cancer and all-cause mortality between estrogen plus progestin hormone therapy and placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-off between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years at the end of the intervention phase (HR, 1.12 [95% CI, 1.02 to 1.24]). After 18 years of cumulative followup, no statistically significant differences between groups were still apparent.

For women who were randomized to estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03 [95% CI, 0.93 to 1.13]). Long-term followup also did not show any statistically significant differences between groups.

Conclusions

Hormone therapy plays an important role in the clinical management of menopausal symptoms, but it has a complex pattern of risks and benefits in the primary prevention of chronic conditions. Depending on the treatment regimen, the risk-benefit profile of hormone therapy for the prevention of chronic conditions differs for women ages 50 to 79 years. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risk of fractures or diabetes) but also an increased risk of harms (e.g., higher risk of stroke, thromboembolic events, gallbladder disease, and possibly urinary incontinence), particularly among women older than age 60 years. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profile (with more favorable results in younger women), particularly for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

13.1.10 Characteristics of included studies

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022
WHI Estrogen-only trial Women's Health Initiative (WHI) Anderson et al, 2004; (244) Bonds et al, 2006; (264) Brunner et al, 2005; (77) Chlebowski et al, 2010; (262) Cirillo et al, 2005; (265) Curb et al, 2006; (266) Hendrix et al, 2005; (267) Hendrix et al, 2006; (268) Hsia et al, 2006; (269) Manson et al, 2013; (197) Ritenbaugh et al, 2008; (258) Rossouw et al, 2007 (270) RCT	n= 10739	• United States • Postmenopausal • Ages 50–79 years • Prior hysterectomy • 3-month washout period required for women using hormone therapy at baseline	Median 7.2 years	CEE 0.625 mg/day (N=5,310) Placebo (N=5,429)	The assessment is not entirely clear in Gartlehner 2022. The following quality rating was provided: -WHI (U.S.): Fair -WHI (U.S.) – breast cancer: Fair -WHI (U.S.) – breast cancer, CHD, stroke, hip fracture, non-Hodgkin's lymphoma: Fair -WHI (U.S.) – fractures: Fair -WHI (U.S.) – lung cancer: Fair -WHI (U.S.) – stroke, VTE, mortality, breast cancer, CHD: Fair -WHI (U.S.) – mortality: Fair -WHI (U.S.) – endometrial cancer: Fair Details (randomization, allocation concealment, etc.) about the risk of bias can be found in Gartlehner 2022 Quality Rating: Fair (for outcomes mortality and endometrial cancer the quality rating is good)

					FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHI Estrogen-only trial Postintervention and Postintervention Extension Phases Chlebowski et al, 2010;(271) LaCroix et al, 2011;(246) Manson et al, 2013;(197) Manson, 2017;(255) Prentice, 2020;(254) Prentice, 2020(253) RCT	Postintervention phase n= 9666 (90%) had any postintervention followup Postintervention Extension Phase n= 7645 (71%) consented to participate in the extension phase	See above	Postintervention phase Mean 6.6 years	Postintervention followup CEE 0.625 mg/day (N=4,794) Placebo (N=4,872) Postintervention extension followup CEE 0.625 mg/day (N=3,778) Placebo (N=3,867)	
EPAT Estrogen-only trial Estrogen in the Prevention of Atherosclerosis [EPAT] (256) Hodis et al, 2001 (256)	n=222	• United States • Postmenopausal women • Ages 46–80 years • Low-density lipoprotein cholesterol level ≥ 130 mg/dL	2 years	Micronized 17 β -estradiol 1 mg/day (N=111) Placebo (N=111)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes Other biases? Yes Quality Rating: Fair

RCT					FUNDING: investigator initiated trial
ERA Estrogen-only and estrogen plus progestin trial Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis [ERA] Herrington et al, 2000 (215) RCT	n=205	• United States • Ages 41–79 years • Postmenopausal women not currently receiving estrogen replacement therapy • With >1 epicardial coronary stenosis of $\geq 30\%$ of the luminal diameter	3.2 years	CEE 0.625 mg/day (N=100) CEE 0.625 mg/day plus MPA 2.5 mg/day (N=104) Placebo (N=105)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Unclear Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes Other biases? Yes between placebo and CEE in adherence. Quality Rating: Fair FUNDING: National Heart, Lung and Blood Institute
PEPI Estrogen-only and estrogen plus progestin trial Postmenopausal Estrogen and Progestin Interventions Trial [PEPI] PEPI, 1995(257)	n=349	• United States • Ages 45–64 years • With or without a uterus • Naturally or surgically menopausal	3 years	CEE 0.625 mg/day (N=175) CEE 0.625 mg/day plus MPA 10 mg/day for 12 days/month (N=174) CEE 0.625 mg/day plus MP 200 mg/day for 12 days/month (N=178) Placebo (N=174)	Randomization adequate? Yes Allocation concealment adequate? Unclear Groups similar at baseline? Unclear Outcome assessors masked? Yes Care providers masked? Unclear Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Unclear Intention-to-treat analysis? No Other biases? Yes Potential risk of contamination and low adherence to assigned study medications. Study authors noted that in women assigned to CEE,

RCT					continuation rate was lowest and potentially due to endometrial hyperplasia. Some women were also initiated on another hormone regimen (other than the one assigned at randomization); this included up to 18% in some study arms. Quality Rating: Fair FUNDING: National Heart, Lung, and Blood Institute (NHLBI)
Multiethnic Cohort Study Park, 2016(259) <u>Cohort study</u>	n=85734	Postmenopausal women who have ever (n= 46723) or never (n=39011) used hormone therapy	16 years	-Ever used estrogen only -Currently use estrogen only -Ever used estrogen plus progestin - Currently use estrogen plus progestin	-Bias due to confounding: Moderate - Bias in selection of participants into the study: Moderate - Bias in classification of interventions: Moderate - Bias due to deviations from intended interventions: Low - Bias due to missing data: Low -Bias in measurement of outcomes: Low -Bias in selection of the reported result: Low Overall risk of bias: Moderate risk of bias FUNDING: National Cancer Institute, USA

ULTRA Estrogen-only trial Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) Ettinger et al, 2004(272); Johnson et al, 2005(260); Waetjen et al, 2005(273); Yaffe et al, 2006(274) RCT	n=417	• United States • Ages 60–80 years • Intact uterus • ≥5 years past menopause • Bone mineral density normal for age	2 years	Unopposed transdermal estradiol 0.014 mg/day (N=208) Placebo (N=209)	Randomization adequate? Yes Allocation concealment adequate? Unclear Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: Berlex Inc; and in part by grant R01 AG021918 from the National Institute on Aging (Dr Yaffe).
Black Women's Health Study Bethea, 2017(261) <u>Prospective cohort study</u>	n=9002	• United States • Postmenopausal Black women	18 years	2,477 Estrogen only 1,836 Estrogen plus progestin 4,689 Never used or used <1 year	-Bias due to confounding: Moderate - Bias in selection of participants into the study: Low - Bias in classification of interventions: Moderate - Bias due to deviations from intended interventions: Low - Bias due to missing data: Low -Bias in measurement of outcomes: Low -Bias in selection of the reported result: Low Overall risk of bias: Moderate risk of bias

13.2 Estrogen only versus placebo: Cardiovascular disease

Estrogen only versus placebo: cardiovascular disease

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

13.2.1 Coronary heart disease

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=3 n=11310 (EPAT,(256) PEPI(257) and WHI (269))	coronary heart disease (CHD)	3.6% vs 4.0% RR, 0.95 [95% CI, 0.79 to 1.14] NS Heterogeneity: T ² =0.00, I ² =0.00%, H ² =1.00
		N=1 n=10739 Postintervention Followup: n=7645	Overall CHD (nonfatal myocardial infarction or coronary death)	
			Intervention followup: Mean 7.1 years/Median 7.2 years	CEE vs placebo 201 (annualized 0.53%) vs. 217 (annualized 0.56%); HR, 0.95 (95% CI, 0.79 to 1.16) NS
			Postintervention followup: Mean 3.9 years	HR, 0.97 (95% CI, 0.75 to 1.25) NS

		WHI Estrogen-only trial Anderson, 2004;(244) Rossouw, 2007;(270) Hsia, 2006;(269) Prentice, 2009;(247) LaCroix, 2011;(246) Manson, 2013;(197) Manson, 2019;(249) Liu, 2020;(275) Chlebowski, 2017;(252) Prentice, 2020;(253) Manson, 2017(255)	Cumulative followup: Median 13.0 years	363 (0.60% annualized) vs. 393 (0.63% annualized); HR, 0.94 (95% CI, 0.82 to 1.09); p=0.43 NS
			Cumulative followup: Median 19.4 years	521 (9.8% calculated) vs. 550 (10.1%); HR, 0.97 (95% CI, 0.86 to 1.09); p=NR NS
			All cardiovascular events(197) Intervention followup: Mean 7.1 years/Median 7.2 years	877 (2.51% annualized) vs. 813 (2.24%); HR, 1.11 (95% CI, 1.01 to 1.22); p=0.03 SS
			Myocardial infarction	
			Intervention followup: Mean 7.1 years/Median 7.2 years	164 (0.44% annualized) vs. 173 (0.45); HR, 0.97 (95% CI, 0.79 to 1.21); p=0.81 NS
			Cumulative followup: Median 13.0 years	285 (0.47% annualized) vs. 288 (0.47%); HR, 1.01 (95% CI, 0.86 to 1.19); p=0.90 NS
			Total HF	
			Intervention followup: Mean 7.1 years/Median 7.2 years	120 (2.30%) vs. 119 (2.22%); HR, 1.04 (95% CI, 0.81 to 1.34) NS
			Cumulative followup: Median 18.9 years (275)	359 (6.9%) vs. 353 (6.6%); HR, 1.04 (95% CI, 0.90 to 1.20) NS
			Hospitalized HfrEF	
			Intervention followup: Mean 7.1 years/Median 7.2 years	38 (0.75%) vs. 43 (0.82%); HR, 0.91 (95% CI, 0.59 to 1.41) NS

			Cumulative followup: Median 18.9 years (275)	108 (2.2%) vs. 127 (2.5%); HR, 0.87 (95% CI, 0.67 to 1.13) NS
			Hospitalized HfpEF	
			Intervention followup: Mean 7.1 years/Median 7.2 years	49 (0.96%) vs. 50 (0.95%); HR, 1.01 (95% CI, 0.68 to 1.50) NS
			Cumulative followup: Median 18.9 years (275)	168 (3.3%) vs. 151 (2.9%); HR, 1.13 (95% CI, 0.91 to 1.41) NS
			CHD mortality	
			Intervention followup: Mean 7.1 years/Median 7.2 years	66 (0.17%) vs. 67 (0.17%); HR, 1.02 (95% CI, 0.72 to 1.43); p=0.92 NS
			Postintervention followup: Mean 10.8 years	174 (0.36%) vs. 210 (0.42%); HR, 0.84 (95% CI, 0.69 to 1.03); p=0.09 NS
			Cumulative followup: Median 17.7 years	240 (0.28%) vs. 277 (0.31%); HR, 0.89 (95% CI, 0.75 to 1.05), p=0.17 NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; CHD= coronary heart disease; HF=heart failure; HfrEF=heart failure with reduced ejection fraction; HfpEF=heart failure with preserved ejection fraction; NS=not statistically significant, SS=statistically significant

Remarks:

The WHI and EPAT trials defined coronary heart disease as nonfatal myocardial infarction or coronary death;(256) (269) the definition used in the PEPI trial was unclear.(257) The authors did not include the ERA study in the meta-analysis because only women with an elevated cardiovascular risk were eligible for enrollment.¹¹³

13.2.2 Venous Thromboembolism

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=10739 Postintervention followup: n=7645 Cumulative followup (intervention plus postintervention phases): n=9939 WHI Estrogen-only trial LaCroix, 2011(246); Curb, 2006(266); Prentice, 2009(247); Manson, 2013(197); Manson, 2019(249); Chlebowski, 2017(252); Prentice, 2020(253); Prentice, 2020(254)	Venous thromboembolism	
			Intervention followup: Mean 7.1 years/Median 7.2 years	CEE vs placebo 111 (2.1% calculated) vs. 86 (1.6%); HR, 1.32 (95% CI, 1.00 to 1.76); p=NR ¹⁰¹ SS
			Cumulative followup: Median 19.4 years	270 (5.1% calculated) vs. 288 (5.3% calculated); HR, 0.97 (95% CI, 0.82 to 1.14); p=NR NS
			Deep vein thrombosis	
			Intervention followup: Mean 7.1 years/Median 7.2 years	85 (1.6%) vs. 59 (1.0%); HR, 1.48 (95% CI, 1.06 to 2.07); p=0.02 ^{67, 108} SS
			Postintervention followup: Mean 3.9 years	HR, 0.63 (95% CI, 0.41 to 0.98); p=0.003 SS
			Cumulative followup: Median 13.0 years	135 (0.22% annualized) vs. 133 (0.21%); HR, 1.05 (95% CI, 0.82 to 1.33); p=0.71 NS
			Pulmonary embolism	
			Intervention followup: Mean 7.1 years/Median 7.2 years	52 (0.14% annualized) vs. 39 (0.10%); HR, 1.35 (95% CI, 0.89 to 2.05); p=0.15 ⁶⁷ NS
			Postintervention followup: Mean 3.9 years	HR, 0.98 (95% CI, 0.62 to 1.55); p=0.29 NS
			Cumulative followup: Median 13.0 years	107 (0.17% annualized) vs. 96 (0.15%); HR, 1.15 (95% CI, 0.87 to 1.51); p=0.34 NS

		N=1 n=222 EPAT Estrogen-only trial Hodis, 2001 (256)	Deep vein thrombosis or pulmonary embolism Followup: 2 years	0 (0.0%) vs. (0.0%)
		N=1 n=205 ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000(215)	Deep vein thrombosis or pulmonary embolism Followup: Mean 3.2 years	5 vs. 2 vs. 1; p=0.16 (For estrogen vs. placebo, p=0.11) NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks: the authors did not pool trials because of heterogeneity in study duration and outcome measures.

13.2.3 Stroke

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen vs		All stroke (Ischemic or hemorrhagic stroke)	

Design: RCT	placebo	N=1 n=10739 WHI Estrogen-only trial Hendrix, 2006;(268) LaCroix, 2011;(246) Manson, 2013;(197) Prentice, 2009;(247) Manson, 2019;(249) Chlebowski, 2017;(252) Prentice, 2020;(253) Manson, 2017;(255) Prentice, 2020(254)	Intervention followup: Median 7.2 years	CEE vs placebo 169 (3.2% calculated) vs. 129 (2.4%); HR, 1.35 (95% CI, 1.07 to 1.70); p=0.01 SS
			Postintervention followup: Mean 3.9 years	66 (0.36% annualized) vs. 77 (0.41%); HR, 0.89 (95% CI, 0.64 to 1.24); p=NR NS
			Cumulative followup: Median 13.0 years	278 (0.46% annualized) vs. 253 (0.41%); HR, 1.15 (95% CI, 0.97 to 1.37); p=0.10 NS
			Cumulative followup: Median 19.4 years	399 (7.5% calculated) vs. 392 (7.2%); HR, 1.06 (95% CI, 0.92 to 1.22); p=NR NS
			Stroke mortality	
			Intervention followup: Median 7.2 years	23 (0.060%) vs. 24 (0.060%); HR, 1.00 (95% CI, 0.57 to 1.78); p=0.99 NS
			Cumulative followup: Median 10.8 years	103 (0.21%) vs. 108 (0.22%); HR, 0.98 (95% CI, 0.75 to 1.28); p=0.86 NS
			Cumulative followup: Median 17.7 years	126 (0.14%) vs. 132 (0.15%); HR, 0.98 (95% CI, 0.77 to 1.26); p=0.89 NS
		N=1 n=222 EPAT Estrogen-only trial Hodis, 2001(256)	Cerebrovascular accidents Followup: 2 years	0/111 vs. 1/111

		N=1 n=205 ERA Estrogen-only and estrogen plus progestin trial	Stroke or transient ischemic attack Followup: Mean 3.2 years	5 vs. 6 vs. 6; p=1.0

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks: the authors did not pool trials because of heterogeneity in study duration and outcome measures.

13.2.4 Peripheral Arterial Disease

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=10739 WHI Estrogen-only trial Hsia 2006(276)	Peripheral Arterial Disease (incident carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease) Followup: Mean 7.1 years	82/5310 vs. 62/5429; HR, 1.35 (95% CI, 0.97 to 1.88) NS

13.2.5 Author's conclusions

Summary of review findings

Results of our review indicate some benefits of hormone therapy regarding the prevention of chronic conditions ([KQ 1](#)). For women using estrogen only, risk of diabetes (134 fewer cases per 10,000 women over 7.1 years) and risk of fractures (388 fewer cases per 10,000 women over 7.2 years) were statistically

significantly reduced compared with women taking placebo. The risk for invasive breast cancer was numerically reduced in women using estrogen only, but the difference compared with placebo did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]). Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years), diabetes (78 fewer cases per 10,000 women over 5.6 years), and fractures (230 fewer cases per 10,000 women over 2 to 5.6 years) compared with women in the placebo groups. Benefits of hormone therapy for colorectal cancer attenuated with extended followup and were no longer statistically significant.

Our review also documented several important harms of hormone therapy ([KQ 2](#)). Women taking estrogen-only therapy had a statistically significant increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.2 years), urinary incontinence (885 more cases per 10,000 women over 1.0 year), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years) compared with women in the placebo groups.

Likewise, for women taking estrogen plus progestin therapy, risks of invasive breast cancer (51 more cases per 10,000 women over 5.6 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (260 more cases per 10,000 women over 5.6 years), stroke (52 more cases per 10,000 women over 5.6 years), urinary incontinence (562 more cases per 10,000 women over 1 year), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years) were statistically significantly increased compared with women taking placebo. A Danish retrospective cohort study also reported an increased risk for endometrial cancer (RR, 1.71 [1.58 to 1.86] over 9.8 years).

Based on high- or moderate-strength evidence, the risks for coronary heart disease and all-cause mortality were similar between estrogen-only hormone therapy and placebo. Likewise, high- or moderate-strength evidence indicates similar risks for lung cancer and all-cause mortality between estrogen plus progestin hormone therapy and placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-off between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years at the end of the intervention phase (HR, 1.12 [95% CI, 1.02 to 1.24]). After 18 years of cumulative followup, no statistically significant differences between groups were still apparent. For women who were randomized to estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03 [95% CI, 0.93 to 1.13]). Long-term followup also did not show any statistically significant differences between groups.

