INSTITUT NATIONAL D'ASSURANCE
MALADIE-INVALIDITE
SERVICE DES SOINS DE SANTE
Comité d' évaluation des pratiques
médicales en matière de médicaments

THE RATIONAL USE OF LIPID LOWERING DRUGS

Systematic literature review: full report

Consensus conference
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Abbreviations

A to Z=Aggrastat to Zocor.
ACS = acute coronary syndrome
AE= adverse events
AF=atrial fibrillation
AFCAPS/TexCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study
ALERT=Assessment of Lescol in Renal Transplantation.
ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.
ALLIANCE=Aggressive Lipid-Lowering Initiation Abates New Cardiac Events.
ALT=alanine aminotransferase
ARR= absolute risk reduction
ASCOT-LLA= Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm
ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus.
ATP II = Adult Treatment Panel II
ATV= Atorvastatine
AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis= an Assessment of Survival and Cardiovascular Events.
BE= Barret's oesophagus
BMI=body-mass index.
CABG=coronary artery bypass grafting.
CARDS=Collaborative Atorvastatin Diabetes Study.
CARE=Cholesterol And Recurrent Events.
CHD= Coronary heart disease
CI= confidence interval
CO= crossover RCT
CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure.
CV=cardiovascular.
CVD= cardiovascular disease
DB= double blind
DBP=diastolic blood pressure.
DM= diabetes mellitus
ECG=echocardiogram.
EZE= Ezetimibe
GFR= glomerular filtration rate
GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca.
GISSI-P=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.
HbA1c=glycated haemoglobin.
HPS=Heart Protection Study.
HR= Hazard ratio
HTN= Hypertension
ICD-9= International Classification of Diseases-Ninth Revision
ICR= illustrative comparative risk
IDEAL=Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group.
IHD=ischaemic heart disease.
IR= Incidence Rate
IRR= Incidence Rate Ratio
ITT= intention-to-treat analysis

JUPITER=Justification for the Use of Statins in Prevention= an Intervention Trial Evaluating Rosuvastatin.
LDL-C= low-density lipoprotein cholesterol;
LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease.
LIPS=Lescol Intervention Prevention Study.
LVEF=left ventricular ejection fraction.
m=months.
MA= meta-analysis
MACE= Major adverse cardiovascular events
MEGA= Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
MI= Myocardial infarction
MI=myocardial infarction.
MTM= mixed treatment meta-analyse (or network meta-analysis)
MVE= major vascular event
n= number of patients
NA= not available/not applicable
NCEP= National Cholesterol Education Program
NR= not reported
NS= not statistically significant
NT= no statistical test
OHG=oral hypoglycaemics.
OL= open label
PCI= percutaneous coronary intervention
PE= primary endpoint
PG= parallel group RCT
Post-CABG=Post-Coronary Artery Bypass Graft.
PROSPER= Prospective Study of Pravastatin in the Elderly at Risk
PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy.
PTCA= percutaneous transluminal coronary angioplasty
Py=person-years
RR= relative risk
RRR= relative risk reduction
RT= Randomized trial
SB= single blind
SBP=systolic blood pressure.
SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine.
SIR= Standardized incidence ratio
SS= statistically significant
SSSS=Scandinavian Simvastatin Survival Study.
TC= total cholesterol
TIA=transient ischaemic attack.
TNT=Treating to New Targets.
trig=triglyceride
ULN= upper limit of the normal range
w=weeks.
WHtR=waist-to-height ratio
WOSCOPS=West of Scotland Coronary Prevention Study.
y=years

1 Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Rational use of lipid lowering drugs' which will take place on May 22 2014.

1.1.1 Questions to the jury

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

Question – Vraag 1

Dyslipidémies et risque cardiovasculaire

Dyslipidemieën en cardiovasculair risico

- quelle est l'importance relative des différents paramètres lipidiques (LDL-C, HDL-C, non HDL-C,…) dans le risque vasculaire global ?
  wat is het belang van de verschillende lipideparameters (LDL-C, HDL-C, non-HDL-C,…) in geval van een globaal vasculair risico?
- quels sont les outils (tests, scores) les plus performants pour l'évaluation de ce risque global pour le médecin généraliste belge ?
  welke zijn voor de Belgische huisarts de meest performante instrumenten (tests, scores) om dat globaal risico te evalueren?

Question – Vraag 2

Efficacité des statines et d'autres hypolipidémiants pour la diminution du risque cardiovasculaire

Werkzaamheid van de statines en andere hypolipemiërende middelen voor de vermindering van het cardiovasculair risico

- quelle est l'efficacité des statines en termes de prévention d'évènements cardiovasculaires dans la population générale (càd hors sous-populations particulières au point 4), en fonction du risque cardiovasculaire avant traitement ?
  wat is de werkzaamheid van de statines op het vlak van de preventie van cardiovasculaire evenementen bij de bevolking in het algemeen (dus buiten de specifieke subpopulaties vermeld in punt 4), rekening houdende met het cardiovasculair risico vóór de behandeling?
- existe-il des preuves d'une différence entre statines et/ou doses de statines dans la prévention des évènements cardiovasculaires ?
  bestaan er bewijzen voor een verschil tussen statines en/of dosissen van statines in de preventie van cardiovasculaire evenementen?
- quelle est l'efficacité d'autres hypolipidémiants (fibrates, ézétimibe, acipimox, résines échangeuses d'ions) en termes de prévention d'évènements cardiovasculaires dans la population générale (càd hors sous-populations particulières au point 4), en fonction du risque cardiovasculaire avant traitement ?
  wat is de werkzaamheid van andere hypolipemiërende middelen (fibraten, ezetimibe, acipimox, ionenwisselende harsen) op het vlak van de preventie van cardiovasculaire evenementen bij de bevolking in het algemeen (dus buiten de specifieke subpopulaties vermeld in punt 4), rekening houdende met het cardiovasculair risico vóór de behandeling?
- existe-t-il des valeurs cibles validées pour les composantes lipidiques (LDL-c, HDL-c, non HDL-c, autres…) ?
  bestaan er specifieke waarden die voor de bestanddelen van de lipiden (LDL-C, HDL-C, non-HDL-C, andere…) zijn gevalideerd?

- quels doivent être le monitoring et une éventuelle adaptation du traitement (dose, changement de médicament) dans le cadre de l'évaluation de l'efficacité du traitement ?
  hoe moeten de monitoring en een eventuele aanpassing van de behandeling (dosis, verandering van geneesmiddel) eruitzien in het kader van de evaluatie van de werkzaamheid van de behandeling?

Question – Vraag 3

Sécurité des statines et d'autres hypolipidémiants en prévention cardiovasculaire

Veiligheid van de statines en andere hypolipemiërende middelen in het kader van de cardiovasculaire preventie

- quels sont les effets indésirables observés avec les statines en prévention vasculaire quelle est leur fréquence et ceux-ci sont-ils variables en fonction d'autres facteurs (type de statine, dose, durée de traitement, sexe, âge, comorbidité, comédication, génétique…).
  welke zijn de neveneffecten die met de statines in het kader van de vasculaire preventie worden vastgesteld, wat is hun frequentie en verschillen ze naar gelang van de factoren (soort statine, dosis, behandelingsduur, geslacht, leeftijd, comorbiditeit, co-medicatie, erfelijkheid,…)?
- quel est le monitoring adéquat d'un traitement par statines dans le cadre d'une surveillance des effets indésirables potentiels ?
  welke is de geschikte monitoring van een behandeling met statines in het kader van een toezicht op de mogelijke neveneffecten?
- quels sont les alertes devant conduire à l'arrêt d'une statine et/ou de toute statine ?
  welke zijn de alarmsignalen die moeten leiden tot de stopzetting van een statine en/of van alle statines?
- comment les prendre en charge ?
  hoe moeten die ten laste worden genomen?
- quels sont les effets indésirables observés avec les autres hypolipidémiants en prévention vasculaire et ceux-ci sont-ils variables en fonction d'autres facteurs (type d'hypolipidémiant, dose, durée de traitement, sexe, âge, comorbidité, comédication,…)
  welke zijn de neveneffecten die met de andere hypolipemiërende middelen in het kader van de vasculaire preventie worden vastgesteld, en verschillen ze naar gelang van de factoren (soort statine, dosis, behandelingsduur, geslacht, leeftijd, comorbiditeit, co-medicatie,…)?

Question – Vraag 4

Efficacité et sécurité pour certains sous-groupes de patients

Werkzaamheid en veiligheid voor bepaalde subgroepen van patiënten

l'efficacité et la sécurité des statines en termes de prévention d'évènement cardiovasculaire présentent-t-elles des particularités chez des patients

vertonen de werkzaamheid en de veiligheid van de statines op het vlak van de preventie van cardiovasculaire evenementen bijzondere kenmerken bij patiënten

- âgés de plus de 60-65 ans (mais moins de 80 ans)
  ouder dan 60-65 jaar (maar jonger dan 80 jaar)?
- âgés de plus de 80 ans ?
  ouder dan 80 jaar?
- présentant un diabète ?
  met diabetes?
- présentant une insuffisance rénale ?
  met nierinsufficiëntie?
- présentant une insuffisance hépatique ?
  met leverinsufficiëntie?

Question – Vraag 5

Usage rationnel des statines (et autres hypolipidémiants)

Rationeel gebruik van de statines (en andere hypolipemiërende middelen)

- quelles sont les indications validées de l'initiation d'un traitement par statine, et laquelle ?
  Welke zijn de gevalideerde indicaties voor het starten van een behandeling met statines? Welke statine dient hierbij opgestart te worden?
- un arrêt (temporaire ou définitif) d'un traitement par hypolipidémiant est-il rationnel dans certaines circonstances ?

Is een (tijdelijke of definitieve) stopzetting van een hypolipemiërende behandeling onder bepaalde omstandigheden rationeel?

1.1.2 Research task of the literature group

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

- **To discuss selected guidelines regarding juryquestions numbers 2 to 5.**

- To search for systematic reviews, meta-analyses, RCTs (and large observational studies for rare safety endpoints) for the following populations, comparisons and endpoints:

1.1.2.1 Populations

The following populations are to be evaluated.

- 'General population'. No formal definition was given by the organising committee. The idea is to include all trials on hypolipemic drugs, except in specific subgroups (see below for excluded populations).
- Specific populations
  - Specific attention to the elderly (population > 65 y and > 80y)
  - Excluded from literature search: diabetics, patients with decreased renal function, people with familial hypercholesterolaemia, patients with cardiac failure

1.1.2.2 Interventions

Only products with a registered indication in Belgium will be considered. These are listed here:

○ Statins	Atorvastatin Fluvastatin Pravastatin Rosuvastatin Simvastatin
○ Fibrates	Bezafibrate Ciprofibrate Fenofibrate
○ Cholesterol absorption inhibitors	Ezetimibe

The following product are excluded from the literature search:

○ Nicotinic acid and acipimox	
○ Bile acid sequestrants	Colestipol Cholestyramine
○ Omega-3 fatty acids	
○ Food supplements	Red yeast rice, phytosterols….

1.1.2.3 Comparisons

The following comparisons are to be reported

	PLacebo	Statin	Fibrate	Ezetimibe	Statin + fibrate	Statin + ezetimibe
Statin						
Fibrate						
Ezetimibe						
Statin + fibrate						
Statin + ezetimibe						

1.1.2.4 Endpoints

The following endpoints are to be reported from RCTs:

- All cause mortality
- Cardiovascular mortality
- Cardiovascular disease
- Coronary heart disease
- Stroke
- Peripheral aterial disease
- Haemorrhagic stroke (as adverse event)

The following endpoint are to be reported from RCTs but also from observational cohort studies:

- Type 2 diabetes
- Cognitive function
- Cancer
- Cataract
- Musculoskelettal problems (myalgia and muscle damage)
- All-cause mortality

1.1.2.5 Study criteria

- Efficacy
    - Design
        - RCT
        - Double blind
    - Duration of RCT: minimum 1 year.
    - Minimum number of participants: minimum 40 per study arm. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.
    - Phase III trials (no phase II trials)

- Safety
    - Information from the selected RCTs
    - Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), European Medicines Agency (EMA), Meyler's Side Effects of Drugs (15th edition), Martindale: The complete drug reference (36th edition), Farmacotherapeutisch Kompas.
    - Additional information from large observational cohort studies.

1.1.2.6 Guidelines

Only guidelines that report levels of evidence/recommendation are to be selected.
Only guidelines from 2009 onwards are to be selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
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.

1.2 Search strategy

1.2.1 Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link “evidence-based guidelines” on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to ‘guideline search engines’, like National Guideline Clearinghouse and G-I-N.

1.2.2 Search strategy details

As a source document, the following systematic reviews or meta-analyses were selected

1. Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, et al. Comparative Effectiveness of Lipid-Modifying Agents. 2009.
2. Fodor G. Primary prevention of CVD: treating dyslipidaemia. Clinical evidence. 2010.
3. Lip GY, Kalra L. Stroke: secondary prevention. Clinical evidence. 2010.
4. Skinner JS, Cooper A. Secondary prevention of ischaemic cardiac events. Clinical evidence. 2011.

A search strategy was developed in Pubmed to find relevant RCTs that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
In some cases, when the selected systematic reviews were not sufficient (e.g. no search for all drugs), an additional search was conducted for RCTs that appeared before the search date of the selected systematic review.
The search for observational studies in pubmed was limited to the last 3 years, due to large amount of publications on statins, but reference lists of the selected publications were also screened for relevant earlier publications.

The following search strategy was used:

((((("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin*[tiab] OR "reductase inhibitor*"[tiab] OR Simvastatin[Mesh] OR Simvastatin[tiab] OR Atorvastatin[tiab] OR Rosuvastatin[tiab] OR Pravastatin[Mesh] OR Pravastatin[tiab] OR Fluvastatin[tiab] OR ezetimibe[Supplementary Concept] OR ezetimibe[tiab]) AND ("2009/12"[PDat] : "2013/12/31"[PDat])) OR ((fibrate*[tiab] OR fibric acids[Mesh] OR fibric acid*[tiab] OR Clofibric acid[Mesh] OR Clofibric acid[tiab] OR clofibrate[tiab] OR fenofibrate[MH] OR fenofibrate[tiab] OR bezafibrate[Mesh] OR bezafibrate[tiab]) AND ("2010/05"[PDat] : "2013/12/31"[PDat])) OR ((ezetimibe[Supplementary Concept] OR ezetimibe[tiab] OR fibrates[tiab] OR fibric acids[Mesh] OR fibric acid*[tiab] OR Clofibric acid[Mesh] OR Clofibric acid[tiab] OR clofibrate[tiab] OR fenofibrate[MH] OR fenofibrate[tiab] OR bezafibrate[Mesh] OR bezafibrate[tiab]) AND ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin*[tiab] OR "reductase inhibitor*"[tiab] OR Simvastatin[Mesh] OR Simvastatin[tiab] OR Atorvastatin[tiab] OR Rosuvastatin[tiab] OR Pravastatin[Mesh] OR Pravastatin[tiab] OR Fluvastatin[tiab]) AND ("2008/8"[PDat] : "2013/12/31"[PDat]))) AND ((("Cardiovascular Diseases/blood"[Mesh] OR "Cardiovascular Diseases/mortality"[Mesh] OR "Cardiovascular Diseases/prevention and control"[Mesh] OR "Mortality"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors/adverse effects"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use"[Mesh] OR "Primary Prevention"[Mesh] OR "Secondary Prevention"[Mesh] OR "Stroke/prevention and control"[Mesh]) AND (mortality[tiab] OR death[tiab] OR cardiovascular[tiab] OR MI[tiab] OR myocardial infarct*[tiab] OR coronary[tiab] OR "vascular event"[tiab] OR stroke[tiab])) OR ((mortality[tiab] OR death[tiab] OR cardiovascular[tiab] OR MI[tiab] OR myocardial infarct*[tiab] OR coronary[tiab] OR "vascular event"[tiab] OR stroke[tiab]) AND ("2013/05"[PDat] : "2013/12/31"[PDat]))) AND (((systematic[sb] OR medline[TIAB]) NOT (renal[ti] OR "chronic kidney"[ti] OR endothel*[ti] OR valv*[ti])) OR ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial) NOT (renal[ti] OR endothel*[ti] OR valv*[ti] OR niacin[ti] OR resin*[ti] OR cholestyramin*[ti] OR omega-3[ti] OR "chronic kidney"[ti]))) NOT (animals[Mesh] NOT humans[Mesh]))
OR
("Hydroxymethylglutaryl-CoA Reductase Inhibitors/adverse effects"[Mesh] OR statin*[tiab] OR "Simvastatin/adverse effects"[Mesh] OR Simvastatin [tiab] OR Atorvastatin [tiab] OR Rosuvastatin [tiab] OR

“Pravastatin/adverse effects"[Mesh]OR Pravastatin [tiab] OR Fluvastatin [tiab] OR ezetimibe[Supplementary Concept] OR ezetimibe [tiab] OR fibrate* [tiab] OR “fibric acids/adverse effects"[Mesh] OR fibric acid*[tiab]) AND (Cohort[TIAB] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study" [Publication Type] OR systematic[sb] OR medline[TIAB]) AND ((("Diabetes Mellitus, Type 2"[Mesh] OR (diabetes[TIAB] AND ("type II"[TIAB] OR "type 2"[TIAB]))) AND ("2012"[PDat] : "2013”[PDat])) OR ((cognit*[TIAB] OR Alzheimer*[TIAB] OR dementia[TIAB] OR "Dementia"[Mesh]) AND ("2012"[PDat] : "2013”[PDat])) OR ((cancer [TIAB] OR "Neoplasms"[Mesh]) AND ("2011"[PDat] : "2013”[PDat])) OR ((cataract[TIAB] OR "Cataract"[Mesh]) AND ("2011"[PDat] : "2013”[PDat])) OR ((muscle*[TIAB] OR "Myalgia"[Mesh] OR "Musculoskeletal Pain"[Mesh] OR "Myositis"[Mesh] OR "Rhabdomyolysis"[Mesh] OR Myopathy[TIAB]OR Myalgia [TIAB] OR myositis [TIAB] OR Rhabdomyolysis [TIAB] OR Tendinitis [TIAB] OR Muscle weakness [TIAB]) AND ("2011"[PDat] : "2013”[PDat])) OR ((mortality[TIAB] OR "mortality"[MeSH Terms]) AND ("2011"[PDat] : "2013”[PDat])))

Search results:
1911 records after duplicates removed
187 full text articles assessed
112 full text articles excluded
76 articles included

A list of publications that were excluded after reading the full text is available in appendix 1.

1.3 Selection procedure

Inclusion criteria used to select relevant *meta-analyses and systematic reviews*:

- Research question in selected publication matched research question for this literature review
- Systematic search
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes

Inclusion criteria for *randomised controlled trials (RCTs)* are mentioned in chapter 1.1. with relevant interventions, endpoints and study criteria.

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. 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 read to decide on inclusion or exclusion.

Some publications were excluded for practical reasons:

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

1.4 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 enpoint, across studies.
The GRADE system[3,4,5] 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
For observational studies	Evidence of association	+ 1	Strong evidence of assciation (RR of >2 or <0.5)
		+ 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

*** Consistency** refers to the similarity of estimates of effect across studies. if there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the (inevitably somewhat arbitrary) decision about whether important inconsistency exists.

**** Directness:** there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than would be provided by head to head comparisons of the drugs.
The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

*****Imprecision**: When studies include relatively few patients and few events and thus have wide confidence intervals, a guideline panel will judge the quality of the evidence to be lower.

In this literature review the criterium 'pubication bias' and the criteria specifically intended for observational studies (see table above) have not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
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
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

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

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Study design

In this literature review, all studies are RCTs (inclusion criterium). "Study design" is therefore not reported specifically in this report.

Study quality

To assess the methodological quality of RCTs, 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 wit hno 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 and the reading committee 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

If we include systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision. For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

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

1.5 Synopsis of study results

The complete report contains per research question

- 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 per research question

- 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 have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

References

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3. GRADE working group. http://www.gradeworkinggroup.org
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2 Critical reflections of the reading committee and the literature group

2.1 Patient population

2.1.1 Inclusion criteria

The inclusion criteria in the RCTs are very diverse. While some trials do include participants based on a certain level of lipids, a wide range of other inclusion criteria is used (e.g. a previous cardiovascular event, hypertension, microalbuminuria, elevated hs-CRP,…)..

Some RCTs include only patients with no previous history of cardiovascular disease, some include only patients with a history of cardiovascular disease, and some include both. Likewise, some trials include only diabetics, some exclude them, whilst other trials include both diabetics and non-diabetics. We have, between trials an within trials, a population that consists of patients with a very different baseline risk of cardiovascular disease.

This proves a challenge in interpreting the results for clinical practice, especially since most of our information is derived from meta-analyses. Most of these meta-analyses have pooled trials that are clinically very heterogeneous. This poses a problem when we want to estimate the efficacy of a statin in an individual patient. (See also below: clinical relevance, number needed to treat)

In clinical practice, risk prediction models (e.g. SCORE in Europe) are used to predict the risk of cardiovascular disease in an individual patient and as a decision aid whether or not to start treatment. Almost no trials include patients based on such a risk prediction model.

2.1.2 Primary prevention?

A number of meta-analyses have been published on the use of statins in primary prevention.

This raises some questions for the clinician. How is primary prevention defined? In the selected meta-analyses, this is usually on clinical grounds (No history of clinical CVD). But what about patients with atherosclerosis (e.g. asymptomatic cartotid stenosis) on imaging techniques?

The meta-analysis by Taylor 2013 included some trials with patients who had evidence of subclinical carotid atherosclerosis. It also allowed trials with a low number of patients with clinical CVD.

The only meta-analysis that excluded all patients with clinical CVD is Ray 2010. Interestingly, this meta-analysis did not find a statistically significant effect of statins on all-cause mortality.

2.1.3 Elderly

One of the questions that the jury needs to address, is the use of lipid-lowering drugs in the elderly. Unfortunately, data are somewhat limited. Statins have been studied in a relatively young population (mean age below 60y in most trials). We included 2 meta-analyses in the elderly that include mostly subgroup analyses of larger trials (mean age in these meta-analyses: +/- 73 y in primary prevention and +/- 70y in secondary prevention). .

We have not enough data in the very old (>80y).

2.1.4 Run in

A lot of trials use a run-in period: patients that are candidates for inclusion in the trial are given placebo treatment (or a statin in other trials) for a certain time, to eliminate participants with poor compliance.
In placebo-controlled statin trials, there is often a placebo run-in period used.

In trials of high dose statin versus a lower dose, a statin run-in period is sometimes used. In this case (as in patients that have received statins before entering the trial), adverse events cannot reliably be estimated, since patients that have experienced adverse events are not likely to be included in the trial.

2.2 Comparisons

Trials that compare a higher dose of statin to a lower dose (moderate dose) of statin have only been conducted in participants with a history of cardiovascular disease.
In patients with no history of cardiovascular disease, it is therefore not clear whether a higher dose statin leads to any relevant benefit in cardiovascular disease risk and mortality.

There are many trials on statin treatment. Our evidence base for other lipid-lowering drugs such as fibrates and ezetimibe is much more limited. More studies are needed to determine the role of these drugs.

2.3 Endpoints

2.3.1 Adverse events

Reporting of adverse events in the trials is not very good. Meta-analyses do not always analyse adverse events. The use of run-in periods also leads to considerable bias.

2.4 Interpreting the results

2.4.1 Statistically significant - clinically relevant

The main focus of an RCT is usually to establish whether a treatment is statistically significantly better than a comparator (placebo or other treatment).
However, some differences may be statistically significant due to a large sample size, but the clinical relevance may be limited (Willenheimer 2001(1), Chevalier 2009(2)).
If the absolute risk reduction is very small and the number needed to treat very high, a clinically meaningful result for an individual patient will be doubtful.
It is difficult to say what such a cut-off margin of clinical relevance may be. It will depend on the gravity of the event that is prevented, and has to be balanced with the risk/adverse events of the treatment. A risk- benefit assessment will involve an evaluation of the magnitude of the treatment effect, of adverse events, cost of the treatment (and choices of society), and also involves the notion of medicalization of a relatively healthy population. Many of these factors are not well studied or hard to quantify.
Other factors that contribute to the estimation of clinical relevance of a treatment is the general applicability of study results (Willenheimer 2001(1), Chevalier 2009(2)).

- Does the study population represent the individual patient that we want to treat?
- Can a study duration of several years adequately reflect the lifelong use of a drug?
- Is the compliance in the general population comparable to compliance within the study?

2.4.2 Number needed to treat?

The number needed to treat expresses the number of patients who need to be treated to prevent one additional event. Traditionally, it is a way to present the results from a single trial, since it is influenced by the baseline risk of the included patients and by the duration of the intervention. NNTs for meta-analyses are sometimes reported. These NNTs are to be interpreted with caution because they are not very reliable.

Marx 2003(3) phrases the problem as follows: "NNTs derived from meta-analyses are affected by variations in risk differences among the studies, as well as baseline event rates in control groups of randomised controlled trials. Summary estimates of NNTs assume constant risk differences between trials, a problematic assumption because of inevitable variation in baseline event rates between trials, differences in outcomes considered, effects of secular trends on disease risk, and differences in clinical setting as well as duration of follow up (ie, time horizon). In primary prevention of chronic disease, such as cardiovascular disease, the effect of time trends will become noticeable."

Since we know that the meta-analyses on statins pool studies with very different baseline risk, it may be more prudent to look at NNTs of the individual trials.

2.4.3 Observational studies

For adverse events, we have included the results of observational studies.

An observational study cannot prove a causal link, it can merely establish an association between the use of a drug and a specific outcome. The quality of evidence in the GRADE approach for observational studies is LOW by default, although upgrading or downgrading according to certain rules is possible.

3 Guidelines

3.1 Criteria for guideline selection

In order to be included, the guideline had to be of recent date (not published before 2010) and had to report levels of evidence and/or grades of recommendation.
The following guidelines fulfilled these criteria:

3.2 Selected guidelines

3.2.1 Dyslipidemia

ESC-EAS 2011	European Society of Cardiology / European Atherosclerosis Society guidelines for the management of dyslipidaemias Reiner Z, Catapano AL, De Backer G et al. ECS/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769-1818. doi:10.1093/eurheartj/ehr158 http://eurheartj.oxfordjournals.org
AACE 2012	American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and atherosclerosis Jellinger PS, Smith DA, Mehta AE et al. Lipid and atherosclerosis guidelines. Endocrine Practice 2012; 18 (1): 1-78.
ESC 2013	Chapter 6.4. Prevention of cardiovascular disease in patients with diabetes and dyslipidaemia ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with EASD (European Association for the Study of Diabetes) Eur Heart J 2013 Advance Access published August 30, 2013 doi:10.1093/eurheartj/eht108 http://eurheartj.oxfordjournals.org
UMHS 2012	Screening and management of lipids, guidelines for clinical care by University of Michigan Health System Original: 2009, minor revisions in 2011 and 2012 Barrie WE, Van Harrison R, Khanderia UB et al. Screening and management of lipids. UMHS Lipid Therapy Guideline update, November 2012: 1-16.
CCS 2013	Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult Anderson TJ, Grégoire J, Hegele RA et al. 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia

	for the prevention of cardiovascular disease in the adult. Canadian Journal of Cardiology 2013; 29: 151–167.
ACC AHA 2013 bc	Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation

3.2.2 Cardiovascular prevention

ESC 2012	European guidelines on cardiovascular disease prevention in clinical practice Perk J, De Backer G, Gohlke H et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J 2012;33:1635-1701. doi: 10.1093/eurheartj/ehs092
NICE 2010	Prevention of cardiovascular disease (NICE public health guidance 25) Issued June 2010 National Institute for Health and Clinical Excellence. Prevention of cardiovascular disease. NICE Clinical Guideline PH25. Issue date: June 2010 http://guidance.nice.org.uk/PH25
ACC AHA 2013 cvr	Guideline on the assessment of cardiovascular risk Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437741.48606.98.citation
Domus Medica 2007	Globaal cardiovasculair risicobeheer Boland B, Christiaens T, Goderis G et al. Globaal cardiovasculair risicobeheer. Aanbeveling voor goede praktijkvoering Domus Medica. *Huisarts Nu* 2007;36:339-69. http://www.domusmedica.be/documentatie/richtlijnen/overzicht/cardiovasculair-horizontaalmenu-381.html

3.2.3 Lifestyle Management

ACC AHA 2013 Lifestyle Management	Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Eckel RH, Jakicic JM, Ard, JD,et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology American/Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437740.48606.d1.citation

3.3 Summary of guidelines

3.3.1 Dyslipidemia

3.3.1.1 ESC-EAS 2011

Grades of recommendation:

1) **Class I:** evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
   ⇨ Is recommended/indicated
2) **Class II**: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
   a. weight of evidence/opinion is in favor of usefulness/efficacy.
   ⇨ Should be considered
   b. usefulness/efficacy is less well established by evidence/opinion.
   ⇨ May be considered
3) **Class III**: evidence and/or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
   ⇨ Is not recommended

Levels of evidence:

1) **Level A**: Data derived from multiple randomized clinical trials or meta-analyses.
2) **Level B**: Data derived from a single randomized clinical trial or large non-randomized studies.
3) **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Included populations, interventions, outcomes:

- Patients with dyslipidaemias. Specific subpopulations: familial dyslipidaemia, metabolic syndrome and diabetes, acute coronary syndrome and patients undergoing percutaneous coronary intervention, heart failure and valvular diseases, autoimmune diseases, renal disease, transplantation patients, peripheral arterial disease, stroke, HIV patients.
- Lifestyle modifications, statins, bile acid sequestrants, cholesterol absorption inhibitors, nicotinic acid, LDL apheresis, fibrates, n-3 fatty acids, cholesteryl ester transfer protein inhibitors.
- Total cardiovascular risk, level of total cholesterol, level of low-density lipoprotein LDL cholesterol, level of very low-density lipoprotein VLDL cholesterol, level of high-density lipoprotein HDL cholesterol, triglycerides, apolipoproteins.

Members of development group, target population:

- Professionals involved with the medical care of patients with this pathology.
- Patients with dyslipidaemias and therefore are at risk for coronary artery disease (CAD), ischaemic stroke, and peripheral arterial disease (PAD).

Recommendations:

Prevention and treatment of dyslipidaemias should always be considered within the broader framework of cardiovascular disease (CVD) prevention.

Recommendations: risk assessment:

Who?

Risk factor screening, including the lipid profile, may be considered (class IIb) in) in adult men ≥40 years of age, and in women ≥50 years of age or post-menopausal, particularly in the presence of other risk factors.
In addition, all subjects with evidence of atherosclerosis in any vascular bed or with type 2 diabetes, irrespective of age, are regarded as being at high risk; it is recommended to assess their lipid profile.
(class I)

Patients with chronic kidney disease (CKD) (GFR ,60 mL/min/1.73 m2) are also at increased risk for CVD events and should be screened for dyslipidaemias.

What?

Total cholesterol (TC) is recommended to be used for the estimation of total CV risk by means of the SCORE system.
(**class I**)

LDL-C is recommended to be used as the primary lipid analysis for screening and risk estimation.
(class I)

Triglycerides (TG) adds information on risk and is indicated for risk estimation.
(class I)

HDL-C is a strong risk factor and is recommended to be used for risk estimation.
(class I)

Non-HDL-C should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the metabolic syndrome or chronic kidney disease.
(class IIa)

Lipoprotein a, Lp(a), should be recommended is selected cases at high risk and in subjects with a family history of premature CVD.
(class IIa)

*Apolipoprotein B, Apo B***,** should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the metabolic syndrome or chronic kidney disease.
(class IIa)

The ratio Apo B/Apo AI combines the risk information of Apo B and Apo AI and may be recommended as an alternative analysis for risk screening.
(class IIb)

The ratio non-HDL-C/HDL-C may be recommended as an alternative analysis for risk screening.
(class IIb)

How?

Very simple principles of risk assessment can be defined as follows:
(1) Those with
† known CVD
† type 2 diabetes or type 1 diabetes with microalbuminuria
† very high levels of individual risk factors
† chronic kidney disease (CKD)
are automatically at VERY HIGH or HIGH TOTAL CARDIOVASCULAR RISK and need active management of all risk factors.
(2) For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.

SCORE differs from earlier risk estimation systems in several important ways, and has been modified somewhat for the present guidelines.
The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe (see Figures 1 and 2)(Belgium should consider the low risk chart). All International Classification of Diseases (ICD) codes that could reasonably be assumed to be atherosclerotic are included. Most other systems estimate CAD risk only.
Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low.
Charts including HDL-C are available as Addendum I to these guidelines on the ESC website (www.escardio.org/guidelines)

Very high risk:
Subjects with any of the following:

- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, PAD.
- Patient with type 2 diabetes, patients with type 1 diabetes with target organ damage (such as microalbuminuria)
- Patients with moderate severe CKD (GFR<60ml/min/1.73m²)
- A calculated 10 year risk SCORE 10 %

High risk:
Subjects with any of the following:

- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension
- A calculated SCORE 5 % and < 10 % for 10 year risk of fatal CVD

Moderate risk:
Subjects are considered to be at moderate risk when their SCORE is >1 % and < 5 % at 10 years. Many middle-aged subjects belong to this risk category. This risk is further modulated by a family history of premature CAD, abdominal obesity, physical activity pattern, HDL-C, TG, hs-CRP, Lp(a), fibrinogen, homocysteine, apo B ad social class.

Low risk:
The low risk category applies to individuals with SCORE < 1 %.