Conclusions

Hormone therapy plays an important role in the clinical management of menopausal symptoms, but it has a complex pattern of risks and benefits in the primary prevention of chronic conditions. Depending on the treatment regimen, the risk-benefit profile of hormone therapy for the prevention of chronic conditions differs for women ages 50 to 79 years. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risk of fractures or diabetes) but also an increased risk of harms (e.g., higher risk of stroke, thromboembolic events, gallbladder disease, and possibly urinary incontinence), particularly among women older than age 60 years. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profile (with more favorable results in younger women), particularly for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

13.2.6 Characteristics of included studies

See appendix cancer

13.3 Estrogen only versus placebo: Cognition and dementia

Estrogen only versus placebo: Dementia

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

13.3.1 Dementia and mild cognitive impairment incidence

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=10739 WHI Estrogen-only trial Manson, 2017(255)	Alzheimer's disease or other dementia mortality	
			Intervention followup: Median 7.2 years	CEE vs placebo 5 (0.013% annualized) vs. 6 (0.015%); HR, 0.90 (95% CI, 0.27 to 2.95); p=0.86 NS
			Postintervention followup: Median 10.8 years	122 (0.25% annualized) vs. 169 (0.34%); HR, 0.73 (95% CI, 0.58 to 0.92); p=0.008 SS
			Cumulative followup: Median 17.7 years	278 (0.46% annualized) vs. 253 (0.41%); 127 (0.15% annualized) vs. 175 (0.20%); HR, 0.74 (95% CI, 0.59 to 0.94); p=0.01 SS
			Probable dementia	28 (1.9%) vs. 19 (1.3%); cumulative HR, 1.49 (95% CI, 0.83 to 2.66); p=0.18

		N=1 n=2947 WHIMS Estrogen-only trial Shumaker, 2004(277)	Intervention followup: 5.2 years (277)	NS
			Mild cognitive impairment Intervention followup: 5.2 years (277)	76 (5.2%) vs. 58 (3.9%); cumulative HR, 1.34 (95% CI, 0.95 to 1.89); NS
			Probable dementia or Mild cognitive impairment Intervention followup: 5.2 years (277)	93 (6.4%) vs. 69 (4.7%); cumulative HR, 1.38 (95% CI, 1.01 to 1.89); p=0.04 SS
		N=1 n=886 WHISCA Estrogen-only trial Resnick, 2009(278)	Probable dementia Intervention followup: 2.7 years (during WHISCA, after being enrolled in WHI for 3 years)(278)	4 (0.9%) vs. 2 (0.4%); calculated RR, 2.08 (95% CI, 0.38 to 11.31); p=0.40 NS
			Mild cognitive impairment Intervention followup: 2.7 years (during WHISCA, after being enrolled in WHI for 3 years)(278)	18 (4.1%) vs. 15 (3.3%); calculated RR, 1.25 (95% CI, 0.64 to 2.45); p=0.52 NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen;

Remarks:/

Author's conclusions:

The WHI estrogen-only trial (n=10,739) evaluated Alzheimer's disease or other dementia mortality following the intervention phase (median 7.2 years), postintervention phase (median 10.8 years), and cumulative follow-up of 17.7 years (median).(255) There was no difference in dementia-related mortality at the end of the intervention phase (5 vs. 6 deaths). However, participants randomized to estrogen were less likely to have dementia-related mortality compared with the placebo group at postintervention follow-up at 10.8 years (122 vs. 169; HR, 0.73 [95% CI, 0.58 to 0.92]) and cumulative follow-up (127 vs. 175; HR, 0.74 [95% CI, 0.59 to 0.94]).(255)

13.3.2 Global cognitive function

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=2947 WHIMS Estrogen-only trial Espeland, 2004(279)	Modified Mini-Mental State Examination Followup: Mean 5.4 years	Mean difference in change from baseline, -0.26 (95% CI, -0.52 to 0.00); p=0.04 SS
		N=1 n=1213 WHISCA Estrogen- only trial	Mean decrement in global cognitive function, Modified Mini-Mental State Examination	
		Espeland, 2010(280)	Followup: 3.6 years (during WHISCA, after being enrolled in WHI for 3 years)(280)	-0.092 (SE, 0.039); p=0.02 SS

			Postintervention followup: Mean 2.4 years (after being enrolled in WHI for 3 years and WHISCA for 3.6 years)(280)	-0.081 (SE, 0.047); p=0.09 NS
		N=1 n=1326 WHIMSY Estrogen-only trial Espeland, 2013;(281) Espeland, 2017(282)	TICS=Telephone Interview for Cognitive Status Postintervention followup: 7.2 years	37.67 (SE, 0.26) vs. 37.28 (SE, 0.27); p=NR
		N=1 n=417 enrolled ULTRA Estrogen-only trial Yaffe, 2006(274)	Baseline Modified Mini-Mental State Examination ≤90	5.90 vs. 7.10; difference, -1.21 (95% CI, -5.05 to 2.64); p=0.53 NS
			Baseline Modified Mini-Mental State Examination >90	0.57 vs. 0.87; difference, -0.30 (95% CI, -0.74 to 0.14); p=0.18 NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen;

Remarks:

Four trials (WHIMS [N=4,344],(279) WHISCA [N=1,213],(280) Women’s Health Initiative Memory Study of Younger Women [WHIMSY] [N=1,326],(281) and ULTRA [N=417](274)) measured global cognitive functioning using the Modified Mini-Mental State (3MSE) examination or the Telephone Interview for Cognitive Status-modified (TICS-m); heterogeneity in timing precluded meta-analysis. The WHIMS and WHISCA trials are described above. The WHIMSY trial, an extension of the WHI trial, was limited to 1,326 enrolled active participants in treatment or placebo arms in the WHI trials who were ages 50 to 55 years at enrollment and agreed to be contacted for recruitment (N by treatment regimen not reported); women in this extension were followed for 7.2 years after the end of the trials.(281) The ULTRA trial randomized women to estrogen only or placebo transdermal patches, with all participants receiving 400 mg of calcium twice daily and 400 IU of vitamin D once daily.(274) The ULTRA trial followed participants for 2 years.

Author’s conclusions:

The WHI trials found larger cognitive deficits among the intervention group (change in 3MSE score at 3.6 years during the WHISCA trial, –0.092; p=0.02;(280) change in 3MSE score at 5.4 years at the end of the WHIMS trial, –0.26 [95% CI, –0.52 to 0.00]; p=0.04(279)). In a long-term extension of the WHISCA trial, with outcomes measured at 2.4 years after stopping therapy, these differences were not sustained.(280) The ULTRA and WHIMSY studies found no differences.(281) (274)

13.3.3 Other Cognitive Measures

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=1213 WHISCA Estrogen- only trial Espeland, 2010(280)	Other Cognitive Measures	
			Followup: Mean 3.6 years	Verbal knowledge –0.100 (SE, 0.051); p=0.05 Verbal fluency –0.118 (SE, 0.054); p=0.03 Figural memory

				-0.132 (SE, 0.048); p=0.006 Spatial ability -0.137 (SE, 0.057); p=0.02 Verbal Memory No significant differences by group. Attention No significant differences by group. Working Memory No significant differences by group.
			Postintervention followup: 2.4 years (280)	Spatial ability -0.179 (SE, 0.063); p=0.004 Verbal Knowledge No significant differences by group. Verbal Fluency No significant differences by group. Verbal Memory No significant differences by group. Figural Memory No significant differences by group.

				Attention No significant differences by group. Working Memory No significant differences by group.
		N=1 n=1326 WHIMSY Estrogen-only trial Espeland, 2013;(281) Espeland, 2017(282)	Other Cognitive Measures Postintervention followup: 7.2 years	Verbal Fluency No significant differences by group. Verbal Memory No significant differences by group. Attention No significant differences by group. Executive function No significant differences by group. Working Memory No significant differences by group. East Boston Memory Test No significant differences by group. Composite cognitive function No significant differences by group.

		N=1 n=643 ELITE-Cog Henderson, 2016(283)	Change in verbal episodic memory Followup: Mean 4.8 years	0.33 (SE, 0.06) vs. 0.40 (SE, 0.07); difference, -0.07 (95% CI, -0.25 to 0.10); p=0.25 NS
			Change in executive functions	-0.08 (SE, 0.04) vs. -0.05 (SE, 0.05); difference, -0.03 (95% CI, -0.15 to 0.10); p=0.085 NS
			Change in global cognition	0.36 (SE, 0.06) vs. 0.39 (SE, 0.07); difference, -0.03 (95% CI, -0.21 to 0.15); p=0.75 NS
		N=1 n=417 enrolled ULTRA Estrogen-only trial Yaffe, 2006(274)	Other Cognitive Measures Followup: 2 years	Logical Memory No significant differences by group. Brief Visuospatial Memory Test No significant differences by group. Word List No significant differences by group. Trials B No significant differences by group. Modified Boston Naming Test No significant differences by group.

				Verbal Fluency No significant differences by group.

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen;

Remarks:

Four trials (WHISCA [N=1,213],(278)· (280) WHIMSY [N=1,326],(281) , Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints [ELITE-Cog] [N=643],(283) and ULTRA [N=417](274)) evaluated other measures of cognitive functioning (e.g., spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention, and working memory); heterogeneity in outcome measures precluded meta-analysis. The WHISCA, WHIMSY, and ULTRA trials are described above. ELITE-Cog examined differences in cognitive changes for women enrolled in the ELITE trial, which was designed to test the timing hypothesis.(283)

Author's conclusions:

All four trials found no differences between women receiving estrogen only or placebo for the majority of outcomes.

13.3.4 Characteristics included trials

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022
WHI Estrogen-only trial	See appendix cancer				
WHIMS Estrogen-only trial Women's Health Initiative Memory Study (WHIMS) Espeland et al, 2004;(279) Shumaker et al, 2004(277) RCT	n=2947	• United States • WHI participants enrolled in the estrogen-only trial • Ages 65–79 years • Free of probable dementia • Able and willing to undergo annual cognitive assessment	5.2 years	CEE 0.625 mg/day (N=1,464) Placebo (N=1,483)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for history of stroke and hypertension Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHISCA Estrogen-only trial Women's Health Initiative Study of Cognitive Aging (WHISCA)	n=886	• United States • WHIMS E-only trial participants • Free of probable dementia • At 1 of 14 WHIMS centers • Began 3 years after enrollment in WHI	3.6 years	CEE 0.625 mg/day (N=434) Placebo (N=452)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for smoking status Outcome assessors masked? Yes

Espeland et al, 2010;(280) Resnick et al, 2009(278) RCT					Care providers masked? Yes Patient masked? Yes Loss to follow-up $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHISCA Estrogen-only trial Post intervention Phase Espeland et al, 2010;(280) RCT	n=886	See above	2.4 years	See above	
WHIMSY Estrogen-only trial Women's Health Initiative Memory Study of Younger Women (WHIMSY) Espeland, 2013;(281)	n=1326	• United States • Postmenopausal • Ages 50–55 years • 3-month washout period for women using hormone therapy at baseline	7.2 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=696) Placebo (N=630)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up $\leq 20\%$ and differential attrition $\leq 15\%$? No Intention-to-treat analysis? Yes

Espeland, 2017(282) RCT					Other biases? No Quality Rating: Fair FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
ULTRA Estrogen-only trial Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) Ettinger et al, 2004(272); Johnson et al, 2005(260); Waetjen et al, 2005(273); Yaffe et al, 2006(274) RCT	n=417	• United States • Ages 60–80 years • Intact uterus • ≥5 years past menopause • Bone mineral density normal for age	2 years	Unopposed transdermal estradiol 0.014 mg/day (N=208) Placebo (N=209)	Randomization adequate? Yes Allocation concealment adequate? Unclear Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: Berlex Inc; and in part by grant R01 AG021918 from the National Institute on Aging (Dr Yaffe).
ELITE-Cog Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog)	n= 643	• United States • Ages 41–84 years • Within 6 years of natural or surgical menopause (early postmenopause group) or at least 10 years beyond natural or surgical menopause (late menopause group)	Mean 4.8 years	17β-estradiol 1 mg/day (N=323) Placebo (N=320) Women with a uterus: cyclic micronized	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes

Henderson, 2016(283) RCT		Serum estradiol level <25 pg/mL		progesterone (45 mg) as a 4% vaginal gel	Loss to followup ≤20% and differential attrition ≤15%? No Intention-to-treat analysis? Yes Other biases? No Quality Rating: Fair FUNDING: NIH. Study drugs and placebo were supplied without charge or restriction by Teva Pharmaceuticals, Watson Pharmaceuticals, Inc., and Abbott Laboratories.

13.4 Estrogen only versus placebo: Fractures

Estrogen only versus placebo: Fractures

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1	Fractures - Total	
		n=10739	Intervention follow-up: Median 7.2 years	CEE vs placebo 544 (1.53% annualized) vs. 767 (2.14% annualized); HR, 0.72 (95% CI, 0.64 to 0.80); p<0.001 SS
		WHI Estrogen-only trial	Postintervention follow-up: Calculated mean 4.3 years (285)	321 (3.11% annualized) vs. 378 (3.69% annualized); HR, 0.85 (95% CI, 0.73 to 0.98); p=0.03 SS
		LaCroix, 2011;(246) Anderson, 2004;(284) Manson, 2013;(197) Manson, 2019;(249) Watts, 2017;(285) Prentice, 2020;(253) Chlebowski, 2017;(252) Prentice, 2020(254)	Fractures - Hip(197) (246)	
			Intervention follow-up: Median 7.2 years	48 (0.13% annualized) vs. 74 (0.19% annualized); HR, 0.67 (95% CI, 0.46 to 0.96); p=0.03 SS
		RCT	Postintervention follow-up: Mean 3.9 years	66 (0.36% annualized) vs. 53 (0.28% annualized); HR, 1.27 (95% CI, 0.88 to 1.82); p=NR NS

			Postintervention follow-up: Calculated mean 4.3 years (285)	30 (0.28% annualized) vs. 29 (0.27% annualized); HR, 1.04 (95% CI, 0.62 to 1.73); p=0.89 NS
			Cumulative follow-up: Mean 10.7 years (246)	114 (0.20% annualized) vs. 127 (0.22% annualized); HR, 0.92 (95% CI, 0.71 to 1.18); p=NR NS
			Cumulative follow-up: Mean 13.0 years	134 (0.22% annualized) vs. 148 (0.24% annualized); HR, 0.91 (95% CI, 0.72 to 1.15); p=0.44(197) NS
			Cumulative follow-up: Mean 19.4 years	208 (3.9% calculated) vs. 229 (4.2% calculated); HR, 0.92 (95% CI, 0.76 to 1.11); p=NR NS
			Fractures - Vertebral (197) Intervention follow-up: Median 7.2 years	44 (0.12% annualized) vs. 70 (0.18% annualized); HR, 0.64 (95% CI, 0.44 to 0.93); p=0.02 SS
		N=1 n=205 ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000(215)	Fractures (all sites) Intervention follow-up: 3.2 years	Calculated RR, 0.42 (95% CI, 0.17 to 1.04); p=0.06 NS

Abbreviations: CEE=conjugated equine estrogen;

Remarks: /

Author's conclusions:

The WHI found a reduced risk of total fractures in the estrogen-only arm compared with placebo during the 7.2-year intervention phase (1.53% annualized vs. 2.14% annualized; HR, 0.72 [95% CI, 0.64 to 0.80])(197) and after 4.3 years of postintervention follow-up (3.11% annualized vs. 3.69% annualized; HR, 0.85 [95% CI, 0.73 to 0.98]).(285) The ERA trial randomized women to the same treatment regimen as the WHI and followed them for 3.2 years. The study found fewer fractures at all sites in the estrogen-only arm (6.0% vs. 14.3%), but the difference was not statistically significant (calculated RR, 0.42 [95% CI, 0.17 to 1.04]).(215)

Characteristics included trials

See appendix cancer.

13.5 Estrogen only versus placebo: Diabetes

Estrogen only versus placebo: Diabetes

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=9917 WHI Estrogen-only trial Bonds, 2006;(264) Manson, 2013;(197) Prentice, 2020(253) RCT	Self-reported treated diabetes (197)	
			Intervention followup: Mean 7.1/median 7.2 years	CEE vs placebo 449 (1.34% annualized) vs. 527 (1.55% annualized); HR, 0.86 (95% CI, 0.76 to 0.98); p=0.02 SS
			Postintervention followup: Median 6.6 years	323 (1.64% annualized) vs. 306 (1.54% annualized); HR, 1.07 (95% CI, 0.92 to 1.25); p=0.39 NS
			Cumulative followup: Median 13.0 years	772 (1.45% annualized) vs. 833 (1.55% annualized); HR, 0.94 (95% CI, 0.85 to 1.04); p=0.22 NS

Abbreviations: CEE=conjugated equine estrogen;

Remarks:

The WHI (N=9,917)(197) (264) was the only trial that reported on the incidence of diabetes among women not receiving treatment for diabetes at baseline. Incident diabetes was self-reported and defined as a new diagnosis of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin.(264)

Characteristics included trials

See appendix cancer.

13.6 Estrogen only versus placebo: Galbladder disease

Estrogen only versus placebo: Galbladder disease

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

The authors did not pool trial results because of heterogeneity in study duration and outcome measures.

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1 n=8376 WHI Estrogen-only trial Cirillo, 2005;(265) LaCroix, 2011;(246) Manson, 2013;(197) Prentice, 2020(253)	Intervention follow-up: Mean 7.1 years	
			Gallbladder event incidence (265)	CEE vs placebo 228 (5.5%) vs. 143 (3.4%); HR, 1.67 (95% CI, 1.35 to 2.06); p<0.001 SS
			Cholecystectomy (265)	192 (4.6%) vs. 104 (2.5%); HR, 1.93 (95% CI, 1.52 to 2.44); p<0.001 SS
			Global gallbladder disease (197)	461 (1.64% annualized) vs. 312 (1.06% annualized); HR, 1.55 (95% CI, 1.34 to 1.79); p<0.001 SS
		RCT	Cholecystitis (265)	186 (4.5%) vs. 107 (2.5%); HR, 1.80 (95% CI, 1.42 to 2.28); p<0.0010 SS

			Gallbladder disease Postintervention follow-up: Median 6.6 years (197)	57 (1.65% annualized) vs. 61 (1.66% annualized); HR, 0.98 (95% CI, 0.68 to 1.41); p=0.92 NS
		N=1 n=349 PEPI Estrogen-only and estrogen plus progestin trial PEPI, 1995(257)	Gallbladder disease Intervention follow-up: 3 years	2 (estrogen: 1.1%) vs. 9 (estrogen plus progestin: 2.6%) vs. 4 (estrogen plus micronized progestin: 2.2%) vs. 2 (placebo: 1.1%)

Abbreviations: CEE=conjugated equine estrogen;

Remarks:

The definition of gallbladder disease used in PEPI is unclear; for WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all gallbladder or biliary tract stone disease.(257) (197) (265)

Author's conclusions:

The larger of the two trials, WHI, reported global gallbladder disease after 7.1 years of treatment for 1.64 percent (annualized) of women receiving estrogen therapy and 1.06 percent (annualized) of those taking placebo.(197) The difference in global gallbladder disease between these groups was statistically significant (HR, 1.55 [95% CI, 1.34 to 1.79]).(197) However, the risk of gallbladder disease was no longer significant 6.6 years postintervention (HR, 0.98 [95% CI, 0.68 to 1.41]).(197)

The PEPI trial had few cases of gallbladder disease and reported inconclusive results.(257)

Characteristics included trials

See appendix cancer.

13.7 Estrogen only versus placebo: Urinary incontinence

Estrogen only versus placebo: Urinary incontinence

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=1	Intervention followup: 1 year	
		n=6767 for total urinary incontinence at year 1	Weekly total urinary incontinence(197) 3,316 Estrogen (all continent at baseline) 3,451 Placebo (all continent at baseline)	CEE vs placebo 773 (22.6% annualized) vs. 499 (14.0% annualized); HR, 1.61 (95% CI, 1.46 to 1.79); p<0.001 SS
		At year 3 n=232 Postintervention n=5644 WHI Estrogen-only trial	Incident urinary incontinence (≥1 episode/year) (267) 1,526 Estrogen (all continent at baseline) 1,547 Placebo (all continent at baseline)	557 (36.5%) vs. 368 (23.8%); RR, 1.53 (95% CI, 1.37 to 1.71); p=NR SS

		Hendrix, 2005;(267) Manson, 2013(197) RCT	Stress urinary incontinence (≥1 episode/year) (267) 1,526 Estrogen (all continent at baseline) 1,547 Placebo (all continent at baseline)	266 (17.4%) vs. 131 (8.5%); RR, 2.15 (95% CI, 1.77 to 2.62); p<0.001 SS
			Urge urinary incontinence (≥1 episode/year) (267) 1,526 Estrogen (all continent at baseline) 1,547 Placebo (all continent at baseline)	210 (13.8%) vs. 184 (11.9%); RR, 1.32 (95% CI, 1.10 to 1.58); p=0.003 SS
			Mixed urinary incontinence (≥1 episode/year) (267) Intervention followup: 3 years (267) 96 Estrogen (all continent at baseline and 1 year) 136 Placebo (all continent at baseline and 1 year)	27 (28.1%) vs. 26 (19.1%); RR, 1.47 (95% CI, 0.92 to 2.36); p=NR NS
			Weekly total urinary incontinence(197) Postintervention followup: Median 6.6 years (197) 2,781 Estrogen (all continent at baseline) 2,863 Placebo (all continent at baseline)	795 calculated (28.6%) vs. 661 calculated (23.1%); HR, 1.24 (95% CI, 1.13 to 1.35); p<0.001 SS

		N=1 n=239 continent ULTRA Estrogen-only trial Waetjen, 2005(273)	Weekly total urinary incontinence Followup: 2 years 122 Estrogen (calculated) 117 Placebo (calculated)	39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7 to 2.2); p=0.74 NS

Abbreviations: CEE=conjugated equine estrogen;

Remarks:/

Both studies defined urinary incontinence as at least one episode weekly.(197) (273) The WHI also evaluated various subtypes of urinary incontinence.(267)

Author's conclusions:

The WHI found a higher risk of urinary incontinence in the estrogen-only treatment arm at 1 year (22.6% annualized vs. 14.0% annualized; HR, 1.61 [95% CI, 1.46 to 1.79]) and 6.6 years after stopping treatment (28.6% vs. 23.1%; HR, 1.24 [95% CI, 1.13 to 1.35]).(197) Results from the smaller ULTRA trial at 2 years did not find a statistically significant difference between groups (39.0% vs. 36.8%; odds ratio [OR], 1.2 [95% CI, 0.7 to 2.2]). (273)

Characteristics included trials

See appendix cancer.

13.8 Estrogen only versus placebo: Quality of life

Estrogen only versus placebo: Health-Related Quality of Life

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

The authors did not pool trial results because of heterogeneity in study duration and outcome measures.

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen vs placebo	N=1 n=10739 WHI Estrogen-only trial Manson, 2013(197)	Quality of Life Followup: Mean 7.2 years	CEE vs placebo SF-36: Similar scores on all items except for emotional role (81.0 vs. 82.2; p=0.04) and social functioning (85.8 vs. 86.9; p=0.01), for which women taking placebo had statistically significantly better scores than women taking estrogen-only therapy
Design: RCT				
Search date: (Jun-2022)		RCT		

Abbreviations: CEE=conjugated equine estrogen;

Remarks:

The WHI (N=10,739)(197) was the only trial that reported on health-related quality of life. It used the Short Form Health Survey (SF-36) form, which assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health.

Author's conclusions:

At post-intervention (mean 7.2 years), women in both groups had similar scores on all items except for emotional role and social functioning, for which women taking placebo had statistically significantly better scores than women taking estrogen-only therapy ($p=0.04$ and $p=0.01$, respectively).