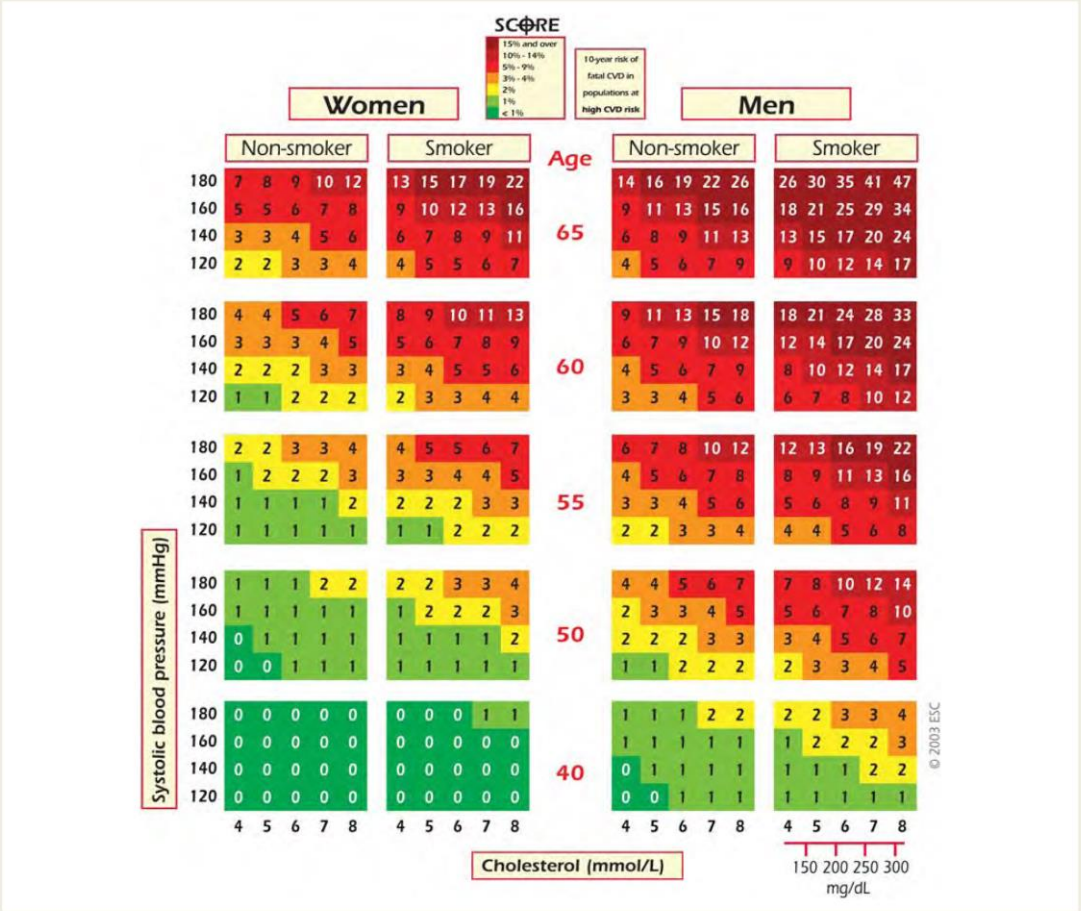


Figure 1 SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at **high CVD risk** based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice.

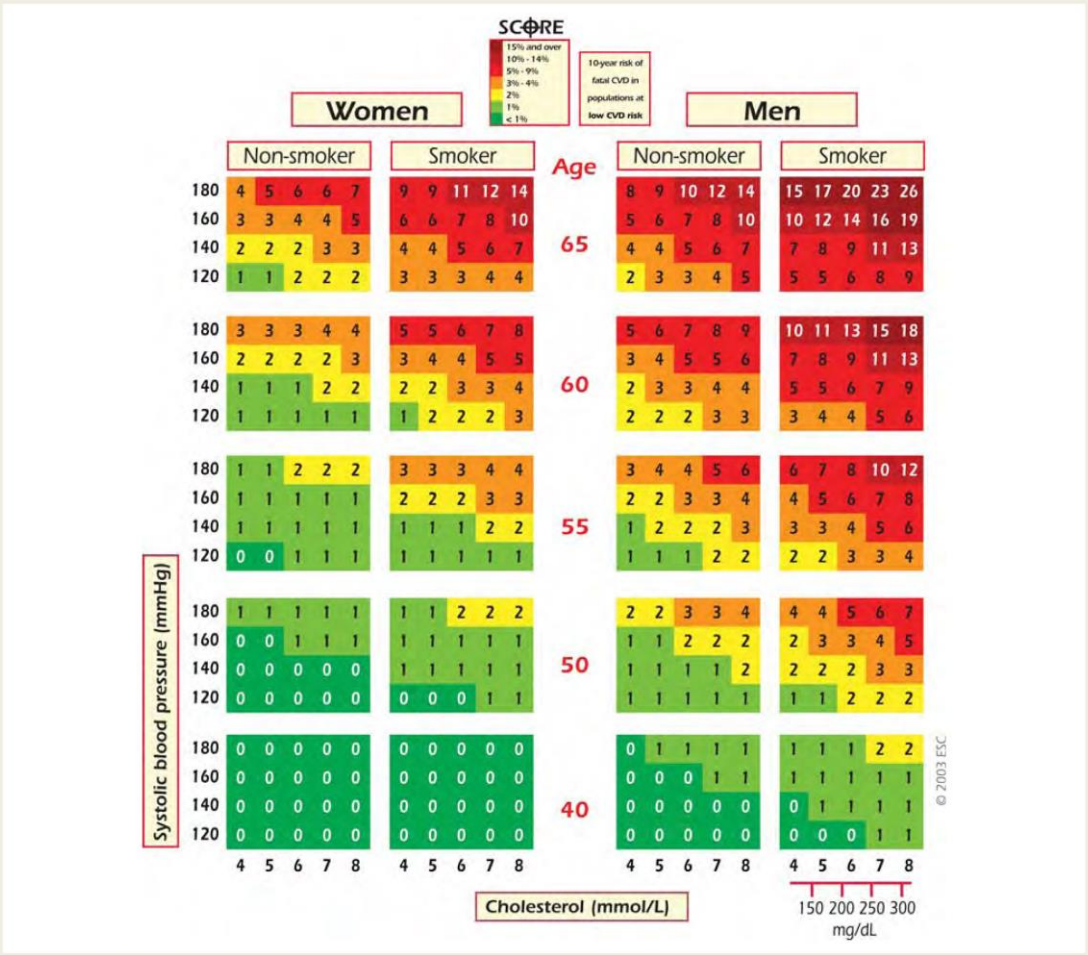


Figure 2 SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at **low CVD risk** based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice.

Recommendations: targets:

LDL-C is recommended as target for treatment.
(class I)
Total cholesterol should be considered as treatment target if other analyses are not available.
(class IIa)
Triglycerides should be analysed during the treatment of dyslipidaemias with high triglyceride level.
(class IIa)
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the metabolic syndrome or chronic kidney disease (CKD).
(class IIa)
Apo B should be considered as a secondary treatment target.
(class IIa)
HDL-C is not recommended as a target treatment.
(class III)
The ratios Apo B/Apo AI and non-HDL-C/HDL-C are not recommended as targets for treatment.
(class III)

In patients at very high cardiovascular risk (established CVD, type 2 diabetes mellitus, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%), the LDL-C goal is < 1.8 mmol/l (less than 70 mg/dl) and/or ≥ 50% LDL-C reduction when target level cannot be reached.
(class I)

In patients at high cardiovascular risk (markedly elevated single risk factors, a SCORE level ≥ 5 to < 10%) an LDL-C goal < 2.5 mmol/l (less than 100 mg/dl) should be considered.
(class IIa)

In subjects at moderate risk (SCORE level > 1 to ≤ 5%) an LDL-C goal < 3.0 mmol/l (less than 115 mg/dl) should be considered.
(class IIa)

To date, no specific targets for HDL-C or TG levels have been determined in clinical trials.

Recommendations: treatment:
Those with
† known CVD
† type 2 diabetes or type 1 diabetes with microalbuminuria
† very high levels of individual risk factors
† chronic kidney disease (CKD)
are automatically at VERY HIGH or HIGH TOTAL CARDIOVASCULAR RISK and need active management of all risk factors.

Intervention strategies as a function of total CV risk and LDL-C level

Table 3 Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

*In patients with MI, statin therapy should be considered irrespective of LDL-C levels.[13,14]
[a]Class of recommendation
[b]Level of evidence. References to level A: 15–41.
CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction.

Pharmacological interventions:

Table 14 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

Lifestyle modifications:

There is strong evidence showing that dietary factors may influence atherogenesis directly or through effects on traditional risk factors such as lipid levels, blood pressure, or glucose levels.

Most evidence linking nutrition to CVD is based on observational studies and on investigations of the effects of dietary changes on lipid levels. The influence of lifestyle changes and of functional foods on lipoproteins is considered and summarized in Table 9.

Table 9 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence	References
Lifestyle interventions to reduce TC and LDL-C levels			
Reduce dietary saturated fat	+++	A	63
Reduce dietary trans fat	+++	A	64
Increase dietary fibre	++	A	65
Reduce dietary cholesterol	++	B	66
Utilize functional foods enriched with phytosterols	+++	A	67
Reduce excessive body weight	+	B	68
Utilize soy protein products	+	B	69
Increase habitual physical activity	+	A	70
Utilize red yeast rice supplements	+	B	71, 72
Utilize polycosanol supplements	-	B	73
Lifestyle interventions to reduce TG levels			
Reduce excessive body weight	+++	A	68
Reduce alcohol intake	+++	A	74
Reduce intake of mono- and disaccharides	+++	A	75, 76
Increase habitual physical activity	++	A	77
Reduce total amount of dietary carbohydrate	++	A	78
Utilize supplements of *n*-3 polyunsaturated fat	++	A	79
Replace saturated fat with mono- or polyunsaturated fat	+	B	63
Lifestyle interventions to increase HDL-C levels			
Reduce dietary trans fat	+++	A	64
Increase habitual physical activity	+++	A	77
Reduce excessive body weight	++	A	68
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A	78
Use alcohol with moderation	++	B	80
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+	C	-
Quit smoking	+	B	81
Reduce intake of mono- and disaccharides	+	C	-

+++ = general agreement on the effects on lipid levels.
++ = less pronounced effects on lipid levels; weight of evidence/opinion is in favour of efficacy.
+ = conflicting evidence; efficacy is less well established by evidence/opinion.
– = not effective and/or uncertainties regarding safety.
HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride.

Summary of lifestyle measures and healthy food choices for managing total CV risk:

- Dietary recommendations should always take into account local food habits. However, interest in healthy food choices from other cultures should be promoted.
- A wide variety of foods should be eaten. Energy intake should be adjusted to prevent overweight and obesity.
- Consumption of fruit, vegetables, legumes, nuts, wholegrain cereals and bread, fish (especially oily) should be encouraged.
- Saturated fat should be replaced with the above foods and with monounsaturated and polyunsaturated fats from vegetable sources, in order to reduce energy intake from total fat to < 35% of energy, saturated fat to < 7% of total energy, trans fats to < 1% of total energy, and dietary cholesterol to < 300 mg/day.

- Salt intake should be reduced to < 5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods. Many processed and convenience foods, including bread, are high in salt.
- For those who drink alcoholic beverages, moderation should be advised (< 10-20 g/day for women and < 20-30 g/day for men) and patients with hypertriglyceridaemia should abstain.
- The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, particularly for patients with hypertriglyceridaemia.
- Physical activity should be encouraged, aiming at regular physical exercise for at least 30 minutes/day every day.
- Use and exposure to tobacco products should be avoided.

Recommendations: specific populations:

Elderly

The strongest driver of CVD risk is age, which may be regarded as 'exposure time' to risk factors. This raises the issue that Table 3 might suggest that most older men in high risk countries who smoke would be candidates for drug treatment, even if they have satisfactory blood pressure and lipid levels. To date, this is not supported by trial evidence, and the clinician is strongly recommended to use clinical judgement in making therapeutic decisions in older people, with a firm commitment to lifestyle measures such as smoking cessation in the first instance.
Elderly individuals (older than 65 years) are a high risk group who could benefit significantly from lipid-lowering therapy to reduce CV morbidity and mortality.
Evidence for treatment above the age of 80–85 years is very limited, and clinical judgement should guide decisions in the very old.
In some age categories the vast majority, especially of men, will have estimated CV death risks exceeding the 5–10% level, based on age (and gender) only, even when other CV risk factor levels are relatively low. This could lead to excessive usage of drugs in the elderly and should be evaluated carefully by the clinician.

Recommendation:
Treatment with statin is recommended for elderly patients with established CVD in the same way as for younger patients.
(class I)
Since elderly people often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to achieve target lipid levels which are the same as in younger subjects.
(class I)
Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age.
(class IIb)

Diabetes

Recommendation:
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.
(class I)

In patients with type 2 diabetes and chronic cardiovascular or kidney disease (CVD or CKD) and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is < 1.8 mmol/l (less than 70 mg/dl) and the secondary goal for non-HDL-C is < 2.6 mmol/l (100 mg/dl) and for apo B is < 80

mg/dl.
(class I)

In all people with type 2 diabetes LDL-C < 2.5 mmol/l (less than 100 mg/dl) is the primary target. Non-HDL-C < 3.3 mmol/l (130 mg/dl) and apo B < 100 mg/dl are the secondary targets.
(class I)

Renal disease:

Recommendations for lipid lowering drugs in patients with moderate to severe chronic kidney disease CKD (stages 2-4, GFR 15-89 mL/min/1.73 m2):

Recommendation:
CKD is acknowledged as a coronary artery disease (CAD) risk equivalent; in these patients LDL-C reduction is recommended as the primary target of therapy.
(class I)
LDL-C lowering reduces CVD risk in CKD subjects and should be considered.
(class IIa)
Statins should be considered to slow the rate of kidney function loss modestly and thus protect against the development of end-stage renal disease (ESRD) requiring dialysis.
(class IIa)
Since statins have a beneficial effect on pathological proteinuria (> 300 mg/day) they should be considered in patients with stage 2-4 CKD.
(class IIa)
In moderate to severe CKD statins as monotherapy or in combination with other drugs should be considered to achieve LDL-C < 1.8 mmol/l (less than 70 mg/dl).
(**class IIa)**

Recommendations: monitoring, compliance

Monitoring:

Table 33 Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy

Testing lipids
How often should lipids be tested? • Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks , with the exception of conditions where immediate drug treatment is suggested such as in ACS.
How often should patients' lipids be tested after starting lipid-lowering treatment? • 8 (±4) weeks after starting drug treatment. • 8 (±4) weeks after adjustments to treatment until within the target range.
How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol? • Annually (unless there is adherence problems or another specific reason for more frequent reviews).
Monitoring liver and muscle enzymes
How often should liver enzymes (ALT) be routinely measured in patients taking lipid-lowering drugs? • Before treatment • 8 weeks after starting drug treatment or after any dose increase • Annually thereafter if liver enzymes are <3×ULN
What if liver enzymes become raised in a person taking lipid-lowering drugs? If <3×ULN: • Continue therapy • Recheck liver enzymes in 4–6 weeks If values rise to ≥3×ULN: • Stop statin or reduce dose, recheck liver enzymes within 4–6 weeks • Cautious reintroduction of therapy may be considered after ALT has returned to normal
How often should CK be measured in patients taking lipid-lowering drugs? *Pre-treatment* • Before starting treatment • If baseline CK level >5×ULN, do not start drug therapy; recheck *Monitoring* • Routine monitoring of CK is not necessary • Check CK if patient develops myalgia Increase alertness regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease.
What if CK becomes raised in a person taking lipid-lowering drugs? If >5×ULN: • Stop treatment, check renal function and monitor CK every 2 weeks. • Consider the possibility of transient CK elevation for other reasons such as muscle exertion. • Consider secondary causes of myopathy if CK remains elevated. If ≤5×ULN: • If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider further checks of CK) • If muscle symptoms, monitor symptoms and CK regularly

ACS = acute coronary syndrome; ALT = alanine aminotransferase; CK = creatine phosphokinase; ULN = upper limit of normal.

Compliance:

Table 34 Hints to help adherence to lifestyle changes

• Develop a good alliance with the patient.
• Make sure that the patient understands how lifestyles affect cardiovascular disease and use this to gain commitment to the change in behaviour.
• Explore potential barriers to the change.
• Design with the patient a lifestyle change plan that is realistic and encouraging.
• Reinforce the patient's efforts to change.
• Involve other experts wherever needed and possible.
• Arrange a schedule of follow-up visits.

Table 35 Tips to help compliance with multiple drug therapies

• Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
• Choose cheaper alternatives.
• Provide clear written and oral instructions.
• Undertake a dialogue with the patient regarding adherence.
• Tailor the regimen to the patient's lifestyle and needs.
• Involve the patient as partner in the treatment.
• Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement)

3.3.1.2 AACE 2012

Grades of recommendation (see table 3 in original guideline):

1) **Grade A**:
   Evidence level 1 or Evidence level 2 with positive subjective factor
2) **Grade B**:
   Evidence level 1 with negative subjective factor
   Evidence level 2
   Evidence level 3 with positive subjective factor
3) **Grade C**:
   Evidence level 2 with negative subjective factor
   Evidence level 3
   Evidence level 4 with positive subjective factor
4) **Grade D**:
   Evidence level 3 with negative subjective factor or Evidence level 4
   Evidence levels 1, 2, 3 or 4 without two-thirds consensus

Table 3
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade[a,b]

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).
[b] Reprinted from *Endocr Pract.* 2010;16:270-283 (9 [EL 4]).

Levels of evidence:

1) **Strong evidence**: meta-analysis of randomized controlled trials; randomized controlled trial
2) **Intermediate evidence**: meta-analysis of nonrandomized prospective or case-controlled trials; nonrandomized controlled trial; prospective cohort study; retrospective case-control study
3) **Weak evidence**: cross-sectional study; surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database); consecutive case series; single case reports
4) **No evidence** (theory, opinion, consensus, review or preclinical study)

Included populations, interventions, outcomes:

- Patients with dyslipidaemias. Specific subpopulations: women, diabetics and children.
- Physical activity, nutrition, smoking cessation, pharmacologic therapy: statins, fibrates, niacin, bile acid sequestrants, cholesterol absorption inhibitors

- Total cardiovascular risk, level of total cholesterol, level of low-density lipoprotein LDL cholesterol, level of high-density lipoprotein HDL cholesterol, level of non-high-density lipoprotein non-HDL cholesterol, triglycerides, apolipoproteins.

Members of development group, target population:
- Endocrinologists
- Endocrinologists and other clinicians

Recommendations: screening

How?

Recommendation:
Identify risk factors and categorize degrees of risk (Table 6) which enables the physician to personalize therapy for dyslipidemia according to each patient's risk level and thereby maximize treatment effectiveness
(Grade A)
Major risk factors include advancing age, high serum total cholesterol levels, high non-HDL-C levels, high LDL-C levels, established CAD, family history of CAD, presence of hypertension or diabetes mellitus and cigarette smoking. *Additional risk factors* (obesity, family history, elevated apo B, increased LDL particle number, small dense LDL, fasting/postprandial hypertriglyceridemia, polycystic ovary syndrome in women, dyslipidemic triad) should be considered, as should *nontraditional risk factors* (e.g. inflammatory markers, highly sensitive C-reactive protein [CRP], lipoprotein-associated phospholipase A2 [Lp-PLA2], lipoprotein [a], hyperhomocysteinemia, hyperuricemia).
(Grade A)

Determine the *10-year risk* (high, intermediate, low) of a coronary event using the Framingham Risk Assessment Tool or Reynolds Risk Score (www.reynoldsriskscore.org), (the latter includes highly sensitive CRP and family history of premature CAD)
(Grade A).

Because of the diagnostic difficulties and differences in clinical presentation, AACE recommends that special attention be given to *assessing women for CAD risk*. Determine the 10-year risk (high, intermediate, low) of a coronary event using Reynolds Risk Score (www.reynoldsriskscore.org) or the Framingham Risk Assessment Tool.
(Grade A)

The Framingham Risk Score provides 10-year probability of women experiencing a coronary event in the presence of specific clinical diagnoses or scenarios (Evidence level 3-4) but unlike the Reynolds Risk Score, it appears to underestimate CAD risk in women with 2 risk factors.

Categorize lipid-related risks as optimal/near-optimal, borderline, and high risk (Evidence level 4). An HDL-C concentration greater than 60 mg/dL is an independent negative risk factor in both sexes, and when the HDL-C concentration is greater than 60 mg/dL, 1 risk factor can be subtracted from a patient's overall risk profile
(Grade A).

AACE recommends classifying *elevated triglycerides* (Evidence level 4) to aid in treatment decisions.
(Grade A)

Table 6
Coronary Artery Disease Risk Categories and Low-Density Lipoprotein Treatment Goals
(20 [EL 4], 22 [EL 4], 23 [EL 4])

Risk category	Risk factors[a]/10-year risk[b]	LDL-C treatment goal
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20% or CHD risk equivalents[c], including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10%-20%	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10%	<130 mg/dL
Low risk	≤1 risk factor	<160 mg/dL

Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.
[a] Major independent risk factors are high low-density lipoprotein cholesterol, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of coronary artery disease (n male first-degree relative younger than 55 years; in female first-degree relative younger than 65 years), and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high high-density lipoprotein cholesterol (≥60 mg/dL) (10 [EL 4], 11 [EL 4]).
[b] Framingham risk scoring is applied to determine 10-year risk (10 [EL 4]).
[c] Coronary artery disease risk equivalents include diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease).

Who?

Recommendation:
AACE recommends more frequent assessments for <u>all patients with a family history</u> of premature CAD (definite myocardial infarction [MI] or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative) **(Grade C)**.
AACE suggest considering more frequent testing for individuals with <u>CAD risk factors</u>
(Grade C)

<u>Adults With Diabetes</u>: Annually screen all adult patients with diabetes mellitus for dyslipidemia
(Grade B)

*<u>Young Adults</u> (Men Aged 20-45 Years, Women Aged 20-55 Years):*Evaluate all adults 20 years of age for dyslipidemia every 5 years as part of a global risk assessment
(Grade A)

<u>Middle-Aged Adults</u> (Men Aged 45-65 Years, Women Aged 55-65 Years): In the absence of CAD risk factors, screen middle-aged persons for dyslipidemia at least every 1 to 2 years. AACE recommends more frequent lipid testing when multiple global CAD risk factors are present **(Grade C)**. The frequency of testing should be based on individual clinical circumstances and the clinician's best judgment
(Grade C).

*Older Adults (Older Than 65 Years):*Annually screen older adults with 0 to 1 CAD risk factor for dyslipidemia.
(Grade C)
In addition, older patients should undergo lipid assessment if they have multiple CAD global risk factors (i.e. risk factors other than age).
(Grade C)

AACE believes that screening recommendations apply based on age and risk, not based on sex; therefore, women should be screened in the same way as men.
(Grade A)

What?

Recommendation:
Fasting Lipid Profile:
Use a fasting lipid profile to ensure the most precise lipid assessment. This should include total cholesterol, LDL-C, triglycerides, and HDL-C.
(Grade C)

Low-Density Lipoprotein Cholesterol :Calculated
AACE does not recommend estimating LDL-C values in certain clinical circumstances. LDL-C is frequently and inexpensively estimated using the Friedewald equation :
(Grade A)
LDL-C = [(total cholesterol – HDL-C) – triglycerides]/5
However, this method is valid only for values obtained during the fasting state. It becomes increasingly inaccurate when triglyceride levels are greater than 200 mg/dL, and the equation is no longer valid when triglyceride levels are greater than 400 mg/dL.

Low-Density Lipoprotein Cholesterol :Direct Measurement
AACE recommends direct measurement of LDL-C in certain high-risk patients, such as those with fasting triglyceride levels greater than 250 mg/dL or those with diabetes mellitus or known vascular disease
(Grade C).

High-Density Lipoprotein Cholesterol:
AACE recommends measurement of HDL-C as a screening test for dyslipidemia. Low HDL-C can act synergistically with other lipid risk factors to increase CAD risk. An HDL-C concentration greater than 60 mg/dL is an independent *negative* risk factor in both sexes.

Non–High-Density Lipoprotein Cholesterol:
Calculate non–HDL-C (total cholesterol minus HDL-C) in patients with moderately elevated triglycerides (200 to 500 mg/dL), diabetes mellitus, and/or established CAD
(Grade C).
If insulin resistance is suspected, AACE recommends evaluating non–HDL-C to gain useful information regarding the patient's total atherogenic lipoprotein burden. In addition, in any circumstance when triglycerides are 200 mg/dL or greater but less than 500 mg/dL, a non–HDL-C calculation will provide better risk assessment than LDL-C alone.
(Grade C)
Non–HDL-C targets are 30 mg/dL higher than established LDL-C risk levels.
(Grade C)

Recommendation:

*Triglycerides***:**
Increasing clinical evidence suggests that elevated triglycerides may be an independent risk factor for CAD; therefore, AACE recommends screening of triglycerides as a component of lipid screening. Triglycerides levels that are even moderately elevated (>150 mg/dL) may identify individuals at risk for the insulin resistance syndrome. Triglyceride levels 200 mg/dL or greater may indicate a substantial increase in CAD risk. (Evidence level 4)

Apolipoproteins:
AACE recommends that optimal apo B levels for patients at risk of CAD, including those with diabetes, are less than 90 mg/dL, while patients with established CAD or diabetes who have 1 or more additional risk factor(s) should have an apo B goal of less than 80 mg/dL
(Grade D).
When the triglyceride level is greater than 150 mg/dL or the HDL-C level is less than 40 mg/dL, AACE believes that the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in patients at risk for CAD *(even when LDL-C levels are controlled)*; this includes patients with established CAD, type 2 diabetes, or the insulin resistance syndrome who are at high risk for CAD. AACE therefore recommends apo B testing in such patients
(Grade B).
AACE recommends apo B measurements to assess the success of LDL-C–lowering therapy. Apo B reflects LDL particle number, which may be elevated in patients at or below LDL-C goal. While LDL-C and LDL particle *size* (e.g. small dense LDL) are associated with atherogenicity, LDL particle *number* as reflected by apo B is a more potent measure of cardiovascular disease (CVD) risk than either of these 2 measures **(Grade B)**.
AACE believes that assessment of apo AI may be useful in certain cases.
(Grade B)
A normal apo AI level in a patient with low HDL-C suggests the existence of an adequate number of HDL-C particles that contain less cholesterol and may be an indication of less risk. The INTERHEART study found that the apo B to apo AI ratio was among the most significant risk factors for MI (Evidence level 2).

Additional Tests:
Assess *markers of inflammation* in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA2 provide useful additional information in these instances and appear to be synergistic in predicting risk of CVD and stroke
(**Grade B**).
Use *highly sensitive CRP* to stratify CVD risk in patients with a standard risk assessment that is borderline, or in those with an LDL-C concentration less than 130 mg/dL (Grade 2; BEL B).
Measure Lp-PLA2, which in some studies has demonstrated more specificity than highly sensitive CRP, when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations.
(Grade 2; BEL B)
AACE does not recommend routine measurement of *homocysteine, uric acid, plasminogen activator inhibitor 1, or other inflammatory markers* because the benefit of doing so is unclear.
(Grade 4; BEL D)
Noninvasive measures of atherosclerosis such as *carotid intima media thickness* (IMT) and *coronary artery calcification* should not be performed routinely, but may be used in certain clinical situations as adjuncts to standard CVD risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies. Although coronary calcium correlates strongly with coronary atherosclerosis, there is a lack of definite evidence that this risk factor independently predicts coronary events.
(Grade 4; BEL D)

Recommendations: targets:

See also table 6 in the chapter: screening

Lipid parameter	Goal
TC, mg/dL	<200
LDL-C, mg/dL	<100; <70 (*all* very high risk patients) (**Grade A)**
HDL-C, mg/dL	As high as possible, but at least >40 in both men and in women **(Grade C)**
Non–HDL-C, mg/dL	30 above LDL-C goal **(Grade A)**
TG, mg/dL	<150 **(Grade A)**
Apo B, mg/dL	<90 (patients at risk of CAD, including those with diabetes) <80 (patients with established CAD or diabetes plus ≥1 additional risk factor) **(Grade D)**

Recommendations: treatment:

Pharmacological therapy:

Recommendation:
AACE recommends aggressive lipid-modifying therapy to lower LDL-C to less than 100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk
(Grade A)
and to decrease coronary death, MI, or any cardiovascular events in patients on aggressive statin therapy.
(Grade A)
AACE recommends an LDL-C goal less than 70 mg/dL as an appropriate goal for *all* patients with established CAD. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective.
(Grade A).
Reducing lipids to levels even below recommended targets may be beneficial for certain patients (e.g. those with metabolic syndrome).
Patients for whom AACE recommends aggressive therapy:

- Patients undergoing coronary artery bypass graft **(Grade A)**
- Patients with acute coronary syndrome **(Grade A)**
- Certain healthy and functional older patients at high risk who may be appropriate candidates for aggressive therapy **(Grade A)**

Statins:
AACE recommends statins as the drug of choice for LDL-C reduction on the basis of findings from

morbidity and mortality outcome trials
(Grade A)

Fibrates:
AACE recommends fibrates for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL)
(Grade A)

Cholesterol absorption inhibitor (ezetimibe):
Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. AACE recommends combination therapy with statins because current research indicates that this enhances these benefits and further improves the beneficial effects of statins on triglycerides and HDL-C.
(Grade A)
It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events
(Grade B)

Combination therapy:
Certain clinical situations warrant the use of a combination of lipid-lowering agents. Because the adverse effects of 2 or more drugs may be additive, clinical judgment is needed to balance the risks and benefits of combination therapy.
AACE recommends that combination therapy be considered in the following circumstances:

- When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal.
  (Grade A)
  The recent SHARP trial (Study of Heart and Renal Protection) demonstrated a reduction of LDL-C via treatment with simvastatin, 20 mg daily, plus ezetimibe, 10 mg daily, which safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.
- When mixed dyslipidemia is present
  (Grade C)

Lifestyle

Recommendation:
Physical Activity: AACE recommends a reasonable and feasible approach to fitness therapy, ie, exercise programs that include at least 30 minutes of moderate-intensity physical activity (consuming 4-7 kcal/min) 4 to 6 times weekly, with an expenditure of at least 200 kcal/day. Suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities
(Grade A; BEL 2)
Daily *physical activity* goals can be met in a single session or in multiple sessions throughout the course of a day (10 minutes minimum). For some patients, breaking activity up throughout the day may help improve adherence to physical activity programs (Grade B; BEL 4). In addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week.
(Grade B; BEL 2)

Medical Nutrition Therapy: for adults, AACE recommends a reduced-calorie diet consisting of fruits and vegetables (≥5 servings/day),
(Grade A; BEL 2)
grains (≥6 servings/day, one-third of those as whole grains), fish, and lean meats.
(Grade B; BEL 2)

Intake of saturated fats, trans fats, and cholesterol should be limited, while LDL-C–lowering macronutrient intake should include plant stanols/sterols (~2 g/day) and soluble fiber (10-25 g/day). **(Grade A; BEL 1)**

Smoking Cessation: every effort should be made to support patients in their efforts to cease smoking **(Grade A; BEL 3)**
Cigarette smoking is a powerful risk factor, especially for MI, peripheral vascular disease, and stroke. Smoking accelerates coronary plaque development and may lead to plaque rupture and is particularly dangerous in persons with advanced coronary atherosclerosis. Numerous studies have shown that smoking has a substantial, negative effect on HDL-C levels and the LDL-C to HDL-C ratio. Smoking also appears to have a negative effect on postprandial lipids, including triglycerides. However, smoking cessation significantly increases HDL-C, with improvement observed in as few as 30 days.

Recommendations: follow-up and monitoring:

Recommendation:
AACE recommends reassessing patients' *lipid status* 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved. Thereafter, AACE recommends that patients be tested at 6- to 12-month intervals. The specific interval should depend on patient adherence to therapy and lipid profile consistency. If adherence is a concern or the lipid profile is unstable, the patient will probably benefit from biannual assessment.
(Grade C; BEL 4)
AACE recommends more frequent lipid status evaluation in the following clinical circumstances:

- Deterioration of diabetes control.
- The use of a new drug known to affect lipid levels.
- Progression of atherothrombotic disease.
- Considerable weight gain.
- An unexpected adverse change in any lipid parameter.
- Development of a new CAD risk factor.
- Convincing new clinical trial evidence or guidelines that suggest stricter lipid goals.

Recommendation:
AACE recommends that a *liver transaminase* level be measured before and 3 months after statin or fibric acid treatment initiation, because most liver abnormalities occur within 3 months of treatment initiation. AACE recommends that this test be repeated periodically (eg, semiannually). **(Grade A; BEL 3)**
AACE recommends that transaminase level assessment be repeated at these intervals whenever lipid-altering therapy is restarted, increased, changed, or combined.
(Grade A; BEL 3)

Recommendation:
AACE recommends assessment of *creatine kinase* levels whenever a patient reports clinically significant myalgias or muscle weakness.
(Grade A; BEL 3)

3.3.1.3 ESC 2013 (chapt. 6.4)

From the ESC 2013 guidelines on diabetes, pre-diabetes and cardiovascular diseases only the chapter about dyslipidemia is discussed here.

Grades of recommendation:

1) **Class I**: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
2) **Class II:** conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
   a. weight of evidence/opinion is in favor of usefulness/efficacy.
   b. usefulness/efficacy is less well established by evidence/opinion.
3) **Class III:** evidence and/or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Levels of evidence:

1) **Level A**: Data derived from multiple randomized clinical trials or meta-analyses.
2) **Level B**: Data derived from a single randomized clinical trial or large non-randomized studies.
3) **Level C**: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Included populations, interventions, outcomes:

- Patients with type 1 and type 2 diabetes mellitus
- Physical activity, diet, weight reduction, smoking cessation, pharmacologic therapy: statins, ezetimibe, fibrates
- Cardiovascular events, level of LDL-C, HDL-C, triglycerides, all-cause mortality, progression of atheroma, adverse events: muscle symptoms

Members of development group, target population:

- Cardiologists, endocrinologists
- Health professionals

Recommendation:

Statin therapy is recommended in patients with type 1 and type 2 diabetes at very high risk (i.e. if combined with documented CVD, severe CKD or with one or more cardiovascular risk factors and/or target organ damage) with an LDL-C target of < 1.8 mmol/l (< 70 mg/dl) or at least ≥ 50% LDL-C reduction if this target goal cannot be reached.
(Class I, level A)

Statin therapy is recommended in patients with type 2 diabetes at high risk (without any other cardiovascular risk factor and free of target organ damage) with an LDL-C target of < 2.5 mmol/l (< 100 mg/dl).
(Class I, level A)

Statins may be considered in type 1 diabetes patients at high risk for cardiovascular events irrespective of the basal LDL-C concentration.
(Class IIb, level C)

It may be considered to have a secondary goal of non-HDL-C < 2.6 mmol/l (< 100 mg/dl) in patients with diabetes mellitus at very high risk and of < 3.3 mmol/l (< 130 mg/dl) in patients at high risk.
(Class IIb, level C)

Intensification of statin therapy should be considered before the introduction of combination therapy with the addition of ezetimibe.
(Class IIa, level C)

The use of drugs that increase HDL-C to prevent CVD in type 2 diabetes is not recommended.
(Class III, level A)

3.3.1.4 UMHS 2012

Grades of recommendation:

1) **Class I**: treatment or procedure generally should be performed.
2) **Class II**: treatment or procedure may be reasonable to perform.
3) **Class III**: treatment or procedure should not be performed.

Levels of evidence:

1) **Level A:** Data derived from randomized controlled trials
2) **Level B:** Data derived from non-randomized controlled trials
3) **Level C:** Data derived from observational trials
4) **Level D**: Opinion of expert panel

Included populations, interventions, outcomes:

- Adults 20-75 years without familial or severe dyslipidemias
- Lifestyle modification (smoking cessation, diet, exercise, weight reduction) and drug therapy (statins, fibrates, niacin, resins, ezetimibe)
- Lipid and CHD profile, level of LDL-C, HDL-C, triglycerides, non-HDL-C

Members of development group, target population:

- Family doctors and cardiologists
- Primary care providers

Recommendations: primary prevention: screening

Screen men age 35 and older and age 20 to 35 if at increased risk for CHD. Screen women only if at increased risk for CHD.
(Class I, level C)

Repeat screening in 5 years in patients with normal lipids
(Class II, level D)

Screening with fasting lipid profile is advised. If screened non-fasting for patient convenience, follow-up on abnormal non-fasting lipids with a fasting lipid profile.

Recommendations: primary prevention: risk assessment:

Risk factors are cigarette smoking, hypertension (blood pressure 140/90 mm Hg or on antihypertensive medication) low HDL cholesterol (< 40 mg/dl), family history of premature CHD (CHD in first-degree relative: male <55 years or female <65 years), age (men ≥ 45 years: women ≥ 55 years)

Determination of risk can be facilitated by using the Framingham based Global Risk Score, which predicts 10 year risk of a coronary event (level C).

Note: Framingham 10-Year Risk Score can be calculated at http://cvdrisk.nhlbi.nih.gov/calculator.asp

Recommendations: primary prevention: treatment:

Initial treatment:
lifestyle modification - smoking cessation, diet, exercise, and weight reduction
(Class I, level A)

Evaluate LDL-C response in 6 weeks to 6 months based on patient's cardiovascular risk.
(Class I, level D)

Drug therapy: consider if LDL-C remains above threshold
patients with low risk ≥ 190 mg/dl, moderate risk ≥ 160 mg/dl, moderately high risk ≥ 130 mg/dl
(Class II, level A)

Evidence is insufficient to recommend drug therapy for low HDL-C or high triglycerides for primary prevention.

Table 1. Overview of Primary Prevention *

1. Candidates. Confirm appropriate for primary prevention.
- Men age 35 and older; age 20–35 if increased risk for CHD
- Women age 20 and older if increased risk for CHD

For candidates, go to next step.

2. Laboratory testing. Obtain lipid/CHD profile – fasting advised. If screened non-fasting and lipids abnormal, perform fasting lipid panel.

3. Abnormal levels? Is: HDL-C ≤ 40 mg/dl or TC ≥ 240 mg/dl or TC . 200 mg/dl with 2 or more CHD risks (Table 3)?
If normal levels: reinforce lifestyle education (as appropriate: smoking cessation, diet, exercise, weight loss) and repeat screen in 5 years.
If abnormal levels, go to next step.

4. Secondary causes? Consider and treat any secondary causes (Table 4).

5. Lifestyle modifications. As appropriate, address smoking cessation, diet, exercise, weight loss, reduce excessive alcohol.

6. Lipid profile. Obtain a lipid profile periodically (6 weeks to 6 months) to assess efficacy of lifestyle / lipid lowering therapy.

7. Triglycerides elevated? If triglycerides > 400 mg/dl, see text for triglyceride management. If triglycerides ≥200 mg/dL, calculate non-HDL cholesterol. Non-HDL cholesterol = total cholesterol – HDL cholesterol. If triglycerides ≤ 400 mg/dl go to next step.

8. Risks sufficient to start drug therapy? See Table 5 for risks levels to initiate drug therapy. (Continues on next column.)

(Step 8 continued)
If not starting drug therapy:
- Reinforce lifestyle modifications (as appropriate: smoking cessation, diet, exercise, weight loss, reduce excessive alcohol)
- Follow-up lipids in 1 to 2 years.

If risk sufficient to start drug therapy, go to next step.

9. Initiate drug therapy.
- Check baseline ALT.**
- Treat with statin (see Tables 6, 7, and 8)

10. Initial follow-up. Check lipids in 6–12 weeks. Check ALT as indicated.** Check creatinine kinase (CK) only if patient has symptomatic muscle aches and weakness.

11. Lipid goal met? See Table 5 for lipid goals.
If lipid goal not met:
- Address adherence
- Reinforce lifestyle modifications
- Modify drug treatment, e.g., increase statin. See Table 9 for statin intolerance.
- Consider referral to specialist in lipid management.
- Follow-up in 6–12 weeks and reassess whether lipid goal met (repeat step 11).

If lipid goal met or no further reduction likely, go to next step.

12. Longer term follow-up. Follow-up lipids at least annually.

* Assumes candidate does not already have a disease that requires lipid measurement for secondary prevention, e.g., CHD, athlerosclerotic cardiovascular disease, and diabetes mellitus.

** Careful follow-up of liver tests is indicated for those with known liver disease, risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications. For other patients, if baseline liver function tests (LFTs) are normal, no further monitoring is required. If baseline LFTs are mildly abnormal (over upper limit of normal but < 5 X upper limit of normal): monitor LFTs during first 6 months of statin treatment for stability. Abnormal baseline liver biochemistries can frequently improve with statin therapy.

Recommendations: secondary prevention: screening:

Recommendation:
Screen with a full lipid panel all patients with CHD, other atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus (DM), or Framingham 10 year risk >20%.
(Class I, level A)

Recommendations: secondary prevention: risk assessment:

Determine whether patient risk for cardiovascular events is:
• High: CHD without major risk factors or other risks associated with "very high" risk.
• Very high: CHD or other atherosclerotic vascular disease plus one or more of: major risk factors (e.g. diabetes, metabolic syndrome, active cigarette smoking), or acute coronary syndrome.

Recommendations: secondary prevention: treatment:

All patients: lifestyle modification
(Class I, level A)

Drug therapy:

- *Statin* therapy should be considered for all patients. Statins reduce mortality and CHD/ASCVD endpoints, including if LDL-C < 100 mg/dl
  (level A).
  High potency statins (atorvastatin, rosuvastatin) at high doses reduce events more than low potency statins or high potency statins at low doses.
  (level A)
  Prescribe moderate dose of high potency statin (e.g. atorvastatin 20 mg daily or higher) even if low LDL-C
  (Class I, level A).
  Note: in DM patients age <40 with no other CHD risk, statin is only marginally cost-effective.
  LDL-C goals: high risk ≤ 100 mg/dl, very high risk substantially < 100 mg/dl
  (Class II, level A)
  Note: lower doses in special situations (elderly, renal insufficiency, cytochrome 3A4 inhibitors,…)
- *Non statin* lipid agents (fibrates, niacin, resins, ezetimibe) have less or no evidence for improved outcomes compared to statins.
  (level A)
- *Combination therapy* (statin + any other lipid agent) improves lipids, but may increase myopathy risk, and has not yet been shown to improve outcomes compared to statins.
  (Class II, level C)

Table 5. Risk Categories for Initiating Lifestyle Change, Considering Drug Therapy, and LDL-C Goals

Risk Category	LDL-C to Initiate Lifestyle Changes [a]	LDL-C to Consider Drug Therapy	LDL-C Goal
Primary Prevention			
Low risk: 0–1 risk factors [b]	≥ 130 mg/dl	≥ 190 mg/dl	< 160 mg/dl
Moderate risk: 2+ risk factors & 10-year risk < 10% [c]	≥ 130 mg/dl	≥ 160 mg/dl	< 130 mg/dl
Moderately high risk: 2+ risk factors & 10-year risk 10 to 20% [c]	All	≥ 130 mg/dl (option: ≥ 100 mg/dl)	< 100 mg/dl
Secondary Prevention			
CHD or CHD risk equivalent [d] without risk factors that are major or severe/poorly controlled [e]	All	All – at least moderate statin	< 100 mg/dl
CHD or CHD risk equivalent [d] with risk factors that are major or severe/poorly controlled [e]	All	All – at least moderate statin	Substantially < 100 mg/dl (option: < 70 mg/dl)

Note: This table was modified from ATP, based on HPS.

[a] As appropriate, address smoking cessation, diet, exercise, weight loss, reduce excessive alcohol.

[b] Almost all people with 0–1 risk factor have a 10-year risk ≤ 10%; thus 10-year risk assessment is not necessary.

[c] Major risk factors are listed in Table 3. Electronic 10-year risk calculators are available at "www.nhlbi.nih.gov/guidelines/cholesterol".

[d] CHD includes history of myocardial infarction, unstable angina. Stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include diabetes and clinical manifestations of non-coronary forms of atherosclerotic cardiovascular disease (ASCVD) such as peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, or Framingham score ≥20%.

[e] Very high risk is established CHD (see above) plus one or more of: major risk factors (e.g. diabetes, metabolic syndrome – especially triglycerides ≥ 200 plus non-HDL-C ≥ 130 plus HDL-C < 40), current cigarette smoking or acute coronary syndrome.

Recommendations: specific populations:

Renal disease:

End Stage Renal Disease. A large RCT comparing atorvastatin (20 mg/d) to placebo in a diabetic dialysis population did not find a significant reduction in cardiovascular events with statin therapy. Atorvastatin was well tolerated, however.

Diabetes:

For patients with diabetes and no other CHD risk factors, statin therapy may reasonably be delayed until age 40 since statin use in this population is only marginally cost-effective.

Recommendations: adverse effects:

Table 9. Management of Statin Intolerant (muscle aches/myopathy) Patients

1. **Reversible causes**. Check for reversible causes of muscle aches/myopathy while on statin (hypothyroidism, cytochrome 3A4 inhibitors). Consider drug interactions (cyclosporine and concomitant use of certain statins (atorvastatin, lovastatin, simvastatin) and other agents that are metabolized by the cytochrome P450 3A4 system.
2. **Alternative statin.** Trial alternative low dose statin, and titrate up slowly.
3. **Alternate day dosing.** If failing a second statin, consider a trial of alternate day dosed long acting statin (atorvastatin/rosuvastatin).
4. **Non-statin agents.** If failing alternate day statin, consider one or more non-statin lipid lowering agents, including niacin, bile acid sequestrants, fibrates (if low HDL-C, high triglycerides), that have some evidence of CHD event reduction.
5. **Consider ezetimibe.** If intolerant to second line agents, consider ezetimibe (LDL-C reduction but no data showing event reduction).

3.3.1.5 CCS 2013

This is an update of the CCS guideline on dyslipidemia 2009

Grades of recommendation:

GRADE methodology

1) **Strong recommendation**: based on the available evidence, if clinicians are very certain that benefits do, or do not, outweigh risks and burdens they will make a strong recommendation.

2) **Weak recommendation**: based on the available evidence, if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks, they must offer a weak recommendation.

Levels of evidence:

1) **High quality evidence**: we are very confident that the true effect lies close to that of the estimate of the effect
2) **Moderate quality evidence**: we are moderately confident in the effect of estimate; the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different
3) **Low quality evidence**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
4) **Very low quality evidence**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

Included populations, interventions, outcomes:

- Men ≥ 40 years of age, women ≥ 50 years of age, up until 75 years.
- Nutrition therapy, exercise, psychological factors, smoking cessation, statin therapy, non-statin therapy (combination with ezetimibe, niacin, bile acid resins, fibrates, gemfibrozil
- Level of LDL-C, HDL-C, non-HDL-C, Apo B

Members of development group, target population:

- Developed by family doctors and cardiologists, multidisciplinary experts
- Aimed for primary care providers and specialists
- Target population: Canadian population

Recommendations: screening:

Who?

Men ≥ 40 years of age and women ≥ 50 years of age or postmenopausal
(consider earlier in ethnic groups at increased risk such as South Asians or First Nations individuals)
or
All patients with any of the following conditions, regardless of age:

- Current cigarette smoking
- Diabetes mellitus
- Arterial hypertension
- Family history of premature cardiovascular disease
- Family history of hyperlipidemia
- Erectile dysfunction
- Chronic kidney disease
- Inflammatory disease
- HIV infection
- Chronic obstructive pulmonary disease
- Clinical evidence of atherosclerosis or abdominal aneurysm
- Clinical manifestation of hyperlipidemia

- Obesity (BMI > 27)

How?

For all:
- History and examination, LDL, HDL, TG, non-HDL (will be calculated from profile), glucose, eGFR

Optional:
- apoB (instead of standard lipid panel), urine albumin:creatinine ratio (if eGFR < 60, hypertension, diabetes)

Apply Framingham Risk Score.

We recommend that *secondary testing* be considered for further risk assessment in "IR" patients (10%-19% FRS after adjustment for family history) who are not candidates for lipid treatment based on conventional risk factors or for whom treatment decisions are uncertain
(Strong Recommendation, Moderate-Quality Evidence)

We suggest that secondary testing be considered for a selected subset of "LR to IR" patients (5%-9% FRS after adjustment for family history) for whom further risk assessment is indicated (eg, strong family history of premature CAD, abdominal obesity, South Asian ancestry,or impaired glucose tolerance)
(Weak/Conditional Recommendation, Low-Quality Evidence)

How often?

If Framingham risk score is < 5%, repeat every 3-5 years.
If Framingham risk score is ≥ 5%, repeat every year.

We recommend that a cardiovascular risk assessment, using the "10-Year Risk" provided by the Framingham model be completed every 3-5 years for men age 40-75, and women age 50-75 years. This should be modified (percent risk doubled) when family history of premature CVD is positive (i.e. first-degree relative < 55 years for men and < 65 years of age for women). A risk assessment might also be completed whenever a patient's expected risk status changes. Younger individuals with at least 1 risk factor for premature CVD might also benefit from a risk assessment to motivate them to improve their lifestyle
(**Strong Recommendation, Moderate-Quality Evidence**).

We recommend calculating and discussing a patient's "Cardiovascular Age" to improve the likelihood that patients will reach lipid targets and that poorly controlled hypertension will be treated
(**Strong Recommendation, High-Quality Evidence**).

Recommendation: risk stratification:
- *Low risk:*
  No high risk features
  FRS < 10%
- *Intermediate risk:*
  No high risk features
  FRS 10-19%
- *High risk:*
  FRS ≥ 20%

Clinical vascular disease
Abdominal Aortic Aneurysm
Diabetes and age ≥ 40 yrs or >15 yrs duration and age ≥ 30 yrs or microvascular disease
Chronic kidney disease
High risk hypertension

Recommendations: targets:

Summary in figure 4 of original guideline. More details in figures 2 and 3.

Risk level	Initiate therapy if	Primary target LDL-C	Alternate target
High **FRS ≥ 20%**	Consider treatment in all (Strong, High)	≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, High)	*Apo B ≤ 0.8 g/L *Non HDL-C ≤ 2.6 mmol/L (Strong, High)
Intermediate **FRS 10%-19%**	*LDL-C ≥ 3.5 mmol/L (Strong, Moderate) *For LDL-C < 3.5 consider if: Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 4.3 mmol/L (Strong, Moderate)	≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, Moderate)	*Apo B ≤ 0.8 mg/L *Non HDL-C ≤ 2.6 mmol/L (Strong, Moderate)
Low **FRS < 10%**	*LDL-C ≥ 5.0 mmol/L *Familial hypercholesterolemia (Strong, Moderate)	≥ 50% reduction in LDL-C (Strong, Moderate)	

Recommendations: treatment:

Lifestyle

Recommendation:
All individuals be encouraged to adopt healthy eating habits to lower their CVD risk: (1) moderate energy (caloric) intake to achieve and maintain a healthy body weight; (2) emphasize a diet rich in vegetables, fruit, whole-grain cereals, and polyunsaturated and monounsaturated oils, including omega-3 fatty acids particularly from fish;(3) avoid trans fats, limit saturated and total fats to < 7% and < 30% of daily total energy (caloric) intake, respectively; (4) increase daily fibre intake to > 30 g; (5) limit cholesterol intake to 200 mg daily for individuals with dyslipidemia or at increased CVD risk **(Conditional Recommendation, Moderate-Quality Evidence)**

We recommend the Mediterranean, Portfolio, or Dietary Approach to Stop Hypertension (DASH) diets to improve lipid profiles or decrease CVD risk,
(Strong Recommendation, High-quality Evidence)
and for cholesterol-lowering consider increasing phytosterols, soluble fibre, soy, and nut intake.

We recommend that adults should accumulate at least 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of 10 minutes or more to reduce CVD risk.
(Strong Recommendation, High-Quality Evidence)

We recommend smoking cessation
(**Strong Recommendation, Moderate-Quality Evidence**),
and limiting alcohol intake to 30 g or less per day (1-2 drinks).
(**Conditional Recommendation, Moderate-Quality Evidence**)

Pharmacological treatment

Low Risk:
We recommend pharmacotherapy in LR individuals with LDL-C 5.0 mmol/L, or if there is evidence of genetic dyslipidemia (such as familial hypercholesterolemia)
(**Strong Recommendation, Moderate-Quality Evidence**)

We recommend 50% reduction of LDL-C in LR individuals for whom treatment is initiated
(**Strong Recommendation, Moderate-Quality Evidence**)

Intermediate Risk:
We recommend that the IR category include individuals with adjusted FRS 10% and 20%
(Strong Recommendation, Moderate-Quality Evidence)

We recommend treating IR individuals with LDL-C 3.5 mmol/L .
(Strong Recommendation, Moderate-Quality Evidence)

In IR individuals with LDL-C 3.5 mmol/L, apo B 1.2 g/L, or non-HDL-C 4.3 mmol/L is suggested to identify patients who might benefit from pharmacotherapy.
(**Strong Recommendation, Moderate-Quality Evidence**)

We recommend a target LDL-C 2.0 mmol/L or 50% reduction of LDL-C for IR individuals in whom treatment is initiated
(**Strong Recommendation, Moderate-Quality Evidence**).

Alternative target variables are apo B0.8 g/L or non-HDL-C2.6 mmol/L
(**Strong Recommendation, Moderate-Quality Evidence**).

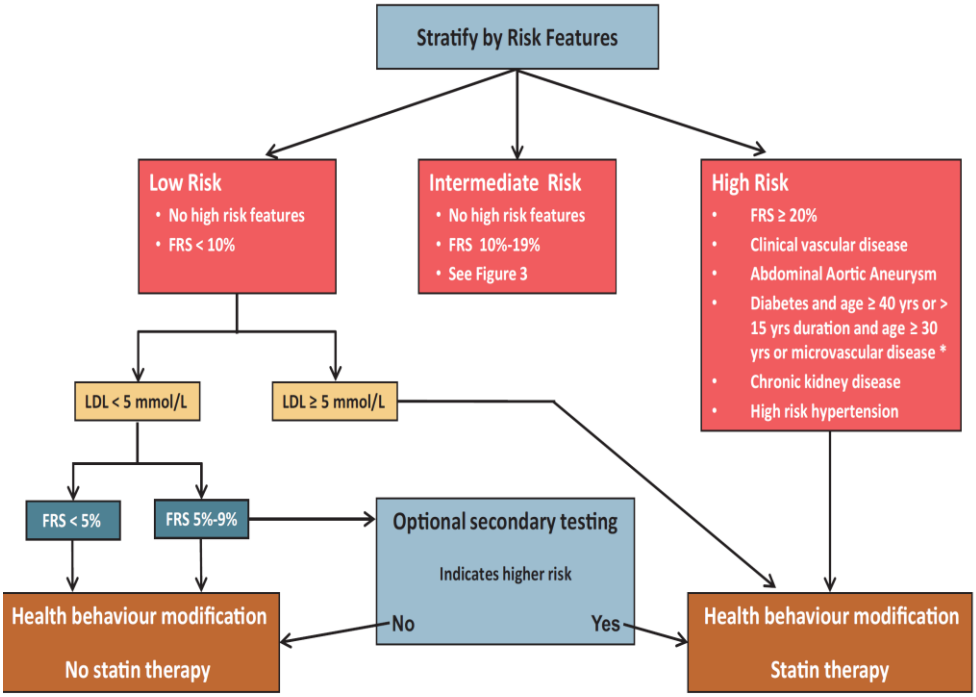
High Risk:
We recommend that high risk be defined in subjects who have clinical atherosclerosis, abdominal aortic aneurysm, or an adjusted FRS of 20%.
(Strong Recommendation, High-Quality Evidence)

We have also included diabetes of 15 years duration and age older than 30 years, diabetes with age older than 40 years, or the presence of microvascular disease, high risk kidney disease, or high risk hypertension.
(Strong Recommendation, Moderate-Quality Evidence)

We recommend a target LDL-C 2.0 mmol/L or 50% reduction of LDL-C for IR individuals in whom treatment is initiated.
(Strong Recommendation, Moderate-Quality Evidence)

We recommend that apo B 0.80 g/L or non-HDL-C 2.6 mmol/L be considered as alternative treatment targets for optimal risk reduction.
(Strong Recommendation, High-Quality Evidence)

In function of risk stratification. See figure 2 of original guideline.



isk stratification by Framingham Risk Score (FRS) and phenotype.*Not all subjects with diabetes are at high 10-year risk; included for based on randomized studies and high long-term risk.

Recommendations: specific populations

Elderly

For patients older than 75 years of age, the Framingham model is not well validated. Though clinical studies are currently under way to address this group, at this point clinical judgement is required in consultation with the patient to determine the value of pharmacotherapy. One approach is extrapolation of the modified FRS, and this approach identifies most subjects as having intermediate- to high-risk based on age.

Recommendations: monitoring adverse effects:

Because overall risk/benefit favours therapy in patients meeting criteria for lipid lowering therapy and cardiovascular risk reduction, we recommend that:

(1) despite concerns about a variety of other possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, reinitiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use **(Strong Recommendation, Very Low-Quality Evidence**);
and
(2) statins not be withheld on the basis of a potential, small risk of new-onset diabetes mellitus emerging during long-term therapy
(**Strong Recommendation, Very Low-Quality Evidence**).

We do not recommend vitamins, minerals, or supplements for symptoms of myalgia perceived to be statin-associated.
(Strong Recommendation, Very Low-Quality Evidence)

3.3.1.6 ACC AHA 2013 (bc)

Grades of recommendation (see tables 1a and 1b in original document):

1) **Grade A**: strong recommendation: there is high certainty based on evidence that the net benefit is substantial.
2) **Grade B**: moderate recommendation: there is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is a high certainty that the net benefit is moderate.
3) **Grade C**: weak recommendation: there is at least moderate certainty based on evidence that there is a small net benefit.
4) **Grade D:** recommendation against: there is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
5) **Grade E**: Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
6) **Grade N**: No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no
evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

Levels of evidence:

1) **High**:
Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. MAs of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect
2) **Moderate:**
RCTs with minor limitations affecting confidence in, or applicability of, the results. Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. MAs of such studies.
Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate
3) **Low:**
RCTs with major limitations. Nonrandomized controlled studies and observational studies with major
limitations affecting confidence in, or applicability of, the results. Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). Physiological studies in humans. MAs of such studies.
Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate

An alternative system of levels of recommendation is proposed in the guideline tables. We will not report this. Further information can be found in the original guideline.

Included populations, interventions, outcomes:

- Patients : secondary prevention and primary prevention adult patients
- Interventions: statins, fibrates, nicotinic acid, bile acid sequestrants, ezetimibe, omega-3 fatty acids.
- Outcomes: treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD). ASCVD includes coronary heart disease (CHD), stroke, and peripheral

arterial disease, all of presumed atherosclerotic origin.

Members of development group, target population:

- Cardiologists, endocrinologists, primary care physicians, experts clinical lipidology, clinical trials, cardiovascular epidemiology, guideline development
- Adults >21 years of age

Recommendations: risk assessment:

4 major statin benefit groups:

4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events. Individuals

1) with clinical ASCVD,
2) primary elevations of LDL–C >190 mg/dL,
3) diabetes aged 40 to 75 years with LDL–C 70 to189 mg/dL and without clinical ASCVD,
4) without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk >7.5%.

Recommendations: treatment:

Pharmacological treatment

Figure 2. Major recommendations for statin therapy for ASCVD prevention

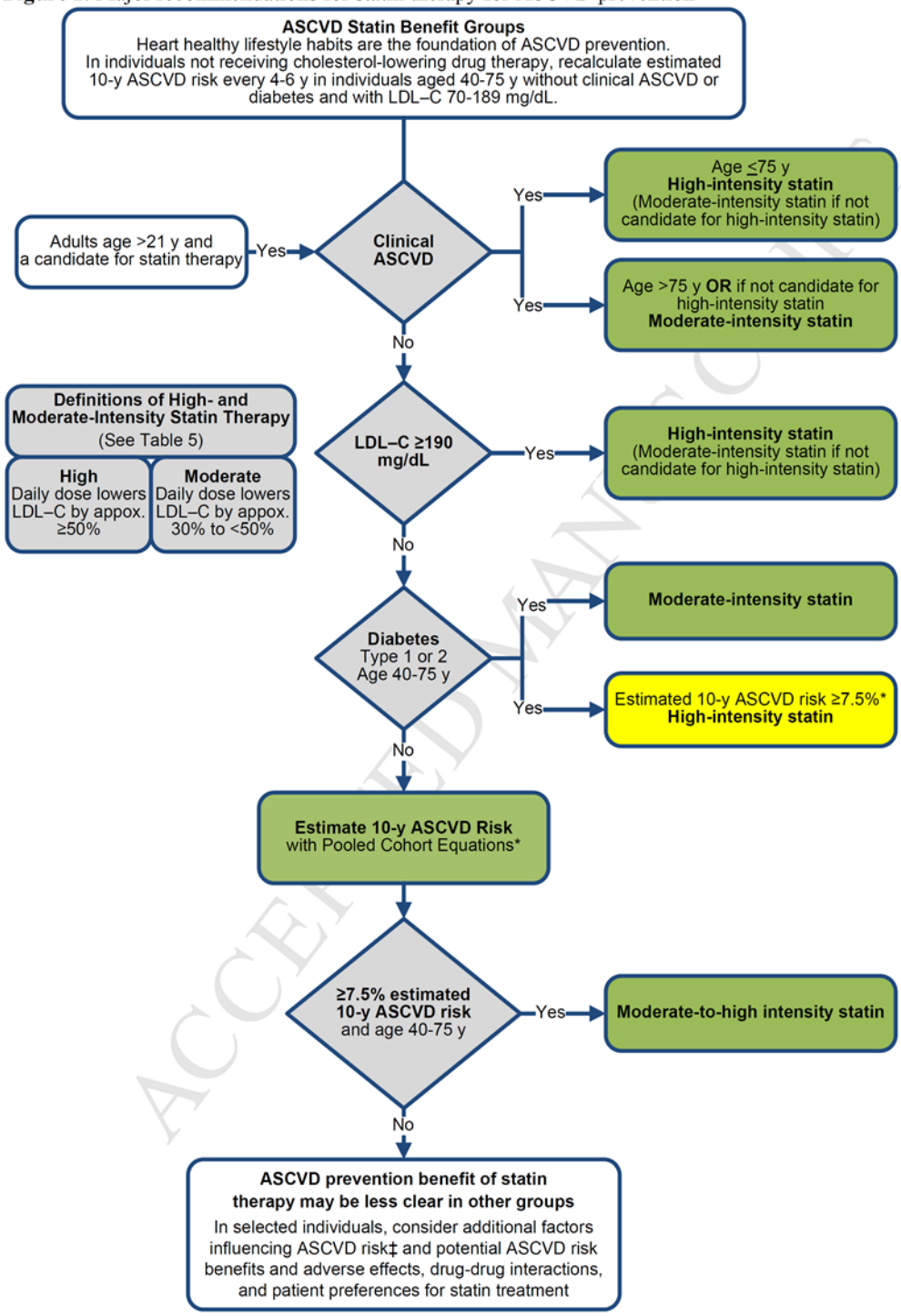


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Table 4. Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults—Statin Treatment
(High-, moderate-, and low-statin intensities are defined in Table 5)

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Treatment Targets				
1. The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)	1-4	N/A	N/A
Secondary Prevention				
1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD**, unless contraindicated.	A (Strong)	1, 6-8, 10-23, 26-28	I	A
2. In individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1).	A (Strong)	13-22, 24, 27, 28	I	A
3. In individuals with *clinical* ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	E (Expert Opinion)	---	IIa	B (16,20-43)
Primary Prevention in Individuals ≥21 Years of Age With LDL–C ≥190 mg/dL				
1. Individuals with LDL–C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia (Table 6).	B (Moderate)	75	I‡	B (44,45)
2. Adults ≥21 years of age with primary LDL–C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): • Use high-intensity statin therapy unless contraindicated. • For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.	B (Moderate)	6, 19, 28, 33-35, 37, 38	I§	B

3. For individuals ≥21 years of age with an untreated primary LDL–C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL–C reduction.	E (Expert Opinion)	---	IIa	B (20,46-50)
4. For individuals ≥21 years of age with an untreated primary LDL–C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL–C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences.	E (Expert Opinion)	---	IIb	C (51)
Primary Prevention in Individuals With Diabetes Mellitus and LDL–C 70-189 mg/dL				
1. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.	A (Strong)	19, 29-34, 40	I	A
2. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk‖ unless contraindicated.	E (Expert Opinion)	---	IIa	B (49,52)
3. In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.	E (Expert Opinion)	---	IIa	C (53-62)
Primary Prevention in Individuals Without Diabetes Mellitus and With LDL–C 70 to 189 mg/dL				
1. The Pooled Cohort Equations should be used to estimate 10-year ASCVD‖ risk for individuals with LDL–C 70 to 189 mg/dL without *clinical ASCVD** to guide initiation of statin therapy for the primary prevention of ASCVD.	E (Expert Opinion)	---	I	B (11)
2. Adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without *clinical* ASCVD* or diabetes and an estimated 10-year ASCVD‖ risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.	A (Strong)	28, 34-36, 38, 42-44, 47, 49-56, 76	I	A
3. It is reasonable to offer treatment with a moderate-intensity statin to adults 40 to 75 years of age, with LDL–C 70 to 189 mg/dL, without *clinical* ASCVD* or diabetes and an estimated 10-year ASCVD‖ risk of 5% to <7.5%.	C (Weak)	28, 34-36, 38, 42-44, 47, 49-56, 76	IIa	B
4. Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL–C 70-189 mg/dL without *clinical* ASCVD* or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment.	E (Expert Opinion)	---	IIa	C (63)
5. In adults with LDL–C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional	E (Expert Opinion)	---	IIb	C (11,13)

factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences.				
Heart Failure and Hemodialysis				
1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No Recommendation)	71, 72	---	---

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
† Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information (64-70).
‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. Triglycerides >500 mg/dL were an exclusion criteria for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.
§No RCTs included only individuals with LDL–C ≥190 mg/dL. However, many trials did include individuals with LDL–C ≥190 mg/dL and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the CTT meta-analyses have shown that each 39 mg/dL reduction in LDL–C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL–C levels. Therefore, individuals with primary LDL–C ≥190 mg/dL should be treated with statin therapy.
‖Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.
¶These factors may include primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years in a first degree male relative or <65 years in a first degree female relative, high sensitivity-C-reactive protein >2 mg/L, CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

ALT indicates alanine transaminase; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; CAC, coronary artery calcium; CK, creatine kinase; COR, Class of Recommendation; HDL–C, high-density lipoprotein cholesterol; LDL–C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; TIA, transient ischemic attack; ULN, upper limit of normal; and ---, not applicable.

Lifestyle

Lifestyle modification (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies. Healthy diet or lifestyle modifications were recommended as background therapy for the RCTs of cholesterol-lowering drug therapy. See the 2013 Lifestyle Management Work Group Guideline (10) for lifestyle recommendations for healthy adults.

Recommendations: specific population:

Elderly

Fewer people >75 years of age were included in the statin RCTs reviewed. RCT evidence does support the *continuation* of statins beyond 75 years of age in persons who are already taking and tolerating these drugs.

A larger amount of data supports the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD >75 years of age. However, the few data available did not clearly support *initiation* of high-intensity statin therapy *for secondary prevention* in individuals >75 years.

Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD. Therefore, *initiation of statins for primary prevention* of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. The Pooled Cohort Equations can also provide information on expected 10-year ASCVD risk for those 76 to 79 years of aged that may inform the treatment decision. These factors may influence decisions about cholesterol-lowering drug therapy, especially in the primary prevention setting. Accordingly, a discussion of the potential ASCVD risk reduction benefits, risk of adverse effects, drug-drug interaction, and patient preferences precede the initiation of statin therapy for primary prevention in older individuals.