Characteristics included trials

See appendix cancer.

13.9 Estrogen only versus control: Asthma

Hormone therapy vs control: onset of asthma

Hormone replacement therapy and asthma onset in menopausal women: National cohort study(196)					
Design	N/n	Population	Risk factor	Outcome	Results*
Design: Retrospective cohort study UK	N= 1 n= 353173 17 years of follow-up	peri-menopausal women	HRT	Asthma	Previous users vs non-users Adjusted HR 0.83 (95% CI : 0.79-0.88) SS
		postmenopausal women			Current users vs non-users Adjusted HR 0.79 (95% CI : 0.74-0.85) SS
		aged 46–70 years			
		Primary care practices	Estrogen only	Asthma	Previous users vs non-users Adjusted HR 0.89 (95% CI : 0.84-0.95) SS Current users vs non-users Adjusted HR 0.80 (95% CI : 0.73-0.87) SS
			Estrogen plus progestin	Asthma	Previous users vs non-users Adjusted HR 0.82 (95% CI : 0.76-0.88) SS Current users vs non-users Adjusted HR 0.78 (95% CI : 0.70-0.87) SS
*Adjusted for age, smoking, Charlson Comorbidity Index score, BMI, gravidity, any gynecologic condition, and IMD (index of multiple deprivation) quintile.					

Remarks:

- The AHRQ review from Garthlehner 2022 mentioned in their appendix of eligible observational studies two studies with outcome asthma. This is not further studied in the review without mentioning a reason for this. We included one of the studies here and excluded the other study in our report due to the studied population (women with asthma).
- Use of HRT was associated with a reduced risk of asthma only in all women, but not when the women were stratified by menopausal status.

- The authors observed a dose-response association (Kandall τ statistic = -1 [$P = .089$]) between duration of HRT use and risk of asthma onset: women with 1 to 2 years of HRT use had a 7% (95% CI = 13-1) lower risk than women who did not use HRT, women with 3 or 4 years of use had a 23% lower risk (95% CI = 30-16), and those with 5 or more years of use had a 29% (95% CI = 36-22) lower risk. “This effect becomes insignificant, however, when patients are stratified by age, BMI, and smoking, possibly because of lack of sufficient power to detect significant effect after stratification.”

13.10 Estrogen only versus placebo: COPD

Estrogen only versus placebo: COPD

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.

- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

“For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization’s International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.”

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date:	Estrogen vs placebo	N=1 n=10739 WHI Estrogen-only trial Manson, 2017(255)	COPD incidence	No eligible studies
			COPD-specific mortality	
			Intervention followup: Median 7.2 years (255)	6 (0.016% annualized) vs. 8 (0.020% annualized); HR, 0.76 (95% CI, 0.26 to 2.20); p=0.62 NS
			Postintervention followup: Median 10.8 years (255)	77 (0.16% annualized) vs. 71 (0.14% annualized); HR, 1.09 (95% CI, 0.79 to 1.51); p=0.60 NS

(month-year)		RCT		
			Cumulative followup: Median 17.7 years(255)	83 (0.095% annualized) vs. 79 (0.088% annualized); HR, 1.07 (95% CI, 0.78 to 1.45); p=0.68 NS

Remarks: No eligible studies reported on COPD incidence. The WHI [N=10,739](255)) was the only trial that provided information about the prevention of COPD mortality with estrogen only. COPD mortality was measured at multiple time points and identified via data linkage to the U.S. National Death Index (NDI).

Characteristics included trials

See appendix cancer.

13.11 Estrogen only versus placebo: All-cause mortality

Estrogen only versus placebo: All-cause mortality

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen vs placebo	N=3 n=11587 WHI Estrogen-only trial ELITE-Cog Henderson, 2016 (283) ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000 (215) RCT	All-cause mortality	CEE vs placebo RR, 1.04 [95% CI, 0.89 to 1.21) NS Heterogeneity: T ² =0.00, I ² =0.00%, H ² =1.00
		N=1 n=10739	All-cause mortality	
			Intervention followup: Mean 7.2 years	300 (5.6%) vs. 297 (5.5%);

		Postintervention n=7645		HR, 1.04 (95% CI, 0.89 to 1.22); p=NR NS
		Cumulative follow-up n=9939	Postintervention followup: Mean 3.9 years (246)	277 (1.47% annualized) vs. 284 (1.48% annualized); HR, 1.00 (95% CI, 0.84 to 1.18); p=NR NS
		WHI Estrogen-only trial LaCroix, 2011;(246) Manson, 2013;(197) Prentice, 2009;(247) Manson, 2019;(249) Prentice, 2020;(253) Chlebowski, 2017;(252) Manson, 2017;(255) Prentice, 2020(254)	Postintervention followup: Median 10.8 years (255)	1,204 (2.48% annualized) vs. 1,331 (2.69%); HR, 0.92 (95% CI, 0.85 to 0.99); p=0.03 NS
			Cumulative followup: Mean 10.7 years (246)	577 (1.02% annualized) vs. 581 (1.00% annualized); HR, 1.02 (95% CI, 0.91 to 1.15); p=NR NS
			Cumulative followup: Median 13.0 years (197)	704 (1.14% annualized) vs. 725 (1.14% annualized); HR, 0.99 (95% CI, 0.90 to 1.10); p=0.92 NS
			Cumulative followup: Median 17.7 years (255)	1,505 (1.73% annualized) vs. 1,630 (1.83% annualized); HR, 0.94 (95% CI, 0.88 to 1.01); p=0.11 NS
		RCT	Cumulative followup: Median 19.4 years (253)	1,899 (35.8% calculated) vs. 2,004 (36.9% calculated); HR, 0.97 (95% CI, 0.91 to 1.03); p=NR NS

Abbreviations: CEE=conjugated equine estrogen

Remarks: /

13.12 Estrogen plus progestin versus placebo: Cancer

Estrogen + Progestin versus placebo: cancer and cancer mortality

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force (2, 5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: most yes

Other methodological remarks:

13.12.1 Breast cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022(5) Design: RCT Search date: (Jun-2022)	Estrogen + progestin vs placebo	N= 1 n= 16608 Postintervention extension followup: n= 12788 Cumulative followup(249, 251, 255): n= 16608	<u>Invasive breast cancer</u>	
			Intervention followup: Median 5.6 years(197)	CEE + MPA vs placebo 206 (0.43% annualized) vs. 155 (0.35% annualized); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 206/8506 vs 155/8102 RR 1.27 (95%CI, 1.03-1.56) SS
			Postintervention followup: Median 2.4 years(287)	HR, 1.27 (95% CI, 0.91 to 1.78) NS
			Postintervention followup: Median 8.2 years(197)	228 (0.43% annualized) vs. 168 (0.33% annualized); HR, 1.32 (95% CI, 1.08 vs. 1.61); p=0.007

		WHI Estrogen plus progestin trial		SS
		Writing Group for the WHI, 2002(286); Heiss, 2008(287); Chlebowski, 2003(288); Chlebowski, 2010(271); Gramling, 2009(289); Prentice, 2009(247); Manson, 2013(197); Chlebowski, 2015(248); Chlebowski, 2016(250); Chlebowski, 2020(251); Prentice, 2019(253); Prentice, 2020(254)	Cumulative followup: 13.2 years	434 (0.43% annualized) vs. 323 (0.34% annualized); HR, 1.28 (95% CI, 1.11 to 1.48); p<0.001 SS
			Cumulative followup: Median 18.0 years(254)	574 (0.45% annualized) vs. 432 (0.36% annualized)
			Cumulative followup: Median 18.9 years(251)	584 (0.45%) vs. 447 (0.36%); HR, 1.28 (95% CI, 1.13 to 1.45); p<0.001 SS
			Cumulative followup: Median 19.4 years(253)	574 (6.7% calculated) vs. 432 (5.3% calculated); HR, 1.28 (95% CI, 1.13 to 1.45); p=NR SS
		N= 1 n= 777 EPHT Estrogen plus progestin trial Veerus, 2006(290)	Breast cancer (not defined) Intervention followup: Mean 3.4 years	1 (0.2%) vs. 2 (0.5%); HR, 0.55 (95% CI, 0.05 to 6.06) NS
		N= 1 n= 309 ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000(215)	Breast cancer (not defined) Intervention followup: Mean 3.2 years	1 (CEE) vs. 0 (CEE + MPA) vs. 0 (placebo); p=0.35

		N= 1 n= 701 PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995(257)	Breast cancer (not defined) Intervention followup: Mean 3 years	1 (estrogen) vs. 2 (estrogen plus progestin) vs. 4 (estrogen plus micronized progestin) vs. 1 (placebo); p=0.29
		N= 1 n= 2763 HERS Estrogen plus progestin trial Hulley, 2002(291)	Breast cancer (not defined) Intervention followup: Mean 4.1 years	34 (2.5%) vs. 25 (1.8%); HR, 1.38 (95% CI, 0.82 to 2.31); p=0.22 NS
			Breast cancer (not defined) Postintervention followup: Mean 2.7 years	HR, 1.08 (95% CI, 0.52 to 2.24); p=0.83 NS
			Breast cancer (not defined) Cumulative followup: Mean 6.8 years	HR, 1.27 (95% CI, 0.84 to 1.94); p=0.26 NS
		N= 1 n= 4385 WISDOM Estrogen plus progestin trial Vickers, 2007(292)	Breast cancer incidence Intervention followup: Mean 1 year	5 (0.2%) vs. 7 (0.3%)
		N= 1	<u>Breast cancer mortality</u>	

		n= 16608	Intervention followup: Median 5.6 years(197)	5 (0.010% annualized) vs. 4 (0.009%); HR, 1.08 (95% CI, 0.29 to 4.03); p=0.91 NS
		Postintervention extension followup: n= 12788	Postintervention followup: Median 12.5 years(255)	56 (0.060% annualized) vs. 36 (0.041%); HR, 1.50 (95% CI, 0.98 to 2.27); p=0.06 NS
		Cumulative followup(250, 251, 255) n= 16608	Cumulative followup: Mean 11.0 years	25 (0.03% annualized) vs. 12 (0.02% annualized); HR, 1.96 (95% CI, 1.00 to 4.04); p=0.049 SS
		WHI Estrogen plus progestin trial	Cumulative followup: Median 17.7 years(255)	61 (0.043% annualized) vs. 40 (0.030%); HR, 1.44 (95% CI, 0.97 to 2.15); p=0.07 NS
			Cumulative followup: Median 20.3 years(251)	71 (0.045%) vs. 53 (0.035%); HR, 1.35 (95% CI, 0.94 to 1.95); p=0.11 NS
		N= 1 n= 4385 WISDOM Estrogen plus progestin trial Vickers, 2007(292)	Breast cancer mortality	0 vs 0

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks: The authors did not pool trial results because of heterogeneity in study duration and outcome measures.

13.12.2 Colorectal cancer

Ref	Comparison	N/n	Outcomes	Result
		N=1	Colorectal cancer	

Gartlehner 2022 Design: RCT + cohort study Search date: (Jun-2022)	Estrogen + Progestin vs placebo	n=16608	Intervention followup: Median 5.6 years(Manson, 2013 #47	50 (0.59%) vs. 75 (0.93%); HR, 0.62 (95% CI, 0.43 to 0.89); p=0.009 SS
		Postintervention followup: n=15747	Postintervention followup: Median 8.2 years	HR, 0.97 (95% CI, 0.70 to 1.33); p=0.83 NS
		Postintervention extension followup: (The mean followup for this analysis was 5.5 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson (2013)(197)) n=12788	Cumulative followup: Median 13.2 years(197)	HR, 0.80 (95% CI, 0.63 to 1.01); p=0.06 NS
		WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002(286); Chlebowski, 2004(293); Heiss, 2008(287); Prentice, 2009(247); Manson, 2013(197); Prentice, 2020(254); Manson, 2017(255)	Colorectal cancer mortality	
			Intervention followup: Median 5.6 years	11 (0.022% annualized) vs. 12 (0.026%); HR, 0.87 (95% CI, 0.38 to 1.98); p=0.74 NS
			Cumulative followup: Median 12.5 years(255)	42 (0.045% annualized) vs. 38 (0.043%); HR, 1.06 (95% CI, 0.68 to 1.64); p=0.80 NS
			Cumulative followup: Median 17.7 years	53 (0.037% annualized) vs. 50 (0.037%); HR, 1.01 (95% CI, 0.69 to 1.49); p=0.96 NS
			Other colorectal cancer outcomes(258)	
			Intervention followup: Median 5.6 years	Invasive colorectal cancer HR, 0.56 (95% CI, 0.38 to 0.81); p=0.003 SS
			The analysis was based on 122 centrally adjudicated colorectal cancers, which were diagnosed before 7/8/2002, the date participants were instructed to discontinue their study medication.	Invasive colon cancer HR, 0.54 (95% CI, 0.36 to 0.82); p=0.004 SS
				Invasive rectal cancer HR, 0.66 (95% CI, 0.26 to 1.64); p=0.37 NS

		RCT		
		N=1 n=4385 WISDOM Estrogen plus progestin trial Vickers, 2007(292) RCT	Colorectal cancer Intervention followup: Median 11.9 months	2 vs. 2
		N=1 n=2763 HERS Estrogen plus progestin trial Hulley, 2002(291)	Colorectal cancer	Intervention Followup: Mean 4.1 years 11 (0.80%) vs. 16 (1.16%); HR, 0.69 (95% CI, 0.32 to 1.49); p=0.43 NS Cumulative followup: Mean 6.8 years HR, 0.82 (95% CI, 0.46 to 1.47); p=NR NS
		N=1 n=142 EMS Estrogen plus progestin trial Tierney, 2009(294)	Colorectal cancer Intervention Followup: 2 years	0 vs. 0

		Multiethnic Cohort Study Park, 2016(259) <u>Cohort study</u>	Colorectal cancer	<u>Followup: 16 years</u> Ever used estrogen plus progestin: 405 vs. 903 (2.3% calculated); HR, 0.76 (95% CI, 0.68 to 0.86) SS Currently use estrogen plus progestin: 214 vs. 903 (2.3% calculated); HR, 0.72 (95% CI, 0.62 to 0.84) SS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks:/

13.12.3 Cervical cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=16608 WHI Estrogen plus Progestin trial Anderson, 2003(284)	Cervical cancer Intervention followup: Median 5.6 years	8 (0.09%) vs. 5 (0.06%); HR, 1.44 (95% CI, 0.47 to 4.42) NS

		RCT		

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant

Remarks:/

13.12.4 Endometrial cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT + cohort study Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1	Endometrial cancer	
		n=16608	Intervention followup: Median 5.6 years(197)	27 (0.32%) vs. 30 (0.37%); HR, 0.83 (95% CI, 0.49 to 1.40); p=0.49 NS
		Postintervention followup: n=15747	Postintervention only followup: Median 8.2 years(295)	41 (0.08% annualized) vs. 65 (0.13% annualized); HR, 0.59 (95% CI, 0.40 to 0.88); p=0.008 SS
		Postintervention extension followup: (Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the	Cumulative followup: Median 13.2 years(295)	66 (0.06% annualized) vs. 95 (0.10% annualized); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.007 SS

		postintervention extension phase.) n=12788 WHI Estrogen plus Progestin trial Writing Group for the Women's Health Initiative Investigators, 2002(286); Anderson, 2003(284); Heiss, 2008(287); Prentice, 2009(247); Chlebowski, 2010(262); Manson, 2013(197, 295); Chlebowski, 2016(295); Prentice, 2020(254) RCT		
		N=1	Endometrial cancer	
		n=2763	Intervention followup: Mean 4.1 years	2 (0.14%) vs. 5 (0.36%); HR, 0.39 (95% CI, 0.08 to 2.02); p=0.26 NS
		HERS Estrogen plus progestin trial	Cumulative followup: Mean 6.8 years	HR, 0.25 (95% CI, 0.05 to 1.18); p=0.08 NS
		Hulley, 2002(291)		
		RCT		

		N=1 n=643340 Danish Sex Hormone Register Study Morch, 2016(296)	Followup: Mean 9.8 years	Estrogen plus progestin: adjusted RR, 1.71 (95% CI, 1.58 to 1.86) SS Continuous combined estrogen plus progestin: adjusted RR, 1.02 (95% CI, 0.87 to 1.20) NS Cyclic combined regimen: adjusted RR, 2.06 (95% CI, 1.88 to 2.27) SS Long cyclic combined regimen: adjusted RR, 2.89 (95% CI, 2.27 to 3.67) SS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks:/

13.12.5 Ovarian cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT + cohort study	Estrogen + Progestin vs placebo		Ovarian cancer	
		N=1 n=16608	Intervention followup: Median 5.6 years(197)	24 (0.28%) vs.16 (0.20%); HR, 1.41 (95% CI, 0.75 to 2.66); p=0.28 NS
		Postintervention followup:	Postintervention followup: Median 8.2 years(197)	HR, 1.12 (95% CI, 0.65 to 1.90); p=0.69 NS

Search date: (Jun-2022)		n=15747	At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.	
		Postintervention extension followup: (At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.) n=12788 WHI Estrogen plus Progestin trial Anderson, 2003(284); Manson, 2013(197) RCT	Cumulative followup: Median 13.2 years(197)	HR, 1.24 (95% CI, 0.83 to 1.87); p=0.30 NS
		N=1	Ovarian cancer	14 (0.8% calculated) vs. 61 (1.3% calculated) HR, 1.37 (95% CI, 0.73 to 2.55)

		n=6525 Black Women's Health Study Bethea, 2017(261) <u>Prospective cohort study</u>	Follow-up 18 years	NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks: /

13.12.6 Lung cancer

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1	Lung cancer	
		n=16608	Intervention followup: Median 5.6 years(197)	78 (0.92%) vs. 70 (0.86%); HR, 1.05 (95% CI, 0.76 to 1.45); p=0.78 NS
		Postintervention followup: n=15747 Postintervention extension followup:	Intervention and partial postintervention followup: Mean 7.9 years(297) (Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson(197); this would mean these results are for trial and posttrial phases combined together.)	Lung cancer 109 (0.16% annualized) vs. 85 (0.13% annualized); HR, 1.23 (95% CI, 0.92 to 1.63); p=0.16 NS NSCLC 96 (0.14% annualized) vs. 72 (0.11% annualized);

		(Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.) n=12788		HR, 1.28 (95% CI, 0.94 to 1.73); p=0.12 NS
		WHI Estrogen plus Progestin trial Chlebowski, 2009(297); Manson, 2013(197); Chlebowski, 2019(298)	Postintervention followup: Median 8.2 years(197)	SCLC 13 (0.02% annualized) vs. 13 (0.02% annualized); HR, 0.96 (95% CI, 0.44 to 2.07); p=0.91 NS
			Cumulative followup: Median 13.2 years(197)	120 (0.22% annualized) vs. 101 (0.19% annualized); HR, 1.13 (95% CI, 0.86 to 1.47); p=0.38 NS
			Cumulative followup: Median 14 years(298)	198 (0.19% annualized) vs. 171 (0.18% annualized); HR, 1.10 (95% CI, 0.89 to 1.35); p=0.38 NS
				219 (0.19% annualized) vs. 184 (0.17% annualized); HR, 1.12 (95% CI, 0.92 to 1.37); p=0.24 NS
		RCT	Mortality Cumulative followup: Median 14 years(298)	Mortality from lung cancer 153 (0.13% annualized) vs. 132 (0.12% annualized); HR, 1.09 (95% CI, 0.87 to 1.38); p=0.45 NS Mortality from NSCLC 109 (0.09% annualized) vs. 85 (0.08% annualized); HR, 1.23 (95% CI, 0.92 to 1.63); p=0.16 NS Mortality from SCLC 17 (0.02% annualized) vs. 21 (0.02% annualized); HR, 1.16 (95% CI, 0.61 to 2.21); p=0.64 NS Significant linear trend over time in lung cancer mortality (p=0.042), suggesting that the nonsignificant increase in risk of mortality in the hormone therapy group through year 9 decreased after both

				randomization groups stopped taking study pills after active intervention (median 5.6 years)
		N=1 n=2763 HERS Estrogen plus progestin trial Hulley, 2002(291)	Lung cancer	
			Intervention followup: Mean 4.1 years	24 (1.74% calculated) vs. 19 (1.37% calculated); HR, 1.28 (95% CI, 0.70 to 2.33); p=0.43 NS
			Cumulative followup: Mean 6.8 years	37 (3.2% calculated) vs. 27 (2.0% calculated) Unadjusted ITT: HR, 1.39 (95% CI, 0.84 to 2.28); p=0.20 NS Adjusted ITT: HR, 1.43 (95% CI, 0.87 to 2.37) NS Adjusted as-treated: HR, 1.73 (95% CI, 0.93 to 3.21) NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks:/

13.12.7 Non-Hodgkin's Lymphoma

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen + Progestin vs placebo	N=1	Incidence of non-Hodgkin's lymphoma	
Design: RCT		n=16544	Intervention followup: Median 5.6 years	HR, 0.81 (95% CI, 0.51 to 1.29) NS
			Cumulative followup: Median 13.5 years	113 (0.099% annualized) vs. 110 (0.101% annualized);

Search date: (Jun-2022)		WHI Estrogen plus Progestin trial(263) RCT		HR, 0.98 (95% CI, 0.76 to 1.28) NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant

Remarks:/

13.12.8 Total cancer mortality

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (month-year)	Estrogen + Progestin vs placebo	N=1 n=16608	Total cancer mortality	
			Intervention followup: Median 5.6 years(255)	133 (0.27% annualized) vs. 111 (0.24% annualized); HR, 1.10 (95% CI, 0.86 to 1.42); p=0.44 NS
		Postintervention extension followup: n= 16120	Postintervention followup: Median 12.5 years(255)	573 (0.62% annualized) vs. 527 (0.59% annualized); HR, 1.05 (95% CI, 0.93 to 1.18); p=0.43 NS
		Cumulative followup (intervention plus postintervention phases): n= 16608	Cumulative followup: Median 13.2 years(197)	428 (0.42% annualized) vs. 379 (0.39% annualized); HR, 1.07 (95% CI, 0.93 to 1.23); p=0.32 NS
			Cumulative followup: Median 17.7 years(255)	706 (0.50% annualized) vs. 638 (0.47% annualized); HR, 1.06 (95% CI, 0.95 to 1.18); p=0.31 NS
		WHI Estrogen plus progestin trial		

		Manson, 2013(197); Manson, 2017(255) RCT		

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; MPA= medroxyprogesterone acetate, NS=not statistically significant, SS=statistically significant

Remarks:

13.12.9 Author's conclusions

Summary of review findings

Results of our review indicate some benefits of hormone therapy regarding the prevention of chronic conditions. For women using estrogen only, risk of diabetes (134 fewer cases per 10,000 women over 7.1 years) and risk of fractures (388 fewer cases per 10,000 women over 7.2 years) were statistically significantly reduced compared with women taking placebo. The risk for invasive breast cancer was numerically reduced in women using estrogen only, but the difference compared with placebo did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]). Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years), diabetes (78 fewer cases per 10,000 women over 5.6 years), and fractures (230 fewer cases per 10,000 women over 2 to 5.6 years) compared with women in the placebo groups. Benefits of hormone therapy for colorectal cancer attenuated with extended followup and were no longer statistically significant.

Our review also documented several important harms of hormone therapy. Women taking estrogen-only therapy had a statistically significant increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.2 years), urinary incontinence (885 more cases per 10,000 women over 1.0 year), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years) compared with women in the placebo groups.

Likewise, for women taking estrogen plus progestin therapy, risks of invasive breast cancer (51 more cases per 10,000 women over 5.6 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (260 more cases per 10,000 women over 5.6 years), stroke (52 more cases

per 10,000 women over 5.6 years), urinary incontinence (562 more cases per 10,000 women over 1 year), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years) were statistically significantly increased compared with women taking placebo. A Danish retrospective cohort study also reported an increased risk for endometrial cancer (RR, 1.71 [1.58 to 1.86] over 9.8 years).

Based on high- or moderate-strength evidence, the risks for coronary heart disease and all-cause mortality were similar between estrogen-only hormone therapy and placebo. Likewise, high- or moderate-strength evidence indicates similar risks for lung cancer and all-cause mortality between estrogen plus progestin hormone therapy and placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-off between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years at the end of the intervention phase (HR, 1.12 [95% CI, 1.02 to 1.24]). After 18 years of cumulative followup, no statistically significant differences between groups were still apparent.

For women who were randomized to estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03 [95% CI, 0.93 to 1.13]). Long-term followup also did not show any statistically significant differences between groups.

Conclusions

Hormone therapy plays an important role in the clinical management of menopausal symptoms, but it has a complex pattern of risks and benefits in the primary prevention of chronic conditions. Depending on the treatment regimen, the risk-benefit profile of hormone therapy for the prevention of chronic conditions differs for women ages 50 to 79 years. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risk of fractures or diabetes) but also an increased risk of harms (e.g., higher risk of stroke, thromboembolic events, gallbladder disease, and possibly urinary incontinence), particularly among women older than age 60 years. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profile (with more favorable results in younger women), particularly for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

13.12.10 Characteristics of included studies

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022

WHI E+P Trial Anderson et al, 2012(245); Anderson et al, 2003(284); Canonico et al, 2014(299); Cauley et al, 2003(300); Chlebowski et al, 2003(288); Chlebowski et al, 2004(293); Cirillo et al, 2005(265); Cushman et al, 2004(301); Hays et al, 2003(79); Hendrix et al, 2003(302); Hendrix et al, 2005(267); Hsia et al, 2004(303); Manson et al, 2003(304); Manson et al, 2013(197); Margolis et al, 2004(305); Prentice et al, 2009(247); Rossouw et al, 2002(286); Rossouw et al, 2007(270); Tang et al, 2011(306); Toh et al, 2010(307); Wassertheil-Smoller et al, 2003(308) RCT	n=16608	• United States • Postmenopausal • Ages 50–79 years • 3-month washout period required for women using hormone therapy at baseline	Median 5.6 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,506) Placebo (N=8,102)	The assessment is not entirely clear in Garlehner 2022. The following quality rating was provided: -WHI (U.S.): Fair -WHI (U.S.) – breast cancer: Fair -WHI (U.S.) – breast cancer, CHD, stroke, hip fracture, non-Hodgkin’s lymphoma: Fair -WHI (U.S.) – fractures: Fair -WHI (U.S.) – lung cancer: Fair -WHI (U.S.) – stroke, VTE, mortality, breast cancer, CHD: Fair -WHI (U.S.) – mortality: Fair -WHI (U.S.) – endometrial cancer: Fair Details (randomization, allocation concealment, etc.) about the risk of bias can be found in Gartlehner 2022 Quality Rating: Fair (for outcomes mortality and endometrial cancer the quality rating is good) FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHI E+P Postintervention and Postintervention Extension Phases Chlebowski et al, 2009(297); Chlebowski	Postintervention phase n=15747 (95%) Postintervention Extension Phases	• See above	Median 8.2 years	Postintervention followup CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,060) Placebo (N=7,687)	

et al, 2010(271); Gramling et al, 2009(289); Heiss et al, 2008(287); Manson et al, 2013(197); Manson, 2017(255); Prentice, 2020(254); Prentice, 2020(253)	n=12788 (77%) consented to participate in the extension phase			Postintervention extension followup CEE 0.625 mg/day plus MPA 2.5 mg/day (N=6,545) Placebo (N=6,243)	
EPHT Estrogen plus progestin trial Estonian Postmenopausal Hormone Therapy Trial (EPHT) Veerus, 2006(290) RCT	n=777	• Estonia • Ages 50–64 years • An elapsed ≥ 12 months since last period at the randomization stage	Mean 3.4 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=404) Placebo (N=373)	Randomization adequate? Yes Allocation concealment adequate? Unclear Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Fair FUNDING: National Research and Development Centre for Welfare and Health (STAKES) (Finland)
ERA Estrogen-only and estrogen plus progestin trial Effects of Estrogen Replacement on the	n=205	• United States • Ages 41–79 years • Postmenopausal women not currently receiving estrogen replacement therapy	3.2 years	CEE 0.625 mg/day (N=100) CEE 0.625 mg/day plus MPA 2.5 mg/day (N=104)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Unclear Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes

Progression of Coronary-Artery Atherosclerosis [ERA] Herrington, 2000(215) RCT		With >1 epicardial coronary stenosis of $\geq 30\%$ of the luminal diameter		Placebo (N=105)	Other biases? Yes between placebo and CEE in adherence. Quality Rating: Fair FUNDING: National Heart, Lung and Blood Institute
PEPI Estrogen-only and estrogen plus progestin trial Postmenopausal Estrogen and Progestin Interventions Trial [PEPI] PEPI, 1995(257) RCT	n=349	- United States - Ages 45–64 years - With or without a uterus - Naturally or surgically menopausal	3 years	CEE 0.625 mg/day (N=175) CEE 0.625 mg/day plus MPA 10 mg/day for 12 days/month (N=174) CEE 0.625 mg/day plus MP 200 mg/day for 12 days/month (N=178) Placebo (N=174)	Randomization adequate? Yes Allocation concealment adequate? Unclear Groups similar at baseline? Unclear Outcome assessors masked? Yes Care providers masked? Unclear Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Unclear Intention-to-treat analysis? No Other biases? Yes Potential risk of contamination and low adherence to assigned study medications. Study authors noted that in women assigned to CEE, continuation rate was lowest and potentially due to endometrial hyperplasia. Some women were also initiated on another hormone regimen (other than the one assigned at randomization); this included up to 18% in some study arms. Quality Rating: Fair FUNDING: National Heart, Lung, and Blood Institute (NHLBI)
HERS Estrogen plus progestin trial	n=2763 At follow-up (HERS 2):	- United States - Age ≤ 80 years (mean, 66.7) - Intact uterus	Mean 4.1 years HERS was a blinded RCT,	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=1,380) Placebo (N=1,383)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes

Heart and Estrogen/Progestin Replacement Study (HERS) Grady et al, 1998(218); Hulley et al, 1998(222); Kanaya et al, 2003(309); Steinauer et al, 2005(291, 310) RCT	n=2321	• Postmenopausal • Established coronary artery disease	that had a mean followup of 4.1 years. At the end of HERS, participants were unblinded and 93 percent reenrolled in HERS2, an open label study, for an additional 2.7 years.	Mean 4.1 years CEE 0.625 mg/day plus MPA 2.5 mg/day (N=1,156) Placebo (N=1,165) Mean 6.8 years	Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: good FUNDING: Wyeth-Ayerst Laboratories
WISDOM Estrogen plus progestin trial Vickers, 2007(292) RCT	n=3022	• United Kingdom, Australia, New Zealand • Postmenopausal • Ages 50–69 years	1 year	CEE 0.625 mg/day plus MPA 2.5–5.0 mg/day (N=2,196) CEE 0.625 mg/day (N=826) Placebo (N=2,189) 1 year	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Unclear Intention-to-treat analysis? Yes Other biases? No Quality Rating: fair FUNDING: UK Medical Research Council, the UK Departments of

					Health, the British Heart Foundation and the NHS R&D Programme. Wyeth Ayerst US provided trial medication and matched placebo tablets.
Multiethnic Cohort Study Park, 2016(259) <u>Cohort study</u>	n=85734	Postmenopausal women who have ever (n=46723) or never (n=39011) used hormone therapy	16 years	- Ever used estrogen only - Currently use estrogen only - Ever used estrogen plus progestin - Currently use estrogen plus progestin	- Bias due to confounding: Moderate - Bias in selection of participants into the study: Moderate - Bias in classification of interventions: Moderate - Bias due to deviations from intended interventions: Low - Bias due to missing data: Low - Bias in measurement of outcomes: Low - Bias in selection of the reported result: Low Overall risk of bias: Moderate risk of bias FUNDING: National Cancer Institute, USA
Danish Sex Hormone Register Study Morch, 2016(296) <u>Cohort study</u> (retrospective)	n=643340	Women, ages 50 and 79 years without hysterectomy	Mean 9.8 years	22,853 Continuous combined estrogen plus progestin 25,209 Cyclic combined estrogen plus progestin	- Bias due to confounding: Moderate - Bias in selection of participants into the study: Moderate - Bias in classification of interventions: Moderate - Bias due to deviations from intended interventions: Low - Bias due to missing data: Low - Bias in measurement of outcomes: Low - Bias in selection of the reported result: Low

				2,071 Long cyclic combined estrogen plus progestin 593,207 Never hormone use	Overall risk of bias: Moderate risk of bias FUNDING: National Cancer Institute, USA

13.12.11 Update literature search (search date 01/12/2023)

Due to the postponement of the consensus conference, an additional literature search was performed on 01/12/2023.

A retrospective cohort study was identified by Inayama et al. 2023 (311) that evaluated the risk of cancer in perimenopausal Japanese women. In accordance with our methodology, we did not include this observational study given that data from RCT's on this topic was already available. Furthermore, no clear distinction was made between estrogen only and estrogen + progestin therapy and the study focused more on the timing hypothesis which was not included in the questions to the jury.

13.13 Estrogen plus progestin versus placebo: Cardiovascular disease

Estrogen + Progestin versus placebo: cardiovascular disease

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

“For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization’s International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.”

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

13.13.1 Coronary heart disease

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen + Progestin vs placebo	N=3 n=18085 (EPHT(290), PEPI(257), and WHI(197))	coronary heart disease (CHD)	2.8% vs 2.6% RR, 1.12 [95% CI, 0.94 to 1.33] NS
Design: RCT				
Search date: (Jun-2022)			Overall CHD (nonfatal myocardial infarction or coronary death)	

		N=1 n=16608 postintervention followup: n=15730 WHI Estrogen plus progestin trial Writing Group for the WHI, 2002(286); Manson, 2003(304); Rossouw, 2007(270); Heiss, 2008(287); Prentice, 2009(247); Manson, 2013(197); Liu, 2020(275); Prentice, 2020(253); Manson, 2017(255)	Intervention followup: Mean 5.2 years/Median 5.6 years	CEE + progestin vs placebo 196 (0.41% annualized) vs. 159 (0.35% annualized); HR, 1.18 (95% CI, 0.95 to 1.45) NS
			Postintervention followup: Mean 2.4 years	HR, 1.04 (95% CI, 0.89 to 1.21) NS
			Cumulative followup: Median 13.0 years	487 (0.48% annualized) vs. 430 (0.45%); HR, 1.09 (95% CI, 0.96 to 1.24); p=0.19 NS
			Cumulative followup: Median 19.4 years	710 (8.3% calculated) vs. 652 (8.0%); HR, 1.05 (95% CI, 0.95 to 1.17); p=NR NS
			All cardiovascular events(197)	
			Intervention followup: Mean 5.2 years/Median 5.6 years	786 (1.7% annualized) vs. 663 (1.52%); HR, 1.13 (95% CI, 1.02 to 1.25); p=0.02 SS
			Cumulative followup: Median 13.0 years(197)	1,606 (1.7% annualized) vs. 1,446 (1.6% annualized); HR, 1.08 (95% CI, 1.00 to 1.15); p=0.05 SS
			Myocardial infarction	
			Intervention followup: Mean 5.2 years/Median 5.6 years	168 (0.35% annualized) vs. 129 (0.29%); HR, 1.24 (95% CI, 0.98 to 1.56); p=0.07 NS
			Cumulative followup: Median 13.0 years	389 (0.39% annualized) vs. 324 (0.34%); HR, 1.15 (95% CI, 0.99 to 1.34); p=0.06 NS
			Total HF	
			Intervention followup: Mean 5.2 years/Median 5.6 years	32 (0.38%) vs. 28 (0.35%); HR, 1.06 (95% CI, 0.64 to 1.76) NS

			Cumulative followup: Median 18.9 years(275)	433 (5.1%) vs. 418 (5.2%); HR, 0.98 (95% CI, 0.86 to 1.13) NS
			Hospitalized HfrEF	
			Intervention followup: Mean 5.2 years/Median 5.6 years	32 (0.38%) vs. 28 (0.35%); HR, 1.06 (95% CI, 0.64 to 1.76) NS
			Cumulative followup: Median 18.9 years(275)	139 (1.7%) vs. 143 (1.8%); HR, 0.93 (95% CI, 0.73 to 1.17) NS
			Hospitalized HfpEF	
			Intervention followup: Mean 5.2 years/Median 5.6 years	31 (0.37%) vs. 31 (0.39%); HR, 0.93 (95% CI, 0.57 to 1.53) NS
			Cumulative followup: Median 18.9 years(275)	205 (2.5%) vs. 196 (2.5%); HR, 0.99 (95% CI, 0.82 to 1.21) NS
			CHD mortality	
			Intervention followup: Mean 5.2 years/Median 5.6 years	40 (0.082% annualized) vs. 40 (0.087%); HR, 0.94 (95% CI, 0.60 to 1.45); p=0.77 NS
			Postintervention followup: Mean 12.5 years	270 (0.29%) vs. 245 (0.28%); HR, 1.08 (95% CI, 0.91 to 1.28); p=0.39 NS
			Cumulative followup: Median 17.7 years	310 (0.22%) vs. 285 (0.21%); HR, 1.05 (95% CI, 0.89 to 1.23); p=0.57 NS

		WISDOM Estrogen plus progestin trial Vickers, 2007(292)	Cardiovascular events Followup: Mean 1 year	Estrogen vs estrogen+progestin vs placebo 2 (0.2%) vs. 7 (0.3%) vs. 0 (0.0%); p=0.016 SS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; CHD= coronary heart disease; HF=heart failure; HfrEF=heart failure with reduced ejection fraction; HfpEF=heart failure with preserved ejection fraction; NS=not statistically significant, SS=statistically significant

Remarks:

“Overall, six trials (EMS, EPHT, PEPI, WHI, WISDOM, and ERA) provided information about preventing coronary heart disease with estrogen plus progestin.”

“Of these, three trials (EPHT, PEPI, and WHI) were similar enough to be combined in a meta-analysis. We did not include the ERA study, which enrolled only women with an elevated cardiovascular risk; the EMS trial because its definition of cardiovascular events also included deep vein thrombosis and cerebrovascular events; and the WISDOM trial because it had a followup time of only 1 year.”

13.13.2 Venous Thromboembolism

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=16608 Postintervention followup n=15730	Venous thrombosis	
			Intervention followup: Median 5.6 years	CEE + progestin vs placebo 167 (1.96% calculated) vs. 76 (0.94%); HR, 2.06 (95% CI, 1.57 to 2.70) SS
			Cumulative followup: Median 19.4 years	416 (4.9% calculated) vs. 348 (4.3%); HR, 1.14 (95% CI, 0.99 to 1.31); p=NR NS
		WHI Estrogen plus progestin trial	Deep vein thrombosis	

		Heiss, 2008(287); Cushman, 2004(301); Manson, 2013(197); Prentice, 2009(247); Prentice, 2020(253); Prentice, 2020(254)	Intervention followup: Median 5.6 years	122 (1.4% calculated) vs. 61 (0.8%); HR, 1.87 (95% CI, 1.37 to 2.54); p<0.001 SS
			Postintervention followup: Mean 2.4 years(287)	HR, 1.07 (95% CI, 0.66 to 1.75) NS
			Cumulative followup: Median 13.2 years	212 (0.21% annualized) vs. 162 (0.17%); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 SS
			Pulmonary embolism	
			Intervention followup: Median 5.6 years	87 (1.0% calculated) vs. 41 (0.5%); HR, 1.98 (95% CI, 1.36 to 2.87); p<0.001 SS
			Postintervention followup: Mean 2.4 years(287)	HR, 1.07 (95% CI, 0.62 to 1.86) NS
			Cumulative followup: Median 13.2 years	172 (0.17% annualized) vs. 128 (0.13%); HR, 1.26 (95% CI, 1.00 to 1.59); p=0.05 SS
		N=1 n=2763 Cumulative follow-up: n=2539 HERS Estrogen plus progestin trial Hulley, 2002(291)	Total thromboembolic events	
			Intervention followup: Mean 4.1 years	34 (2.5% calculated) vs. 13 (0.9% calculated); HR, 2.66 (95% CI, 1.41 to 5.04); p=0.003 SS
			Cumulative followup: Mean 6.8 years	49 (4.2% calculated) vs. 24 (1.7% calculated); HR, 2.06 (95% CI, 1.26 to 3.36); p=NR SS
			Deep vein thrombosis	25 (1.8% calculated) vs. 9 (0.7% calculated); HR, 2.82 (95% CI, 1.32 to 6.04); p=0.008 SS
			Intervention followup: Mean 4.1 years	

		Tierney, 2009(294)		

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; ; NS=not statistically significant, SS=statistically significant

Remarks: the authors did not pool trial results because of heterogeneity in study duration and outcome measures.