Diabetes:

See previously: table 4

Recommendations: adverse events:

Statin safety recommendations

To maximize the safety of statins, selection of the appropriate statin and dose in men andnonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present.
Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
· Multiple or serious comorbidities, including impaired renal or hepatic function.
· History of previous statin intolerance or muscle disorders.
· Unexplained ALT elevations >3 times ULN.
· Patient characteristics or concomitant use of drugs affecting statin metabolism.
· >75 years of age.
Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
· History of hemorrhagic stroke.
· Asian ancestry.
(Grade A)

CK should not be routinely measured in individuals receiving statin therapy.
(Grade A)
Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy.
(Grade E)
During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.
(Grade E)

Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy.
(Grade B)

During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, darkcolored urine or yellowing of the skin or sclera).
(Grade E)

Decreasing the statin dose may be considered when 2 consecutive values of LDL–C levels are <40 mg/dL.
(Grade C)

It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
(Grade B)

Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines (93). Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.
(Grade B)

For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug.
(Grade E)

It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:
· To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.
· If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.
· If mild to moderate muscle symptoms develop during statin therapy:
– Discontinue the statin until the symptoms can be evaluated.
– Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases.)
– If muscle symptoms resolve, and if nocontraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
– If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
– Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.
– If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original

dose.
(Grade E)

For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy
(Grade E)

Nonstatin safety recommendations

Ezetimibe:
It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations >3 times ULN occur.
(Grade C)

Fibrates:
Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.
(Grade B)
Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effects.
(Grade E)
Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.
• Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m2, is present.
• If eGFR is between 30 and 59 mL/min per 1.73 m2, the dose of fenofibrate should not exceed 54 mg/day.
• If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m2, fenofibrate should be discontinued.
(Grade B)

Recommendations: monitoring:

Monitoring statin therapy

Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. Other safety measurements should be measured as clinically indicated.
(Grade A)

Optimizing statin therapy:

The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated.
(Grade B)

Insufficient respons to statin therapy

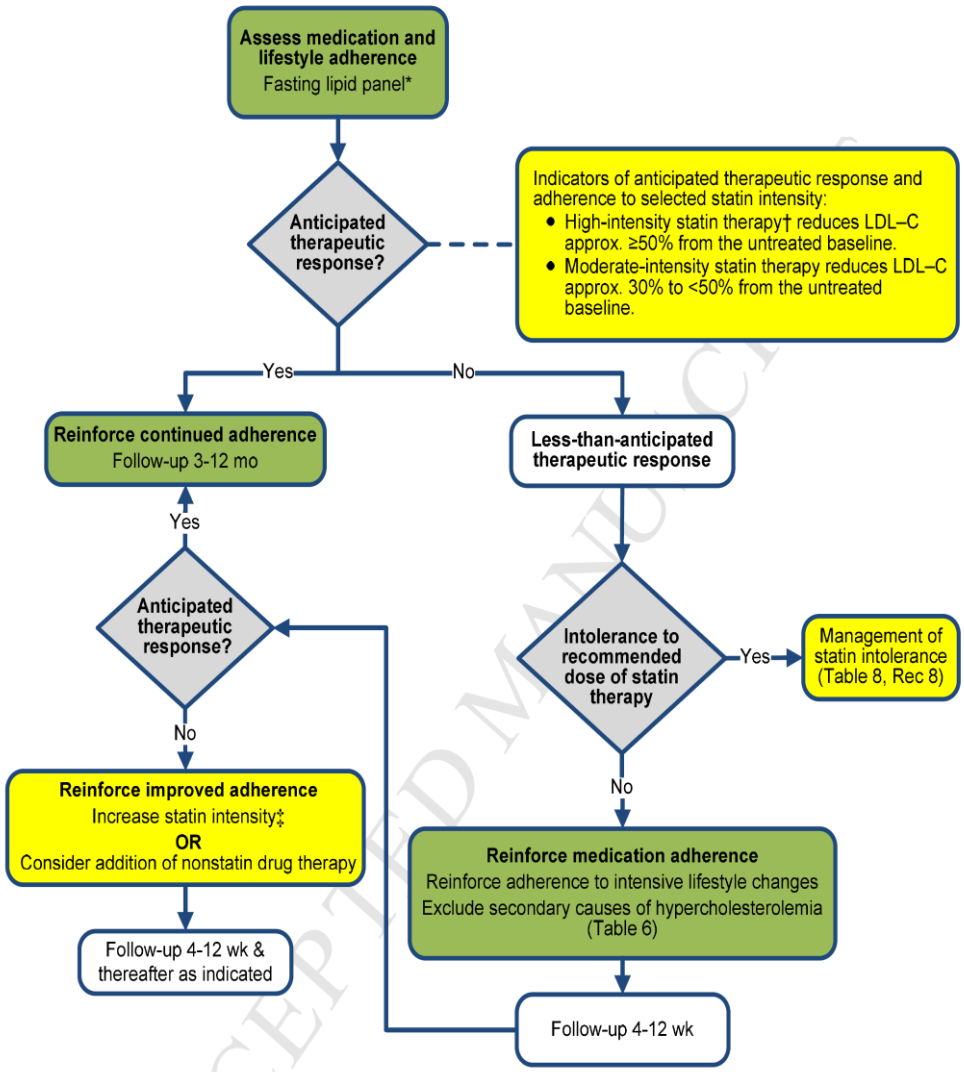
In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:
· Reinforce medication adherence.
· Reinforce adherence to intensive lifestyle changes.
· Exclude secondary causes of Hyperlipidemia
(Grade A)

It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
· High-intensity statin therapy† generally results in an average LDL–C reduction of ≥50% from the untreated baseline;
· Moderate-intensity statin therapy generally results in an average LDL–C reduction of 30 to <50% from the untreated baseline;
· LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.
(Grade E)

In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
Higher-risk individuals include:
· Individuals with clinical ASCVD‡ <75 years of age.
· Individuals with baseline LDL–C ≥190 mg/dL.
· Individuals 40 to 75 years of age with diabetes mellitus.
Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.
(Grade E)

In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
(Grade E)

Figure 5. Statin Therapy: Monitoring therapeutic response and adherence



Colors correspond to the class of recommendations in the ACC/AHA Table 1.
*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.
†In those already on a statin, in whom baseline LDL–C is unknown, an LDL–C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
‡See Section 6.3.1

3.3.2 Cardiovascular prevention

3.3.2.1 ESC 2012

Grades of recommendation:

1. **Class I:** evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
2. **Class II:** conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
   a. weight of evidence/opinion is in favor of usefulness/efficacy.
   b. usefulness/efficacy is less well established by evidence/opinion.
3. **Class III:** evidence and/or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Levels of evidence:

1) **Level A:** Data derived from multiple randomized clinical trials or meta-analyses.
2) **Level B:** Data derived from a single randomized clinical trial or large non-randomized studies.
3) **Level C:** Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Included populations, interventions, outcomes:

- Apparently healthy people
- Lifestyle modification and drug therapy (statins, non-statin treatment, combination)
- Lipid profile, level of LDL-C, HDL-C, triglycerides

Members of development group, target population:

- Cardiologists
- Primary care providers

Recommendations: screening:

Who?

In apparently healthy persons, CVD risk is most frequently the result of multiple interacting risk factors.
A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under- and overtreatment.
Certain individuals are at high CVD risk without needing risk scoring and require immediate intervention for all risk factors.
In younger persons, a low absolute risk may conceal a very high relative risk, and use of the relative risk chart or calculation of their 'risk age' may help in advising them of the need for intensive lifestyle efforts.
While women appear to be at lower CVD risk than men, this is misleading as risk is deferred by ca. 10 years rather than avoided.
All-risk estimation systems are relatively crude and require attention to qualifying statements.
Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org).
The total risk approach allows flexibility: if perfection cannot be achieved with one risk factor, risk can still be reduced by trying harder with others.

Recommendation:
Total risk estimation using multiple risk factors (such as SCORE) is recommended for asymptomatic adults without evidence of CVD.
(Class I, level C, strong recommendation)

High-risk individuals can be detected on the basis of established CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, or a high SCORE risk, and are a high priority for intensive advice about all risk factors.
(Class I, level C, strong recommendation)

How?

Note: The detailed SCORE charts with integrated HDL-cholesterol values can be found on http://www.escardio.org/guidelines-surveys/escguidelines/Pages/cvd-prevention.aspx in the related materials section. See also appendices.

To estimate a person's 10-year risk of CVD death, find the correct table for their gender, smoking status, and age. Within the table find the cell nearest to the person's BP and total cholesterol or cholesterol:HDL cholesterol ratio. Risk estimates will need to be adjusted upwards as the person approaches the next age category.

Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk. In general, those with a risk of CVD death of ≥5% qualify for intensive advice, and may benefit from drug treatment.

At risk levels > 10%, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are 'normal'.

The relative risk chart may be helpful in identifying and counseling in young persons, even if

absolute risk levels are low † The charts may be used to give some indication of the effects of reducing risk factors, given that there will be a time lag before risk reduces and the results of RCTs in general give better estimates of benefits. Those who stop smoking in general halve their risk.

The charts can assist in risk assessment and management but must be interpreted in the light of the clinician's knowledge and experience, especially with regard to local conditions.

Risk will be overestimated in countries with a falling CVD mortality, and underestimated in countries in which mortality is increasing.

At any given age, risk estimates are lower for women than for men. Inspection of the charts indicates that risk is merely deferred in women, with a 60-year-old woman resembling a 50-year-old man in terms of risk.

Recommendations: risk assessment:

It is suggested that total risk assessment be offered during a consultation if:
- The person asks for it.
- One or more risk factors such as smoking, overweight, or hyperlipidaemia are known.
- There is a family history of premature CVD or of major risk factors such as hyperlipidaemia.
- There are symptoms suggestive of CVD.

Special efforts should be made to assess risk in the socially deprived who are more likely to carry a heavy burden of risk factors.

4 risk categories:

1) Very high risk

Subjects with any of the following:
- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction, ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, peripheral artery disease (PAD).
- Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h).
- Severe chronic kidney disease (CKD) (GFR <30 mL/min/1.73 m2).
- A calculated SCORE ≥10%.

2) High risk

Subjects with any of the following:
- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage.
- Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m2).
- A calculated SCORE of ≥5% and <10% for 10-year risk of fatal CVD.

3) Moderate risk

Subjects are considered to be at moderate risk when their SCORE is ≥1 and <5% at 10 years. Many middle-aged subjects belong to this category. This risk is further modulated by factors mentioned above.

4) Low risk

The low-risk category applies to individuals with a SCORE <1% and free of qualifiers that would put them at moderate risk.

These risk categories are compatible with the joint European Atherosclerosis Society/ESC lipid guidelines. The joint guidelines offer further advice on lipid intervention based on these risk categories.

Recommendation: targets:

LDL cholesterol is recommended as the primary lipid analysis for screening and risk estimation as well as target for treatment.

HDL cholesterol is also a strong risk factor and is recommended to be used for risk estimation, but is not recommended as a target for treatment.

The recommended target levels are <5 mmol/L (less than ~190 mg/dL) for total plasma cholesterol and <3 mmol/L (less than ~115 mg/dL) for LDL cholesterol for subjects at low or moderate risk.
(Class I, level A)

In patients at high CVD risk, an LDL cholesterol goal <2.5 mmol/L (less than ~100 mg/dL) is recommended.
(Class I, level A)

In patients at very high CVD risk, the recommended LDL cholesterol target is <1.8 mmol/L (less than ~70 mg/dL) or a ≥50% LDL cholesterol reduction when the target level cannot be reached.
(Class I, level A)

Recommendations: treatment:

Intervention strategies:

Table 16 Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

Total CV risk (SCORE) %	LDL-C lvels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug	Lifestyle intervention, consider drug	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Reference table.[42]
CV = cardiovascular; LDL = low-density lipoprotein.
[a]Class of recommendation.
[b]Level of evidence.

In patients with an acute coronary syndrome, statin treatment in high doses has to be initiated while the patients are in hospital.
(Class I, level A)

Prevention of non-haemorrhagic stroke: treatment with statins must be started in all patients with established atherosclerotic disease and in patients at high risk for developing CVD. Treatment with statins must be started in patients with a history of non-cardioembolic ischaemic stroke.
(Class I, level A)

Occlusive arterial disease of the lower limbs and carotid artery disease are CHD risk-equivalent conditions and lipid-lowering therapy is recommended.
(Class I, level A)

Drug treatment:

Statin treatment
Statins, by decreasing LDL cholesterol, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. Statins at doses that effectively reduce LDL cholesterol by 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis. Therefore, they should be used as the drugs of first choice in patients with hypercholesterolaemia or combined hyperlipidaemia.

Non-statin treatment

Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL cholesterol concentrations.

Bile acid sequestrants also decrease total and LDL cholesterol but tend to increase triglyceride concentrations.

Fibrates and niacin are used primarily for triglyceride lowering and increasing HDL cholesterol, while *fish oils* (omega-3 fatty acids) in doses of 2–4 g/day are used for triglyceride lowering.

When triglycerides exceed 10 mmol/L (900 mg/dL), in order to prevent pancreatitis triglycerides must be reduced not only by drugs but also by restriction of alcohol, treatment of diabetes with insulin, withdrawal of oestrogen therapy, etc. In the rare patients with severe primary hypertriglyceridaemia, it is necessary to restrict absolutely the intake of alcohol and severely restrict long-chain fat of both animal and vegetable origin. Fibrates are the drugs of choice for these patients, and prescription omega-3 fatty acids might be added if elevated triglycerides are not decreased adequately.

Drug combinations

Patients with dyslipidaemia, particularly those with established CVD, diabetes, or asymptomatic high-risk individuals, may not always reach treatment targets. Therefore, combination treatment may be needed.

Combinations of a statin and a bile acid sequestrant or a *combination of a statin and ezetimibe* can be used for greater reduction of LDL cholesterol than can be achieved with either drug alone. Another advantage of combination therapy is that lower doses of statins can be used, thus diminishing the risk of adverse effects associated with high doses. However, statins should be used in the highest tolerable doses to reach the LDL cholesterol target level before combination therapy.

Combinations of niacin and a statin increase HDL cholesterol and decrease triglycerides better than either of these drugs alone, but flushing is the main adverse effect of niacin, which may affect compliance. Adding laropiprant to niacin might help in reducing the incidence of this adverse effect.

Fibrates, particularly fenofibrate, may be useful, not only for decreasing high triglyceride concentrations and increasing low HDL cholesterol, but can further lower LDL cholesterol when applied *together with a statin*.

If target levels cannot be reached even on maximal doses of lipid-lowering therapy or drug combinations, patients will still benefit from treatment to the extent to which dyslipidaemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.

Lifestyle

Established cognitive-behavioural strategies (e.g. motivational interviewing) to facilitate lifestyle change are recommended.
(Class I, level A)

In individuals at very high CVD risk, multimodal interventions, integrating education on healthy lifestyle and medical resources, exercise training, stress management, and counseling on psychosocial risk factors, are recommended.
(Class I, Level A)

All smokers should be given advice to quit and be offered assistance
(Class I, Level A)

A healthy diet is recommended as being the cornerstone of CVD prevention.
(Class I, Level)

• Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans-unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.
• <5 g of salt per day.
• 30–45 g of fibre per day, from wholegrain products, fruits, and vegetables.
• 200 g of fruit per day (2–3 servings).
• 200 g of vegetables per day (2–3 servings).
• Fish at least twice a week, one of which to be oily fish.
• Consumption of alcoholic beverages should be limited to two glasses per day (20 g/day of alcohol) for men and one glass per day (10 g/day of alcohol) for women.

Healthy adults of all ages should spend 2.5–5 h a week on physical activity or aerobic exercise training of at least moderate intensity, or 1–2.5 h a week on vigorous intense exercise. Sedentary subjects should be strongly encouraged to start light-intensity exercise programmes.
(Class I, Level A)

Physical activity/aerobic exercise training should be performed in multiple bouts each lasting ≥10 min and evenly spread throughout the week, i.e. on 4–5 days a week
(Class IIa, Level A)

Patients with previous acute myocardial infarction, CABG, PCI, stable angina pectoris, or stable chronic heart failure should undergo moderate-to-vigorous intensity aerobic exercise training ≥3 times a week and 30 min per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification.
(Class I, Level A)

Multimodal behavioural interventions, integrating health education, physical exercise, and psychological therapy for psychosocial risk factors and coping with illness, should be prescribed**.**
(Class I, Level A)

In the case of clinically significant symptoms of depression, anxiety, and hostility, psychotherapy, medication, or collaborative care should be considered. This approach can reduce mood symptoms and enhance health-related quality of life, although evidence for a definite beneficial effect on cardiac endpoints is inconclusive.

(Class IIa, Level A)

Weight reduction in overweight and obese people is recommended as this is associated with favourable effects on blood pressure and dyslipidaemia, which may lead to less CVD.
(Class I, Level A)

Elevated blood pressure (BP) is a major risk factor for CHD, heart failure, cerebrovascular disease, PAD, renal failure, and atrial fibrillation.
Individuals with an elevated BP more commonly have other risk factors for CVD (diabetes, insulin resistance, dyslipidaemia) and target organ damage. Because risk factors may interact, the overall risk of hypertensive patients is increased although the BP elevation is only mild or moderate.

All hypertensive patients with established cardiovascular disease, or with type 2 diabetes, or with an estimated 10-year risk of cardiovascular death ≥5% (based on the SCORE chart) should be considered for statin therapy.
(Class IIa, Level B)

Recommendations: specific subpopulations:

Elderly

Women and older people should be included in CVD risk assessments in the same way as other groups to determine need for specific treatments.
(Class I, level B)

Chronic kidney disease:

Recommendation:
In patients with chronic kidney disease, risk factors have to be attended to in the same way as for very high risk persons.
(Class I, level B)

Hypertension, dyslipidaemia, and diabetes mellitus are common among patients with CKD. They are major risk factors for the development and progression of endothelial dysfunction and atherosclerosis, and contribute to the progression of renal failure—yet these patients tend to be less intensely treated than patients with normal renal function. Inflammatory mediators and promoters of calcification are increased and inhibitors of calcification are reduced in CKD, which favours vascular calcification and vascular injury. Microalbuminuria increases cardiovascular risk two- to four-fold. A decreasing GFR is an indicator of increased risk for CVD and all-cause mortality. There is a quantitative association between decreased GFR and cardiovascular risk: patients with moderately decreased renal function (stage 3, GFR 30–59 mL/min/1.73 m2) have a two- to four-fold increased risk in comparison with persons free of CKD.
Lipid lowering appears useful in a wide range of patients with advanced CKD but with no known history of myocardial infarction or coronary revascularization: a reduction of low-density lipoprotein (LDL) cholesterol by 0.85 mmol/L (33 mg/dL) with daily 20 mg simvastatin plus 10 mg ezetimibe reduced the incidence of major events: non-fatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any arterial revascularization procedure.

Chronic kidney disease is characterized by mixed dyslipidaemia (high triglycerides, high LDL cholesterol, and low HDL cholesterol). Microalbuminuria is a risk factor for CVD, which rises progressively from a normal GFR to end-stage renal disease. CKD (stages 2–5, i.e. GFR ,90

mL/min/1.73 m2) is acknowledged as a CHD risk-equivalent, and the LDL cholesterol target in these patients has been adapted to the degree of renal failure (see page 1653).The statin dose should be modified according to GFR. Statin therapy has a beneficial effect on CVD outcomes in CKD stages 2 and 3 and slows the rate of kidney function loss.

CHD risk-equivalent and the LDL cholesterol target in these patients should be adapted to the degree of renal failure.**(Class IIa, level C)**

Diabetes mellitus type 2:

The target HbA1c for the prevention of CVD in diabetes of <7.0% (<53 mmol/mol) is recommended.
(Class I, level A)

Statins are recommended to reduce cardiovascular risk in diabetes.
(Class I, level A)

Hypoglycaemia and excessive weight gain must be avoided and individual approaches (both targets and drug choices) may be necessary in patients with complex disease.
(Class I, level B)

Metformin should be used as first-line therapy if tolerated and not contraindicated.
(Class IIa, level B)

Further reductions in HbA1c to a target of <6.5% (<48 mmol/mol) (the lowest possible safely reached HbA1c) may be useful at diagnosis. For patients with a long duration of diabetes this target may reduce risk of microvascular outcomes.
(Class IIb, level B)

BP targets in diabetes are recommend to be <140/80 mmHg.
(Class I, level A)

Target LDL cholesterol is <2.5 mmol/L, for patients without atherosclerotic disease total cholesterol may be <4.5 mmol/L, with a lower LDL cholesterol target of <1.8 mmol/L (using higher doses of statins) for diabetic patients at very high CVD risk.
(Class IIb, level B)

Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease.
(Class III, level A)

Recommendations: adverse effects, monitoring:

Statins

Higher activity of liver enzymes in plasma occurs occasionally, and in most cases is reversible: 5–10% of patients receiving statins develop myopathy, but rhabdomyolysis is extremely rare. The risk of myopathy can be minimized by identifying vulnerable patients and/or by avoiding statin interactions with specific drugs. Because statins are prescribed on a long-term basis, possible

interactions with other drugs deserve particular and continuous attention, as many patients will receive pharmacological therapy for concomitant conditions. In general, the safety profile of statins is acceptable, and earlier observations that lipid-lowering treatment may contribute an increase in non-cardiovascular mortality (e.g. cancers, suicides, depression) or mental disorders have not been confirmed. There are reports indicating increased blood sugar and HbA1c levels, i.e. increased risk of type 2 diabetes, as a possible adverse effect of long-term statin therapy, but the benefits of statins far outweigh the risks for the vast majority of patients.

Fibrates plus statin

Other drugs metabolized through cytochrome P450 should be avoided when this combination is prescribed. Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations and decrease the risk of myopathy. Patients have to be instructed about warning symptoms (myalgia) even though these adverse effects are very rare.

Recommendations: adherence, programmes:

Physicians must assess adherence to medication, and identify reasons for nonadherence in order to tailor further interventions to the individual needs of the patient or person at risk.
(Class I, Level A)

In clinical practice, reducing dosage demands to the lowest acceptable level is recommended. In addition, repetitive monitoring and feedback should be implemented. If feasible, multisession or combined behavioural interventions should be offered in the case of persistent non-adherence.
(Class IIa, Level A)

Table 19 Recommendations for promoting medication adherence

• Provide clear advice regarding the benefits and possible adverse effects of the medication, and the duration and timing of dosing.
• Consider patients' habits and preferences.
• Reduce dosage demands to the lowest feasible level.
• Ask patients in a non-judgemental way how the medication works for them, and discuss possible reasons for non-adherence (e.g. side effects, worries).
• Implement repetitive monitoring and feedback.
• In the case of lack of time, introduce physicians assistants and/or trained nurses whenever its necessary and feasible.
• In the case of persistent non-adherence, offer multisession or combined behavioural interventions.

Actions to prevent cardiovascular disease should be incorporated into everyone's daily lives, starting in early childhood and continuing throughout adulthood and senescence.
(Class IIa, Level B)

Nurse-co-ordinated prevention programmes should be well integrated into healthcare systems.
(Class IIa, Level B)

Patients with cardiac disease may participate in self-help programmes to increase or maintain awareness of the need for risk factor management, for maintaining physical fitness, or for diligent self-management of oral anticoagulation.
(Class IIa, Level B)

All patients with cardiovascular disease must be discharged from hospital with clear guideline orientated treatment recommendations to minimize adverse events.
(Class I, Level B)

All patients requiring hospitalization or invasive intervention after an acute ischaemic event should participate in a cardiac rehabilitation programme to improve prognosis by modifying lifestyle habits and increasing treatment adherence.
(Class IIa, Level B)

3.3.2.2 NICE 2010

NICE 2010 offers guidelines on the *population-based* prevention of cardiovascular disease for public health policy and the development of a national framework of action.

Levels of evidence:

Included papers were assessed for methodological rigour and quality using the NICE methodology checklist, as set out in the NICE technical manual 'Methods for the development of NICE public health guidance'. Each study was graded (++, +, –) to reflect the risk of potential bias arising from its design and execution.

Study quality

++: All or most of the checklist criteria have been fulfilled. Where they have not been fulfilled, the conclusions are very unlikely to alter.

+: Some of the checklist criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are unlikely to alter the conclusions.

–: Few or no checklist criteria have been fulfilled. The conclusions of the study are likely or very likely to alter.

Grades of recommendation:

Interventions that must be used: when the recommendation links to enforceable legislation (such as health and safety regulations). It can also be used if the committee believes there will be serious repercussions if the recommendation is not followed.

Interventions that should be used: the intervention will do more good than harm and is likely to be cost effective.

Interventions that could be used: the intervention is effective and/or cost effective, but other options may be similarly effective and/or cost effective. Or the choice of intervention (or the decision whether to have one at all) is likely to vary depending on the client's values and preferences.

Interventions that should not be used: a particular action should not be carried out or should be stopped (because it is ineffective or not cost effective, or harmful).

Included populations, interventions, outcomes:

- Entire population
- Lifestyle modification (smoking cessation, diet, exercise, weight reduction,…)
- Cardiovascular risk

Members of development group, target population:

- The development group is multidisciplinary, comprising public health practitioners, clinicians (both specialists and generalists), local authority officers, teachers, social care professionals, representatives of the public, patients, carers, academics and technical experts.
- The guidance is for *government, the NHS, local authorities, industry and all those whose actions influence the population's cardiovascular health* .

Recommendations: risk assessment:

CVD risk factors:
Lifetime risk of CVD is strongly influenced by diet and physical activity levels since childhood (National Heart Forum 2003). The risk among adults is determined by a variety of 'upstream' factors (such as food production and availability, access to a safe environment that encourages physical activity and access to education). It is also influenced by 'downstream' behavioural issues (such as diet and smoking).

Potentially modifiable risk factors:

- smoking/tobacco use
- poor diet
- high blood cholesterol
- high blood pressure
- insufficient physical activity
- overweight/obesity
- diabetes
- psychosocial stress (linked to people's ability to influence the potentially stressful environments in which they live)
- excess alcohol consumption

Many of the risk factors that the guideline developers considered are also associated with other health-related conditions including some common cancers, chronic respiratory disease, obesity, diabetes, kidney disease and mental wellbeing.
The strategies discussed in this guidance are likely to help prevent some of these other health conditions. (Certainly, they are not likely to increase the risk of any common chronic diseases.) However, it was not possible to consider each of these other health conditions in detail.

Recommendations: lifestyle:

Salt: Accelerate the reduction in salt intake among the population. Aim for a maximum intake of 6 g per day per adult by 2015 and 3 g by 2025.

Satured fats: Reducing general consumption of saturated fat is crucial to preventing CVD. Reduce population intake of saturated fat from 13.3% to below 11% of food energy.

Trans fats: Ensure all groups in the population are protected from the harmful effects of IPTFAs. Industrially-produced trans fatty acids (IPTFAs)

Ensure all food procured by, and provided for, people working in the public sector and all food provided for people who use public services: is low in salt and saturated fats is nutritionally balanced and varied, in line with recommendations made in the 'eatwell plate' does not contain industrially produced trans fatty acids (IPTFAs).

Promote physical activity.

3.3.2.3 ACC AHA 2013 (cvr)

Grades of recommendation:

Grades of recommendation (see tables 2 and 3 in original document):

1) **Grade A:** strong recommendation: there is high certainty based on evidence that the net benefit is substantial.

2**) Grade B**: moderate recommendation: there is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is a high certainty that the net benefit is moderate.

3) **Grade C**: weak recommendation: there is at least moderate certainty based on evidence that there is a small net benefit.

4**) Grade D**: recommendation against: there is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.

5**) Grade E**: Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.

6**) Grade N**: No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no

evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

Levels of evidence:

1) **High**:

Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. MAs of such studies.

Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect

2) **Moderate**:

RCTs with minor limitations affecting confidence in, or applicability of, the results. Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. MAs of such studies.

Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate

3) **Low**:

RCTs with major limitations. Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). Physiological studies in humans. MAs of such studies.

Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate

Included patients, interventions, outcomes:

- Non-Hispanic African-American and non-Hispanic White men and women from 40 to 79 years of age.

Members of development group, target population:

- Internists, cardiologists, endocrinologists, experts in CV epidemiology, biostatistics, healthcare management and economics and guideline development
- Adult population without clinical signs or symptoms of ASCVD, who merit evaluation for the primary prevention of ASCVD (atherosclerotic cardiovascular disease).

Recommendations:

Recommendations for Assessment of 10-Year Risk for a First Hard ASCVD Event

The race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD* event should be used in nonHispanic African Americans and nonHispanic Whites, 40 to 79 years of age.
(Grade B)

Use of the sex-specific Pooled Cohort Equations for nonHispanic Whites may be considered when estimating risk in patients from populations other than African Americans and nonHispanic Whites.
(Grade E)

Rem: a downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/scienceand-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.
Rem: *Ten-year risk was defined as the risk of developing a first ASCVD event, defined as nonfatal myocardial infarction or CHD death, or fatal or nonfatal stroke, over a 10-year period among people free from ASCVD at the beginning of the period.

Recommendations for CQ1: Use of Newer Risk Markers After Quantitative Risk Assessment

If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.
(Grade E)

CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.
(Grade N)

The contribution to risk assessment for a first ASCVD event using ApoB, chronic kidney disease, albuminuria, or cardiorespiratory fitness is uncertain at present.
(Grade N)

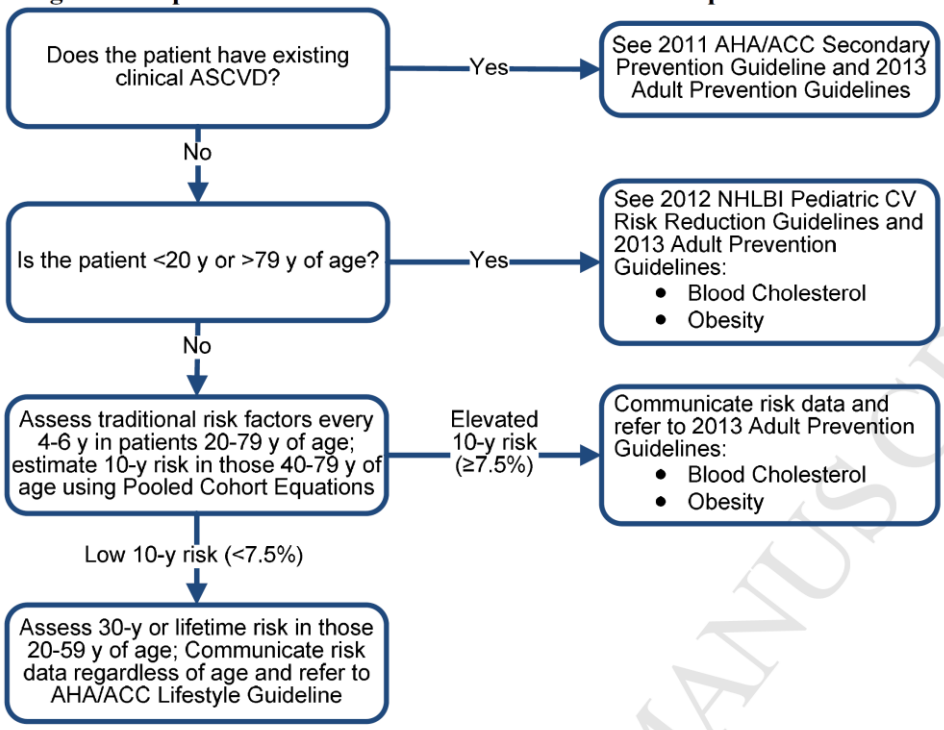
Recommendations for CQ2: Long-Term Risk Assessment

It is reasonable to assess traditional ASCVD risk factors every 4 to 6 years in adults 20 to 79 year of age who are free from ASCVD and estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age who are free from ASCVD.
(Grade B)

Assessing 30-year or lifetime ASCVD risk based on traditional risk factors† may be considered in adults 20 to 59 years of age who are free from ASCVD and who are not at high short-term risk.
(Grade C)

Rem: traditional risk factors: age, sex, total and HDL–cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking

Figure 1. Implementation of Risk Assessment Work Group Recommendations



ACC indicates American College of Cardiology; AHA, American Heart Association; and ASCVD, atherosclerotic cardiovascular disease.

3.3.2.4 Domus Medica 2007

This guideline does not fulfill inclusion criteria (>5y), but is added and discussed here because it is the only full Belgian guideline and differs in some areas from the other guidelines that are discussed here.

Grades of recommendation/ Levels of evidence (niveaus van bewijskracht):

Niveau 1

Voor niveau 1 is de voorwaarde dat er ten minste twee onafhankelijk van elkaar uitgevoerde onderzoeken met gelijklopende resultaten bestaan die behoren tot één van de volgende types:
een RCT van goede kwaliteit, een onafhankelijk blinde vergelijking van een diagnostische test met de referentietest van goede kwaliteit (dit wil zeggen bij een doelgroep van opeenvolgende patiënten die zowel de diagnostische als de referentietest hebben ondergaan), een prospectief cohortonderzoek van goede kwaliteit met een follow-up van 80% of meer.
Voor dit niveau van bewijskracht is een systematische review of een meta-analyse van dit soort artikels met een hoge consistentiegraad tevens voldoende.
Als besluit van dergelijke studies stellen we 'dat het aangetoond is dat ...'

Niveau 2

Voor niveau 2 is de voorwaarde dat er ten minste twee onafhankelijk van elkaar uitgevoerde onderzoeken met gelijklopende resultaten bestaan die behoren tot één van de volgende types:
een RCT van matige kwaliteit, een onafhankelijk blinde vergelijking van een diagnostische test met de referentietest van matige kwaliteit (dit wil zeggen bij een beperkt deel van de doelgroep of wanneer de referentietest niet bij iedereen werd uitgevoerd), een (retrospectief) cohortonderzoek van matige kwaliteit of patiëntcontroleonderzoek.
Voor dit niveau van bewijskracht is een systematische review of meta-analyse van dit soort artikels met een hoge consistentiegraad voldoende. Indien er één onderzoek van de onder niveau 1 vermelde types beschikbaar is, spreken we van niveau 2.
Als besluit van dergelijke studie stellen we 'dat het aannemelijk is dat ...'