13.13.3 Stroke

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=16608 Postintervention: n=15730 WHI Estrogen plus progestin trial Wassertheil-Smoller, 2003(308); Heiss, 2008(287); Cushman, 2004(301); Manson, 2013(197); Prentice, 2020(275); Manson, 2017(255); Prentice, 2020(254)	All stroke (Ischemic or hemorrhagic stroke)	
			Intervention followup: Median 5.6 years	CEE + progestin vs placebo 159 (1.9% calculated) vs. 109 (1.3%); HR, 1.37 (95% CI, 1.07 to 1.76); p=0.01(197) SS
			Postintervention followup: Mean 2.4 years	217 (0.40% annualized) vs. 202 (0.39%); HR, 1.04 (95% CI, 0.86 to 1.26); p=0.67 NS
			Cumulative followup: Median 13.2 years	376 (0.37% annualized) vs. 311 (0.32%); HR, 1.16 (95% CI, 1.00 to 1.35); p=0.06 NS
			Cumulative followup: Median 19.4 years	579 (6.8% calculated) vs. 492 (6.1%); HR, 1.13 (95% CI, 1.00 to 1.27); p=NR SS
			Ischemic stroke(308) Intervention followup: Median 5.6 years	125 vs. 81; HR, 1.44 (95% CI, 1.09 to 1.90) SS

			Hemorrhagic stroke(308) Intervention followup: Median 5.6 years	18 vs. 20; HR, 0.82 (95% CI, 0.43 to 1.56) NS
			Stroke mortality	
			Intervention followup: Median 5.6 years	27 (0.055% annualized) vs. 16 (0.035%); HR, 1.58 (95% CI, 0.85 to 2.94); p=0.14 NS
			Cumulative followup: Median 12.5 years	161 (0.17%) vs. 145 (0.16%); HR, 1.08 (95% CI, 0.86 to 1.35); p=0.52 NS
			Cumulative followup: Median 17.7 years	188 (0.13% annualized) vs. 161 (0.12%); HR, 1.12 (95% CI, 0.91 to 1.38); p=0.29 NS
		N=1 n=777 EPHT Estrogen plus progestin trial Veerus, 2006(290)	Any cerebrovascular disease Defined as diagnoses of one of the following (ICD-10 or 160-169 codes): subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral arteries, occlusion and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, or sequelae of cerebrovascular disease. Followup: Mean 3.4 years	23 (5.7%) vs. 9 (2.4%); HR, 2.46 (95% CI, 1.14 to 5.34); p=NR SS
			Stroke Followup: Mean 3.4 years	1 (0.2%) vs. 1 (0.3%); HR, 1.06 (95% CI, 0.07 to 17.2); p=NR NS

		N=1 n=205 (Women with angiographically verified coronary disease) ERA Estrogen-only and estrogen plus progestin trial	Stroke or transient ischemic attack Followup: Mean 3.2 years	5 vs. 6 vs. 6; p=1.0
		N=1 n=142 EMS Estrogen plus progestin trial Tierney, 2009(294)	Intracerebral hemorrhage Followup: 2 years	1 (1.4%) (fatal) vs. 0; p=NS
			Transient ischemic attack Followup: 2 years	1 (1.4%) vs. 1 (1.4%); p=NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks: the authors did not pool trial results because of heterogeneity in study duration and outcome measures.

13.13.4 Peripheral Arterial Disease

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT	Estrogen + progestin vs placebo	N=1 n=16608	Peripheral Arterial Disease (incident carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease)	48 vs. 50; HR, 0.89 (95% CI, 0.60 to 1.32); p=0.57 NS

Search date: (Jun-2022)		WHI Estrogen plus progestin trial Hsia 2004(303)	Followup: Mean 5.6 years	

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant

Remarks:/

13.13.5 Author's conclusions

Summary of review findings

Results of our review indicate some benefits of hormone therapy regarding the prevention of chronic conditions. For women using estrogen only, risk of diabetes (134 fewer cases per 10,000 women over 7.1 years) and risk of fractures (388 fewer cases per 10,000 women over 7.2 years) were statistically significantly reduced compared with women taking placebo. The risk for invasive breast cancer was numerically reduced in women using estrogen only, but the difference compared with placebo did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]). Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years), diabetes (78 fewer cases per 10,000 women over 5.6 years), and fractures (230 fewer cases per 10,000 women over 2 to 5.6 years) compared with women in the placebo groups. Benefits of hormone therapy for colorectal cancer attenuated with extended followup and were no longer statistically significant.

Our review also documented several important harms of hormone therapy. Women taking estrogen-only therapy had a statistically significant increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.2 years), urinary incontinence (885 more cases per 10,000 women over 1.0 year), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years) compared with women in the placebo groups.

Likewise, for women taking estrogen plus progestin therapy, risks of invasive breast cancer (51 more cases per 10,000 women over 5.6 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (260 more cases per 10,000 women over 5.6 years), stroke (52 more cases per 10,000 women over 5.6 years), urinary incontinence (562 more cases per 10,000 women over 1 year), and venous thromboembolism (120 more cases

per 10,000 women over 5.6 years) were statistically significantly increased compared with women taking placebo. A Danish retrospective cohort study also reported an increased risk for endometrial cancer (RR, 1.71 [1.58 to 1.86] over 9.8 years).

Based on high- or moderate-strength evidence, the risks for coronary heart disease and all-cause mortality were similar between estrogen-only hormone therapy and placebo. Likewise, high- or moderate-strength evidence indicates similar risks for lung cancer and all-cause mortality between estrogen plus progestin hormone therapy and placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-off between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years at the end of the intervention phase (HR, 1.12 [95% CI, 1.02 to 1.24]). After 18 years of cumulative followup, no statistically significant differences between groups were still apparent. For women who were randomized to estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03 [95% CI, 0.93 to 1.13]). Long-term followup also did not show any statistically significant differences between groups.

Conclusions

Hormone therapy plays an important role in the clinical management of menopausal symptoms, but it has a complex pattern of risks and benefits in the primary prevention of chronic conditions. Depending on the treatment regimen, the risk-benefit profile of hormone therapy for the prevention of chronic conditions differs for women ages 50 to 79 years. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risk of fractures or diabetes) but also an increased risk of harms (e.g., higher risk of stroke, thromboembolic events, gallbladder disease, and possibly urinary incontinence), particularly among women older than age 60 years. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profile (with more favorable results in younger women), particularly for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

13.13.6 Characteristics of included studies

See appendix cancer.

Other trials not included in appendix cancer: EMS study.

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022
EMS Estrogen plus progestin trial Tierney, 2009(294) RCT	n= 142	- Canada - Ages 61–87 years - Last menstrual cycle >12 months before screening - Fluent in English and could read normal print and hear normal speech	2 years	17 β -estradiol 1 mg/day for 4 days then 17 β -estradiol 1 mg plus norethindrone 0.35 mg/day for 3 days, repeated every week (N=70) Placebo (N=72)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for prior HT use and amnesic mild cognitive impairment. Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup $\leq$ 20% and differential attrition $\leq$ 15%? Yes Intention-to-treat analysis? Unclear Other biases? No Quality Rating: Fair FUNDING: the Canadian Institutes of Health Research (CIHR) (Grant 15222). The Institute of Neurosciences, Mental Health and Addiction (CIHR), and Shire Biochem provided additional funding. Estrace (17- β estradiol) was provided by Shire Biochem and norethindrone was provided by Janssen-Ortho.

Author's conclusions:

"Results of the meta-analysis showed a numerically higher (but not statistically significant) risk of coronary heart disease in women treated with hormone therapy than in those treated with placebo (2.8% vs. 2.6%; RR, 1.12 [95% CI, 0.94 to 1.33]) during a mean followup of 4 years.

Postintervention followup of women in the WHI showed that 2.4 years after stopping therapy, the risk of coronary heart disease was similar between women who took estrogen plus progestin during the trial and those who received placebo (HR, 1.04 [95% CI, 0.89 to 1.21]).(287) Risk remained similar between treatment groups at 13 and 19.4 years of cumulative followup (HR, 1.09 [95% CI, 0.96 to 1.24] and HR, 1.05 [95% CI, 0.95 to 1.17], respectively).(197), (253)

The WISDOM trial was prematurely closed because of findings of the WHI. However, after 1 year of followup (6,498 women-years), women taking estrogen plus progestin had a statistically significantly higher risk of cardiovascular events (0.3% vs. 0.0%; $p=0.016$) than women taking placebo.(292)

Only the WHI reported mortality due to coronary heart disease. Death from coronary heart disease was similar between the estrogen plus progestin and placebo groups during the 5.6-year intervention phase (40 vs. 40 events), at 12.5 years postintervention (270 vs. 245 events), and after 17.7 years of cumulative followup (310 vs. 285 events).(255)"

13.14 Estrogen plus progestin versus placebo: Cognition and dementia

Estrogen + Progestin versus placebo: Dementia

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

The authors did not pool trial results because of heterogeneity in study duration and outcome measures.

13.14.1 Dementia and mild cognitive impairment incidence

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=16608 WHI Estrogen plus progestin trial Manson, 2017(255)	Alzheimer's disease or other dementia mortality	
			Intervention followup: Median 5.6 years	CEE vs placebo 0 (0% annualized) vs. 0 (0%); HR not estimatable
			Postintervention followup: Median 12.5 years	223 (0.24% annualized) vs. 233 (0.26%); HR, 0.94 (95% CI, 0.78 to 1.13); p=0.52 NS
			Cumulative followup: Median 17.7 years	223 (0.16% annualized) vs. 233 (0.17%); HR, 0.93 (95% CI, 0.77 to 1.11); p=0.42 NS
			Probable dementia	40 (1.8%) vs. 21 (0.9%);

		N=1 n=4532 WHIMS Estrogen plus progestin trial Shumaker, 2003;(312) Shumaker, 2004(277)	Intervention followup: ~4 years	cumulative HR, 2.05 (95% CI, 1.21 to 3.48); p=0.01 SS
			Mild cognitive impairment Intervention followup: ~4 years	56 (2.5%) vs. 55 (2.4%); cumulative HR, 1.07 (95% CI, 0.74 to 1.55); p=0.72 NS
			Probable dementia or Mild cognitive impairment Intervention followup: ~4 years	85 (3.8%) vs. 66 (2.9%); cumulative HR, 1.37 (95% CI, 0.99 to 1.89) NS
		N=1 n=1416 WHISCA Estrogen plus progestin trial Resnick, 2006(313)	Probable dementia Intervention followup:1.4 years (during WHISCA, after being enrolled in WHI for 3 years)	5 (0.7%) vs. 6 (0.8%); calculated RR, 0.88 (95% CI, 0.27 to 2.86); p=0.83 NS
			Mild cognitive impairment Intervention followup:1.4 years (during WHISCA, after being enrolled in WHI for 3 years)	6 (0.9%) vs. 13 (1.8%); calculated RR, 0.49 (95% CI, 0.19 to 1.27); p=0.14 NS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks: /

13.14.2 Global cognitive function

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=1328 HERS Estrogen plus progestin trial Grady, 2002(314)	Modified Mini-Mental State Examination Followup: 4.2 years	93.1 (SD, 6.4) vs. 93.4 (SD, 6.4); difference, -0.4 (95% CI, -1.1 to 0.4); p=0.36 NS
		N=1 n=4344 WHIMS Estrogen plus progestin trial Rapp, 2003;(315) Espeland, 2004(279)	Modified Mini-Mental State Examination Followup: 5.4 years	Mean difference in change from baseline, -0.18 (95% CI, -0.37 to 0.00); p=0.055 NS
		N=1 n=1213 WHISCA Estrogen plus progestin trial	Mean decrement in global cognitive function, Modified Mini-Mental State Examination	
		Espeland, 2010(280)	Followup: mean 2 years (during WHISCA, after being enrolled in WHI for 3 years)	-0.080 (SE, 0.034); p=0.02 SS

			Postintervention followup: Mean 4 years (after being enrolled in WHI for 3 years and in WHISCA for 2 years)	-0.059 (SE, 0.032); p=0.06 NS
		N=1 n=1326 WHIMSY Estrogen + progestin trial Espeland, 2013;(281) Espeland, 2017(282)	TICS =Telephone Interview for Cognitive Status Postintervention followup: 7.2 years	38.08 (SE, 0.20) vs. 38.26 (SE, 0.21); p=NR No difference
		N=1 n=693 KEEPS-Cog Estrogen plus progestin trial Gleason, 2015(316)	Modified Mini-Mental State Examination Followup: 4 years	Oral estrogen: Beta estimate, 1.02×10^{-2} (95% CI, -4.45×10^{-3} to 2.48×10^{-2}); p=0.178 NS Transdermal estrogen: Beta estimate, -9.40×10^{-4} (95% CI, -1.57×10^{-2} to 1.38×10^{-2}); p=0.840 NS
		N=1 n=101 KEEPS-MRI Kantarci, 2016(317)	Modified Mini-Mental State Examination Followup: 4 years	No significant differences in changes in global cognitive function. (Authors did not report absolute values of 3MS by group, visual display only.)

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks:/

Author's conclusions:

HERS found no difference in 3MSE scores between groups through 4 years of follow-up (-0.4 , $p=0.36$). Similarly, there were no significant difference in change in 3MSE scores in the WHIMS estrogen plus progestin trial during 5.4 years of follow-up (-0.18 , $p=0.055$). In WHISCA, the WHIMS ancillary study, differences in 3MSE scores during the 2-year intervention period among participants for the estrogen and progestin arm (-0.09 , $p=0.02$) were not sustained at the postintervention follow-up (-0.081 , $p=0.09$). The WHIMSY trial, a subset of the WHI limited to women ages 50 to 55 years at enrollment, found no difference in mean TICS-m scores with adjustment for age and visit year between women assigned to estrogen plus progestin and women assigned placebo 7.2 years after stopping therapy. Neither KEEPS-Cog, an ancillary study that recruited patients from all sites of the KEEPS trial, nor KEEPS-MRI, an ancillary study that recruited patients from one site of the KEEPS trial, found differences between women randomized to either estrogen plus progestin therapy and women randomized to placebo in change in 3MSE score over a 4-year period of observation for either oral or transdermal estrogen.

13.14.3 Other Cognitive Measures

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=142 EMS Estrogen plus progestin trial Tierney, 2009(294)	Short-delay verbal recall of the California Verbal Learning Test (CVLT) Followup: 1 year	No significant differences by group.
			Short-delay verbal recall of the California Verbal Learning Test (CVLT) Followup: 1 year	No significant differences by group.
		N=1 n=1328 HERS Estrogen plus progestin trial Grady, 2002(314)	Other cognitive measures Followup: 4.2 years	Verbal fluency 15.9 (SD, 4.8) vs. 16.6 (SD, 4.8); difference, -0.7 (95% CI, -1.3 to -0.1); p=0.02 SS Boston Naming Test No significant differences by group. Word List Memory No significant differences by group. Word List Recall No significant differences by group. Trials B No significant differences by group.

		N=1 n=1213 WHISCA Estrogen plus progestin trial Espeland, 2010(280)	Other Cognitive Measures Followup: Mean 3 years (pre-WHISCA, 2 years during WHISCA trial)	Spatial Ability No significant differences by group. Verbal Knowledge No significant differences by group. Verbal Fluency No significant differences by group. Verbal Memory No significant differences by group. Figural Memory No significant differences by group. Attention No significant differences by group. Working Memory No significant differences by group.
			Other Cognitive Measures Postintervention followup: Mean 4 years	Spatial Ability No significant differences by group. Verbal Knowledge No significant differences by group. Verbal Fluency

				No significant differences by group. Verbal Memory No significant differences by group. Figural Memory No significant differences by group. Attention No significant differences by group. Working Memory No significant differences by group.
		N=1 n=1326 WHIMSY Estrogen plus progestin trial Espeland, 2013;(281) Espeland, 2017(282)	Other Cognitive Measures Postintervention followup: 7.2 years	Verbal Fluency No significant differences by group. Verbal Memory No significant differences by group. Attention No significant differences by group. Executive function No significant differences by group. Working Memory No significant differences by group. East Boston Memory Test

				No significant differences by group. Composite cognitive function No significant differences by group.

Remarks:/

13.14.4 Characteristics of included studies

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022
WHI Estrogen plus progestin trial	See appendix cancer				
WHIMS Estrogen plus progestin trial Women's Health Initiative Memory Study (WHIMS) Culhane, 2003;(318) Rapp et al, 2003;(315) Shumaker et al, 2003(312) RCT	n=4532	• United States • WHI participants enrolled in the E+P trial • Age >65 years • Free of probable dementia • Able and willing to undergo annual cognitive assessment	5.4 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=2,229) vs Placebo (N=2,303)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for history of stroke and hypertension Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHISCA Estrogen plus progestin trial	n=1416	• United States • WHIMS E+P trial participants • Free of probable dementia	2 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=690)	Randomization adequate? Yes Allocation concealment adequate? Yes

Women's Health Initiative Study of Cognitive Aging (WHISCA) Espeland et al, 2010;(280) Resnick et al, 2006(313) RCT		- At 1 of 14 WHIMS centers - Began 3 years after enrollment in WHI		vs Placebo (N=726)	Groups similar at baseline? Mostly, except for smoking status Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Yes Other biases? No Quality Rating: Good FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
WHISCA Estrogen plus progestin trial Post intervention Phase Espeland et al, 2010;(280) RCT	n=1416	See above	4 years	See above	
WHIMSY Estrogen + progestin trial	n=1326	- United States - Postmenopausal - Ages 50–55 years	7.2 years	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=696) Placebo (N=630)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes

Women's Health Initiative Memory Study of Younger Women (WHIMSY) Espeland, 2013;(281) Espeland, 2017(282) RCT		3-month washout period for women using hormone therapy at baseline			Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up $\leq 20\%$ and differential attrition $\leq 15\%$? No Intention-to-treat analysis? Yes Other biases? No Quality Rating: Fair FUNDING: National Heart, Lung, and Blood Institute, or NHLBI
KEEPS-Cog Estrogen plus progestin trial Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog) Gleason, 2015(316) RCT	n=693	- United States - Ages 42–58 years - Intact uterus - Recently postmenopausal - At risk for cardiovascular disease	4 years	CEE 0.45 mg/day plus MP 200 mg/day for 12 days/month (N=220) Transdermal estradiol 50 µg/day plus MP 200 mg/day for 12 days/month (N=211) Placebo (N=262)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up $\leq 20\%$ and differential attrition $\leq 15\%$? No Intention-to-treat analysis? Yes Other biases? No Quality Rating: Fair FUNDING: National Institutes of Health. Bayer HealthCare Pharmaceuticals, Inc. supplied

					the CLIMARA estradiol and placebo patches and Abbott Laboratories (formerly Solvay Pharmaceuticals) provided the micronized progesterone (PROMETRIUM) and placebo capsules.
KEEPS-MRI Kronos Early Estrogen Prevention Study-MRI Kantarci, 2016(317)	n=101	• United States • Ages 42–59 years • In good cardiovascular health • 5–36 months past menopause • No MRI contraindications for safety and neurological disorders	4 years	CEE 0.45 mg/day plus MP 200 mg/day for 12 days/month (N=31) Transdermal 17β-estradiol 50 µg/day plus MP 200 mg/day for 12 days/month (N=31) Placebo (N=39)	<u>Global cognition score</u> Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to follow-up ≤20% and differential attrition ≤15%? No Intention-to-treat analysis? Unclear Other biases? yes Quality Rating: Poor <u>Global cognitive function</u> Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Yes Outcome assessors masked? Yes Care providers masked? Yes

					Patient masked? Yes Loss to follow-up $\leq 20\%$ and differential attrition $\leq 15\%$? No Intention-to-treat analysis? Yes Other biases? No Quality Rating Fair FUNDING: National Institutes of Health
EMS Estrogen plus progestin trial Tierney, 2009(294) RCT	n= 142	• Canada • Ages 61–87 years • Last menstrual cycle >12 months before screening • Fluent in English and could read normal print and hear normal speech •	2 years	17β-estradiol 1 mg/day for 4 days then 17β-estradiol 1 mg plus norethindrone 0.35 mg/day for 3 days, repeated every week (N=70) Placebo (N=72)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for prior HT use and amnesic mild cognitive impairment. Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup $\leq 20\%$ and differential attrition $\leq 15\%$? Yes Intention-to-treat analysis? Unclear Other biases? No Quality Rating: Fair FUNDING: the Canadian Institutes of Health Research (CIHR) (Grant 15222). The Institute of Neurosciences, Mental Health and Addiction (CIHR), and Shire Biochem provided additional funding. Estrace (17-β estradiol) was

					provided by Shire Biochem and norethindrone was provided by Janssen-Ortho.

13.15 Estrogen plus progestin versus placebo: Fractures

Estrogen + Progestin versus placebo: Fractures

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

“For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization’s International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.”