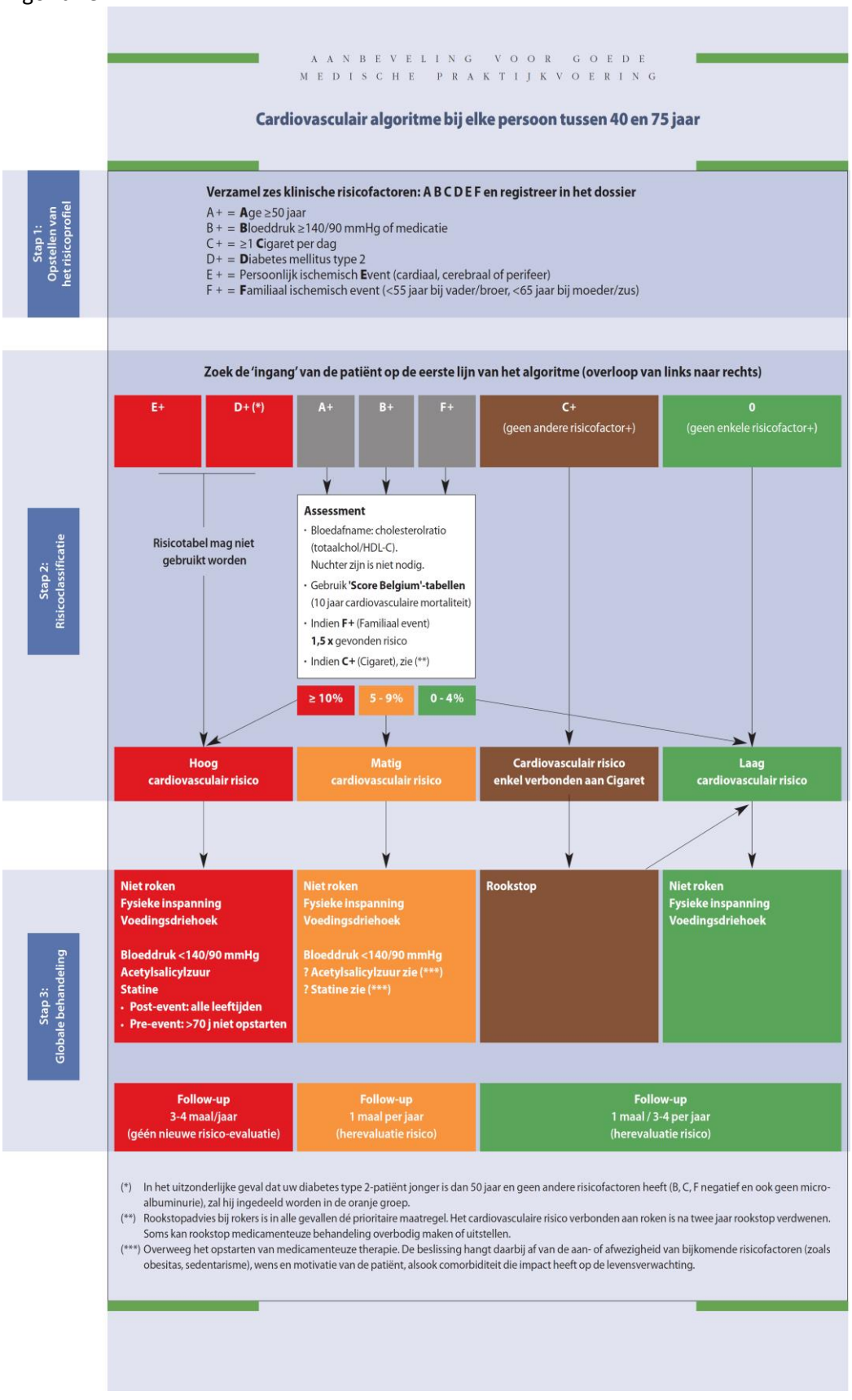
Niveau 3

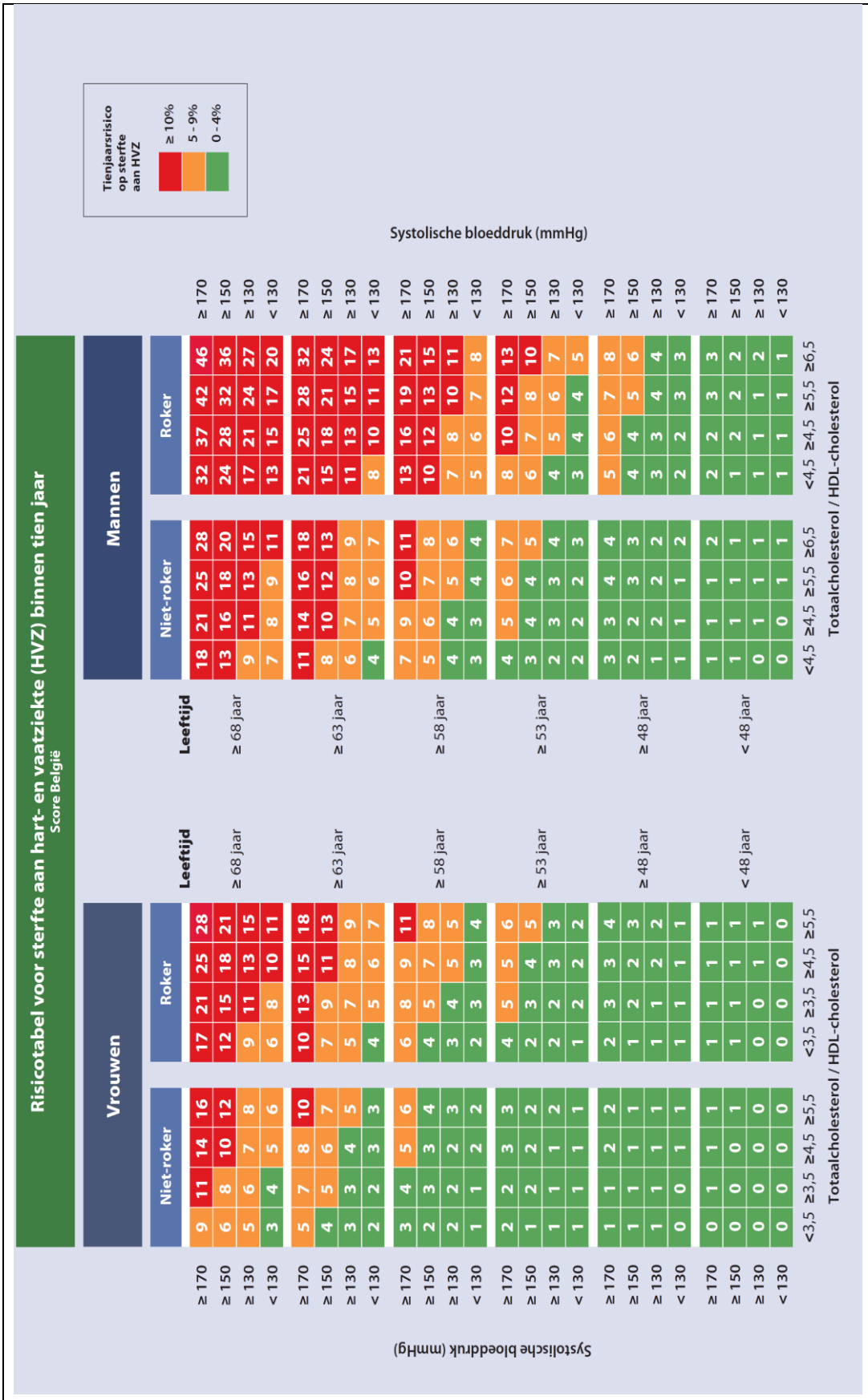
Ontbreekt er vergelijkend onderzoek van goede kwaliteit, dan spreken we van het derde niveau van bewijskracht:
er zijn geen RCT's van goede kwaliteit, er bestaat slechts één onderzoek van matige kwaliteit en er zijn geen meta-analyses van onderzoeken met matige kwaliteit voorhanden, de uitkomsten van RCT's of meta-analyses zijn tegenstrijdig.
Tot dit niveau behoren ook de consistente mening van ten minste twee deskundigen, een aanbeveling of conclusie bekomen na het bekijken van alle beschikbaar materiaal en een consensus binnen de auteursgroep.
In al deze gevallen spreken we enkel van 'een aanwijzing dat ...'of 'dat de werkgroep van mening is dat ...'

Included populations, interventions, outcomes:

- Interventions: dietary interventions, statins in primary prevention

Algoritme:


AANBEVELING VOOR GOEDE MEDISCHE PRAKTIJKVOERING
Cardiovasculair algoritme bij elke persoon tussen 40 en 75 jaar
Stap 1: Opstellen van het risicoprofiel
Verzamel zes klinische risicofactoren: A B C D E F en registreer in het dossier
A + = Age ≥50 jaar
B + = Bloeddruk ≥140/90 mmHg of medicatie
C + = ≥1 Cigaret per dag
D + = Diabetes mellitus type 2
E + = Persoonlijk ischemisch Event (cardiaal, cerebraal of perifeer)
F + = Familiaal ischemisch event (<55 jaar bij vader/broer, <65 jaar bij moeder/zus)
Stap 2: Risicoclassificatie
Zoek de 'ingang' van de patiënt op de eerste lijn van het algoritme (overloop van links naar rechts)
E+
D+ (*)
A+
B+
F+
C+ (geen andere risicofactor+)
0 (geen enkele risicofactor+)
Risicotabel mag niet gebruikt worden
Assessment
• Bloedafname: cholesterolratio (totaalchol/HDL-C). Nuchter zijn is niet nodig.
• Gebruik 'Score Belgium'-tabellen (10 jaar cardiovasculaire mortaliteit)
• Indien F+ (Familiaal event) 1,5 x gevonden risico
• Indien C+ (Cigaret), zie (**)
≥ 10%
5 - 9%
0 - 4%
Hoog cardiovasculair risico
Matig cardiovasculair risico
Cardiovasculair risico enkel verbonden aan Cigaret
Laag cardiovasculair risico
Stap 3: Globale behandeling
Niet roken
Fysieke inspanning
Voedingsdriehoek
Bloeddruk <140/90 mmHg
Acetylsalicylzuur
Statine
• Post-event: alle leeftijden
• Pre-event: >70 j niet opstarten
Niet roken
Fysieke inspanning
Voedingsdriehoek
Bloeddruk <140/90 mmHg
? Acetylsalicylzuur zie (***)
? Statine zie (***)
Rookstop
Niet roken
Fysieke inspanning
Voedingsdriehoek
Follow-up 3-4 maal/jaar (géén nieuwe risico-evaluatie)
Follow-up 1 maal per jaar (herevaluatie risico)
Follow-up 1 maal / 3-4 per jaar (herevaluatie risico)
(*) In het uitzonderlijke geval dat uw diabetes type 2-patiënt jonger is dan 50 jaar en geen andere risicofactoren heeft (B, C, F negatief en ook geen micro-albuminurie), zal hij ingedeeld worden in de oranje groep.
(**) Rookstopadvies bij rokers is in alle gevallen dé prioritaire maatregel. Het cardiovasculaire risico verbonden aan roken is na twee jaar rookstop verdwenen. Soms kan rookstop medicamenteuze behandeling overbodig maken of uitstellen.
(***) Overweeg het opstarten van medicamenteuze therapie. De beslissing hangt daarbij af van de aan- of afwezigheid van bijkomende risicofactoren (zoals obesitas, sedentarisme), wens en motivatie van de patiënt, alsook comorbiditeit die impact heeft op de levensverwachting.



Recommendations:

Recommendation: Screening: bij alle patiënten tussen 40 en 75 jaar die de huisarts consulteren, zal bij gelegenheid het cardiovasculaire risicoprofiel opgesteld worden door het inventariseren van de risicofactoren.**(niveau 3)**

Recommendation: De risicobepaling kan gebeuren op basis van de Score-risicotabellen, aangepast aan de Belgische populatie **(niveau 2)**

Recommendation: De opsporing en risicoclassificatie kunnen ook gebeuren aan de hand van een nieuw stappenplan dat een combinatie is van een klinisch algoritme (Boland et al. 2004) met de Score Belgium-risicotabellen. Dit vergemakkelijkt de implementatie van een globaal cardiovasculair risicobeheer in de huisartsenpraktijk.**(niveau 2)**

- Eerste stap: screening van zes klinische risicofactoren (ABCDEF*) bij personen tussen 40 en 75 jaar **(niveau 2)**
- Tweede stap: risicoclassificatie
    - Patiënten met een persoonlijke cardiovasculaire voorgeschiedenis lopen een hoog risico op een nieuw incident (E+ in het algoritme).
    - Patiënten met diabetes mellitus type 2 met nog één bijkomende risicofactor (ouder dan 50 jaar, hoge bloeddruk, hart- en vaatziekten in voorgeschiedenis, familiale anamnese van hart- en vaatziekten én microalbuminurie) lopen eveneens een hoog risico op een eerste ischemisch incident (D+ in het algoritme).
    - Patiënten zonder risicofactoren (bij wie geen enkele van de bovengenoemde klinische risicofactoren aanwezig is) hebben een laag cardiovasculair risico, ook al zijn hun cholesterolwaarden niet gekend.
    - Rokers zonder andere risicofactoren (bij wie geen enkele van de bovengenoemde klinische risicofactoren aanwezig is) zullen een laag risico bereiken na één tot twee jaar rookstop.
    - Elk ander risicoprofiel is onbepaald en vereist een bloedafname met lipidenprofiel om tot een risicobepaling te komen met de Score Belgium-risicotabellen gebaseerd op de cholesterolratio (totaalcholesterol/HDL-cholesterol).
    - Het risico is hoog indien de kans op het doormaken van een fataal cardiovasculair incident binnen 10 jaar >= is aan 10%.
    - Het risico is matig indien de kans op het doormaken van een fataal cardiovasculair incident binnen 10 jaar tussen 5 en 9% ligt.
    - Het risico is laag indien de kans op het doormaken van een fataal cardiovasculair incident binnen 10 jaar tussen 0 en 4% ligt.
- Derde stap: risicoreductie door behandeling

De hoogte van het individuele absolute risico op hart- en vaatziekten bepaalt het te volgen beleid **(niveau 3).**

Recommendation: *Hoogrisicopatiënten* (incident in de voorgeschiedenis, diabetes type 2 of volgens Scoretabel >=10%) moeten intensief begeleid worden om een gezonde leefstijl aan te nemen **(niveau 3)**

- Niet roken **(niveau 2)**
- Regelmatige lichamelijke activiteit: **(niveau 2)**
    - minstens 5 keer per week matige fysieke activiteit gedurende 30 minuten,
    - personen die hiervoor te weinig tijd hebben, kunnen hun activiteit opbouwen via

meerdere korte oefensessies van 8 tot 10 minuten **(niveau 2)**
    - voor patiënten met een cardiovasculaire voorgeschiedenis wordt eerst het advies van een cardioloog gevraagd vooraleer ze met intensieve fysieke training starten **(niveau 3)**
    - fysieke oefening bij personen met coronair lijden moet beginnen aan lage intensiteit en geleidelijk toenemen, gespreid over verschillende weken **(niveau 3)**
- Gezonde gevarieerde voeding waarbij de voedingsdriehoek als voedingsvoorlichtingsmodel gebruikt kan worden **(niveau 3)**
- BMI <=25 kg/m behouden of 10% gewichtsverlies bij obesitas **(niveau 3)**

Recommendation: Elke *hoogrisicopatiënt* (incident in voorgeschiedenis, diabetes type 2 of volgens Scoretabel >=10%) moet volgende medicamenteuze behandeling krijgen:

- Acetylsalicylzuur : 75 mg tot 150 mg per dag (behalve indien tegenaangewezen) **(niveau 1)**
- Statine **(niveau 1)**
    - eerste keuze: simvastatine of pravastatine 40 mg **(niveau 3)**
    - streefwaarde totaalcholesterol <190 mg/dl en LDL-C<115 mg/dl **(niveau 3)**
- Indien ook hypertensie: strikte tensieregeling Bloeddruk <140/90 mmHg **(niveau 1):**
    - eerste stap: thiazidediureticum (chlortalidone 25 mg),
    - tweede stap: ACE-I, bètablokker (niet atenolol) of calciumantagonist.
- Indien diabetes: nog striktere tensieregeling bloeddruk<130/80 mmHg, bij microalbuminurie zeker mét ACE-I **(niveau 3)**
- Indien postinfarctpatiënten: bètalyticum (metoprolol 200 mg , propranolol 160 mg of timolol 20 mg), te overwegen ACEI (perindopril 8 mg of ramipril 10 mg).

Recommendation: Patiënten met een *matig* risico (Score 5-9%) worden begeleid om een gezonde leefstijl aan te nemen zoals de hoogrisicopatiënten **(niveau 3)**

Overweeg bij deze patiënten een medicamenteuze therapie als bijkomende risicofactoren zoals (abdominale) obesitas of sedentarisme aanwezig zijn. Houd rekening met de wens en de motivatie van de patiënt alsook met de comorbiditeit die een impact heeft op de levensverwachting.

- Acetylsalicylzuur **(niveau 3)**
- Statine (simvastatine of pravastatine 40 mg) **(niveau 2).**
- Normale bloeddruk (<140/ 90 mmHg), met behulp van medicatie indien nodig **(niveau 2)**

Een nieuwe risicobepaling bij deze patiënten is zinvol na 1 jaar **(niveau 3).**

Recommendation: Patiënten met een *laag* risico (Score 0-4%): een gezonde leefstijl wordt aanbevolen **(niveau 3).**
Bij deze patiënten is een nieuwe risicobepaling na 3 tot 4 jaar zinvol **(niveau 3).**

Recommendation: Om veranderingen in gedrag te kunnen bewerkstelligen en consolideren moet worden rekening gehouden met de motivatie van de patiënt om te veranderen ('stages of change'-model van Prochaska en Di Clemente). Om een patiënt te motiveren tot gedragsverandering is het 'motivationele interview' een goede manier **(niveau 3).**

Recommendation: Als therapie aangewezen is, wordt een individueel behandelplan opgesteld waarbij wordt rekening gehouden met bepaalde medische prioriteiten (rookstop, gezonde voeding, lichaamsbeweging, acetylsalicylzuur, statine) en de wens van de patiënt.
In vervolgconsulten wordt nagegaan of de streefdoelen worden bereikt en zo nodig wordt het beleid bijgestuurd **(niveau 3).**

3.3.3 Lifestyle Management

3.3.3.1 ACC AHA 2013 Lifestyle management

Grades of recommendation:

1) **Grade A**: strong recommendation: there is high certainty based on evidence that the net benefit is substantial.

2) **Grade B**: moderate recommendation: there is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is a high certainty that the net benefit is moderate.

3) **Grade C**: weak recommendation: there is at least moderate certainty based on evidence that there is a small net benefit.

4) **Grade D**: recommendation against: there is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.

5) **Grade E**: Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.

6) **Grade N**: No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting."): Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

Levels of evidence:

1) **High**:

Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. MAs of such studies.

Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect

2) **Moderate:**

RCTs with minor limitations affecting confidence in, or applicability of, the results. Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. MAs of such studies.

Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate

3) **Low:**

RCTs with major limitations. Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). Physiological studies in humans. MAs of such studies.

Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate

Included populations, interventions, outcomes:

- Populations: adults ≥18 years of age and <80 years of age.
- Interventions: particular dietary patterns, nutrient intake, and levels and types of physical activity
- Outcomes: CVD prevention and treatment through effects on modifiable CVD risk factors (i.e., blood pressure [BP] and lipids).

Members of development group, target population:

- Physicians and experts in BP, blood cholesterol, obesity, and lifestyle management; from primary care, nursing, pharmacology, nutrition, exercise, behavioral science, and epidemiology disciplines and senior scientific staff from NHLBI and the National Institutes of

Health.
- adults (≥18 years) with or without established coronary heart disease (CHD)/CVD, with or without CHD/CVD risk factors, and who were of normal weight, overweight, or obese.

Recommendations: Dietary Patterns and Macronutrients: BP and Lipids

Advise adults who would benefit from LDL–C lowering to:
• Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats.
o Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).
o Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.
(Grade: A)

Advise adults who would benefit from LDL–C lowering to:
• Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat.
(Grade A)

Advise adults who would benefit from LDL–C lowering to:
• Reduce percent of calories from saturated fat.
(Grade A)

Advise adults who would benefit from LDL–C lowering to:
• Reduce percent of calories from trans fat.
(Grade A)

Recommendations: Sodium and Potassium: BP and CVD Outcomes

Advise adults who would benefit from BP lowering to:
a. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats.
i. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).
ii. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.
(Grade A)

Advise adults who would benefit from BP lowering to:
a. Lower sodium intake
(Grade A)

Advise adults who would benefit from BP lowering to:
a. Consume no more than 2,400 mg/day of sodium;
b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with an even greater reduction in BP; and
c. Reduce sodium intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not yet achieved.
(Grade B)

Advise adults who would benefit from BP lowering to:
a. Combine the DASH dietary pattern with lower sodium intake.
(Grade A)

Recommendations: Physical Activity: Lipids and BP

In general, advise adults to engage in aerobic physical activity to reduce LDL–C and non-HDL–C: 3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity.
(Grade B)

In general, advise adults to engage in aerobic physical activity to lower BP: 3 to 4 sessions a week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity.
(Grade B)

3.4 Conclusions from guidelines

See Dutch and French summary reports for more details.

3.4.1 Assessment of cardiovascular risk and treatment

To assess the cardiovascular risk, each guidelines chooses a specific system, often adapted to te risk of the local population. We have for example SCORE in Europe (ESC 2011 and 2012), Framingham-based risk scores in English-speaking regions, and a new model proposed by thet ACC AHA 2013.

3.4.2 Pharmacological treatment

Statins are the first choice in all guidelines. Other lipid-lowering drus in monotherapy have a very limited place. Combination therapy is considered an option by most guidelines, but it is acknowledged that the evidence is limited.

3.4.3 Monitoring of adverse events

The guidelines are almost unanimous about the checking of liver enzymes before starting statin treatment, but they differ in the extent of follow up of these values.
Most guidelines recommend CK measurements before starting statin treatment only when there are risk factors for myopathy.

3.4.4 Elderly

Age is a non-modifiable risk factor for cardiovascular disease.
There is little data from studies in the elderly (>75 or >80years). According to the guidelines, elderly patients with an existing cardiovascular disease will benefit from statin therapy. In primary prevention, this is less certain. The advice is to consider all patient-related factors and to use one's clinical judgement.

3.4.5 Chronic renal insufficiency

Most guidelines mention chronic kidney disease as a risk factor for cardiovascular disease. Some guidelines automatically consider chronic kidney disease as 'high risk' for cardiovascular disease.

3.4.6 Type 2 diabetes

The cardiovascular risk of diabetics is considered high to very high. Targets for LDL-C or intensity of statin therapy depend on additional risk factors.

3.4.7 Treatment targets and monitoring the lipid-lowering effect

Depending on the guideline, LDL-C targets are chosen (sometimes also TC and other secondary targets). Some recent guidelines focus more on intensity of statin therapy (with an expected % decrease of LDL-C).
Monitoring the lipid-lowering effect is generally recommended, but the frequency differs between guidelines.

3.4.8 Guidance of the patient

Each guidelines addresses the importance of lifestyle changes (nutrion, physical activity, smoking cessation). Communication with the patient and a fixed plan for follow-up and treatment are considered important.

4 Evidence tables and conclusions : Efficacy of statins

4.1 Statin versus placebo

4.1.1 CTT 2012 Individual patient data meta-analysis

4.1.1.1 Evidence tables

Statin versus control (22 trials) and statin high dose versus statin low dose (5 trials)

Meta-analysis of individual patient data

Inclusion criteria

- RCT
- Lipid modification therapy at least 1 treatment arm, no multiple interventions
- >= 2y scheduled duration
- Aim >= 1000 patients
- Results not known at time of protocol description (1995)

Search strategy "Potentially eligible studies are to be identified prospectively by a range of methods, including computer-aided literature searches, manual searches of journals, scrutiny of the reference lists of trials and review articles, scrutiny of abstracts and meeting proceedings, collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, and by inquiry among colleagues, collaborators, and manufacturers of lipid-modifying agents."

Note: no further information on the methods of the computer-aided literature search

Assessment of quality of included trials: no

ITT analysis: yes

Other methodological remarks

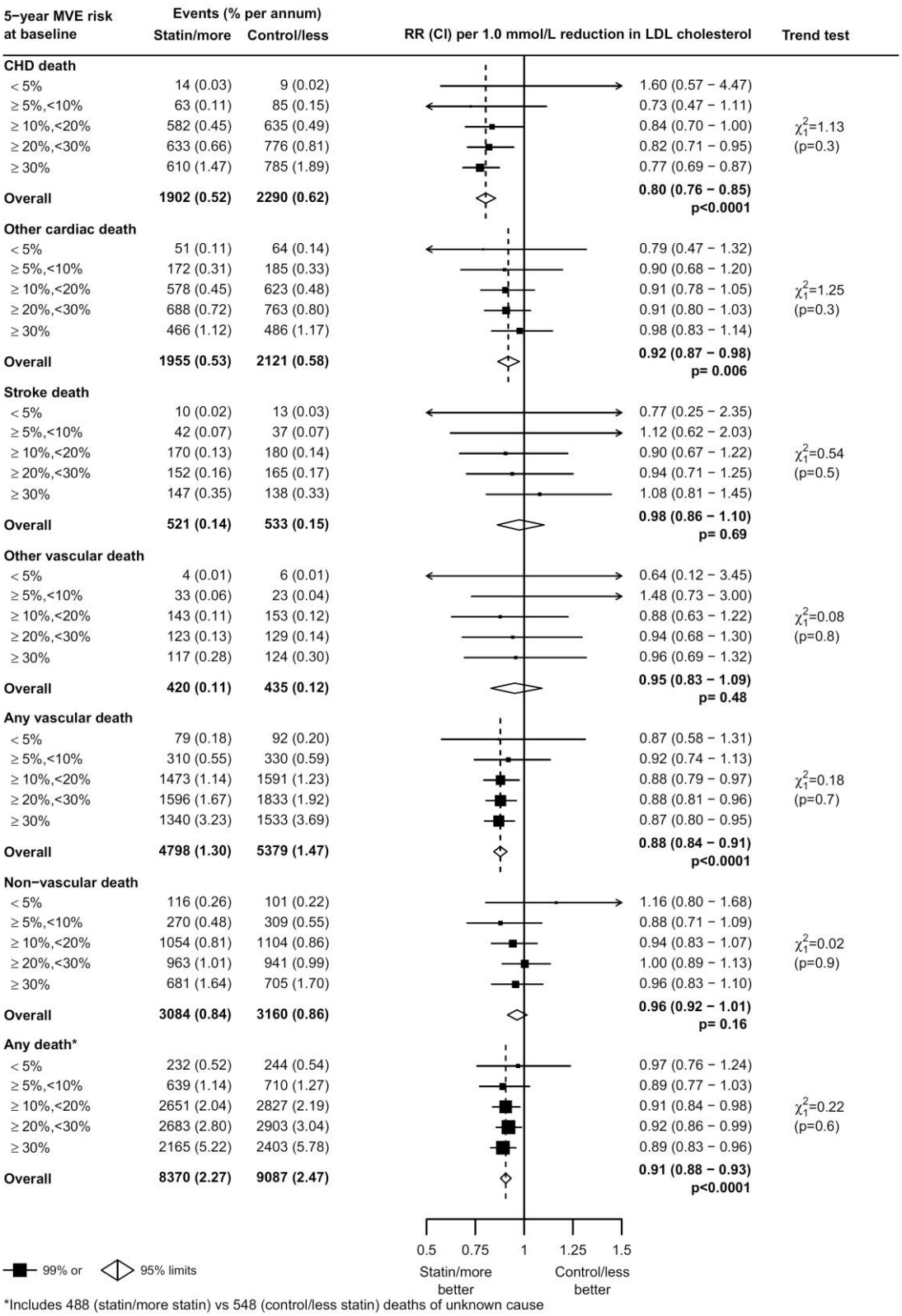
- Risk modelling calculation with cox proportional hazards model
- No mention of analysis according to baseline risk in original protocol.
- Meta-analyses were weighted by the absolute LDL cholesterol difference in that trial at 1 year (mmol/l)
- Authors' note: Predicted risk compared well with observed risk for each trial, as well as within each 5-year risk group.
- Authors' note: Individual participant data were unavailable from only two eligible trials in 6331 higher-risk patients with pre-existing vascular disease (SPARCL36 and GREACE37)..

Ref	Comparison	N/n	Outcomes	Result			
CTT 2012(4) Design: individual patient data MA Search date: (reported end of 2009, trial had to provide data before june 2011) N=27 n=174149 median follow-up duration in survivors 4·8 years	Statins Vs placebo or statin high dose vs low dose	N= 27 n= 174149		5-y MVE risk at baseline	Events/y (%) Statin/more	Events/y (%) Controll/less	RR (CI) per 1·0 mmol/L reduction in LDL cholesterol
			Major vascular event (MVE) (major coronary events (ie, non-fatal myocardial infarction or coronary death, strokes, or coronary revascularisations)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	167 (0.38) 604 (1.10) 3614 (2.96) 4108 (4.74) 2787 (7.64) 11 280 (3·27)	254 (0.56) 847 (1.57) 4195 (3.50) 4919 (5.80) 3458 (9.82) 13 673 (4·04)	**0.62 (0.47–0.81)** **0.69 (0.60–0.79)** **0.79 (0.74–0.85)** **0.81 (0.77–0.86)** **0.79 (0.74–0.84)** **0.79 (0.77–0.81) p<0.0001**
			Major vascular event - Participants without vascular disease	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	148 (0.35) 487 (1.02) 854 (2.52) 294 (4.40) 121 (7.29) 1904 (1·44)	229 (0.53) 716 (1.53) 1003 (2.98) 351 (5.28) 126 (8.16) 2425 (1·84)	**0.61 (0.45–0.81)** **0.66 (0.57–0.77)** **0.82 (0.72–0.93)** 0.81 (0.65–1.01) 0.83 (0.58–1.18) **0.75 (0.70–0.80) p<0·0001**
			Major vascular event - Participants with vascular disease	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	19 (0.87) 117 (1.56) 2760 (3.13) 3814 (4.77) 2666 (7.66) 9376 (4·41)	25 (1.18) 131 (1.80) 3192 (3.71) 4568 (5.85) 3332 (9.90) 11 248 (5·43)	0.73 (0.33–1.61) 0.84 (0.62–1.14) **0.78 (0.72–0.85)** **0.81 (0.76–0.86)** **0.79 (0.74–0.84)** **0.80 (0.77–0.82) p<0·0001**
			Major vascular event - Participants >70y (web appendix) remark: protocol stated analysis for > and < 65j	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	5 (0.25) 97 (1.43) 898 (3.48) 1061 (4.83) 891 (8.19) 2952 (4.37)	17 (0.81) 119 (1.82) 958 (3.66) 1235 (5.87) 1056 (9.96) 3385 (5.09)	0.37 (0.13 – 1.08) 0.79 (0.56 – 1.10) 0.90 (0.79 – 1.04) **0.81 (0.72 – 0.91)** **0.81 (0.71 – 0.91)** **0.83 (0.78 – 0.87) p<0.0001**
			Major coronary event (non-fatal myocardial infarction or coronary death)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	50 (0·11) 276 (0·50) 1644 (1·29) 1789 (1·93) 1471 (3·73) 5230 (1·45)	88 (0·19) 435 (0·79) 1973 (1·57) 2282 (2·49) 1887 (4·86) 6665 (1·87)	**0·57 (0·36–0·89)** **0·61 (0·50–0·74)** **0·77 (0·69–0·85)** **0·77 (0·71–0·83)** **0·78 (0·72–0·84)** **0·76 (0·73–0·79) p<0·0001**

			Any stroke	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	71 (0·16) 190 (0·34) 797 (0·62) 781 (0·84) 571 (1·45) 2410 (0·67)	90 (0.20) 240 (0.43) 907 (0.71) 900 (0.97) 661 (1.68) 2798 (0·78)	0.74 (0.46–1.19) **0.77 (0.60–0.98)** **0.86 (0.75–0.98)** **0.86 (0.75–0.97)** **0.86 (0.75–0.99)** **0.85 (0.80–0.89) p<0·0001**
			Any vascular death -	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	79 (0・18) 310 (0・55) 1473 (1・14) 1596 (1・67) 1340 (3・23) 4798 (1·30)	92 (0・20) 330 (0・59) 1591 (1・23) 1833 (1・92) 1533 (3・69) 5379 (1·47)	0・87 (0・58‑1・31) 0・92 (0・74‑1・13) **0・88 (0・79‑0・97)** **0・88 (0・81‑0・96)** **0・87 (0・80‑0・95)** **0.88 (0.84–0.91) p<0·0001**
			Any vascular death - Participants without vascular disease	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	31 (0・07) 117 (0・24) 307 (0・87) 164 (2・32) 93 (5・21) 712 (0·53)	40 (0·09) 153 (0·32) 342 (0·96) 168 (2·34) 98 (5·84) 801 (0·59)	0·80 (0·43–1·47) 0·75 (0·55–1·04) 0·84 (0·67–1·05) 0·97 (0·72–1·32) 0·88 (0·59–1·33) **0.85 (0.77–0.95) p=0·004**
			Any vascular death - Participants with vascular disease	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	48 (2・16) 193 (2・52) 1166 (1・24) 1432 (1・61) 1247 (3・14) 4086 (1·76)	52 (2·40) 177 (2·35) 1249 (1·34) 1665 (1·89) 1435 (3·60) 4578 (1·98)	0・93 (0・53‑1・62) 1・07 (0・81‑1・41) 0・89 (0・79‑1・00) **0・87 (0・80‑0・95)** **0・87 (0・79‑0・95)** **0·88 (0·84–0·92) p<0·0001**
			All-cause mortality (web appendix)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	232 (0.52) 639 (1.14) 2651 (2.04) 2683 (2.80) 2165 (5.22) 8370 (2.27)	244 (0.54) 710 (1.27) 2827 (2.19) 2903 (3.04) 2403 (5.78) 9087 (2.47)	0.97 (0.76 – 1.24) 0.89 (0.77 – 1.03) **0.91 (0.84 – 0.98)** **0.92 (0.86 – 0.99)** **0.89 (0.83 – 0.96)** **0.91 (0.88 – 0.93) p<0.0001**

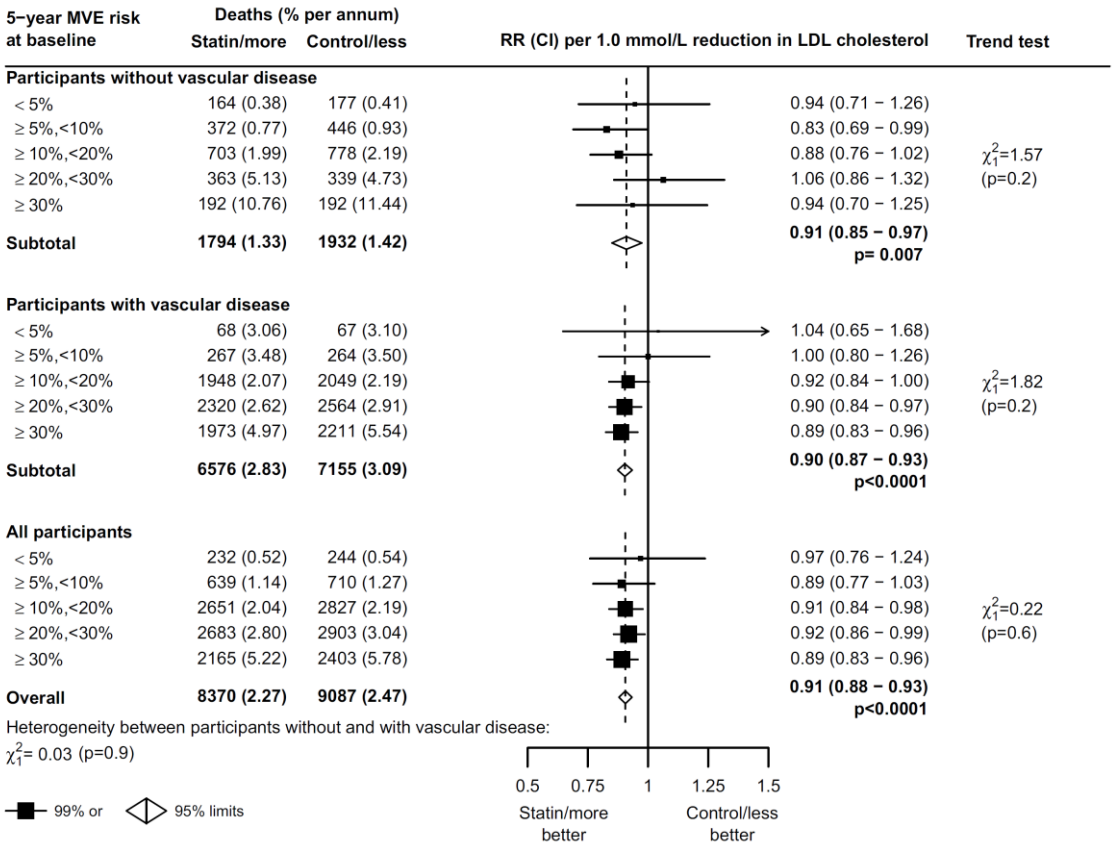
			All-cause mortality - Participants without vascular disease (web appendix)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	164 (0.38) 372 (0.77) 703 (1.99) 363 (5.13) 192 (10.76) 1794 (1.33)	177 (0.41) 446 (0.93) 778 (2.19) 339 (4.73) 192 (11.44) 1932 (1.42)	0.94 (0.71 − 1.26) **0.83 (0.69 – 0.99)** 0.88 (0.76 − 1.02) 1.06 (0.86 − 1.32) 0.94 (0.70 − 1.25) **0.91 (0.85 – 0.97) p= 0.007**
			All-cause mortality - Participants with vascular disease (web appendix)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	68 (3.06) 267 (3.48) 1948 (2.07) 2320 (2.62) 1973 (4.97) 6576 (2.83)	67 (3.10) 264 (3.50) 2049 (2.19) 2564 (2.91) 2211 (5.54) 7155 (3.09)	1.04 (0.65 − 1.68) 1.00 (0.80 − 1.26) 0.92 (0.84 − 1.00) **0.90 (0.84 – 0.97)** **0.89 (0.83 – 0.96)** **0.90 (0.87 – 0.93) p<0.0001**
			Cancer incidence	Overall	5221 (1·45)	5210 (1·45)	1·00 (0·96–1·04) p=0·99
			Cancer death	Overall	1834 (0·50)	1849 (0·50)	0·99 (0·93–1·06) p=0·86
			mean baseline LDL cholesterol	mean baseline LDL cholesterol 3·70 [SD 0·7] mmol/L; mean difference at 1 year 1·08 mmol/L; median follow-up			

Webfigure 8: Effects on cause−specific mortality per 1.0 mmol/L reduction in LDL cholesterol at different levels of



*Includes 488 (statin/more statin) vs 548 (control/less statin) deaths of unknown cause

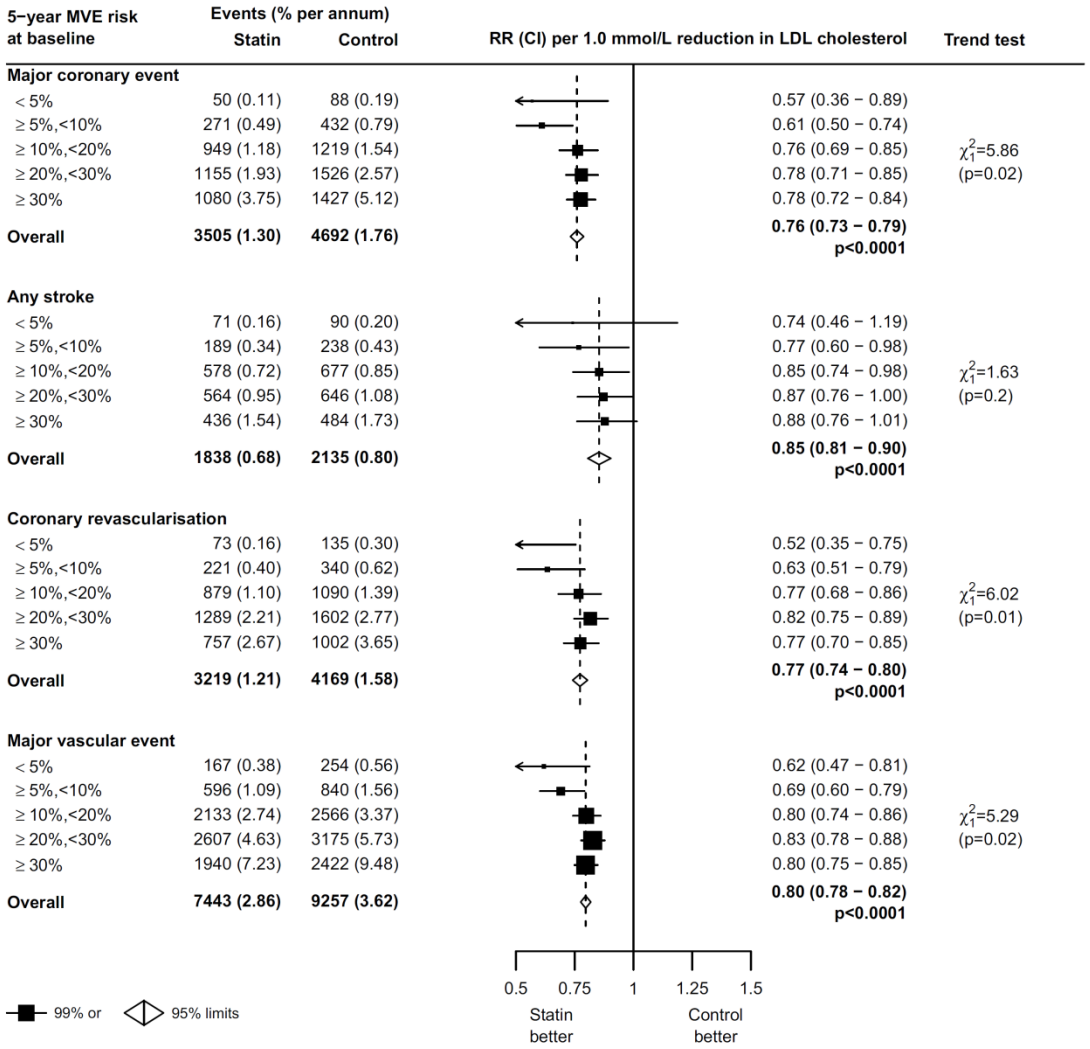
Webfigure 9: Effects on any deaths per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by history of vascular disease and overall



179 (statin/more statin) vs 210 (control/less statin) deaths of unknown cause are included among participants without vascular disease.
309 (statin/more statin) vs 338 (control/less statin) deaths of unknown cause are included among participants with vascular disease.

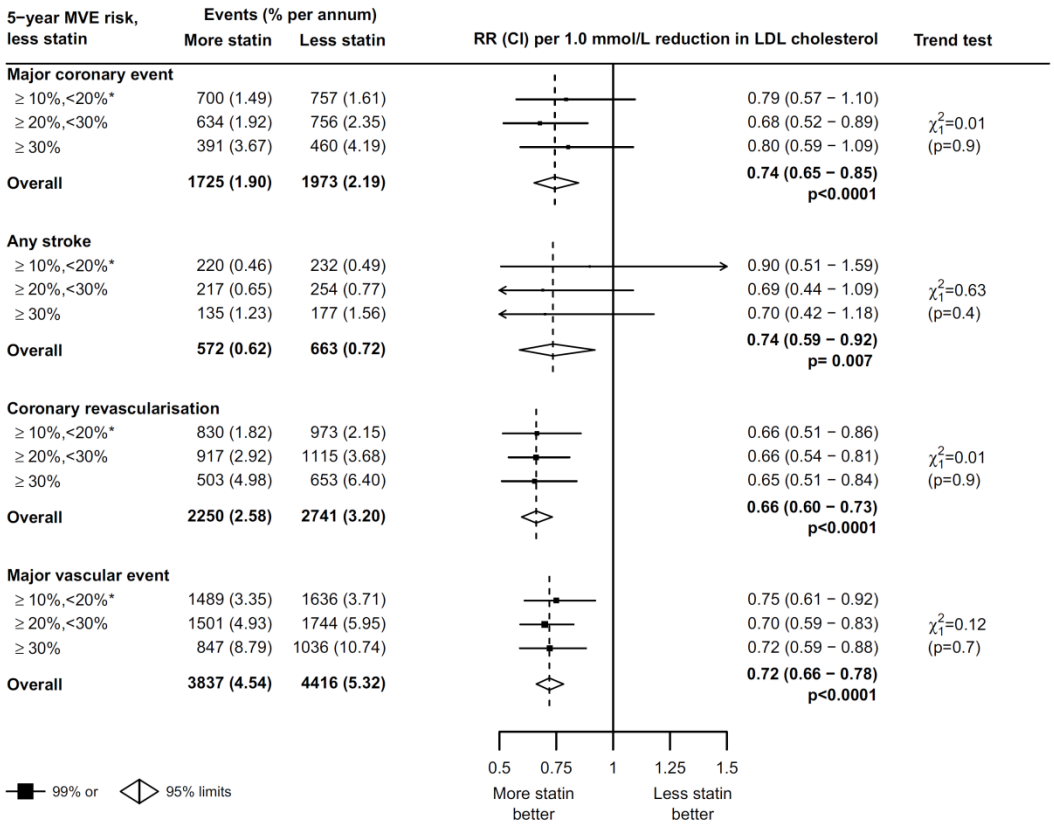
Ref	Comparison	N/n	Outcomes	Result	
CTT 2012 Design: individual patient data MA Search date: (reported end of 2009, trial had to provide data before june 2011)	Statins Vs placebo	N= 22 n= 134 537		5-y MVE risk at baseline	RR (CI) per 1·0 mmol/L reduction in LDL cholesterol
			Major vascular event (major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	**0.62 (0.47 – 0.81)** **0.69 (0.60 – 0.79)** **0.80 (0.74 – 0.86)** **0.83 (0.78 – 0.88)** **0.80 (0.75 – 0.85)** **0.80 (0.78 – 0.82) p<0.0001**
			Major coronary event (non-fatal myocardial infarction or coronary death)	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	**0.57 (0.36 – 0.89)** **0.61 (0.50 – 0.74)** **0.76 (0.69 – 0.85)** **0.78 (0.71 – 0.85)** **0.78 (0.72 – 0.84)** **0.76 (0.73 – 0.79) p<0.0001**
			Any stroke	<5% ≥5% to <10% ≥10% to <20% ≥20% to <30% ≥30% Overall	0.74 (0.46 – 1.19) **0.77 (0.60 – 0.98)** **0.85 (0.74 – 0.98)** 0.87 (0.76 – 1.00) 0.88 (0.76 – 1.01) **0.85 (0.81 – 0.90) p<0.0001**

Webfigure 5: Effects on major coronary events, strokes, coronary revascularisation procedures and major vas events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk in the 22 statin vs control trials



Ref	Comparison	N/n	Outcomes	Result	
CTT 2012 Design: MA Search date: (june 2011)	Statins high Vs Statins low	N= 5 n= 39 612		5-y MVE risk at baseline	RR (CI) per 1·0 mmol/L reduction in LDL cholesterol
			Major vascular event (major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations	≥10% to <20% ≥20% to <30% ≥30% Overall	**0.75 (0.61 – 0.92)** **0.70 (0.59 – 0.83)** **0.72 (0.59 – 0.88**) **0.72 (0.66 – 0.78) p<0.0001**
			Major coronary event (non-fatal myocardial infarction or coronary death)	≥10% to <20% ≥20% to <30% ≥30% Overall	0.79 (0.57 – 1.10) **0.68 (0.52 – 0.89)** 0.80 (0.59 – 1.09) **0.74 (0.65 – 0.85) p<0.0001**
			Any stroke	≥10% to <20% ≥20% to <30% ≥30% Overall	0.90 (0.51 – 1.59) 0.69 (0.44 – 1.09) 0.70 (0.42 – 1.18) **0.74 (0.59 – 0.92) p= 0.007**

Webfigure 6: Effects on major coronary events, strokes, coronary revascularisation procedures and major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk in the 5 trials of more vs less statin



*Includes 141 participants (48 from A to Z and 93 from SEARCH) with an estimated 5−year risk of MVE less than 10%.

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Statin versus control (22 trials)					
4D 2005(5) multicenter, randomized, double-blind, prospective study	1255	- persons with type 2 diabetes mellitus - receiving maintenance hemodialysis - at high risk for cardiovascular disease and death,	median follow-up period of four years	20 mg of atorvastatin per day or matching placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP:30% discontinued before end of study (6% medical reasons, 10% wish of patient,…) ITT:yes note: 4 week run-in placebo FUNDING: Pfizer
AFCAPS/ TexCAPS (6) 1998 RCT, double blind	6606	participants in Texas, USA; mean age 58; 57.5% men; 89%Caucasian. None with any clinical evidence of CVD	5.2 years	20-40 mg lovastatin vs placebo; all participants received advice on diet	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Trial was stopped prematurely. To be terminated when 320 participants had experienced primary outcome event. Stopped when 267 had done at 5.2 years
ALERT 2003(7) multicentre, randomised, double-blind, placebo-	2102	renal transplant recipients with total cholesterol 4·0–9·0 mmol/L	mean follow-up of 5·1 years	fluvastatin or placebo The primary endpoint was the occurrence of a major adverse	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING :

controlled trial				cardiac event, defined as cardiac death, non-fatal myocardial infarction (MI), or coronary intervention procedure	Adequate ITT:yes FUNDING:Novartis we doubled study-medication dose after around 2 years. This rise in dose of fluvastatin from 40 to 80 mg daily was predicted to reduce LDL-cholesterol concentrations by an additional 6%.
ALLHAT-LLT 2002(8) Multicenter (513 primarily community-based North American clinical centers), randomized, nonblinded trial	10355	"older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor" The specific eligibility criteria for the ALLHAT-LLT included prior enrollment in ALLHAT (age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting LDL-C level of 120 to 189 mg/dL (3.1 to 4.9 mmol/L) for those with no known CHD, or 100 to 129 mg/dL (2.6 to 3.3 mmol/L) for those with known CHD (the upper limit was 159 mg/dL [4.1 mmol/L] prior to April 5, 1994, but was changed in light of 4S[4] findings); and fasting triglyceride levels lower than 350 mg/dL (3.9 mmol/L) Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; and triglycerides, 152 mg/dL. Mean age was 66 years, 49% were women, 38% black and 23% Hispanic, 14% had a history of CHD, and 35% had type 2 diabetes.	mean follow-up was 4.8 years	Pravastatin, 40 mg/d vs usual care The usual care group was treated for LDL-C lowering according to the discretion of their primary care physicians. However, vigorous cholesterol-lowering therapy in the usual care group was discouraged unless warranted by a change in clinical circumstances.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : no FOLLOW-UP: At the end of the trial, 84.8% of participants were known to be alive, 12.3% were confirmed dead, 0.5% were reported dead with confirmation pending, and 2.4% had unknown vital status. ITT:yes FUNDING: Methodological remarks: because of the modest cholesterol differential between pravastatin and usual care, ALLHAT-LLT lacked the power to discriminate between the expected reductions in mortality and CHD events and the null hypothesis. The primary outcome was all-cause mortality, with follow-up for up to 8 years.

ALLIANCE 2004(9)	2442	CHD patients with hyperlipidemia	51.5 months on average	Atorvastatin- titrated to LDL-C goals of <80 mg/dl (2.1 mmol/l) or a maximum atorvastatin dose of 80 mg/day versus Usual-care (any treatment deemed appropriate by their regular physicians)	ALLOCATION CONC: unclear RANDO: unclear BLINDING : inadequate FOLLOW-UP: End point assessments were complete in 958 atorvastatin-group and 941 usual-care patients. Partial assessments occurred in 259 patients in the atorvastatin group and 284 patients in the usual care group who did not complete four years of study participation because of adverse events, withdrawn consent, or follow-up loss. ITT:yes The primary efficacy parameter was time to first cardiovascular event.
ASCOT-LLA 2003(10) multicentre randomised controlled trial	10305	Hypertensive patients (aged 40–79 years with at least three other cardiovascular risk factors) with non-fasting total cholesterol concentrations 6·5 mmol/L or less	median follow-up of 3·3 years	Atorvastatin 10 mg versus placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : assessors: yes FOLLOW-UP: 99% ITT:yes Note: 4 week run-in FUNDING:Pfizer
ASPEN 2006(11) RCT, double blind	2410	participants with type 2 diabetes based in 16 developed countries with mean age 60; 62.5% men; 84% Caucasian. < 10% with clinical evidence of CVD	2.4 years	10 mg atorvastatin Vs placebo;	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate

					FOLLOW-UP: 22% drop outs reported ITT:yes FUNDING: unclear risk (funded by pharm industry)
AURORA 2009(12) international, multicenter, randomized, double-blind, prospective trial	2776	50 to 80 years of age, who were undergoing maintenance hemodialysis	median follow-up period of 3.8 years	rosuvastatin, 10 mg daily, or placebo The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors not described FOLLOW-UP: no patients lost ITT:yes) FUNDING:AstraZeneca
CARDS 2004(13)	2838	participants with diabetes based in UK and Ireland aged 40-75 years (mean 61.7) ; 68% men; 94.5% Caucasian. None with any clinical evidence of CVD	3.9-4 years	10 mg atorvastatin versus placebo all patients were given counselling on cessation of smoking	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate (triple blind part/pers/assess) FOLLOW-UP: 0% dropped out ITT:yes FUNDING: unclear risk (funded by pharm industry) Trial stopped prematurely due to large beneficial treatment effect
CARE 1996(14)	4159	3583 men and 576 women with myocardial infarction who had plasma	5 years	Pravastatin 40mg versus	ALLOCATION CONC: Adequate

double-blind trial		total cholesterol levels below 240 mg per deciliter (mean, 209) and low-density lipoprotein (LDL) cholesterol levels of 115 to 174 mg per deciliter (mean, 139).		placebo The primary end point was a fatal coronary event or a nonfatal myocardial infarction.	RANDO: Adequate BLINDING : Adequate FOLLOW-UP: 8% discontinued study medication and started open label treatment ITT:yes FUNDING:Bristol-Myers Squibb
CORONA 2007(15)	5011	patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure	median follow-up of 32.8 months	10 mg of rosuvastatin or placebo per day The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel:Adequate Assessors: unclear FOLLOW-UP: ? ITT:yes note: 2-4 week placebo run-in FUNDING:AstraZeneca
GISSI-HF 2008(16) randomised, double-blind, placebo-controlled trial	4574	patients aged 18 years or older with chronic heart failure of New York Heart Association class II–IV, irrespective of cause and left ventricular ejection fraction	median of 3·9 years (IQR 3·0–4·4)	rosuvastatin 10 mg daily or placebo Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors FOLLOW-UP: ITT:yes FUNDING: Società Prodotti Antibiotici (SPA; Italy), Pfizer, Sigma Tau, and AstraZeneca.
GISSI-P 2000(17)	4271	recent acute myocardial infarction patients (< or = 6 months) with total	Mean follow-up time was 23.0 +/-	pravastatin 20 mg daily or no treatment	ALLOCATION CONC: inadequate

open trial		blood cholesterol > or = 200 mg/dl	6.7 months (median 24.3 months)		RANDO: ? BLINDING : inadequate FOLLOW-UP: ? ITT:yes/no ('author's definition') FUNDING: Methodological remarks:GISSI-P was started in 1993 and its story was crossed by the publication of the results of similarly designed clinical trials. The publication of 4S results in 1994 prompted the Data Safety and Monitoring Board (DSMB) and the Steering Committee (SC) ; decreased statistical power due to its premature stopping
HPS 2002(18) randomised placebo controlled trial	20536	UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes	scheduled 5-year treatment period	40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%).	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? There was a change in the protocol so that only patients whose total blood cholesterol was < 250 mg/dl could be randomized whilst patients with total blood cholesterol > 250 mg/dl who had already been enrolled in the

					study had to be re-evaluated and, if appropriate, pharmacologically treated. The DSMB and the SC agreed to stop randomization prematurely in late 1996 after the publication of CARE results. Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.
JUPITER 2008(19) RCT, double blind	17.802	Apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher participants > 50 years. None with any clinical evidence of CVD	1.9 years	Rosuvastatin 20 mg daily versus placebo At the time the study was terminated, 75% of participants were taking their study pills.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/ assessors Adequate FOLLOW-UP: drop outs unclear ITT: yes FUNDING: High risk (funded by pharm industry) Other remarks: Stopped early with a follow-up of 1.9 years. Run-in : 4-week run-in phase during which they received placebo. Only subjects who successfully completed the run-in phase were enrolled (19323 received run-in, of which 1521 excluded =7.8%) Primary endpoint event rate higher than predicted. Mortality higher than predicted (by comparison to other

					trials)
LIPID 2002(20)	9014	Patients with previous myocardial infarction or unstable angina and a baseline plasma cholesterol concentration of 4·0–7·0 mmol/L	6 years (+ open-label pravastatin for 2 more years) (3766 (86%) of those assigned placebo and 3914 (88%) assigned pravastatin agreed to take open-label pravastatin)	pravastatin 40 mg versus placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:?
LIPS 2002(21) Randomized, double-blind, placebo-controlled trial 77 referral centers in Europe, Canada, and Brazil.	1677	patients (aged 18-80 years) with stable or unstable angina or silent ischemia following successful completion of their first PCI who had baseline total cholesterol levels between 135 and 270 mg/dL (3.5-7.0 mmol/L), with fasting triglyceride levels of less than 400 mg/dL (4.5 mmol/L)	median follow-up was 3.9 years.	fluvastatin, 80 mg/d (n = 844), or matching placebo (n = 833) Main Outcome Measure: Survival time free of major adverse cardiac events (MACE), defined as cardiac death, nonfatal myocardial infarction, or reintervention procedure, compared between the treatment and placebo groups	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP: >90% completed trial ITT:yes FUNDING:Novartis *"patients whose total cholesterol exceeded 7.2 mmol l^{-1} for 3 months or longer could discontinue study therapy at the investigator's discretion and receive an open-label statin or other lipid-lowering therapy. As a result, 10.7% of patients in the treatment arm and 24% in the placebo arm started taking other lipid-lowering medications (mainly statins) before their first major adverse cardiac event or completion*

					of follow-up." *"anecdotal evidence that many patients were aware of their total cholesterol levels as these had been tested by primary care physicians who were not involved in LIPS; as a result, these patients were no longer blinded to their treatment allocation"*
MEGA 2006(22) prospective, randomised, open-labelled, blinded study	7832	Asian patients with hypercholesterolaemia (total cholesterol 5·69–6·98 mmol/L) and no history of coronary heart disease or stroke	Mean follow-up was 5·3 years The follow-up period was initially scheduled for 5 years; however, on the basis of recommendations from the data and safety monitoring committee, the study was continued for an additional 5 years to increase the number of events.	Diet versus Diet +10–20 mg pravastatin	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : assessors Adequate FOLLOW-UP: 87.3% At the end of study, 471 and 522 patients had withdrawn, died, or been lost to follow-up in the diet and diet plus pravastatin groups, respectively ITT:yes FUNDING: Japanese Ministry of Health, Labor and Welfare and Sankyo Co Ltd, Tokyo The primary endpoint was the first occurrence of coronary heart disease
Post-CABG 1997(23) RCT	1351	Patients who had undergone bypass surgery 1 to 11 years before base line and who had an LDL cholesterol level between 130 and 175 mg per deciliter and at least one patent vein graft as seen on angiography.	Angiography was repeated an average of 4.3 years after base line. The primary angiographic	Aggressive lowering versus moderate lowering of cholesterol: Lovastatin 40mg or higher (+/- cholestyramin) (target LDL<85mg/dl) versus Lovastatin 2.5mg or higher	ALLOCATION CONC: unclear RANDO: unclear BLINDING : no blinding reported FOLLOW-UP: 98% clinical follow-up ITT:yes FUNDING: National Heart, Lung, and Blood Institute and by Merck &

			outcome was the mean percentage per patient of grafts with a decrease of 0.6 mm or more in lumen diameter.	(target LDL <140mg/dl) two-by-two factorial design to assign patients to aggressive or moderate treatment to lower LDL cholesterol levels (with lovastatin and, if needed, cholestyramine) and to treatment with warfarin or placebo	Company. The primary angiographic outcome was the mean percentage per patient of grafts with a decrease of 0.6 mm or more in lumen diameter.
PROSPER 2002(24) randomised controlled trial	5804	5804 men (n=2804) and women (n=3000) aged 70–82 years with a history of, or risk factors for, vascular disease Baseline cholesterol concentrations ranged from 4·0 mmol/L to 9·0 mmol/L.	Follow-up was 3·2 years on average	pravastatin 40 mg versus placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP: 25% did not complete trial (due to adverse event, death, refusal or lost) 13% refusal or lost to follow-up ITT:yes FUNDING: Bristol- Myers Squibb, USA. Primary endpoint was a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke
SSSS 1994(25) randomised double-blind trial	4444	Patients with angina pectoris or previous myocardial infarction and serum cholesterol 5·5-8·0 mmol/L on a lipid-lowering diet	5·4 years median follow-up period	simvastatin versus placebo	ALLOCATION CONC: /unclear RANDO: unclear BLINDING : Participants/personnel/assessors

					unclear FOLLOW-UP: note 2 week placebo run in FUNDING:Merck
WOSCOPS 1995(26) RCT, double blind	6595	men with hypercholesterolaemia based in Scotland aged 45-64 (mean age 55). ≤ 10% with clinical evidence of CVD	4.9 years	40 mg pravastatin Vs Placebo Primary outcome: composite of non-fatal MI andCHD death. Single outcomes included totalmortality, fatal CVD events, cholesterol, revascularisations, non-fatalMI and CHD death and adverse events	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 30% drop-outs reported ITT: yes FUNDING: unclear risk (funded by pharm industry)

statin high dose versus statin low dose (5 trials)					
A to Z 2004(27) International, randomized, double-blind trial	4497	Patients with acute coronary syndrome (ACS) Age, mean, years: 61 Men, %: 76 Prior CHD, %: 100 Diabetes, %: 24 Hypertension, %: 50 Current smokers, %: 41 Baseline, mean mg/dL (change): LDL:111 (-37) HDL: 39 (-0.7)	Follow-up was for at least 6 months and up to 24 months	40 mg/d of simvastatin for 1 month followed by 80 mg/d vs placebo for 4 months followed by 20 mg/d of simvastatin	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blinded FOLLOW-UP: adequate reporting 33% discontinued prematurely 3% lost to follow-up or follow-up too short for primary endpoints ITT:yes FUNDING: Merck

					note: lower start dose The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke.
IDEAL 2005(28) prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe	8888	Patients aged 80 years or younger with a history of acute MI Age, mean, years:62 Men, %:81 Prior CHD, %: 100 Diabetes, %:12 Hypertension, %:33 Current smokers, %:21 Baseline, mean mg/dL (change): LDL:121 (-22) HDL:46 (-0.5)	Median follow-up of 4.8 years	high dose of atorvastatin (80 mg/d), versus usual-dose simvastatin (20 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : endpoint-evaluation FOLLOW-UP: <1% lost to follow-up ITT:yes FUNDING: Pfizer note: no run-in Main Outcome Measure: Occurrence of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation
PROVE-IT 2004(29) RCT, Noninferiority trial	4162	Patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days Age, mean, years:58 Men, %:78 Prior CHD, %: 100 Diabetes, %:18 Hypertension, %:50 Current smokers, %:37 Baseline, mean mg/dL (change): LDL:106 (-33)	Follow-up lasted 18 to 36 months (mean, 24)	40 mg of pravastatin daily (standard therapy) versus 80 mg of atorvastatin daily (intensive therapy)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blind FOLLOW-UP: - The rates of discontinuation of treatment because of an adverse event or the patient's preference or for other reasons were 21.4 percent in the pravastatin

		HDL:39 (0.65)			group and 22.8 percent in the atorvastatin group at one year (P=0.30) and 33.0 percent and 30.4 percent, respectively, at two years (P=0.11). - 0.2% lost to follow-up ITT:yes FUNDING: ? note: no run-in The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke
SEARCH 2010(30) double-blind randomised trial	12064	Men and women aged 18-80 years with a history of myocardial infarction, were either currently on or had clear indication for statin therapy, and had a total cholesterol concentration of at least 3·5 mmol/L if already on a statin or 4·5 mmol/L if not Age, mean, years: - Men, %:83 Prior CHD, %: 100 Diabetes, %:- Hypertension, %:- Current smokers, %:- Baseline, mean mg/dL (change): LDL:97 (-14)	Mean follow-up of 6·7 (SD 1·5) years	80 mg simvastatin versus 20 mg simvastatin	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : yes FOLLOW-UP: 37% not eligible after run-in phase 2% lost to follow-up 30% stopping before end of study ITT:yes FUNDING: Merck The primary endpoint was major vascular events, defined as coronary

		HDL:39 (-)			death, myocardial infarction, stroke, or arterial revascularisation
TNT 2005(31) double blind RCT	10001	patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) Age, mean, years:61 Men, %:81 Prior CHD, %: 100 Diabetes, %:15 Hypertension, %:54 Current smokers, %:13 Baseline, mean mg/dL (change): LDL:98 (-22) HDL:47 (0)	median of 4.9 years.	10 mg atorvastatin versus 80 mg atorvastatin	ALLOCATION CONC: unclear RANDO: unclear BLINDING : 'double blind', blinded assessors FOLLOW-UP: 35% excluded after run-in (mainly due to not meeting randomization criteria) 3.6% of excluded run-in patients had ischemic event 3.6% of excluded run-in patients had adverse events <1% lost to follow-up ITT:yes FUNDING: Industry-funded note: washout period of one to eight weeks eight-week run-in period of open-label treatment with 10 mg of atorvastatin per day. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

Webtable 3: Mean difference in plasma lipid concentrations at 1 year in participants at different levels of risk

Estimated 5-year risk of major vascular event	Total cholesterol (mmol/L*)	LDL cholesterol (mmol/L*)	HDL cholesterol (mmol/L*)	Triglycerides (mmol/L*)
Statin vs. Control				
<5%	-0.94	-0.88	0.034	-0.19
≥5%, <10%	-1.08	-0.96	0.031	-0.25
≥10%, <20%	-1.14	-0.99	0.045	-0.27
≥20%, <30%	-1.26	-1.10	0.032	-0.24
≥30%	-1.31	-1.21	0.034	-0.23
Subtotal (22 trials)	**-1.22**	**-1.08**	**0.038**	**-0.26**
More vs. Less statin				
≥10%, <20%†	-0.52	-0.44	0.006	-0.19
≥20%, <30%	-0.65	-0.53	-0.011	-0.24
≥30%	-0.70	-0.58	-0.013	-0.30
Subtotal (5 trials)	**-0.61**	**-0.51**	**-0.005**	**-0.23**

LDL= low-density lipoprotein cholesterol. HDL= high-density lipoprotein cholesterol.

* To convert values from mmol/L to mg/dL, divide triglycerides by 0.01129 and other lipids by 0.02586.

Estimating the five year risk of major vascular event among the 174,149 participants in 27 randomised trials of statin therapy

The 5-year risk of a major vascular event (first non-fatal myocardial infarction, coronary death, stroke or coronary revascularisation procedure) was estimated using separate Cox proportional hazards models for the 67,000 patients allocated the control regimen in the 22 trials of statin versus control (model 1) and the 20,000 patients allocated the less intensive statin regimen in the 5 trials of more versus less statin (model 2). The results from these two regression models were then applied to all patients (including those in the active treatment arms), as described below.

For patient *i* in study *j* with allocated treatment *k* (where *k*=0 corresponds to the control/less statin treatment and *k*=1 corresponds to the statin/more statin treatment), the hazard function in the control/less statin group was modelled by the regression equation:

$$h_{ij0}(t) = h_0(t)exp\ (\alpha + \beta_j + \boldsymbol{\gamma}(\boldsymbol{x_{ij0}} - \overline{\boldsymbol{x}}_{.j0}) + \boldsymbol{\delta}(\boldsymbol{w_{ij0}}) + \boldsymbol{\theta}(\boldsymbol{z_j}(t)))$$

where $h_0(t)$ is the baseline hazard function, α is an overall intercept term, β_j represents the effect of study j relative to the Heart Protection Study for model 1 or the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine for model 2 (see Webtable 1, terms C), $\boldsymbol{\gamma}$ represents a vector of log hazard ratios corresponding to the patient's set of baseline characteristics $\mathbf{x_{ij0}}$ (centred around study means $\overline{\boldsymbol{x}}_{.j0}$ where appropriate: see Webtable 1, terms A), $\boldsymbol{\delta}$ represents a vector of log hazard ratios corresponding to interactions $\mathbf{w_{ij0}}$ between various baseline characteristics (see Webtable 1, terms B), and $\boldsymbol{\theta}$ represents a vector of log hazard ratios corresponding to trial-specific time dependent effects $\mathbf{z_j}(t)$ (defined for initial six-monthly time periods: see Webtable 1, terms D).

For each of the two regression models, the baseline characteristics $\mathbf{x_{ij}}$ and interactions $\mathbf{w_{ij}}$ were selected using backward elimination, with factors remaining in the model if they were statistically significant at the 1% level (age and sex were to be included in both models irrespective of statistical significance). The baseline characteristics included in the final models are shown in Webtable 1. The trial-specific time dependent effects $\mathbf{z_j}(t)$ were defined for initial six-monthly time periods and a backwards elimination strategy with statistical significance at 1% was employed to select the effects remaining in the models.