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen+Progestin vs placebo	N=5 n=20499 WHI Estrogen plus progestin trial Heiss, 2008;(287) Cauley, 2003;(300) Rossouw, 2002;(286) Manson, 2013;(197) Watts, 2017;(285) Prentice, 2020;(253) Prentice, 2020(254)	Fractures During or at the end of the intervention period	CEE vs placebo 8.7% vs 10.9%; RR, 0.79 (95% CI, 0.66 to 0.94) SS Heterogeneity: $T^2=0.01$, $I^2=34.24\%$, $H^2=1.52$

		HERS Estrogen plus progestin trial Hulley, 2002(291) ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000(215) EPHT Estrogen plus progestin trial Veerus, 2006(290) EMS Estrogen plus progestin trial Tierney, 2009(294)		
		Studies with postintervention data: WHI		
		N=1 n=16608 Postintervention follow-up: n=15730 WHI Estrogen plus progestin trial Heiss, 2008;(287) Cauley,	Fractures – total	
			Intervention followup: Mean 5.6 years	741 (1.61% annualized) vs. 903 (2.12% annualized); HR, 0.76 (95% CI, 0.69 to 0.83); p<0.001 SS
			Postintervention followup: Mean 2.4 years	337 (1.95% annualized) vs. 346 (2.16% annualized); HR, 0.91 (95% CI, 0.78 to 1.06); p=0.06 NS
			Postintervention followup: Calculated mean 4.2 years (285)	572 (2.89% annualized) vs. 612 (2.99% annualized); HR, 0.97 (95% CI, 0.87 to 1.09); p=0.63 NS

		2003;(300) Rossouw, 2002;(286) Manson, 2013;(197) Watts, 2017;(285) Prentice, 2020;(253) Prentice, 2020(254)		
			Fractures - Hip	
			Intervention followup: Mean 5.6 years(197)	53 (0.11% annualized) vs. 75 (0.17% annualized); HR, 0.67 (95% CI, 0.47 to 0.96); p=0.03 SS
			Postintervention followup: Mean 2.4 years(287)	54 (0.28% annualized) vs. 57 (0.31% annualized); HR, 0.92 (95% CI, 0.64 to 1.34); p=0.20 NS
			Postintervention followup: Calculated mean 4.2 years(285)	50 (0.24% annualized) vs. 56 (0.26% annualized); HR, 0.93 (95% CI, 0.63 to 1.36); p=0.70 NS
			Cumulative followup: Mean 13.2 years(197)	232 (0.23% annualized) vs. 270 (0.28% annualized); HR, 0.81 (95% CI, 0.68 to 0.97); p=0.02 SS
			Cumulative followup: Mean 19.4 years(253)	394 (4.6% calculated) vs. 421 (5.2% calculated); HR, 0.90 (95% CI, 0.78 to 1.03); p=NR NS
			Fractures - Vertebral	
			Intervention followup: Mean 5.6 years(197)	56 (0.12% annualized) vs. 78 (0.17% annualized); HR, 0.68 (95% CI, 0.48 to 0.96); p=0.03 SS
			Postintervention followup: Mean 2.4 years(287)	46 (0.24% annualized) vs. 47 (0.26% annualized); HR, 0.96 (95% CI, 0.64 to 1.44); p=0.23 NS
			Other osteoporotic fractures (287) Intervention followup: Mean 5.6 years	650 (1.41% annualized) vs. 800 (1.87% annualized); HR, 0.75 (95% CI, 0.68 to 0.83); p=NR SS

* Characteristics of included studies: see below

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks: /

Author's conclusions:

A random-effects meta-analysis of these five trials measuring total fractures during or at the end of the intervention period (N=20,499) yielded a statistically significant reduction of fractures in women taking estrogen plus progestin (RR, 0.79 [95% CI, 0.66 to 0.94]. In the meta-analysis, 8.7 percent of women taking estrogen plus progestin and 10.9 percent of women taking placebo experienced fractures.

Characteristics included trials

The characteristics of the included trials can be found in appendix cancer.

Trials included for analysis on fractures but not included in appendix cancer: the EMS Estrogen plus progestin trial. See below.

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Gartlehner 2022
EMS Estrogen plus progestin trial Tierney, 2009(294) RCT	n= 142	- Canada - Ages 61–87 years - Last menstrual cycle >12 months before screening - Fluent in English and could read normal print and hear normal speech	2 years	17β-estradiol 1 mg/day for 4 days then 17β-estradiol 1 mg plus norethindrone 0.35 mg/day for 3 days, repeated every week (N=70) Placebo (N=72)	Randomization adequate? Yes Allocation concealment adequate? Yes Groups similar at baseline? Mostly, except for prior HT use and amnesic mild cognitive impairment. Outcome assessors masked? Yes Care providers masked? Yes Patient masked? Yes Loss to followup ≤20% and differential attrition ≤15%? Yes Intention-to-treat analysis? Unclear Other biases? No Quality Rating: Fair FUNDING: the Canadian Institutes of Health Research (CIHR) (Grant 15222). The Institute of Neurosciences, Mental Health and Addiction

					(CIHR), and Shire Biochem provided additional funding. Estrace (17- β estradiol) was provided by Shire Biochem and norethindrone was provided by Janssen-Ortho.

13.16 Estrogen plus progestin versus placebo: Diabetes

Estrogen plus progestin versus placebo: Diabetes

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=15784 WHI Estrogen plus progestin trial Margolis, 2004;(305) Manson, 2013;(197) Prentice, 2020(253) RCT	Self-reported treated diabetes (197)	
			Intervention followup: Mean 5.6 years	CEE vs placebo 328 (0.72% annualized) vs. 373 (0.88% annualized); HR, 0.81 (95% CI, 0.70 to 0.94); p=0.005 SS
			Postintervention followup: Median 8.2 years	603 (1.24% annualized) vs. 482 (1.04% annualized); HR, 1.19 (95% CI, 1.05 to 1.34); p=0.005 SS
			Cumulative followup: Median 13.2 years	931 (0.99% annualized) vs. 855 (0.96% annualized); HR, 1.02 (95% CI, 0.93 to 1.12); p=0.66 NS
		N=1 n=2029	Overall Diabetes Intervention followup: Mean 4.1 years	62 (6.2%) vs. 98 (9.5%); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.006 SS

		HERS Estrogen plus progestin trial Kanaya, 2003(309) RCT		

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks:

Two trials (HERS [N=2,029](309) and WHI [N=15,874](197) (305)) provided information about the prevention of diabetes with estrogen plus progestin among 17,903 women without diabetes or not receiving treatment for diabetes at baseline. Incident diabetes was defined in HERS as having a fasting glucose level of 6.9 mmol/L or greater (≥ 126 mg/dL), self-report of new diabetes or diabetes-related complications (diabetic neuropathy, diabetic retinopathy, diabetic foot ulcer, diabetic renal disease, or hypoglycemia if taking an antidiabetic medication), or initiation of hypoglycemic medication; this analysis was conducted post hoc and should be considered cautiously.(309) In the WHI, incident diabetes was limited to self-reported new diagnoses of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin.(305)

Author's conclusions:

Estrogen plus progestin therapy reduced incident diabetes among women in HERS (mean followup, 4.1 years; HR, 0.65 [95% CI, 0.48 to 0.89]) and the WHI (mean followup, 5.6 years; HR, 0.81 [95% CI, 0.70 to 0.94]) through the end of the intervention phase.(309) (305) In the WHI, the larger trial of the two, new diabetes diagnoses were reported during followup by 0.72 percent (annualized) of women randomized to active treatment and 0.88 percent (annualized) of those taking placebo.(197) (305) However, women receiving active treatment actually experienced an increased risk of diabetes compared with those taking placebo 8.2 years postintervention (HR, 1.19 [95% CI, 1.05 to 1.34]).(197) No between-group difference in risk was observed after 13.2 years of cumulative followup (HR, 1.02 [95% CI, 0.93 to 1.12]).(197)

Characteristics included trials

See appendix cancer.

13.17 Estrogen plus progestin versus placebo: Gallbladder disease

Estrogen + Progestin versus placebo: Gallbladder disease

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=14203 WHI Estrogen plus progestin trial Cirillo, 2005;(265) Manson, 2013;(197) Prentice, 2020 RCT	Intervention followup: Mean 5.6 years	
			Gallbladder event incidence (265)	CEE vs placebo 228 (3.1%) vs. 135 (2.0%); HR, 1.59 (95% CI, 1.28 to 1.97); p<0.001 SS
			Cholecystectomy (265)	190 (2.6%) vs. 107 (1.6%); HR, 1.67 (95% CI, 1.32 to 2.11); p<0.001 SS
			Global gallbladder disease (197)	528 (1.31% annualized) vs. 319 (0.84% annualized); HR, 1.57 (95% CI, 1.36 to 1.80); p<0.001 SS
			Cholecystitis (265)	192 (2.6%) vs. 117 (1.7%); HR, 1.54 (95% CI, 1.22 to 1.94); p<0.001 SS

			Gallbladder disease Postintervention follow-up: Median 8.2 years (197)	213 (1.27% annualized) vs. 166 (1.01% annualized); HR, 1.24 (95% CI, 1.01 to 1.52); p=0.04 SS
		N=1 n=526 PEPI Estrogen-only and estrogen plus progestin trial PEPI, 1995(257)	Gallbladder disease Intervention follow-up: 3 years	2 (estrogen: 1.1%) vs. 9 (estrogen plus progestin: 2.6%) vs. 4 (estrogen plus micronized progestin: 2.2%) vs. 2 (placebo: 1.1%)

Abbreviations: CEE=conjugated equine estrogen; NS=not statistically significant, SS=statistically significant

Remarks:

The definition of gallbladder disease used in PEPI is unclear; for WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all gallbladder or biliary tract stone disease.(257) (197) (265)

Characteristics included trials

See appendix cancer.

13.18 Estrogen plus progestin versus placebo: Urinary incontinence

Estrogen plus Progestin versus placebo: Urinary incontinence

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=1 n=11578 continent	Intervention followup: 1 year	
		At year 3 n=338 Postintervention n=10073	Weekly total urinary incontinence(197) 5,981 Estrogen plus progestin (all continent at baseline) 5,597 Placebo (all continent at baseline)	1,021 (16.6% annualized) vs. 641 (11.1% annualized); HR, 1.49 (95% CI, 1.36 to 1.63); p<0.001 SS
		WHI Estrogen plus progestin trial Hendrix, 2005;(267) Manson, 2013(197)	Incident urinary incontinence (≥1 episode/year) (267) 2,675 Estrogen plus progestin (all continent at baseline) 2,507 Placebo (all continent at baseline)	834 (31.2%) vs. 563 (22.5%); RR, 1.39 (95% CI, 1.27 to 1.52) SS

		RCT	Stress urinary incontinence (≥1 episode/year) (267) 2,675 Estrogen plus progestin (all continent at baseline) 2,507 Placebo (all continent at baseline)	429 (16.0%) vs. 218 (8.7%); RR, 1.87 (95% CI, 1.61 to 2.18); p<0.001 SS
			Urge urinary incontinence (≥1 episode/year) (267) 2,675 Estrogen plus progestin (all continent at baseline) 2,507 Placebo (all continent at baseline)	304 (11.4%) vs. 272 (10.8%); RR, 1.15 (95% CI, 0.99 to 1.34); p=0.06 NS
			Mixed urinary incontinence (≥1 episode/year) (267) Intervention followup: 3 years (267) 153 Estrogen plus progestin (all continent at baseline and 1 year) 185 Placebo (all continent at baseline and 1 year)	39 (25.5%) vs. 26 (14.1%); RR, 1.81 (95% CI, 1.16 to 2.84); p=NR SS
			Weekly total urinary incontinence(197) Postintervention followup: Median 8.2 years (197)	1,221 calculated (23.5%) vs. 990 calculated (20.3%); HR, 1.16 (95% CI, 1.08 to 1.25); p<0.001 SS

			5,194 Estrogen plus progestin (all continent at baseline) 4,879 Placebo (all continent at baseline)	
		N=1 n=1208 continent	Followup: 4.2 years 597 Estrogen plus progestin 611 Placebo	
		HERS Estrogen plus progestin trial	Weekly total urinary incontinence	382 vs. 302; OR, 1.6 (95% CI, 1.3 to 1.9); p<0.001 SS
		Steinauer, 2005(310)	Weekly stress urinary incontinence	OR, 1.7 (95% CI, 1.5 to 2.1); p<0.001 SS
			Weekly urge urinary incontinence	OR, 1.5 (95% CI, 1.2 to 1.8); p<0.001 SS

Abbreviations: NS=not statistically significant, SS=statistically significant

Remarks:

These studies defined urinary incontinence as at least one episode weekly.(197) (310) Both the WHI(267) and HERS(310) also evaluated various subtypes of urinary incontinence.

Characteristics included trials

See appendix cancer.

13.19 Estrogen plus progestin versus placebo: Quality of life

Estrogen plus Progestin versus placebo: Health-Related Quality of Life

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022	Estrogen + Progestin vs placebo	N=1 n=16608 WHI Estrogen plus progestin trial	Quality of Life Followup: Mean 5.6 years	CEE vs placebo SF-36: Similar scores on all items except for physical functioning (82.6 vs. 81.8; p<0.001), physical role (77.4 vs. 76.2; p=0.02), bodily pain (77.6 vs. 75.6; p<0.001), and general health (76.6 vs. 76.1; p=0.02), for which women taking hormone therapy had statistically significantly better scores than women taking placebo
Design: RCT				
Search date: (Jun-2022)		Manson, 2013;(197) Hays, 2003(79) RCT		

Abbreviations: CEE=conjugated equine estrogen

Remarks:

The WHI (N=16,608)(197) was the only trial that reported on health-related quality of life. It used the SF-36 form, which assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health.

Author's conclusions:

Women in both groups had similar scores on all items except for physical functioning ($p<0.001$), physical role ($p=0.02$), bodily pain ($p<0.001$), and general health ($p=0.02$), for which women taking hormone therapy had statistically significantly better scores than women taking placebo.

Characteristics included trials

See appendix cancer.

13.20 Estrogen plus progestin versus control: Asthma

Hormone therapy vs control: onset of asthma

Hormone replacement therapy and asthma onset in menopausal women: National cohort study(196)					
Design	N/n	Population	Risk factor	Outcome	Results*
Design: Retrospective cohort study UK	N= 1 n= 353173 17 years of follow-up	peri-menopausal women postmenopausal women aged 46–70 years	HRT	Asthma	Previous users vs non-users Adjusted HR 0.83 (95% CI : 0.79-0.88) SS Current users vs non-users Adjusted HR 0.79 (95% CI : 0.74-0.85) SS
			Estrogen only	Asthma	Previous users vs non-users Adjusted HR 0.89 (95% CI : 0.84-0.95) SS Current users vs non-users Adjusted HR 0.80 (95% CI : 0.73-0.87) SS
		Estrogen plus progestin	Asthma	Previous users vs non-users Adjusted HR 0.82 (95% CI : 0.76-0.88) SS Current users vs non-users Adjusted HR 0.78 (95% CI : 0.70-0.87) SS	
*Adjusted for age, smoking, Charlson Comorbidity Index score, BMI, gravidity, any gynecologic condition, and IMD (index of multiple deprivation) quintile.					

Remarks:

- The AHRQ review from Garthlehner 2022 mentioned in their appendix of eligible observational studies two studies with outcome asthma. This is not further studied in the review without mentioning a reason for this. We included one of the studies here and excluded the other study in our report due to the studied population (women with asthma).

- Use of HRT was associated with a reduced risk of asthma only in all women, but not when the women were stratified by menopausal status.
- The authors observed a dose-response association (Kandall τ statistic = -1 [$P = .089$]) between duration of HRT use and risk of asthma onset: women with 1 to 2 years of HRT use had a 7% (95% CI = 13-1) lower risk than women who did not use HRT, women with 3 or 4 years of use had a 23% lower risk (95% CI = 30-16), and those with 5 or more years of use had a 29% (95% CI = 36-22) lower risk. “This effect becomes insignificant, however, when patients are stratified by age, BMI, and smoking, possibly because of lack of sufficient power to detect significant effect after stratification.”

13.21 Estrogen plus progestin versus placebo: COPD

Estrogen plus Progestin versus placebo: COPD

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.

- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

“For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization’s International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.”

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT	Estrogen + Progestin vs placebo	N=1 n=16608 WHI Estrogen plus progestin trial	COPD incidence	No eligible studies
			COPD-specific mortality	
			Intervention followup: Median 5.6 years	1 (0.002% annualized) vs. 8 (0.017% annualized); HR, 0.12 (95% CI, 0.01 to 0.93); p=0.01 SS

Search date: (month-year)		Manson, 2017(255) RCT	Postintervention followup: Median 12.5 years	107 (0.12% annualized) vs. 92 (0.10% annualized); HR, 1.13 (95% CI, 0.85 to 1.49); p=0.41 NS
			Cumulative followup: Median 17.7 years	108 (0.076% annualized) vs. 100 (0.074% annualized); HR, 1.03 (95% CI, 0.79 to 1.36); p=0.81 NS

Abbreviations: NS=not statistically significant, SS=statistically significant

Remarks: No eligible studies reported on COPD incidence. The WHI (N=16,608)(255) was the only trial that provided information about the prevention of COPD mortality with estrogen plus progestin. COPD mortality was measured at multiple time points and identified via data linkage to the NDI.

Author's conclusions:

The WHI found a reduced risk of COPD mortality among women who took estrogen plus progestin compared with those who received placebo during the 5.6-year (median) intervention phase (1 vs. 8 events; HR, 0.12 [95% CI, 0.01 to 0.93]). This finding needs to be viewed cautiously because only nine women had died of COPD by this time point. However, the reduction in risk was no longer observed during a 12.5-year (median) postintervention followup (HR, 1.13 [95% CI, 0.85 to 1.49]) or 17.7-year (median) cumulative followup (HR, 1.03 [95% CI, 0.79 to 1.36]).

Characteristics included trials

See appendix cancer.

13.22 Estrogen plus progestin versus placebo: All-cause mortality

Estrogen plus Progestin versus placebo: All-cause mortality

Meta-analysis:

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force(5)

Inclusion criteria:

- Population: generally healthy perimenopausal and postmenopausal women eligible for menopausal HT. Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions
- Interventions: Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States.
- Duration of intervention: ≥ 1 year of treatment.
- Study design:
All outcomes: RCTs, Controlled clinical trials, Systematic reviews.
For outcomes or subgroups with no evidence from trials or systematic reviews: Large cohort studies (more than 10,000 women).
- Setting: primary care or primary-care-like setting.

Exclusion criteria:

- Population: Premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care. Postmenopausal women who use HT for secondary prevention of chronic conditions.
- Interventions: Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved.
- Outcomes: Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level.
- Setting: Inpatient facilities, nursing homes, hormone specialist offices.

Search strategy:

"For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate.

We conducted targeted searches for unpublished literature by searching [ClinicalTrials.gov](https://clinicaltrials.gov), HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and vog.ADF@sgurD. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation."

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Gartlehner 2022 Design: RCT Search date: (Jun-2022)	Estrogen + Progestin vs placebo	N=3 n=19580 WHI Estrogen plus progestin trial HERS Estrogen plus progestin trial Hulley, 2002 (291) ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000 (215) RCT	All-cause mortality	RR, 1.01 [95% CI, 0.88 to 1.16] NS Heterogeneity: $T^2=0.00$, $I^2=0.00\%$, $H^2=1.00$

		WHI Estrogen plus progestin trial Heiss, 2008;(287) Manson, 2013;(197) Prentice, 2009;(247) Prentice, 2020;(253) Manson, 2017;(255) Prentice, 2020(254) RCT	All-cause mortality	
			Intervention followup: Mean 5.6 years	250 (2.9% calculated) vs. 239 (2.9% calculated); HR, 0.97 (95% CI, 0.81 to 1.16) (255) (287) NS
			Postintervention followup: Mean 2.4 years (287)	233 (1.20% annualized) vs. 196 (1.06% annualized); HR, 1.15 (95% CI, 0.95 to 1.39); p=0.27 NS
			Postintervention followup: Median 8.2 years (197)	761 (1.39% annualized) vs. 728 (1.39% annualized); HR, 1.01 (95% CI, 0.91 to 1.11); p=0.90 NS
			Cumulative followup: Mean 12.5 years (255)	1,994 (2.15% annualized) vs. 1,872 (2.11% annualized); HR, 1.04 (95% CI, 0.97 to 1.10); p=0.28 NS
			Cumulative followup: Median 13.2 years (197)	1,011 (0.98% annualized) vs. 966 (0.99% annualized); HR, 0.99 (95% CI, 0.91 to 1.08); p=0.87 NS
			Cumulative followup: Median 17.7 years (255)	2,244 (1.58% annualized) vs. 2,110 (1.57% annualized); HR, 1.02 (95% CI, 0.96 to 1.08); p=0.51 NS
			Cumulative followup: Median 19.4 years (253)	2,802 (32.9% calculated) vs. 2,638 (32.6% calculated); HR, 1.02 (95% CI, 0.97 to 1.08); p=NR NS
		HERS Estrogen plus progestin trial Hulley, 2002 (291)	All-cause mortality	
			Followup: Mean 4.1 years	130 (9.4%) vs. 123 (8.9%); HR, 1.06 (95% CI, 0.83 to 1.36); p=0.62 NS
			Cumulative followup: Mean 6.8 years	261 (22.6%) vs. 239 (17.3%); HR, 1.08 (95% CI, 0.91 to 1.29); p=NR NS

		N=1 n=209 ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000 (215)	All-cause mortality Followup: Mean 3.2 years	8 (8.0%) vs. 3 (2.9%) vs. 6 (5.7%); p=0.28

Abbreviations: NS=not statistically significant, SS=statistically significant

Remarks:/

Characteristics included trials

See appendix cancer.

14 Appendix. Evidence tables. Non-oral HT versus oral HT: Venous thromboembolism

14.1 Non-oral hormone therapy versus control: Venous thromboembolism

Meta-analysis:

Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis

Inclusion criteria:

Data from clinical trials and from case-control and cohort studies designed to assess venous thromboembolism (VTE) (pulmonary embolism and/or deep vein thrombosis) in postmenopausal women using oral or non-oral HT. Women receiving placebo or nonusers of HT were considered as control groups. For clinical trials and cohort studies, only works including postmenopausal women with no previous VTE were selected. For multiple articles on the same sample, we selected the article containing the most complete information. Eligibility assessment was performed independently in an unblinded, standardized manner by two reviewers, and inconsistencies were settled by a third reviewer.

Search strategy:

MEDLINE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed through Wiley Science), and EMBASE were searched for studies published until February 2017. We also searched <http://ClinicalTrials.gov> to retrieve RCTs with unpublished results. The following medical subject headings (MeSH) were used in the search: postmenopause OR menopause AND “estrogen replacement therapy” OR “hormone replacement therapy” AND “pulmonary embolism” OR “venous thromboembolism” OR thromboembolism.