The Cox models provide estimates of log hazard ratios, but provide no direct estimate of the baseline hazard $h_o(t)$. However, an estimate of the cumulative hazard function $H_o(t)$ can be recovered by estimation of baseline hazard contributions at failure times using the Kalbfleisch and Prentice method and, from that, an estimate of the baseline cumulative survival $S_0(t) = exp(-H_0(t))$ can be made.

Separating study participants according to baseline 5-year major vascular event risk

The predicted 5-year risk of a major vascular event for all patients was estimated by:

$$P_{ijk}(t) = 1 - S_0(t)^{exp\,(\alpha+\beta_j+\gamma(x_{ijk}-\bar{x}_{.j0})+\delta(w_{ijk})+\theta(z_j(t)))} \quad \text{at t=5 years}$$

Patients with missing baseline characteristics employed in the risk models were excluded from the estimation of models 1 and 2, but their values were imputed for the purpose of predicting 5-year risk of a major vascular event. Occasional missing age, gender, treatment for hypertension were imputed using study-specific mean (age) or median (gender, treatment for hypertension). Missing data for LDL-C (1.7%), HDL-C (0.7%), blood pressure (0.4%) and creatinine (1.4%) were imputed using study-specific mean values by age, gender and treatment for hypertension.

Trial participants were categorised into one of five baseline categories of 5-year risk: <5%; 5 to <10%; 10 to <20%; 20 to <30%; and 30% or larger. The proportionate and absolute effects of allocation to statin or more statin intervention on specific endpoints was then estimated separately within each of these subgroups (as described in the main statistical methods section).

Webtable 2: Comparison of the observed (95% CI) and predicted rates of major vascular events in participating trials

Study	Duration (years)*	Observed MVEs (%) (95% CI)†	Average predicted MVEs (%)
Statin vs. Control			
SSSS	5	33.8% (31.8% - 35.8%)	33.7%
WOSCOPS	5	10.0% (8.9% - 11.1%)	10.1%
CARE	5	27.3% (25.3% - 29.3%)	27.2%
Post-CABG	5	22.9% (15.5% - 30.4%)	17.4%
AFCAPS/TexCAPS	5	5.4% (4.6% - 6.2%)	5.7%
LIPID	5	22.4% (21.2% - 23.7%)	22.9%
GISSI-P	2	11.1% (9.7% - 12.4%)	10.9%
HPS	5	19.5% (18.7% - 20.3%)	19.5%
ASCOT-LLA	4	6.9% (6.1% - 7.8%)	7.3%
PROSPER	4	19.3% (17.6% - 21.0%)	20.2%
CARDS	5	10.9% (8.9% - 12.9%)	11.4%
ALERT	5	12.5% (10.4% - 14.6%)	12.8%
ALLHAT-LLT	5	16.1% (15.0% - 17.2%)	15.8%
LIPS	4	27.3% (23.9% - 30.7%)	26.8%
ALLIANCE	5	28.0% (25.1% - 30.9%)	27.6%
ASPEN	4	12.3% (10.4% - 14.3%)	12.5%
4D	5	39.9% (33.6% - 46.2%)	39.4%
MEGA	5	3.2% (2.7% - 3.8%)	3.2%
JUPITER	5	5.3% (4.2% - 6.5%)	4.9%
GISSI-HF	5	9.4% (7.9% - 10.8%)	10.6%
AURORA	5	33.9% (30.7% - 37.1%)	34.7%
CORONA	3	15.1% (13.5% - 16.7%)	15.3%
More vs. Less statin			
A to Z	2	13.3% (11.8% - 14.8%)	13.3%
PROVE-IT	2	22.6% (20.7% - 24.5%)	22.7%
TNT	5	23.4% (22.2% - 24.6%)	23.4%
IDEAL	5	25.8% (24.4% - 27.1%)	25.7%
SEARCH	5	17.1% (16.2% - 18.1%)	17.2%
Risk categories			
<5%	5	2.8% (2.4% - 3.2%)	3.4%
≥5%, <10%	5	7.4% (6.9% - 7.9%)	7.3%
≥10%, <20%	5	15.9% (15.5% - 16.4%)	15.4%
≥20%, <30%	5	24.7% (24.0% - 25.3%)	24.3%
≥30%	5	38.1% (37.0% - 39.2%)	38.1%

MVE= major vascular event.

*Duration over which rates of major vascular events compared: 5 years or the latest year with available Kaplan-Meier estimate of MVE within 50 days from end of that year.

†Estimated using Kaplan-Meier survival methods among participants allocated to the control or less statin arm, respectively.

4.1.1.2 Summary and conclusions: CTT 2012. Individual patient data meta-analysis

Statin or high dose statin versus placebo or low dose statin: Cholesterol Treatment Trialist

The following results are from a meta-analysis based on individual patient data, that includes all trials that were published or conducted after 1995. Included trials compare statin versus placebo or high dose statin versus a low dose statin.
The description of the search strategy does not specify how the literature was searched to find all eligible trials.
The authors (Cholesterol Treatment Trialists: CTT) have made previous publications using the same methodology.
Endpoints are reported for the overall population, and also in subgroups based on baseline 5-year risk of (first) major vascular event (MVE; Major vascular event= major coronary events, strokes, or coronary revascularisations).
It is unclear why coronary revascularisations were included as part of this definition.
Five risk categories were defined: <5%; ≥5% to <10%; ≥10% to <20%; ≥20% to <30% and ≥30% risk of a major vascular event in the next 5 years.
To estimate for each individual patient this 5-year risk of MVE, the authors developed a statistical calculation method, based on the event rate in the control group of the studies, the patient's baseline characteristics and the factor 'time'.
To check the accuracy of this calculation model, they compare the estimated MVEs to the observed MVEs in the different trials. They find that their model adequately predicts MVE events.
The analysis of subgroups at different MVE risk was not stated in the original protocol of the CTT. It may therefor be prudent to consider these results as hypothesis-generating.

The authors report all endpoints adjusted for a chosen LDL response of 1mmol/L reduction. This makes interpretation more difficult. Not all patients in the included trials necessarily reached this 1 mmol/L reduction. (particularly in the high dose versus low dose trials).
Besides, it is impossible to predict the LDL decrease from statin therapy in an individual patient.

Unfortunately, the majority of the reported analyses are for both the placebo-controlled trials and for the higher statin dose versus lower statin dose combined. This limits our interpretation of the results.
Only in the appendices do we find separate analyses for the 22 placebo-controlled trials and the 5 trials that compare a higher dose to a lower dose.
In their previous publication, the authors did report separately on placebo-controlled trials and high dose versus low dose trials for all endpoints, and reported the unadjusted relative risks as well as the relative risk per mmol/L reduction in LDL-C. This is a more preferable approach.

Where possible, we have chosen to report the results of the separate analyses for the placebo-controlled comparison. For the endpoints where these data were not available, we will report the results of the combined analysis (placebo-controlled trials and high-dose versus low-dose statin trials together).

4.1.1.2.1 Statin versus placebo

Statin versus placebo in an overall population and in subgroups according to baseline risk			
Bibliography: Individual patient data meta-analysis: CTT 2012(4)			
Outcomes	**N° of participants (studies) Follow up**	**Results** RR (CI) per 1·0 mmol/L reduction in LDL	**Quality of the evidence (GRADE)**
Major vascular event: major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations	134 537 (22 studies)	HR= **0.80 (0.78 – 0.82)** **SS in favour of statin** **SS in all 5-y MVE risk category subgroups**	*Not applied*
Major coronary event: non-fatal myocardial infarction or coronary death	134 537 (22 studies)	HR= **0.76 (0.73 – 0.79)** **SS in favour of statin** **SS in all 5-y MVE risk category subgroups**	*Not applied*
Any stroke	134 537 (22 studies)	**0.85 (0.81 – 0.90)** **SS in favour of statin** **SS in these subgroups:** ≥5% to <10% MVE risk ≥10% to <20% MVE risk	*Not applied*

Statin versus placebo

Individual patient data from 22 trials were included.

There is a statistically significant reduction* in major vascular events in the population taking a statin compared to placebo. This reduction is statistically significant across all risk groups.

GRADE: not applied

There is a statistically significant reduction* in major coronary events in the population taking a statin compared to placebo. This reduction is statistically significant across all risk groups.

GRADE: not applied

There is a statistically significant reduction* in total stroke events in the population taking a statin compared to placebo. However, this reduction is NOT significant in subgroups with risk stratification <5% and ≥20%.

GRADE: not applied

The CTT did not report on frequent adverse events.

** per 1.0 mmol/L reduction in LDL-cholesterol*

4.1.1.2.2 Statin or high dose statin versus placebo or low dose statin

Statin versus placebo or higher dose statin versus lower dose in an overall population and in subgroups according to baseline risk or according to previous vascular disease			
Bibliography: Individual patient data meta-analysis: CTT 2012(4)			
Outcomes	**N° of participants (studies) Follow up**	**Results** RR (CI) per 1·0 mmol/L reduction in LDL	**Quality of the evidence (GRADE)**
All-cause mortality	174149 (27 studies)	Overall HR= **0.91 (0.88 – 0.93)** **SS in favour of statin** 5y-MVE risk subgroups **SS in risk groups ≥10% to <20%; ≥20% to <30%; ≥30%** Patients without vascular disease: **HR= 0.91 (0.85 – 0.97)** **SS in favour of statin** **SS in MVE-risk group ≥5% to <10%** Participants with vascular disease: **0.90 (0.87 – 0.93)** **SS in favour of statin** **SS in MVE-risk group ≥20% to <30%; ≥30**%	*Not applied*
Any vascular death	174149 (27 studies)	Overall HR= **0.88 (0.84–0.91)** **SS in favour of statin** 5y-MVE risk subgroups **SS in risk groups ≥10% to <20%; ≥20% to <30%; ≥30%** Patients without vascular disease: **HR= 0.85 (0.77–0.95)** **SS in favour of statin** NS in all 5y-MVE subgroups Participants with vascular disease: **HR=0·88 (0·84–0·92)** **SS in favour of statin** **SS in MVE-risk group ≥20% to <30%; ≥30%**	*Not applied*

Statin versus placebo, or high dose statin versus low dose statin.
Individual patient data from 27 trials were included.

There is a statistically significant reduction* in all-cause mortality with statin treatment versus placebo or lower dose statin. A statistically significant decrease in all-cause mortality is also observed in the 3 highest MVE risk categories, but not in the 2 lowest MVE risk categories.

In patients without vascular disease, all-cause mortality is also significantly lower with statin therapy compared to placebo or lower dose statin. When this population is divided in subgroups according to 5y MVE risk, only in the risk category of ≥5% to <10% do we find a statistically significant difference.

In patients with vascular disease, all-cause mortality is significantly lower with statin therapy compared to placebo or lower dose statin. When this population is divided in subgroups according to 5y MVE risk, a statistically significant reduction in all-cause mortality is observed only in the 2 highest risk groups.

GRADE: not applied

There is a statistically significant reduction* in vascular death with statin therapy compared to placebo or lower dose statin in the overall study population. A statistically significant decrease in vascular death is also observed in the 3 highest MVE risk categories, but not in the 2 lowest MVE risk categories.

In patients without vascular disease, vascular death is also significantly lower with statin therapy compared to placebo or lower dose statin. When this population is divided in subgroups according to 5y MVE risk, no statistically significant difference in all-cause mortality rates is observed in any risk group.

In patients with vascular disease, vascular death is significantly lower with statin therapy compared to placebo or lower dose statin. When this population is divided in subgroups according to 5y MVE risk, a statistically significant reduction in all-cause mortality is observed only in the 2 highest risk groups.

GRADE: not applied

** per 1.0 mmol/L reduction in LDL-cholesterol*

4.1.2 Statin versus placebo in primary prevention

4.1.2.1 Evidence tables. Taylor 2013

Meta-analysis
Inclusion criteria

- RCT
- >= 12 m treatment, FU>= 6m
- study population to have less than or equal to 10% of a previous history of CVD (this would include previous angina, myocardial infarction and/or stroke). Trials in which statins were used to treat or control chronic conditions (e.g. Alzheimer's disease, rheumatoid arthritis, renal disease, macular degeneration, aortic stenosis) were excluded.
- Comparison: statins vs placebo or usual care
- Concomitant interventions were accepted if given to both arms of the study. Adjuvant treatments with one additional drug where a patient developed excessively high lipids during the trial were accepted.

Search strategy : different databases and reference lists
Assessment of quality of included trials: yes, Cochrane handbook of systematic reviews
ITT analysis: yes
Other methodological remarks:
Trial data were considered to be heterogeneous where the I2 statistic was > 50%.
For analysis: the fixed-effect method was used unless data were heterogenous in which case they used the random-effects model. (This is methodologically unsound.
In our opinion, a random effect model should have been used)
The authors state:
Excluding the five trials that included up to 10%participants with clinical evidence of CVD (none of the trials published the subgroup without any evidence of CVD) demonstrates very similar findings: total mortality RR 0.80 (95% CI 0.70 to 0.91) versus RR(??) 0.86 (0.79 to 0.94) in all trials; total CHD events RR 0.68 (0.59 to 0.77) versus 0.73 (0.67 to 0.80) in all trials; adverse events RR 0.99 (0.96 to 1.02) versus 1.00 (0.97 to 1.03) in all trials.
Sensitivity analysis suggested that early stopping of trials and size of trial did not influence the overall results.

Ref	Comparison	N/n	Outcomes	Result
Taylor 2013(32) Design: SR+MA Search date: (jan-2012) N= 18 n= 56.934	Statins vs placebo or usual care	N= 13 n= 48.060 (ACAPS 1994, Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, ASPEN 2006, Bone 2007, CARDS 2008, CERDIA 2004, JUPITER 2008, KAPS 1995, METEOR 2010, PHYLLIS 2004, PREVEND IT 2004, WOSCOPS)	**All-cause mortality**	**Statin: 1077/24.408** **No statin:1223/23.652** **OR: 0.86 [95%CI 0.79 to 0.94]** **NNT for 5y: 96 [95%CI 64 to 244]** **SS**
		N= 14 n= 48.049 (ACAPS 1994, Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, ASPEN 2006, CAIUS 1996, CARDS 2008, CERDIA 2004, HYRIM 2007, JUPITER 2008, KAPS 1995, METEOR 2010, PHYLLIS 2004, PREVEND IT 2004, WOSCOPS)	**Total number of CHD events**	**Statin: 820/24.217** **No statin: 1114/23.832** **RR: 0.73 (95% CI 0.67 to 0.80)** **NNT for 5y: 56 (95%CI 46 to 75)** **SS**
		N=10 n= 46.094 (ACAPS 1994, Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, ASPEN 2006, CAIUS 1996, CARDS 2008, JUPITER 2008, KAPS 1995, PREVEND IT 2004, WOSCOPS)	**Fatal CHD events**	**Statin: 251/23.019 (1.1%)** **No statin: 306/23.075 (1.3%)** **RR: 0.82 (95% CI 0.70 to 0.96)** **SS**
		N= 9 n= 23.805 (ACAPS 1994, Adult Japanese MEGA Study, CAIUS 1996, CARDS 2008, CERDIA 2004, HYRIM 2007, MRC/BHF heart Protection, PREVEND IT 2004,	**Total number of CVD events**	**Statin: 1103/11.892 (9.3%)** **No statin: 1455/11.913 (12.2%)** **RR: 0.75 (95% CI 0.70 to 0.81)** **SS**

		WOSCOPS)		
		N= 5 n= 34.012 (ACAPS 1994, Adult Japanese MEGA Study, JUPITER 2008, PREVEND IT 2004, WOSCOPS)	**Fatal CVD events**	**Statin: 295/16.962 (17.4%)** **No statin: 355/17.050 (20.8%)** **RR: 0.83 (95% CI 0.72 to 0.96)** **SS**
		N= 10 n= 40.295 (ACAPS 1994, Adult Japanese MEGA Study, ASPEN 2006, Bone 2007, CARDS 2008, JUPITER 2008, KAPS 1995, PHYLLIS 2004, PREVEND IT 2004, WOSCOPS)	**Total number of stroke events**	**Statin: 345/20.302 (17%)** **No statin: 442/19.993 (22%)** **RR: 0.78 (95%CI 0.68 to 0.89)** **SS**
		N=3 n= 27.238 (CARDS 2008, JUPITER 2008, WOSCOPS-)	**Fatal stroke events**	**Statin: 57/13.632 (0.4%)** **No statin: 50/13.606 (0.4%)** **RR: 0.63 (95%CI 0.18 to 2.23)** **NS**
		N= 4 n= 35.254 (Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, CARDS 2008, JUPITER 2008)	**Combined endpoint (fatal and non-fatal CHD, CHD and stroke events)**	**Statin: 438/17.591 (2.4%)** **No statin: 678/17.663 (3.8%)** **RR: 0.65 (95% CI 0.58 to 0.73)** **SS**
		N= 16 n= 41.380 (ACAPS 1994, Adult Japanese MEGA Study, ASPEN 2006, CAIUS 1996, CARDS 2008, CELL A 1996, CELL B 1996, CERDIA 2004, Derosa 2003, HYRIM 2007, JUPITER 2008, KAPS 1995, METEOR 2010, PHYLLIS 2004, PREVEND IT 2004, WOSCOPS)	**LDL cholesterol**	Net difference -1.00 (95% CI -1.16 to -0.85 mmol/L)

		N= 7 n= 42.403 (Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, CAIUS 1996, CARDS 2008, JUPITER 2008, KAPS 1995, WOSCOPS)	***Revascularisation;***	**Statin: 286/ 21.166 (1.4%)** **No statin: 461/21.237 (2.2%)** **RR: 0.62 (95%CI 0.54 to 0.72)** **SS**
		N=2 n=25634 Adult Japanese MEGA study 1998, Jupiter 2008	**Number of study participants who developed haemorrhagic stroke**	OR= 0.97 (0.54-1.75) NS
		N= 11 n= 38.739 (AFCAPS/TexCAPS 1998, ASPEN 2006, Bone 2007, CAIUS 1996, CARDS 2008, CERDIA 2004, JUPITER 2008, KAPS 1995, METEOR 2010, PHYLLIS 2004, WOSCOPS)	**Number of study participants who developed cancer**	Statin: 1180/19.789 (5.96%) No statin: 1075/18.950 (5.67%) RR: 1.01 (95%CI 0.93 to 1.10) NS
		N= 9 n= 37.938 (AFCAPS/TexCAPS 1998, ASPEN 2006, Bone 2007, CARDS 2008, CERDIA 2004, JUPITER 2008, KAPS 1995, METEOR 2010, WOSCOPS)	**Number of study participants who developed myalgia or muscle pain**	Statin: 1847/19.396 (9.52%) No statin: 1704/18.542 (9.18%) RR: 1.03 (95%CI 0.97 to 1.09) NS
		N= 6 n= 38.468 (Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, ASPEN 2006, CARDS 2008, JUPITER 2008, METEOR 2010)	***Number of study participants who developed rhabdomyolysis***	Statin:3/19.410 (0.02%) No statin:3/19.058 (0.02%) RR: 1.00 (95%CI 0.23 to 4.38) NS
		N= 2 n=24.407 (AFCAPS/TexCAPS 1998, JUPITER 2008)	**Number of study participants who developed diabetes**	Statin: 342/12.205 (2.8%) No statin: 290/12.202 (2.4%) RR: 1.18 (95%CI 1.01 to 1.39) SS

		N= 10 n= 40.094 (ACAPS 1994, Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, ASPEN 2006, Bone 2007, CARDS 2008, CERDIA 2004, JUPITER 2008, KAPS 1995, METEOR 2010)	***Number of study participants who had elevated liver enzymes***	Statin:476/20.420 (2.3%) No statin:472/19.674 (2.4%) RR: 1.16 (95%CI 0.87 to 1.54) NS
		N= 8 n= 41.712 (Adult Japanese MEGA Study, AFCAPS/TexCAPS 1998, Bone 2007, JUPITER 2008, KAPS 1995, METEOR 2010, , PREVEND IT 2004, WOSCOPS)	***Treatment compliance***	Statin: 16.438/21.207 (77%) No statin: 14.534/20.505 (70%) RR: 1.08 (95%CI 0.98 to 1.18) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
ACAPS 1994(33) RCT 4x4 factorial design	919	USA patients, mean age 62y, none with any clinical evidence of CVD The study population was men and women, 40 to 79 years old, with early carotid atherosclerosis and moderately elevated LDL cholesterol	34 months	20 mg lovastatin vs placebo (treatment arms with warfarin also in study but not reported here)	Carotid atherosclerosis, cholesterol, fatal + non-fatal CHD events, stroke	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors Carers and patients were blinded FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: 3- to 4-week run-in period during which they were given lovastatin placebo and open-labeled warfarin (1 mg/dL). “One purpose of the run-in phase was to identify and exclude participants who took <80% of their pills” (randomization after run-in)

						"Of the 960 persons returning for the baseline visit, only 4% (n=41) failed to qualify for randomization. The majority (33 of the 41) failed the run-in because of adherence problems."
Adult Japanese MEGA Study(22) RCT, single blind	7832	participants with hypercholesterolaemia based in Japan aged 40-70 (mean age 59) ; 32% men. None with any clinical evidence of CVD	5 years	10-20 mg pravastatin vs placebo; all participants got advice on diet	Primary: composite of major CVD events, sudden cardiac death, angina and revascularisation. Single outcomes included: all-cause mortality, total CVD events, fatal and nonfatal MI, stroke and TIA events, sudden cardiac death, angina and revascularisation, cholesterol, adverse events	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Inadequate; single blinded endpoint committee was blinded only because investigators stated that placebo-controlled trials are regarded with suspicion by Japanese participants FOLLOW-UP: 98 % in efficacy analysis ITT:yes FUNDING: low risk (funded by pharm industry) Selective reporting: high risk. Not all adverse events reported. We wrote to the authors asking for clarity regarding data on serious events. The authors responded saying they were unable to send the data
AFCAPS/TexCAPS 1998(6) RCT, double blind	6606	participants in Texas, USA; Average TC and LDL-C levels and below-averageHDL-C levels Lipid entry criteria(TC,4.65-6.82mmol/L[180-264mg/dL];LDL-C,3.36-4.91 mmol/L [130-190 mg/dL]; HDL-C,≤ 1.16mmol/L [45mg/dL]for men or ≤1.22mmol/L [47 mg/dL] for women; and triglycerides, ≤4.52 mmol/L [400 mg/dL] mean age 58; 57.5% men; 89%Caucasian. None with any clinical evidence of CVD	5.2 years	20-40 mg lovastatin vs placebo; all participants received advice on diet	Primary: composite of fatal and non-fatal MI and fatal CHD events. Single outcomes included: all-cause mortality, fatal and non-fatal CVD + stroke events, heart failure and adverse events	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were

						randomized. No information on how many people were excluded in this step. *Trial was stopped prematurely. To be terminated when 320 participants had experienced primary outcome event. Stopped when 267 had done at 5.2 years*
ASPEN 2006(11) RCT, double blind	2410	participants with type 2 diabetes based in 16 developed countries with mean age 60; 62.5% men; 84% Caucasian. < 10% with clinical evidence of CVD	2.4 years	10 mg atorvastatin Vs placebo;	Primary: composite of fatalMI, stroke, sudden cardiac death, heart failure, CVD death. Single outcomes included: non-fatal or silentMI + stroke, revascularisation, resuscitated cardiac arrest, TIA, unstable angina, peripheral arterial disease, Ischaemic heart failure and adverse events	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 22% drop outs reported ITT:yes Run-in: 6-week, single-blind, placebo-baseline period, at the end of which baseline values for vital signs and lipids were obtained and subjects were randomly assigned excluded if run-in compliance rate <80% 2901 patients received placebo run-in, of which 490 (17%) excluded FUNDING: unclear risk (funded by pharm industry)
Bone 2007(34) RCT, double blind	626	Post-menopausal women aged 40-75 years with dyslipidaemia and no history of CHD or diabetes. None with any clinical evidence of CVD	?	Atorvastatin (10/20/40/80 mg/day) Vs Placebo All patients were instructed to be on NCEP	Primary: Percentage change in lumbar spine bone marrow density Seconday: Percentage change in femoral neck etc BMD by DXA. other; adverse events	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Unclear;states double blind but only reports that the participants were blinded to intervention FOLLOW-UP: 5% dropped out

				ATP III diet		ITT:yes FUNDING: unclear risk (funded by pharm industry)
CAIUS 1996(35) RCT, double blind	305	participants with hypercholesterolaemia based in Italy with mean age 55; 53%men. None with any clinical evidence of CVD	3 years	40 mg pravastatin Vs placebo	Slope of carotid artery, fatal and non-fatal MI, angina, revascularisations, cholesterol and adverse events	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Unclear; double-blind: participants and personnel FOLLOW-UP: 13% dropped out ITT:yes Run-in: 6 week placebo run-in + diet, randomized afterwards FUNDING: unclear risk (funded by pharm industry)
CARDS 2008(13)	2838	participants with diabetes (and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension) based in UK and Ireland aged 40-75 years (mean 61.7) ; 68% men; 94.5% Caucasian. None with any clinical evidence of CVD	3.9-4 years	10 mg atorvastatin, all patients were given counselling on cessation of smoking	Primary: composite of fatal and non-fatal MI, acute CHD death, resuscitated cardiac arrest. Single outcomes included: all-cause mortality, fatal and non-fatal or silent MI + stroke, revascularisation, resuscitated cardiac arrest, total CVD events, adverse events and cholesterol	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate (triple blind part/pers/assess) FOLLOW-UP: 1% lost to follow up ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: excluded if during the baseline phase they had less than 80% compliance with placebo 12% excluded from baseline phase Trial stopped prematurely due to large

						beneficial treatment effect We calculated numbers needed to treat as the reciprocal of the absolute risk reduction for the primary endpoint for a treatment duration of 4 years (the median follow-up time) in 1000 patients. Treatment would be expected to prevent at least 37 major vascular events per 1000 such people treated for 4 years 27 patients would need to be treated for 4 years to prevent one event. However, incidence of first or subsequent major cardiovascular disease events was 31·8 per 1000 person-years at risk in the placebo group and 19·5 per 1000 person years at risk in the atorvastatin group. Therefore, allocation of 1000 such patients to atorvastatin 10 mg daily would be expected to be associated with 50 fewer first or subsequent major cardiovascular disease events over a 4-year period of follow-up..
CELL A 1996(36) RCT, double blind, 2x3 factorial design	228	participants with hyperlipidaemia based in Sweden - at least two cardiovascular risk factors in addition to moderate primary hyperlipidaemia (total cholesterol of at least 6.50 mmol L) with a mean age of 49; 85% men, <10% had clinical evidence of CVD	18 months	10-40 mg pravastatin plus dietary advice vs placebo plus dietary advice	Main outcome measure: changes in the overall Framingham risk score. Fatal MI, cholesterol, quality of life.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 14.5% dropped out ITT:yes Selective reporting: high risk: adverse event rates not provided for each group FUNDING: unclear risk (funded by pharm industry)
CELL B 1996(36)	227	participants with hyperlipidaemia	18	10-40 mg	Main outcome	ALLOCATION CONC:

RCT, double blind, 2x3 factorial design		based in Sweden - at least two cardiovascular risk factors in addition to moderate primary hyperlipidaemia (total cholesterol of at least 6.50 mmol L) with a mean age of 49; 85% men, <10% had clinical evidence of CVD	months	pravastatin plus dietary advice Vs placebo plus dietary advice	measure: changes in the overall Framingham risk score. Fatal MI, cholesterol, quality of life.	Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 6% dropped out ITT:yes Selective reporting: unclear risk: CVD and adverse events rates not provided for each group FUNDING: unclear risk (funded by pharm industry)
CERDIA 2004(37) RCT, double blind	250	patients with type 2 Diabetes aged 30-80 years. None with any clinical evidence of CVD	2y	0.4 mg of Cerivastatin until 08/2001 then Simvastatin 20 mg	Primary outcome: Change inmean common carotid intimamedia thickness (IMT) after 24 months of intervention. Secondary outcomes: Changes in Mean + maximum IMT at 24 months, CVD events, amputation due to atherosclerotic disease, serum levels of LDL and total cholesterol	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors unclear; states double blind but only reported that participants were blinded to intervention FOLLOW-UP: 73 % in efficacy analysis ITT: no FUNDING: unclear risk (funded by pharm industry)
Derosa 2003(38)	47	participants with hypercholesterolaemia based in Italy	1 year	80 mg fluvastatin	Adverse events, cholesterol.	ALLOCATION CONC: Adequate

RCT, single blind		with a mean age of 51; 46% men. None with any clinical evidence of CVD		Vs Placebo all participants were given advice on diet and exercise		RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry)
HYRIM 2007(39) RCT, double blind. 2x2 factorial design	287	men with drug-treated hypertension based in Norway aged 40-75 years (mean age 57). None with any clinical evidence of CVD	4 years	40 mg fluvastatin vs placebo (2x2 design also intensive lifestyle intervention vs usual care)	primary endpoint: development of intima media thickness in the common carotid artery	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: not described and no drop outs reported ITT: unclear FUNDING: unclear risk (funded by pharm industry)
JUPITER 2008(19) RCT, double blind	17802	apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher >50 years. None with any clinical evidence of CVD	median 1.9 years	Rosuvastatin 20 mg daily.	-Primary end point (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes) -adverse events	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 100 % in efficacy analysis ITT: yes Stopped early with a median follow-up of 1.9 years.

						Run-in : 4-week run-in phase during which they received placebo. Only subjects who successfully completed the run-in phase were enrolled (19323 received run-in, of which 1521 excluded =7.8%) Primary endpoint event rate higher than predicted. Mortality higher than predicted (by comparison to other trials) Funding: High risk (funded by pharm industry) "On the basis of Kaplan–Meier estimates (Fig. 1), the number of patients who would need to be treated with rosuvastatin for 2 years to prevent the occurrence of one primary end point is 95, and the number needed to treat for 4 years is 31. If 4-year risks are projected over an average 5-year treatment period, as has been commonly done in previous statin trials according to the method of Altman and Andersen the number needed to treat to prevent the occurrence of one primary end point is 25."
KAPS 1995(40) RCT, double blind	447	men based in Finland aged 44-65 years (mean 57). < 10% with clinical evidence of CVD	3 years	40 mg pravastatin Vs placebo	Carotid atherosclerotic progression, total mortality, fatal and non-fatalMI events, stroke, adverse events, cholesterol, other cardiac death, revascularisations, non cardiac death and heart failure	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 83 % in efficacy analysis ITT: no FUNDING: unclear risk (funded by pharm industry)
METEOR 2010(41)	984	asymptomatic individuals with either age (mean, 57 years) as	2y	Rosuvastatin 40 mg/ day.	Primary:Mean of 12 Carotid Intima	ALLOCATION CONC: Adequate

RCT		the only coronary heart disease risk factor or a 10-year FRS of less than 10%, modest CIMT thickening (1.2-<3.5 mm), and elevated LDL cholesterol (mean, 154 mg/dL) None with any clinical evidence of CVD			media (CIMT) thickness measurements. Secondary: CIMT measurements of left and right common carotid artery. Other relevant outcomes: adverse events, cholesterol levels	RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 25-6% dropped out. ITT:yes FUNDING: unclear risk (funded by pharm industry)
MRC/BHF heart Protection(42) RCT, double blind, 2x2 factorial design	3982	total trial population: 6748 UK adults with PAD and 13,788 other high-risk participants (non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) were eligible provided they had a medical history of coronary disease, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and aged at least 65 years).) patients with no prior CHD with diabetes mellitus as a subset of these 20,536 UK adults aged 40-80 years	5.3 years	40 mg simvastatin Vs placebo and, separately, using a two-by-two factorial design, antioxidant vitamins or matching placebo capsules	Composite of coronary and vascular events, stroke, revascularisations	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: not described ITT:not described Selective reporting: high risk: only CVD event results provided for this subgroup FUNDING: unclear risk (funded by pharm industry)
PHYLLIS 2004(43) RCT , double blind, 4x4 factorial	253	men and women aged 45-70 (mean age 58) with hypertension, hypercholesterolaemia and asymptomatic carotid atherosclerosis based in Italy. None with any clinical evidence of CVD	2.6 years	25 mg hydrochlorothiazide vs fosinopril and 40 mg pravastatin vs placebo	Primary outcomes: carotid atherosclerosis. Secondary outcomes: non-fatal MI, CVD death, stroke,	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate

					cholesterol and cancer	FOLLOW-UP: 20% dropouts reported Run-in: 6-week washout under triple placebo and American Heart Association low-lipid diet. ITT: yes FUNDING: unclear risk (funded by pharm industry)
PREVEND IT 2004(44) RCT, double blind, 2x2 factorial	864	participants with microalbuminuria based in Holland aged 28-75 years (mean age 51); 64.5% men; 96% Caucasian. < 10% with clinical evidence of CVD	3.8 years	40 mg pravastatin Vs placebo (2x2 factorial: also fosinopril vs placebo)	<u>primary end point was cardiovascular mortality and hospitalization for cardiovascular morbidity</u> Cardiovascular hospitalization was defined as hospitalization for documented (1) nonfatal myocardial infarction or myocardial ischemia, (2) heart failure, (3) peripheral vascular disease, and/or (4) cerebrovascular accident. Single outcomes included fatal CVD events, stroke, heart failure, non-fatal MI and cholesterol	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 6% dropped out ITT: yes but confined to CVD events FUNDING: unclear risk (funded by pharm industry) Subjects treated with pravastatin had a 13% lower incidence of the primary end point than subjects in the placebo group (4.8% versus 5.6%, *P*_0.649;NOT STATISTICALLY SIGNIFICANT
WOSCOPS(26)	6595	men with hypercholesterolaemia (the LDL cholesterol level was at least	4.9 years	40 mg pravastatin	<u>Primary outcome: composite of non-</u>	ALLOCATION CONC: Adequate

RCT, double blind		155 mg per deciliter after dietary advice) based in Scotland aged 45-64 (mean age 55). (mean (± SD) plasma cholesterol level of 272 ±23 mg per deciliter (7.0 ±0.6 mmol per liter) < 10% with clinical evidence of CVD		Vs placebo	fatalMI andCHDdeath. Single outcomes included total mortality, fatal CVDevents, cholesterol, revascularisations, non-fatalMI and CHD death and adverse events	RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 30% drop-outs reported ITT: yes FUNDING: unclear risk (funded by pharm industry)

Author's conclusions (Taylor 2013):
"Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins"

The previous edition of this review (2011) also found a statistically significant benefit of statin versus control for all-cause mortality (RR 0,84; 95%BI: 0,73-0,96) and cardiovascular morbidity (RR 0,70; 95%BI: 0,61-0,79). At that time, the authors advised caution in prescribing statins for primary prevention to patients with low cardiovascular risk, given the limited benefit and unclear cost-effectiveness.