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result

Rovinski 2018(198) Design: RCT+cohort studies+case-control studies Search date: (Feb-2017)	Non-oral hormone therapy (estrogen-only AND combined estrogen and progestin therapies) versus control	N=9 n=821155 (Daly 1996; Pérez-Gutthann 1997 ; Douketis 2005 ; ESTHER 2007 ; E3N 2010 ; Renoux 2010 ; MILLION 2012 ; Roach 2013 ; Bergendal 2016)	venous thromboembolism	OR 0.97 [0.9-1.06] NS Heterogeneity: I² 0%
	Non-oral hormone therapy (estrogen-only) versus control	N=6 n=745697 (Scarabin 2003; Douketis 2005; Renoux 2010 ; MILLION 2012 ; Roach 2013 ; Bergendal 2016)	venous thromboembolism	OR 0.95 [0.81-1.10] NS Heterogeneity: I² 14%

	Non-oral hormone therapy (combined estrogen and progestin) versus control	N=5 n=712900 (Scarabin 2003; Renoux 2010; Roach 2013 ; Bergendal 2016 ; MILLION 2012)	venous thromboembolism	OR 0.92 [0.77-1.09] NS Heterogeneity: I ² 0%

* Characteristics of included studies: see below

Abbreviations: RCT: randomized clinical trial; PE: pulmonary embolism; DVT: deep vein thromboembolism; VTE: venous thromboembolism; MI: myocardial infarction; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate, HT: hormone therapy; NETA: norethisterone acetate; DRSP: drospirenone; E2: estradiol; CVD: cardiovascular disease.

Remarks: /

Author's conclusions:

Twelve studies were analyzed, including case-control studies, cohort studies, and RCTs, for a total of 113,059 women using non-oral HT and 281,018 using oral HT. VTE risk was increased with oral HT (OR 1.66 [1.39–1.98], I² 58%). The next step was a sensitivity analysis. This sensitivity analysis was restricted to studies including participants without risk factors for VTE, cancer, previous HT use, or use of other (oral) HT-containing co-medication or other medication (aspirin) that could possibly influence VTE risk. A total of 33,024 users of non-oral HT and 57,793 users of oral HT from seven studies were considered. In this analysis, higher risk of VTE was maintained for oral HT users (OR 1.80 [1.35–2.39] I² 46%).

Publication bias may have occurred in the comparisons of controls vs. combined oral HT users (Fig. 5-F) ($p < 0.10$). Conversely, no publication bias was detected in any other comparisons ($p \geq 0.10$; Fig. 5A–H).

Characteristics included trials

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Rovinski 2018 Newcastle-Ottawa Scale
Scarabin 2003(199) Case-control	N= 536	France 45-70 years Case: VTE Control: no VTE Exclusion: previous VTE or predisposing factor for VTE	3 years	Oral: Low dose CEE 0.625 mg, 1 mg E2 or 1 mg estradiol valerate High dose: CEE 1.25 mg, 1.5-2 mg E2 or 2 mg estradiol valerate Non-oral low dose (<50 mcg E2) high dose (50 -100 mcg E2)	Selection of study groups: *** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Douketis 2005(200); Case-control	n=1168	-Canada, Italy, and the Netherlands -Inclusion: Postmenopausal women, any age Case: DVT Control: no DVT (mean age not informed; 80% of the population between 50 and 79 years) -Exclusion: PE, ovarian failure, language barrier or cognitive impairment	3 years	Oral estrogen only or estrogen plus progestin Vs Transdermal estrogen	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
ESTHER 2007(201) Case-control	n=881	-France -Inclusion: Postmenopausal women, any age Case: VTE (mean age 61.6 ± 6.7 years) -Exclusion:	6 years	Oral estrogen only or associated with progestin (most frequently 17B E2 0.5–2 mg/day) Vs	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

		History of VTE, contraindication for HT or predisposing factor for VTE		Transdermal estrogen alone or associated with progestin (mostly < 50 µg/day)	
Daly 1996(202) Case-control	n=281	-UK -Inclusion: 45–64 years Case: PE, DVT, or both (mean age 53.9 ± 5.9 years) Control: no VTE (mean age 53.9 ± 5.6 years) -Exclusion: History of PE, DVT, or MI and history of surgery in the previous 6 weeks or illness necessitating bed rest for longer than 1 week, history of cancer of the breast, ovary, endometrium or other recent or active cancer, serious heart disease or use of anticoagulants	1.8 years	Low dose: CEE 0.625 mg, 1 mg 17B Estradiol or 1.5 mg piperazine estrone sulphate High dose: CEE 2.5 mg or 2 mg 17B E2 Vs Low dose: Transdermal preparations delivering 50 µg 17B E2 High dose: 100 µg 17B E2	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Pérez Gutthann 1997(203) Case-control	n=347253	-UK -Inclusion: 50–79 years Case: VTE Control: no VTE (mean age not informed; 80% of the population between 50 and 70 years) -Exclusion: History of VTE or risk factors for VTE	3.7 years	Low dose: CEE 0.625 mg High dose: CEE 1.25 mg Vs Low dose: Transdermal E2 25–50 µg High dose: transdermal E2 100 µg	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Renoux 2010(204) Case-control	n=255067	-UK -Inclusion: Postmenopausal women, 50–79 years Cases: VTE (mean age 65.9 ±	20.2 years	Oral estrogen alone or with progestogen Low dose: CEE < 0.625 mg or E2 < 2 mg	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

		8.5 years) Control: no VTE (mean age 65.8 ± 8.5 years) -Exclusion: History of VTE		High dose: CEE 0.625 mg or E2 2 mg Vs Transdermal estrogen alone or with progestogen Low dose: $\leq 50 \mu\text{g}$ High dose: $> 50 \mu\text{g}$	
Roach 2013(205) Case-control	n=2550	-Netherlands -Inclusion: Postmenopausal women, 50–70 years (mean 59 years) Case: VTE Control: no VTE -Exclusion: Severe psychiatric problems and not speaking Dutch	5.5 years	Micronized E2 alone, CEE 0.625 mg + MPA and Micronized E2 (1 mg or 2 mg) + NETA Vs Transdermal patches containing micronized E2	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Bergendal 2016(206) Case-control	n=1729	-Sweden -Inclusion: 40–64 years not using combined hormonal contraception Case: 1st DVT episode (mean age 54.6 ± 6.5 years) Control: no DVT (mean age 54.5 ± 6.5 years) -Exclusion: Not speaking Swedish, previous thrombosis or current malignancy	6 years	17B E2 alone or with NETA or MDX Vs Transdermal estrogen alone or with progestogen	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
E3N 2010(207) Cohort study	n=80308	-France -Inclusion: Postmenopausal women from E3N prospective cohort study (mean age 54 years)	10.1 years	Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

		-Exclusion: History of VTE and cancer other than basal cell carcinoma		derivatives or nortestosterone derivatives Vs Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane derivatives or nortestosterone derivatives	
MILLION 2012(208) Cohort study	n=1058259	-UK -Inclusion: Postmenopausal women, 50–64 years (mean age: 56.7 ± 4.5 years) -Exclusion: Pre or perimenopausal, history of cancer or clotting problem, surgery in the 12 weeks prior to recruitment or unknown use of HT	3.1 years	CEE or E2 isolated or associated with MPA, NETA or norgestrel Vs Patch or gel formulation of 17beta estradiol with or without a progestin (not specified)	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

Newcastle-Ottawa Scale and quality of the study. Quality of selection (minimum 1–maximum 4 stars); comparability (minimum 0–maximum 1 star); exposure (minimum 1–maximum 3 stars)

14.2 Non-oral hormone therapy versus oral hormone therapy: Venous thromboembolism

Meta-analysis:

Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis(198)

Inclusion criteria:

Data from clinical trials and from case-control and cohort studies designed to assess venous thromboembolism (VTE) (pulmonary embolism and/or deep vein thrombosis) in postmenopausal women using oral or non-oral HT. Women receiving placebo or nonusers of HT were considered as control groups. For clinical trials and cohort studies, only works including postmenopausal women with no previous VTE were selected. For multiple articles on the same sample, we selected the article containing the most complete information. Eligibility assessment was performed independently in an unblinded, standardized manner by two reviewers, and inconsistencies were settled by a third reviewer.

Search strategy:

MEDLINE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed through Wiley Science), and EMBASE were searched for studies published until February 2017. We also searched <http://ClinicalTrials.gov> to retrieve RCTs with unpublished results. The following medical subject headings (MeSH) were used in the search: postmenopause OR menopause AND “estrogen replacement therapy” OR “hormone replacement therapy” AND “pulmonary embolism” OR “venous thromboembolism” OR thromboembolism.

Assessment of quality of included trials: yes

ITT analysis: yes/no

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Rovinski 2018(198) Design: RCT+cohort studies+case-control studies	Non-oral hormone therapy versus oral hormone therapy	N=12 n=394077 Douketis 2005(200); ESTHER 2007(201); Daly 1996(202); Pérez Gutthann 1997(203); Renoux 2010(204);	venous thromboembolism	OR 1.66 [1.39–1.98] SS Increased risk with oral HT Heterogeneity: I ² 58%

Search date: (Feb-2017)		Roach 2013(205); Bergendal 2016(206); E3N 2010 Cohort(207); Laliberte 2011 Cohort(209); MILLION 2012 Cohort(208); Dinger 2016 Cohort(210); Simon 2016 Cohort(211)		
		Sensitivity analysis N=7 n=90817 Douketis 2005(200); ESTHER 2007(201); Roach 2013(205); Bergendal 2016(206); Laliberte 2011 Cohort(209); Dinger 2016 Cohort(210); Simon 2016 Cohort(211)	Venous thromboembolism - sensitivity analysis Analysis restricted to studies including participants without risk factors for VTE, cancer, previous HT use, or use of other (oral) HT-containing co-medication or other medication (aspirin) that could possibly influence VTE risk.	OR 1.88 [1.35–2.39] SS Increased risk with oral HT Heterogeneity: I ² 46%

* Characteristics of included studies: see below

Abbreviations: RCT: randomized clinical trial; PE: pulmonary embolism; DVT: deep vein thromboembolism; VTE: venous thromboembolism; MI: myocardial infarction; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate, HT: hormone therapy; NETA: norethisterone acetate; DRSP: drospirenone; E2: estradiol; CVD: cardiovascular disease.

Remarks: /

Author's conclusions:

Twelve studies were analyzed, including case-control studies, cohort studies, and RCTs, for a total of 113,059 women using non-oral HT and 281,018 using oral HT. VTE risk was increased with oral HT (OR 1.66 [1.39–1.98], I² 58%). The next step was a sensitivity analysis. This sensitivity analysis was restricted to studies including participants without risk factors for VTE, cancer, previous HT use, or use of other (oral) HT-containing co-medication or other medication (aspirin) that could possibly influence VTE risk. A total of 33,024 users of non-oral HT and 57,793 users of oral HT from seven studies were considered. In this analysis, higher risk of VTE was maintained for oral HT users (OR 1.80 [1.35–2.39] I² 46%).

Publication bias may have occurred in the comparisons of controls vs. combined oral HT users (Fig. 5-F) ($p < 0.10$). Conversely, no publication bias was detected in any other comparisons ($p \geq 0.10$; Fig. 5A–H).

Characteristics included trials

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Rovinski 2018 Newcastle-Ottawa Scale
Douketis 2005(200); Case-control	n=1168	-Canada, Italy, and the Netherlands -Inclusion: Postmenopausal women, any age Case: DVT Control: no DVT (mean age not informed; 80% of the population between 50 and 79 years) -Exclusion: PE, ovarian failure, language barrier or cognitive impairment	3 years	Oral estrogen only or estrogen plus progestin Vs Transdermal estrogen	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
ESTHER 2007(201) Case-control	n=881	-France -Inclusion: Postmenopausal women, any age Case: VTE (mean age 61.6 ± 6.7 years) -Exclusion: History of VTE, contraindication for HT or predisposing factor for VTE	6 years	Oral estrogen only or associated with progestin (most frequently 17B E2 0.5–2 mg/day) Vs Transdermal estrogen alone or associated with progestin (mostly < 50 $\mu\text{g/day}$)	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Daly 1996(202) Case-control	n=281	-UK -Inclusion: 45–64 years Case: PE, DVT, or both (mean age 53.9 ± 5.9 years) Control: no VTE (mean age $53.9 \pm$ 5.6 years) -Exclusion:	1.8 years	Low dose: CEE 0.625 mg, 1 mg 17B Estradiol or 1.5 mg piperazine estrone sulphate High dose: CEE 2.5 mg or 2 mg 17B E2 Vs	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

		History of PE, DVT, or MI and history of surgery in the previous 6 weeks or illness necessitating bed rest for longer than 1 week, history of cancer of the breast, ovary, endometrium or other recent or active cancer, serious heart disease or use of anticoagulants		Low dose: Transdermal preparations delivering 50 µg 17B E2 High dose: 100 µg 17B E2	
Pérez Gutthann 1997(203) Case-control	n=347253	-UK -Inclusion: 50–79 years Case: VTE Control: no VTE (mean age not informed; 80% of the population between 50 and 70 years) -Exclusion: History of VTE or risk factors for VTE	3.7 years	Low dose: CEE 0.625 mg High dose: CEE 1.25 mg Vs Low dose: Transdermal E2 25–50 µg High dose: transdermal E2 100 µg	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Renoux 2010(204) Case-control	n=255067	-UK -Inclusion: Postmenopausal women, 50–79 years Cases: VTE (mean age 65.9 ± 8.5 years) Control: no VTE (mean age 65.8 ± 8.5 years) -Exclusion: History of VTE	20.2 years	Oral estrogen alone or with progestogen Low dose: CEE < 0.625 mg or E2 < 2 mg High dose: CEE 0.625 mg or E2 2 mg Vs Transdermal estrogen alone or with progestogen Low dose: ≤50 µg High dose: > 50 µg	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Roach 2013(205) Case-control	n=2550	-Netherlands -Inclusion: Postmenopausal women, 50–70 years (mean 59 years)	5.5 years	Micronized E2 alone, CEE 0.625 mg + MPA and Micronized E2 (1 mg or 2 mg) + NETA	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

		Case: VTE Control: no VTE -Exclusion: Severe psychiatric problems and not speaking Dutch		Vs Transdermal patches containing micronized E2	
Bergendal 2016(206) Case-control	n=1729	-Sweden -Inclusion: 40–64 years not using combined hormonal contraception Case: 1st DVT episode (mean age 54.6 ± 6.5 years) Control: no DVT (mean age 54.5 ± 6.5 years) -Exclusion: Not speaking Swedish, previous thrombosis or current malignancy	6 years	17B E2 alone or with NETA or MDX Vs Transdermal estrogen alone or with progestogen	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
E3N 2010(207) Cohort study	n=80308	-France -Inclusion: Postmenopausal women from E3N prospective cohort study (mean age 54 years) -Exclusion: History of VTE and cancer other than basal cell carcinoma	10.1 years	Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane derivatives or nortestosterone derivatives Vs Mostly 17B E2, associated or not with micronized progesterone, pregnane derivatives, norpregnane derivatives or nortestosterone derivatives	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

Laliberte 2011(209) Cohort study	n=54216	-Canada -Inclusion: Postmenopausal women aged ≥ 35 years, recent users of HT, with 2 or more prescription refills (mean age: 48.9 ± 7.1 years) -Exclusion: History of VTE	10.1 (± 4.6) years	Oral estrogen only, conjugated equine estrogens and micronized estradiol 17-beta (Cenestin, Estrace, Premarin) Vs Transdermal estrogen only (E2 transdermal system, Vivelle-Dot)	Selection of study groups: *** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
MILLION 2012(208) Cohort study	n=1058259	-UK -Inclusion: Postmenopausal women, 50–64 years (mean age: 56.7 ± 4.5 years) -Exclusion: Pre or perimenopausal, history of cancer or clotting problem, surgery in the 12 weeks prior to recruitment or unknown use of HT	3.1 years	CEE or E2 isolated or associated with MPA, NETA or norgestrel Vs Patch or gel formulation of 17beta estradiol with or without a progestin (not specified)	Selection of study groups: **** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Dinger 2016(210) Cohort study	n=30597	-7 European countries -Inclusion: HRT starters (first-ever users), HRT switchers or HRT restarters (mean age: 54 ± 7.3 years)	8.5 years	DRSP 2 mg + E2 1 mg, other oral continuous combined HRT preparations containing a progestin other than DRSP or other oral HRT preparations Vs Non-oral estrogen preparations (not specified)	Selection of study groups: ** Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***
Simon 2016(211)	n=5102	-USA	10.6 years	Oral estrogen alone	Selection of study groups: **

Cohort study		-Inclusion: Postmenopausal women, 50 years or more, at least 2 HT prescription refills (mean age: 55 years) -Exclusion: Other type of HT, CVD, cancer, thrombophilia or liver disease		Vs E2 transdermal system, Vivelle-Dot	Comparability of the groups: * Ascertainment of outcome of interest (exposure): ***

Newcastle-Ottawa Scale and quality of the study. Quality of selection (minimum 1–maximum 4 stars); comparability (minimum 0–maximum 1 star); exposure (minimum 1–maximum 3 stars)

15 Appendix. Evidence tables. Levonorgestrel-releasing intrauterine system vs control

Levonorgestrel-releasing intrauterine system vs control in peri-menopausal women: **breast cancer**

Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective Siegelmann 2018(212)					
Design	N/n	Population	Risk factor	Outcome	Results*
Design: Retrospective cohort study Israel	N= 1 n= 40678 (13354 LNG-IUS users and 27324 non- users)	peri-menopausal women aged 40–50 years	levonorgestrel- releasing intrauterine system (LNG-IUS)	Breast cancer	5-year Kaplan–Meier estimates: 1.2% (SE0.1%) vs 1.1% (SE 0.06%); p= 0.23 NS
			vs	ductal carcinoma in situ (DCIS)	5-year Kaplan–Meier estimates: 0.14% (SE 0.03%) vs 0.16% (SE 0.03%); p= 0.22 NS
			age-matched LGN- IUS non-users	Invasive breast cancer	5-year Kaplan–Meier estimates: 1.06% (SE 0.1%) vs 0.93% (SE 0.06%); p= 0.051 NS
*controls were selected sequentially age-matched with the same exclusion criteria as the LNG-IUS group. Exclusion criteria included BC diagnosis at any time before study initiation or within 6 months of inclusion, exposure to female hormones in the form of oral contraceptives (OC), fertility drugs, or hormone-replacement therapy (HRT), or prophylactic use of tamoxifen in the 5 years preceding Day 1 and through November 2015.					

16 Appendix: Evidence tables. Oral hormone therapy versus placebo: secondary prevention of cardiovascular disease

Meta-analysis:

Hormone therapy for preventing cardiovascular disease in postmenopausal women (Review) (3)

Inclusion criteria:

-Type of studies: (RCTs) comparing oral hormone therapy with either placebo or a no treatment control for a follow-up duration of six months or longer. We included RCTs which compared two or more different types of oral hormone therapy, provided that they were additionally compared with a placebo or a no treatment control arm.

-Participants: Post-menopausal women (with either spontaneous or induced cessation of menstrual bleeding for a continuous period of six months or more), either with or without evidence of existing cardiovascular disease.

-Types of interventions: Oral hormone therapy, consisting of either oestrogen alone or in combination with a progestogen, compared with either a placebo or a no treatment control. Combined hormone therapy (oestrogen plus progestogen) could be delivered continuously daily (continuous combined hormone therapy) or sequentially (oestrogen taken daily with progestogens taken for part of the month).

Exclusion criteria:

We excluded RCTs in which hormone therapy was delivered to the body via either patches, tablets, creams, troches, an intrauterine device, vaginal ring, gels or injections compared with placebo or no treatment. Likewise, we excluded RCTs assessing the effects of selective oestrogen receptor modulators (e.g. raloxifene) compared to placebo or a no treatment control.

Search strategy:

We identified randomised controlled trials (RCTs) that assessed the effects of hormone therapy compared to placebo or no treatment with a minimum of six months duration through searching the following electronic databases on 25 February 2014: • Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2014) in The Cochrane Library, • MEDLINE (Ovid; 1946 to week 9 2014), • EMBASE (Ovid; 1980 to week 9 2014), • LILACS (<http://lilacs.bvsalud.org/en/>) (1982 to 25 February 2014). Additionally, we searched the following trials and research registers for any ongoing trials on cardiovascular disease on 25 February 2014: ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictpr/), the UK Clinical Research Network Portfolio Database (<http://public.ukcrn.org.uk>) and Centerwatch (www.centerwatch.com). We did not apply any language restrictions

Assessment of quality of included trials: yes

ITT analysis: yes

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result

Boardman 2015(3) Design: RCT Search date: (Feb-2014)	Hormone therapy vs placebo	N=7 n=5445 ERA 2000; ESPRIT 2002; HERS I 1998; WAVE 2002; WELL- HART 2003; WEST 2001; WHISP 2006	Death (all causes)	RR 1.04 [95%CI: 0.87–1.24] NS Heterogeneity: Tau ² =0; Chi ² =3.7, df=6(P=0.72); I ² =0%
		N=6 n=5259 EAGAR 2006; ERA 2000; ESPRIT 2002; HERS I 1998; WAVE 2002; WEST 2001	Death (cardiovascular causes)	RR 1.00 [95%CI: 0.78–1.29] NS Heterogeneity: Tau ² =0; Chi ² =3.94, df=5(P=0.56); I ² =0%
		N=7 n=5359 EAGAR 2006; ERA 2000; ESPRIT 2002; HERS I 1998; WAVE 2002; WEST 2001; WHISP 2006	Non-fatal myocardial infarction	RR 0.98 [95%CI: 0.81–1.18] NS Heterogeneity: Tau ² =0; Chi ² =2.94, df=6(P=0.82); I ² =0%
		N=5 n=5172 ERA 2000; ESPRIT 2002; HERS I 1998; WAVE 2002; WEST 2001	Stroke	RR 1.09 [95%CI: 0.89–1.33] NS Heterogeneity: Tau ² =0; Chi ² =2.83, df=4(P=0.59); I ² =0%

		N=3 n=3155 EAGAR 2006; ERA 2000; HERS I 1998	Angina	RR 0.91 [95%CI: 0.74–1.12] NS Heterogeneity: Tau2=0; Chi2=1.34, df=2(P=0.51); I2=0%
		N=6 n=4399 ERA 2000; EVTET 2000; HERS I 1998; WAVE 2002; WEST 2001; WHISP 2006	Venous thromboembolism	RR 2.02 [95%CI: 1.13–3.26] SS Heterogeneity: Tau2=0.07; Chi2=5.62, df=5(P=0.34); I2=11.08%
		N=3 n=3920 EVTET 2000; ESPRIT 2002; HERS I 1998	Pulmonary thromboembolism	RR 2.48 [95%CI: 0.92–6.70] NS Heterogeneity: Tau2=0.18; Chi2=2.57, df=2(P=0.28); I2=22.23%
		N=3 n=3155 EAGAR 2006; ERA 2000; HERS I 1998	Revascularisation	RR 0.98 [95%CI: 0.63–1.53] NS Heterogeneity: Tau2=0.08; Chi2=4.96, df=2(P=0.08); I2=59.7%

* Characteristics of included studies: see below

Remarks: /

Author's conclusions:

Our review findings provide strong evidence that treatment with hormone therapy in post-menopausal women for either primary or secondary prevention of cardiovascular disease events has little if any benefit overall, and causes an increase in the risk of stroke, or venous thromboembolic events.

Characteristics included trials

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Boardman 2015
ERA 2000 Herrington 2000(214, 215) RCT	n=309	-post-menopausal women with angiographically verified coronary disease. Coronary artery disease was defined as at least one stenosis of 30% in any single coronary artery -The mean age of the women was 65.8 years (range: 41.8 - 79.9), with a mean number of years since menopause of 22.5. -49% had a history of MI and 47% a history of having undergone an angioplasty -In terms of risk factors for CVD: 28% had diabetes; 67% had hypertension; 18% were current smokers; and 57% had a BMI > 27.5 kg/m². The mean systolic blood pressure of the women was 130 mm Hg and the mean diastolic blood pressure 71.8 mm Hg. There were no statistically significant differences between the three treatment groups at baseline	mean follow-up of 3.2 ± 0.6 years	HT regimen: 1) 0.625 mg conjugated equine oestrogen daily and a placebo tablet daily (continuous dosage regimen) 2) 0.625 mg conjugated equine oestrogen plus medroxyprogesterone acetate and placebo tablet daily (continuous dosage regimen) Comparator: two placebo tablets daily (continuous dosage regimen)	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Low Funding: Grants from National Heart, Lung and Blood Institute and NationalCenter for Research Resources General Clinical Research Center, study medications from Wyeth-Ayerst Research

ESPRIT 2002 Cherry 2002(216) RCT	n=1017	-postmenopausal women who suffered a first MI and were recruited within 31 days of the index event -24% of women (n = 245) had undergone a hysterectomy - 53% were smokers at the time of admission; mean BMI was 40 kg/m ² ; 27% had angina; 44% had high blood pressure (not defined); 7.5% had suffered a previous stroke; 15% had diabetes, and 11% had used HT> 12 months before admission to the trial	2 year follow-up	HT regimen: 2 mg daily tablet of oestradiol valerate (continuous dosage regimen) Comparator: identical placebo capsule daily	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Low Funding: Schering AG provided medication
HERS I 1998 Bibbins-Domingo 2005(217); Grady 1998(218); Grady 2002(219); Grady 2000(220); Hlatky 2002(221); Hulley 1998(222); Khan 2003(223); Shlipak 2000(224); Simon 2001(225); Simon 2006(226);	n=2763	-Postmenopausal women with established coronary disease. Coronary heart disease was defined as evidenced by prior MI, coronary artery bypass graft surgery (CABG), percutaneous transluminal coronary angioplasty, or other mechanical revascularisation, or at least 50% occlusion of a major coronary artery.	Mean followup: 4.1 years	HT regimens: 0.625 mg conjugated oestrogen plus 2.5 mg medroxyprogesterone acetate daily (continuous dosage regimen) Comparator: identical placebo tablet daily	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Low Funding: Pharmaceutical (Wyeth-Ayerst)

Speroff 1998(227)					
RCT					
WAVE 2002 Hsia 2002(228); Waters 2001(229) RCT	n=423	-menopausal women with angiographically verified coronary disease -In terms of risk factors for CVD: 37% had diabetes; 76% had hypertension; 39% were current smokers; 43% had suffered a previous MI, and 37.5% were current HT users. The mean BMI was 30.7 kg/m²; mean systolic blood pressure was 139 (SD: 21) mm Hg and the mean diastolic blood pressure 76 (SD: 10.5) mm Hg. The HT and placebo HT groups were well-balanced in terms of baseline characteristics, apart from the exception of the active HT group having a statistically significantly higher prevalence of diabetes and higher fasting blood glucose levels	Mean follow-up of 2.8 (SD: ± 0.9 years	1) 0.625 mg conjugated equine oestrogen daily plus placebo for women who had undergone a hysterectomy (continuous dosage regimen). 2) 0.625 mg conjugated equine oestrogen plus 2.5 mg medroxyprogesterone acetate daily plus placebo for women who had not undergone a hysterectomy (continuous dosage regimen). 3) 400 IU vitamin E twice daily (800 IU) plus 500 mg vitamin C twice daily (1 g) Comparator: two placebo tablets daily	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Unclear Groups balanced at baseline, apart from HT group had a higher prevalence of diabetes and higher fasting blood glucose levels Funding: : National Heart, Lung and Blood Institute contract, General Clinical Research Center grant, USA.
WELL-HART 2003 Hodis 2003(234) RCT	n=226	-postmenopausal women who had at least one coronary artery lesion. -The mean age of the participants were: 64.2 years in the control group (SD 6.2), 61.8 years in the	median duration 3.3 years	HT regimen: 1 mg of oral micronised 17β-oestradiol [E] (Estrace, Mea Johnson) daily, plus a placebo tablet	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low

		oestrogen group (SD 6.7) [E] and 64.4 years in the oestrogen-progestin group (SD 6.4) [EP] P = 0.02 Years since menopause: 18.3 years in the control group (SD 10.5), 16.7 years in the oestrogen group (SD 10.3) [E] and 19.7 years in the oestrogen-progestin group (SD 10.5) [EP] P = 0.23 - CVS Risk Factors: Smoking status: P = 0.55 Current smoker: 7 (9%) [control], 11 (14%) [E], 8 (11%) [EP] Former smoker: 28 (37%) [control], 27 (36%) [E], 34 (46%) [EP] Never smoked: 41 (54%) [control], 38 (50%) [E], 32 (43%) [EP] Diabetes: 40 (53%) [control], 38 (50%) [E], 37 (50%) [EP] P = 0.93 Blood pressure – systolic: 141.6 (SD 22.4) [control], 138.1 (SD 21.7) [E], 142.3 (SD 24.6) [EP] P = 0.49 Blood pressure – diastolic: 75.9 (SD 10.5) [control], 76.5 (SD 11.1) [E], 75.3 (SD 12.5) [EP] P = 0.82 BMI: 30.0 (SD 5.4) [control], 30.6 (SD 5.6) [E], 30.2 (SD 5.6) [EP] P = 0.83		matching medroxyprogesterone acetate for 12 consecutive days of every month HT regimen 2: 1 mg of oral micronised 17β-oestradiol (Estrace, Mea Johnson) daily, plus 5 mg medroxyprogesterone acetate [P] (Provera, Upjohn) for 12 consecutive days of every month Comparator: two placebo tablets, one matching each of the active drugs for 12 consecutive days of every month	-Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Unclear Death and cardiovascular outcomes were not prespecified as outcomes for this study but were reported afterwards as adverse events Funding: NHLBI, Mead Johnson laboratories and Pharmacia and Upjohn
WEST 2001 Kernan 1998(230);	n=664	-post-menopausal women with a mean age of 71.5 (SD: $\pm$ 10 years) who had undergone either a non-disabling ischaemic stroke or a	mean follow-up duration of 2.8 years $\pm$ 17 months	HT regimen: 1 mg 17β-oestradiol daily (plus a course of 5 mg medroxyprogesterone	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low

Viscoli 2005(231); Viscoli 2001(232) RCT		transient ischaemic attack in the previous 90 days prior to recruitment. -undergone a hysterectomy: 44.5%. 29.5% of the women had previously used oestrogen-replacement therapy - 24% had a previous MI; 14.5% congestive heart failure; 7% atrial fibrillation; 73.5% hypertension; and 28% diabetes. 12.5% were current cigarette smokers, and the mean BMI among the women was 28 kg/m ² (SD: ± 6). - 18.5% had a history of stroke before the index (ischaemic or TIA) event, and 75% had a stroke as the index event.		acetate once a year for 12 days or annual transvaginal ultrasound [to screen for endometrial hyperplasia] for women with a uterus) plus standard care (continuous dosage regimen) Comparator: identical placebo capsule daily plus standard care	-Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Low Funding: National Institute of Neurological Disorders and Stroke grant, Medical Research Council of Canada grant. Mead Johnson laboratories provided support and study drug
WHISP 2006 Collins 2006(233)	n=100	- postmenopausal women > 55 years who were enrolled 2-28 days post-ACS (acute coronary syndrome) - The mean age of participants was: 69.4 years in the HT group (SD 8.6), 68.3 years in the placebo group (SD 9.0) Years since menopause: 21.6 years in the HT group (interquartile range 15.8 to 29.9) [HT], 23.9 years in the placebo group(interquartile range 13.8 to 30.5) - CVS Risk Factors	Follow-up duration was planned for 12 months, but was reported to be a median of seven months.	HT regimen: continuous combined oral oestradiol-17β 1 mg plus norethisterone acetate 0.5 mg daily Comparator: placebo	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Low -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Unclear Staf were blinded. Not stated if personnel assessing outcome were blind. -Incomplete outcome data (attrition bias) All outcomes: High Significant difference between numbers of participants lost to follow-up between different treatment groups, 13 in the treatment group compared to 6 in the control group,

		BMI: 26.0 (SD 3.9) [HT], 26.4 (SD 4.7) [placebo] Smoking (current): 17 (34.7%) [HT], 13 (25.5%) [placebo] Smoking (ex): 14 (28.6%) [HT], 19 (37.2%) [placebo] Smoking (never): 18 (36.7%) [HT], 19 (37.2%) [placebo] Diabetes: 37 (75.5%) [HT], 40 (78.4%) [placebo]			the reasons are not stated. Intention-to-treat analysis was not specified. -Selective reporting (reporting bias): Low -Other bias: Unclear Death and cardiovascular outcomes were not prespecified as outcomes for this study but were reported afterwards as adverse events Funding: UK MRC and Novo Nordisk
EAGAR 2006 Ouyang 2006(213) RCT	n=83	Postmenopausal women (mean age of 64 (SD: $\pm$ 8.5 years)) underwent treatment with either HT or placebo within six months following coronary artery bypass surgery Included women were 78% white, and 22% from an ethnic minority group. 40% had a history of diabetes, 69% hypertension, 81% hyperlipidaemia and 40% MI. In terms of smoking status: 16.5% were current smokers; 59.5% past smokers and 24.5% never smokers. 35% had prior HT use. Mean BMI among the women was 30 kg/m² (SD: 30 $\pm$ 6). Mean systolic blood pressure at baseline was 135 (SD: 6) mm Hg and diastolic blood pressure was 72.5 (SD: 10.5) mm Hg. There were no statistically significant differences between the two groups in terms of baseline demographics	3.5 years	-HT regimen: 1 mg unopposed 17β-oestradiol daily with or without daily 2.5 mg medroxyprogesterone depending on hysterectomy status (continuous dosage regimen) -Comparator: identical placebo capsule daily	-Random sequence generation (selection bias): Unclear -Allocation concealment (selection bias): Unclear -Blinding of participants and personnel (performance bias) All outcomes: Unclear -Blinding of outcome assessment (detection bias) All outcomes: Unclear -Incomplete outcome data (attrition bias) All outcomes: Low -Selective reporting (reporting bias): Low -Other bias: Unclear It is unlikely that the trial was powered to detect differences in clinical events between the HRT and placebo treatment groups. Therefore the lack of significant differences in event rates between the two groups should be treated with caution Funding: Research Council funded

EVTET 2000 Hoibraaten 2000(235) RCT	n=140	-post-menopausal women who had previously had either VTE or PE with a mean age of 55.8 years (range: 42 to 69 years) -In terms of risk factors for CVD 0.7% of women had previous/concomitant MI; 3% had angina; 1.4% had thromboembolic stroke; 3% had a transient ischaemic attack; 17% had hypertension and 2% had diabetes. The time since last DVT was four years (range: 0 - 37 years) and last PE five years (range: 0 - 34 years). There were no statistically significant differences between the two groups in terms of risk factors for CVD. In terms of smoking status: 39% were never smokers; 36% were previous smokers; 14% smoked between one to 10 cigarettes daily, whilst 10% smoked > 10 cigarettes per day. Mean BMI among the women was 27.1 kg/m ² . Systolic blood pressure at baseline was 138 mm Hg and diastolic blood pressure was 83 mm Hg.	1.3 year period, but stopped early as other published trial results (HERS I 1998) indicated an increased risk of venous thromboembolism with use of HT	HT regimen: 2 mg oestradiol plus 1 mg norethisterone acetate (1 tablet) daily (continuous dosage regimen) Comparator: identical placebo capsule daily	-Random sequence generation (selection bias): Low -Allocation concealment (selection bias): Unclear -Blinding of participants and personnel (performance bias) All outcomes: Low -Blinding of outcome assessment (detection bias) All outcomes: Low -Incomplete outcome data (attrition bias) All outcomes: High The main findings were not reported by ITT, as drop-outs from the placebo group were not included in the denominator for the rate of recurrent thromboembolism -Selective reporting (reporting bias): Low -Other bias: Low Funding: Novo-Nordisk Pharmaceutical and research forum Ulleval University Hospital

17 Appendix. Search strategy

The search was performed on 03/07/2023 in MEDLINE via Pubmed.

17.1 Hormone therapy for the treatment of menopausal symptoms

("Menopause"[Mesh] OR "Postmenopause"[Mesh] OR menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab] OR "post menopaus*" [tiab] perimenopaus*[tiab] OR peri-menopaus*[tiab] OR "peri menopaus*" [tiab] OR climacter*[tiab])

AND

("Intrauterine Devices"[Mesh] OR "IUD"[tiab] OR intrauterine device*[tiab] OR "Hormone Replacement Therapy"[Mesh] OR "hormone replacement therapy" [tiab] OR "hormone therap*" [tiab] OR hormon*[tiab] OR HRT[tiab] OR "Estriol"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol"[Mesh] OR "Progesterone"[Mesh] OR "Progestins"[Mesh] OR "Levonorgestrel"[Mesh] OR "Norethindrone"[Mesh] OR "Dydrogesterone"[Mesh] OR estriol*[tiab] OR estradiol[tiab] OR estrogen*[tiab] OR oestriol*[tiab] OR oestradiol*[tiab] OR oestrogen*[tiab] OR progesteron*[tiab] OR progestin*[tiab] OR levonorgestrel*[tiab] OR norethindrone*[tiab] OR norethisteron*[tiab] OR drospirenon*[tiab] OR dydrogesteron*[tiab] OR dienogest[tiab] OR "bioidentical hormon*" [tiab] OR "hormone regimen*" [tiab] OR tibolon*[tiab] OR tibilon*[tiab] OR "Dehydroepiandrosterone"[Mesh] OR prasteron*[tiab] OR DHEA[tiab] OR bazedoxifene[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND

("2014/01/01"[Date - Publication] : "3000"[Date - Publication])

17.2 Hormone therapy for the primary prevention of chronic conditions

("Menopause"[Mesh] OR "Postmenopause"[Mesh] OR menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab] OR "post menopaus*" [tiab] perimenopaus*[tiab] OR peri-menopaus*[tiab] OR "peri menopaus*" [tiab] OR climacter*[tiab])

AND

("Hormone Replacement Therapy"[Mesh] OR "hormone replacement therapy" [tiab:~0] OR "hormone therap*" [tiab] OR hormon*[tiab] OR HRT[tiab] OR "Estriol"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol"[Mesh] OR "Progesterone"[Mesh] OR "Progestins"[Mesh] OR "Levonorgestrel"[Mesh] OR "Norethindrone"[Mesh] OR "Dydrogesterone"[Mesh] OR estriol*[tiab] OR estradiol[tiab] OR estrogen*[tiab] OR oestriol*[tiab] OR oestradiol*[tiab] OR oestrogen*[tiab] OR progesteron*[tiab] OR progestin*[tiab] OR levonorgestrel*[tiab] OR norethindrone*[tiab] OR norethisteron*[tiab] OR drospirenon*[tiab] OR dydrogesteron*[tiab] OR dienogest[tiab] OR "bioidentical hormon*" [tiab] OR "hormone regimen*" [tiab] OR tibolon*[tiab] OR tibilon*[tiab] OR "Dehydroepiandrosterone"[Mesh] OR prasteron*[tiab] OR DHEA[tiab] OR bazedoxifene[tiab])

AND

("randomized controlled trial"[tiab:~0] OR random*[TIAB] OR "controlled clinical trial"[tiab:~0] OR placebo OR systematic[sb] OR medline[TIAB] OR "Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

AND

("2022/07/01"[Date - Publication] : "3000"[Date - Publication])

17.3 Hormone therapy for the secondary prevention of cardiovascular disease

("Menopause"[Mesh] OR "Postmenopause"[Mesh] OR menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab] OR "post menopaus*" [tiab] perimenopaus*[tiab] OR peri-menopaus*[tiab] OR "peri menopaus*" [tiab] OR climacter*[tiab])

AND

("Cardiovascular Diseases"[Mesh] OR "Stroke"[Mesh] OR "Myocardial Infarction"[Mesh] OR cardiovascular[tiab] OR heart[tiab] OR stroke[tiab] OR Myocardial[tiab] OR cardiac*[tiab] OR coronary[tiab] OR angina[tiab] OR mortality[tiab] OR CVA[tiab] OR TIA[tiab] OR cerebrovascular[tiab])

AND

("Hormone Replacement Therapy"[Mesh] OR "hormone replacement therapy"[tiab:~0] OR "hormone therap*" [tiab] OR hormone*[tiab] HRT[tiab] OR "Estriol"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol"[Mesh] OR "Progesterone"[Mesh] OR "Progestins"[Mesh] OR "Levonorgestrel"[Mesh] OR "Norethindrone"[Mesh] OR "Dydrogesterone"[Mesh] OR estriol*[tiab] OR estradiol[tiab] OR estrogen*[tiab] OR oestriol*[tiab] OR oestradiol*[tiab] OR oestrogen*[tiab] OR progesteron*[tiab] OR progestin*[tiab] OR levonorgestrel*[tiab] OR norethindrone*[tiab] OR norethisteron*[tiab] OR drospirenon*[tiab] OR dydrogesteron*[tiab] OR dienogest[tiab] OR "bioidentical hormon*" [tiab] OR "hormone regimen*" [tiab] OR tibolon*[tiab] OR tibilon*[tiab] OR "Dehydroepiandrosterone"[Mesh] OR prasteron*[tiab] OR DHEA[tiab] OR bazedoxifene[tiab])

AND

("randomized controlled trial"[tiab:~0] OR random*[TIAB] OR "controlled clinical trial"[tiab:~0] OR placebo OR systematic[sb] OR medline[TIAB] OR "Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

AND

("2014/02/01"[Date - Publication] : "3000"[Date - Publication])

17.4 Nonpharmacological (black cohosh only)

("Menopause"[Mesh] OR "Postmenopause"[Mesh] OR menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab] OR "post menopaus*" [tiab] perimenopaus*[tiab] OR peri-menopaus*[tiab] OR "peri menopaus*" [tiab] OR climacter*[tiab])

AND

("Cimicifuga"[Mesh] OR cimicifuga[tiab] OR "black cohosh"[tiab])

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND

("2012/02/01"[Date - Publication] : "3000"[Date - Publication])

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