The authors now have changed their conclusions, possibly under pressure from the CTT publication, as can be suspected from the included correspondence.
The authors conclude now that statin treatment reduceces total mortality and cardiovascular morbidity in patients without known cardiovascular disease.
However, they still note their concerns that were the basis of the previous cautious approach: i.e. medicalization of a large part of the elderly population, lifelong treatment, unclear cost-effectieness, risk of undertreating high risk groups. The authors also point out that 47 % of the patients in the meta-analysis came from 3 trials that were stopped early due to a clear benefit in the intervention arm. This may lead to an overestimation of the treatment effect.

4.1.2.2 Summary and conclusions. Taylor 2013. Statins versus placebo or usual care in primary prevention

Statin versus placebo or usual care in patients without a history of cardiovascular disease			
Bibliography: Meta-analysis: Taylor 2013(32)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	48060 (13 studies) 1.9y-5.2y	**OR: 0.86 [95%CI 0.79 to 0.94]** **SS in favour of statins** **Estimated NNT for 5y: 96 [95%CI 64 to 244]**	⊕⊕⊕⊖ **MODERATE** Study quality:- 1 for early stop and use of placebo run-in Consistency:OK Directness:very mixed population… no points deducted but low applicability Imprecision:OK
Fatal CVD events	34012 (5 studies) 1.9y-5y	**RR: 0.83 (95% CI 0.72 to 0.96)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality:- 1 for early stop and use of placebo run-in Consistency:OK Directness:very mixed population… no points deducted but low applicability Imprecision:OK
Total CVD events	23805 (9 studies) 3y-5.3y	**RR: 0.75 (95% CI 0.70 to 0.81)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality:- 1 for early stop and use of placebo run-in Consistency:OK Directness:very mixed population… no points deducted but low applicability Imprecision:OK
Total CHD events	48049 (14 studies) 1.9y-5y	**RR: 0.73 (95% CI 0.67 to 0.80)** **SS in favour of statins** **Estimated NNT for 5y: 56 (95%CI 46 to 75)**	⊕⊕⊕⊖ **MODERATE** Study quality:- 1 for early stop and use of placebo run-in Consistency:OK Directness:very mixed population… no points deducted but low applicability Imprecision:OK
Total stroke events	40295 (10 studies) 1.9y-5y	**RR: 0.78 (95%CI 0.68 to 0.89)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality:- 1 for early stop and use of placebo run-in Consistency:OK Directness:very mixed population… no points deducted but low applicability Imprecision:OK
Haemorrhagic stroke	25634 (2 studies) 1.9y-5y	OR= 0.97 (0.54-1.75) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 incomplete reporting Consistency: OK Directness:-1 varying populations Imprecision: OK
Cancer	38739 (11 studies)	RR: 1.01 (95%CI 0.93 to 1.10) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for reporting issues

	1.9y-5y		Consistency: OK Directness:-1 varying populations Imprecision: OK
Myalgia or muscle pain	37938 (9 studies) 1.9y-4.9y	RR: 1.03 (95%CI 0.97 to 1.09) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for run in and reporting issues Consistency: OK Directness:-1 varying populations Imprecision: OK
Rhabdomyolysis	38468 (6 studies) 1.9y-5.2y	RR: 1.00 (95%CI 0.23 to 4.38) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for run in and reporting issues Consistency: OK Directness:-1 varying populations Imprecision: OK
New onset diabetes	24407 (2 studies) 1.9y-2.8y	**RR: 1.18 (95%CI 1.01 to 1.39)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for premature stopping Consistency: OK Directness:OK Imprecision: OK

This Cochrane systematic review and meta-analysis compared statins to placebo in primary prevention, i.e. in patients with no previous history of cardiovascular disease. However, trials in which there were ≤ 10% of patients with a history of cardiovascular disease, were also included. Populations of included trials were diverse: 14 trials included specific populations (diabetics, people with hypertension or hyperlipidaemia or microalbuminuria). Therefore, included populations could have a substantially different baseline risk of cardiovascular disease. Duration of included trials ranged from 1 year to 5.3 years.
The authors point out that 47% of the patients in this meta-analysis came from 3 trials that were stopped early due to a clear benefit in the intervention group. This may lead to an overestimation of the treatment effect.
An NNT for 5 years of treatment was reported for all-cause mortality and total CHD events. It is unclear how this NNT was calculated.

In this clinically heterogenous population, all-cause mortality is significantly lower with statins compared to placebo, as were fatal CVD events.
GRADE: MODERATE quality of evidence

Total CVD events, total CHD events and total stroke events are also reduced with statins compared to placebo.
GRADE: MODERATE quality of evidence

The pooling of two trials shows no statistically significant difference in the risk of haemorrhagic stroke.
GRADE: LOW quality of evidence

No statistically significant difference between statins and placebo is observed in the incidence of cancer, myalgia or muscle pain and rhabdomyolysis.

However, not all trials reported well on adverse events. Most trials used a placebo run-in period, excluding patients that were not compliant.
No reliable estimate on adverse events can therefore be made.
GRADE: LOW quality of evidence

The pooling of two trials shows an increased risk of new-onset diabetes with statins compared to placebo.
GRADE: MODERATE quality of evidence (see also chapter on adverse events)

4.1.2.3 Other meta-analyses in primary prevention

In recent years several authors have published meta-analyses of statins versus placebo in primary prevention. We decided to report on only the two most recent publications (Taylor 2013 and CTT 2012). We briefly describe 3 other meta-analyses below.

Brugts 2009(45) sought randomized clinical studies with statins vs. control or placebo in patients without established cardiovascular disease, but with cardiovascular risk factors. Studies had to contain at least 80% patients without cardiovascular conditions or report the data of patients without previous cardiovascular disease separately in order to be included. The original authors were contacted in order to obtain any unpublished data. Diabetes was not an exclusion criterion. The follow-up had to last at least 1 year and cardiovascular morbidity and/or mortality had to be the primary outcome measures.
10 studies with in total 70388 participants were included. The average follow-up was 4.1 years. A significant decrease compared to placebo was demonstrated in the number of severe coronary incidents (OR: 0.70; 95%CI 0.61-0.81) and cerebrovascular incidents (OR: 0.81; 95% CI 0.71-0.93) and in the total mortality (OR: 0.88; 95%CI 0.81-0.96). The outcomes were the same when three trials with a small number of patients with known cardiovascular conditions were omitted from the analysis.
The authors concluded that the use of statins in people without cardiovascular disease but with cardiovascular risk factors was associated with a significant decrease in mortality and an important decrease in cardiovascular morbidity. They pointed out however that despite the fact that these were largely studies in primary prevention, the studies clearly included patients with an increased cardiovascular risk, as evidenced by the higher than expected annual incidence of fatal and non-fatal cardiovascular incidents (respectively 1.1 and 0.6%) and an annual mortality of 1.4%; figures that do not differ much from those in some of the secondary prevention studies.

Tonelli 2011(46) included randomized controlled trials with statins in people with a low cardiovascular risk (defined as a 10-year risk of cardiovascular mortality or non-fatal cardiac infarct of less than 20%, calculated by extrapolating the observed risk in the control groups of each study),with a follow-up of at least 6 months. Data from studies in a mixed (primary and secondary prevention) population were included if the 10-year risk was lower than 20% in the control group. Studies specifically about patients with diabetes were excluded, but on the other hand studies in people with Alzheimer's or with chronic kidney failure were included. Outcome measures were both cardiovascular morbidity and cardiovascular and total mortality.
In this way they identified 23 studies with in total 79495 participants and an average follow-up of 2 years. The average 10-year risk of cardiovascular mortality or non-fatal cardiac infarct amounted to 6%. Significant differences between statins and placebo were demonstrated for total mortality (RR 0.90; 95% CI 0.84-0.97) and coronary and cardiovascular morbidity (and further cardiac endpoints) (RR major coronary events 0.63; 95% CI 0.50-0.79), RR of major cerebrovascular events 0.83; 95% CI 0.74-0.93).
The NNT to prevent 1 extra death amounted to 239 (the number needed to treat was calculated based on the pooled risk in the control group of all studies included. The duration of treatment to which the NNT relates, thus appears to be the average duration of the studies included: average 2 years (range 0.5 years to 5.3 years).

Subgroup analyses indicated no relevant differences between so-called high-potency statins and low-potency statins.
The conclusion of the authors is that both high and low-potency statins are effective in the prevention of death and cardiovascular conditions in people with a 10-year risk of cardiovascular death or non-fatal myocardial infarct, most of whom had no known cardiovascular conditions or diabetes, with high NNTs.

Ray 2010(47) also sought randomized clinical studies of statins vs. placebo or control in patients without established cardiovascular disease. They concentrated only on total mortality as the primary endpoint. They also requested and obtained unpublished data. Studies from which it was not possible to separate the primary from the secondary prevention patients were excluded. Diabetes was not an exclusion criterion.
They included largely the same studies as Brugts 2009 but obtained more unpublished data, so that in the end they included 11 studies with in total 65229 patients. The average follow-up amounted to 3.7 years. A non-significant difference was demonstrated between statin and placebo/control regarding total mortality (RR 0.91; 95%CI 0.83-1.01), which made the authors conclude that statins do not affect the total mortality in primary prevention.
The authors postulate that the careful exclusion of patients with previous cardiovascular disease from the different study populations explains the difference between their findings and those of Brugts et al. They also point out the large difference in reduction in mortality between the meta-analysis and the large JUPITER study (that provided a good quarter of the patients in this meta-analysis), which was ended prematurely and the authors suspect that the reduction in mortality in JUPITER (20% after 1.9 years follow-up) is an overestimation and the result of stopping this study prematurely.

4.1.3 Statin versus placebo in patients with a history of stroke or TIA

4.1.3.1 Evidence tabels

Meta-analysis: Interventions in the management of serum lipids for preventing stroke recurrence

Inclusion criteria: Unconfounded randomised trials of participants aged 18 years and over with a history of stroke or transient ischaemic attack (TIA).
Search strategy: adequate. Cochrane Stroke Group Trials Register (last searched December 2008), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2008), MEDLINE (1966 to December 2008) and EMBASE (1980 to December 2008). We contacted pharmaceutical companies known to produce a lipid-lowering agent for information on relevant publications or unpublished work.
Assessment of quality of included trials: yes
ITT analysis: unclear
Other methodological remarks: -

Ref	Comparison	N/n	Outcomes	Result
Manktelow Bradl-2009-(48) Design: Search date: December 2008 (New search for studies and content updated (conclusions changed), published in Issue 3, 2009)	Statins, Fibrates Vs Placebo In patients with history of stroke or TIA	N= 5 (statins) n= 9224 (CARE,1999 ; FASTER, 2007 ; HPS, 2004; LIPID, 2000; SPARCL, 2000)	All ischaemic or haemorrhagic strokes (PO) N=5	501/4645 (Statins) vs 553/4579 (Placebo) OR=0.88 (95% CI 0.77, 1.00) NS p = 0.05
			All-cause mortality, including sudden deaths N=1 (SPARCL, 2000)	216/2365 (Statins) vs 211/2366 (Placebo) OR=1.03 (95% CI 0.84, 1.25) NS p = 0.80
			Serious vascular events N=3 (FASTER, 2007 ; HPS, 2004; SPARCL, 2000)	**959/4209 (Statins) vs 1192/4194 (Placebo)** **OR=0.74 (95% CI 0.67, 0.82)** **SS p<0.00001 in favor of statins**
			Ischaemic strokes N= 2 (HPS, 2004 ; SPARCL, 2000)	**318/4010 (Statins) vs 396/4001 (Placebo)** **OR=0.78 (95% CI 0.67, 0.92)** **SS p=0.0020 in favor of statins**
			Haemorrhagic strokes N= 2 (HPS, 2004; SPARCL, 2000)	**76/4010 (Statins) vs 44/4001 (Placebo)** **OR=1.72 (95% CI 1.20, 2.46)** **SS p=0.0033 in favor of placebo**
		N= 2 (fibrate) n= 627 (Acheson, 1972; VACSA, 1973)	All ischaemic or haemorrhagic strokes N= 2	60/315 (Fibrates) vs 45/312 (Placebo) OR=1.48 (95% CI 0.94, 2.30) NS p = 0.087
			All-cause mortality, including sudden deaths N= 2	45/315 (Fibrates) vs 50/312 (Placebo) OR=0.87 (95% CI 0.55, 1.39)

				NS p = 0.087
			Serious vascular events N=1 (VACSA, 1973)	67/268 (Fibrates) vs 55/264 (Placebo) OR=1.27(95% CI 0.84, 1.89) NS p = 0.25
	Statins, Fibrates Vs Placebo In patients with history of stroke	N= 2 (statins) n= 491 (CARE,1999 ; LIPID, 2000)	All ischaemic or haemorrhagic strokes	29/233 (Statins) vs 41/258 (Placebo) OR=0.73 (95% CI 0.44, 1.22) NS p = 0.23
		N= 1 (clofibrate) n= 485 (VACSA, 1973)	All ischaemic or haemorrhagic strokes	32/241(Fibrates) vs 23/244 (Placebo) OR=1.47(95% CI 0.84, 2.57) NS p = 0.18

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Acheson, 1972(49) RCT (PG) UK	106	Age: 43 to 76 years Male: 68% Inclusion: previous stroke or TIA	between 4 months and 4 years	Clofibrate (250 mg capsules: 4 to 6 daily for females; 6 to 8 daily for males) vs Placebo (corn oil for first 20 months of trial)	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors unclear FOLLOW-UP: 89.7% ITT: ? FUNDING: ?
CARE, 1999(50) RCT (PG) USA	211 =Sub group analysis of trial (4159 whole trial)	211 previous stroke or TIA Age: 21 to 75 years Male: 86% (whole trial) Inclusion: MI 3 to 20 months before randomisation, total cholesterol < 240 mg/dl; LDL 115 to 174 mg/ dl; triglycerides _ 350 mg/dl	median 5.0 years	Pravastatin (40 mg/d) vs Matching placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: >99% ITT:yes FUNDING:?

FASTER, 2007(51) RCT (PG) 2 x 2 factorial design with clopidogrel Canada	392	Age: 40 years or older Male: 53% Inclusion: TIA or minor stroke (NIHSS < 4) within 24 hours of onset	90 day follow-up Trial stopped early because of low recruitment	Simvastatin (40 mg/d) vs Matching placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors unclear FOLLOW-UP:? ITT:yes FUNDING:
HPS, 2004(52) RCT (PG) 2 x 2 factorial design with antioxidant vitamin supplementation UK	3280 =Sub group analysis of trial (20536 whole trial)	3280 with previous cerebrovascular event 64% with a history of ischaemic stroke and 46% with TIA (those with cerebral haemorrhage were excluded) Age: around 40 to 80 years Inclusion: non-fasting total cholesterol _ 135 mg/dL, substantial 5-year risk from CHD	mean of five years	Simvastatin (40 mg/d) vs Matching placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? 35% of patients were enrolled on the basis of noncoronary vascular disease and 1% on the basis of high-risk hypertension. We conducted analyses with and without this trial.
LIPID, 2000(53) RCT (PG) Australia and New Zealand	369 =Sub group analysis of trial (9014 whole trial)	369 with previous stroke Age: 31 to 75 years Male: 83% Inclusion: MI or unstable angina pectoris 3 to 36 months before randomisation; total cholesterol 155 to 271 mg/dl and fasting triglicerides < 445 mg/dl	6 years	Pravastatin (40 mg/d) vs Matching placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:?
SPARCL, 2000(54)	4731	Age: over 18	median 4.9	Atorvastatin (80 mg/d)	ALLOCATION CONC:

RCT (PG) worldwide (205 sites)		Male: 59.8% Inclusion: stroke or TIA in previous 6 months (cardio-embolic strokes excluded) cerebral infarction (67%), TIA (30%) and cerebral haemorrhage (2%)	years	vs Matching placebo	Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: ITT:yes FUNDING:?
VACSA, 1973(55) RCT (PG) USA	541	Age: 70 or under Male: 100% Inclusion: history of cerebral infarction or TIA	up to 4.5 years	Clofibrate (500 mg x 4 daily) Vs Matching placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors? unclear FOLLOW-UP: 98.4% ITT:? FUNDING:?

Author's conclusions (Manktelow-Bradley 2009):

"Implications for practice

There is good evidence for a benefit of statin therapy in those under the age of 80 years with a previous non-disabling stroke or TIA (but not cerebral haemorrhage) who have baseline total cholesterol levels > 3.5 mmols/l in terms of reducing subsequent serious vascular events. The data also suggest a marginal benefit of statins in reducing future cerebrovascular events, but not overall mortality. In view of this evidence it is recommended that all ischaemic stroke or TIA patients aged at least up to 80 years should receive statin therapy as part of a secondary prevention programme

Implications for research

Further work is needed to assess the potential role of statins for those patientswith a previous cerebral haemorrhage,when after the cerebrovascular event therapy to alter lipid levels should be started, atwhat baseline lipid levels treatment should be commenced,what level of reduction should be aimed for or whether the very elderly (those aged over 80 years) stroke patient benefits to the same extent as a younger counterpart."

4.1.3.2 Summary and conclusions. Statin versus placebo in patients with a history of stroke or TIA

Statin vs placebo in patients with a history of stroke or TIA			
Bibliography: Meta-analysis: Manktelow Bradley 2009(48)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	4731 (1 study) median 4.9y	OR=1.03 (95% CI 0.84, 1.25) NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
All ischaemic or haemorrhagic stroke	9224 (5 studies) median +/-5y	OR=0.88 (95% CI 0.77, 1.00) p = 0.05	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Ischaemic stroke	8011 (2 studies) 5y	**OR=0.78 (95% CI 0.67, 0.92)** **SS in favor of statins**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
haemorrhagic stroke	8011 (2 studies) 5y	**OR=1.72 (95% CI 1.20, 2.46)** **SS in favor of placebo**	⊕⊕⊕⊕ **MODERATE** Study quality: OK Consistency: -1 see chapter safety Directness: OK Imprecision: OK
Serious vascular events	8463 (3 studies) 5y	**OR=0.74 (95% CI 0.67, 0.82)** **SS in favor of statins**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

A Cochrane systematic review and meta-analysis compared statins to placebo in patients with a history of stroke or TIA. In most trials, there was an age limit: patients were included up to 75 or 80y.

In patients with a previous stroke or TIA, there is no statistically significant difference in all-cause mortality between statin treatment and placebo.
GRADE: HIGH quality of evidence

The difference in all ischemic or haemorrhagic strokes between statin treatment and placebo is of borderline statistical significance.
GRADE: HIGh quality of evidence

Treatment with statins results in a lower risk of ischaemic stroke compared to placebo.
GRADE: HIGH quality of evidence

Treatment with statins results in a higher risk of hemorrhagic stroke compared to placebo
GRADE: MODERATE quality of evidence

There is a lower risk of serious vascular events with statin treatment compared to placebo
GRADE: HIGH quality of evidence

No information on (other) adverse events was provided.

4.1.4 Statin versus placebo in patients with a history of coronary heart disease

4.1.4.1 Evidence tables

Meta-analysis: A systematic review and economic evaluation of statins for the prevention of coronary events – p.32: Assessment of effectiveness of statins in patients with CHD at baseline (secondary CHD prevention)

Inclusion criteria: randomised controlled trials (RCTs) of at least 6 months' (defined as 26 weeks) duration. Participants: adults (defined as age >18 years) with, or at risk of, CHD
Search strategy: Nine electronic bibliographic databases were searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (NHS HTA) and CINAHL. In addition, the reference lists of relevant articles and sponsor submissions were handsearched.
Assessment of quality of included trials: yes
ITT analysis: unclear
Other methodological remarks: -

Ref	Comparison	N/n	Outcomes	Result
ref*Ward 2007 1426 (56) Design: SR+MA Search date: between November 2003 and April 2004)	Statin vs placebo	N= 11 n= 22686 (FLORIDA 2002, LIPS 2002, CARE 1996, LIPID 1998, PLAC I 1995, PLAC II 1995, PREDICT 1997, REGRESS 1995, 4S 1994, CIS 1997, SCAT 1995)	All-cause mortality	**Treatment: 933/11360** **Control: 1175/11326** **RR: 0.80 (95% CI 0.71 to 0.89)** **SS in favour of statins**
		N= 6 n= 18819 (FLORIDA 2002, CARE 1996, LIPID 1998; PLAC I 1995; 4S 1994, CIS 1997)	CVD mortality	**Treatment: 589/9414** **Control: 786/9405** **RR: 0.75 (95% CI 0.68 to 0.83)** **SS in favour of statins**

		N= 12 n= 23420 (FLORIDA 2002, LIPS 2002, CARE 1996, LIPID 1998, PLAC I 1995, REGRESS 1995, 4S 1994, CIS 1997, SCAT 1995, LiSA 1999, FLARE 1999, MAAS 1994)	CHD mortality	**Treatment:532/11727** **Control: 743/11693** **RR: 0.72 (95% CI 0.64 to 0.80)** **SS in favour of statins**
		N=10 n=21350 (FLORIDA 2002, CARE 1996, LIPID 1998, PLAC I 1995, PREDICT 1997, REGRESS 1995, 4S 1994, SCAT 1995, LiSA 1999, MAAS 1994)	Fatal MI	**Treatment: 114/10692** **Control: 201/10658** **RR: 0.57 (95% CI 0.45 to 0.72)** **SS in favour of statins**
		N=10 n=14180 (LIPS 2002, CARE 1996, PLAC I 1995, PREDICT 1997, REGRESS 1995, 4S 1994, CIS 1997, SCAT 1995, LiSA 1999, FLARE 1999)	Non-fatal MI	**Treatment: 408/7104** **Control: 596/7076** **RR: 0.69 (95% CI 0.59 to 0.79)** **SS in favour of statins**
		N=3 n=8968 (LiSA 1999, CARE 1996, 4S 1994)	Unstable angina	**Treatment: 886/4489** **Control: 1089/4479** **RR: 0.82 (95% CI 0.72 to 0.94)** **SS in favour of statins**
		N=3 n=9728 (LIPID 1998, CIS 1997, SCAT 1995)	Hospitalisation for unstable angina	**Treatment: 1043/4871** **Control: 1153/4857** **RR: 0.90 (95% CI 0.84 to 0.97)** **SS in favour of statins**
		N=3 n=13581 (CARE 1996, LIPID 1998,	Non-fatal stroke	**Treatment: 189/6799** **Control: 250/6782** **RR: 0.72 (95% 0.53 to 0.97)**

		PLAC I 1995)		**SS in favour of statins**
		N=1 n=4444 (4S 1994)	New or worsening intermittent claudication	**Treatment: 52/2221** **Control: 81/2223** **RR: 0.64 (95% CI 0.46 to 0.91)** **SS in favour of statins**
		N=8 n=21068 (LIPS 2002, CARE 1996, LIPID 1998, PREDICT 1997, 4S 1994, CIS 1997, SCAT 1995, LiSA 1999)	Coronary revascularisation	**Treatment: 1382/10551** **Control: 1782/10517** **RR: 0.77 (95% CI 0.69 to 0.85)** **SS in favour of statins**
		N=7 n=20747 (LIPS 2002, CARE 1996, LIPID 1998, 4S 1994, CIS 1997, LiSA 1999, FLARE 1999)	CHD death plus non-fatal MI	**Treatment: 1252/10383** **Control: 1700/10364** **RR: 0.73 (95% CI 0.68 to 0.80)** **SS in favour of statins**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
LiSA 1999(57) Placebo-controlled	365	Stable symptomatic CHD, hyperlipidaemic Europe, mean age 60	1y	40-80mg statin/day vs control	Study quality assessment by Ward 2007(Randomisation and allocation concealment): unclear
FLARE 1999(58) Placebo-controlled	834	CHD (successful balloon angioplasty) Europe mean age 61	40 weeks	80 mg statin/day vs control	Study quality assessment by Ward: unclear
FLORIDA 2002(59) Placebo-controlled	540	Acute MI The Netherlands mean age 60y	1y	80 mg statin/day vs control	Study quality assessment by Ward: unclear
LIPS 2002(21)	1677	Angina or silent ischaemia	3.9y	80 mg statin/day vs	Study quality assessment by Ward: good

Placebo-controlled		Europe, Canada, Brazil mean age 55y	(median)	control	*"patients whose total cholesterol exceeded 7.2 mmol l^{-1} for 3 months or longer could discontinue study therapy at the investigator's discretion and receive an open-label statin or other lipid-lowering therapy. As a result, 10.7% of patients in the treatment arm and 24% in the placebo arm started taking other lipid-lowering medications (mainly statins) before their first major adverse cardiac event or completion of follow-up."* *"anecdotal evidence that many patients were aware of their total cholesterol levels as these had been tested by primary care physicians who were not involved in LIPS; as a result, these patients were no longer blinded to their treatment allocation"*
CARE 1996(14) Placebo-controlled	4159	MI, average cholesterol mean age 59y	5y (median)	40 mg statin/day vs control	Study quality assessment by Ward: good
LIPID 1998(60) Placebo-controlled	9014	MI or unstable angina median age 62y	6.1 y (mean)	40 mg statin/day vs control	Study quality assessment by Ward: unclear *"although study personnel and patients remained unaware of lipid results from the core laboratory,119 the patient's general care was at the discretion of the patient's own doctor, and this allowed changes in lipid treatment to be made in the light of local cholesterol results"*
PLAC I 1995(61) Placebo-controlled	408	CHD mean age 57	3 y	40 mg statin/day vs control	Study quality assessment by Ward: Unclear
PLAC II 1995(62) Placebo-controlled	151	CHD mean age 62	3y	10-40 mg statin/day vs control	Study quality assessment by Ward: Unclear
PREDICT 1997(63) Placebo-controlled	695	CHD (successful PTCA) mean age 58y	6 months	40 mg statin/day vs control	Study quality assessment by Ward: Unclear

REGRESS 1995(64) Placebo-controlled	884	CHD mean age 56y	2y	40 mg statin/day vs control	Study quality assessment by Ward: Unclear *Potential candidates receiving therapy with lipid-lowering agents or drugs that could significantly affect serum lipid levels had their drugs withdrawn (at least 12 weeks for patients receiving HMG-CoA reductase inhibitors, clofibrate, or their analogues and at least 6 weeks for patients receiving bile acid sequestrants, nicotinic acid, or other prohibited drugs*
MAAS 1994(65) Placebo-controlled	381	Moderate hypercholesterolaemia and known CAD mean age 55y	4y	20mg statin/day vs control	Study quality assessment by Ward: Uncleart
4S 1994(25) Placebo-controlled	4444	CHD and moderate hypercholesterolaemia mean age 58y	7.4y (median)	20-40mg statin/day vs control	Study quality assessment by Ward: good
CIS 1997(66) Placebo-controlled	254	CHD and hypercholesterolaemia mean age 49y	2.3y (mean)	20-40mg statin /day vs control	Study quality assessment by Ward: unclear
SCAT 1995 Placebo-controlled	460	CHD Mean age 61y	47.8months (mean)	20-40mg statin/day vs control	Study quality assessment by Ward: good *"the SCAT investigators deemed it unethical to keep on placebo patients whose total cholesterol persistently exceeded 5.5 mmol l–1. Consequently, the protocol was modified to permit such patients to be identified and reallocated, in a double-blind fashion, to simvastatin. It is not stated how many patients this affected"*

Remarks:

-Author's remark: Assessment of effectiveness of statins in patients with CVD (including CHD) at baseline (secondary CVD prevention)

The evidence for the effectiveness of statins in patients with prior CVD is derived primarily from the studies of statins in secondary CHD prevention. However, it also draws on the findings of three relatively small studies (Mohler 2003,21 Aronow 2003118 and Mondillo 2003105) in patients with intermittent claudication. In addition, ASCOTLLA and WOSCOPS reported data relating to subgroups with vascular disease at baseline; however, these results should be treated with caution because, as noted above, the subgroup analysis from WOSCOPS is not, and that from ASCOT-LLA may not be, a true randomized comparison. It might be argued that two of the three studies in patients with intermittent claudication21,105 may be classified as primary CHD prevention, as they do not specify whether any participants had CHD at baseline. However, since all of the participants in these studies had symptomatic CVD at baseline, it seemed more appropriate to categorise them as secondary CVD prevention. As the additional studies

are small, and do not report data relating to all end-points, the changes to the tabulation of the effects of statins in secondary CHD prevention are few and so small as to be barely worth mentioning.
- Author's remarks: "Many studies reported the presence of cointerventions (generally statin or other lipidlowering therapy in the control group), which potentially influenced the study outcome. As a result of such cointerventions, combined with noncompliance with study therapy in the statin group, many studies may underestimate the potential effect of statin therapy in their study populations. However, this may be counterbalanced by the exclusion from some studies of patients who were hypersensitive to, intolerant of or known to be unresponsive to statins, or who were not adequately compliant with study medication during a placebo run-in phase. As the numbers involved may be large, this limits the generalisability of the results of those studies."
- "The results from the placebo-controlled trials are likely to be conservative as a result of the degree of cross-over (use of lipid-lowering therapies, in particular statins, in the placebo arm, and noncompliance with study therapy in the statin arm) reported in many studies. In some studies, the use of lipid-lowering therapy in the placebo arm was preplanned."

- "W Yeo has received speaker fees from Novartis, Pfizer, MSD and AstraZeneca for talks to GPs and prescribing advisors on the National Service Framework for CHD, which includes the use of statins. However, for the duration of his involvement with the preparation of this report, he has declined to comment on statins or attend any advisory boards where statins may have been discussed. His department has received research funding for the Anglo-Scandinavian Cardiac Outcomes Trial, an investigator-led multicentre study in high-risk hypertension patients of older versus more modern blood pressure-lowering drugs, with statin therapy in a factorial design. This study used atorvastatin and was part-funded by Pfizer."

4.1.4.2 Summary and conclusions. Statin versus placebo in patients with a history of coronary heart disease

Statin versus placebo in patients with coronary heart disease			
Bibliography: Meta-analysis Ward 2007(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	22686 (11 studies) 6m-med 6.1y	**RR: 0.80 (95% CI 0.71 to 0.89)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality: unclear rando and allocation concealment in half the trials, Run-in Consistency: OK Directness:OK Imprecision:OK
CVD mortality	18819 (6 studies) 1y-med 6.1y	**RR: 0.75 (95% CI 0.68 to 0.83)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality: unclear rando and allocation concealment in half the trials, Run-in Consistency: OK Directness:OK Imprecision:OK
Non-fatal MI	14180 (10 studies) 1y-med 6.1y	**RR: 0.69 (95% CI 0.59 to 0.79)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality: unclear rando and allocation concealment in half the trials, Run-in Consistency: OK Directness:OK Imprecision:OK
Non-fatal stroke	13581 (3 studies) 3y- med 6.1y	**RR: 0.72 (95% 0.53 to 0.97)** **SS in favour of statins**	⊕⊕⊕⊖ **MODERATE** Study quality: unclear rando and allocation concealment in 2/3 trials Consistency: OK Directness:OK Imprecision:OK
New or worsening intermittent claudication	4444 (1 study) 7.4y	**RR: 0.64 (95% CI 0.46 to 0.91)** **SS in favour of statins**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK

A systematic review and meta-analysis compared statins to placebo in patients with coronary heart disease at baseline. The mean age of included patients ranged from 49 years to 62 years. Follow up ranged from 6 months (1 trial) to 7.4 years. The quality of included trials was mixed: half the trials had inadequate (or unclear) allocation concealment or randomization.

In patients with coronary heart disease, statins significantly reduce all-cause mortality and mortality from cardiovascular disease.
GRADE: MODERATE quality of evidence

The risk of non-fatal myocardial infarction and non-fatal stroke is reduced with statins compared to placebo, in patients with coronary heart disease.

GRADE: MODERATE quality of evidence

In this population, statins reduce the risk of new or worsening intermittent claudication compared to placebo.
GRADE: HIGH quality of evidence

4.1.5 Statin versus placebo in elderly patients without established cardiovascular disease

4.1.5.1 Evidence tables

Meta-analysis: Benefits of statins in elderly subjects without established cardiovascular disease

Inclusion criteria:
Randomized allocation to statin or placebo; report of outcomes in the subgroup of patients with age at randomization ≥65 years and without established CV disease; and report of at least 1 clinical event among all-cause death, CV death, myocardial infarction (MI), stroke, and new cancer onset.
Search strategy:
The study was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement
MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched for articles published until January
"pravastatin" or "lovastatin" or "simvastatin" or "rosuvastatin" or "atorvastatin" or "pitavastatin" or "mevastatin" or "fluvastatin"
No language restrictions were applied.
Assessment of quality of included trials:
yes: The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to summarize the findings and score the overall quality of evidence.
Publication bias evaluated
ITT analysis: yes
Other methodological remarks:
Data synthesis & analysis:

- Overall estimates of effect were calculated with a fixed-effects model or with a random-effects model when heterogeneity could not be explained
- The assumption of homogeneity between the treatment effects in different trials was tested by Q statistic and further quantified by I^2 statistic.

Sensitivity analysis

- To verify the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the 1-study removed sensitivity analysis using the "metaninf" command (STATA)
- To explore the influence of potential effect modifiers on outcomes, weighted random-effects metaregression analysis was performed to test demographic characteristics of the study population, duration of follow-up, CV risk factors (including diabetes mellitus and hypertension), type of statin, concomitant medications, and changes in lipid profile from baseline to the end of follow-up

Table 2 GRADE Method Evidence Summarizing the Outcomes Measured

	Quality Assessment						Summary of Findings			
								Illustrative Comparative Risks (95% CI)		
	No. of Studies (Participants)	Methodological Limitations	Consistency	Directness	Precision	Publication Bias	Relative Effect (95% CI)	Assumed Risk Placebo	Corresponding Risk Statin	Quality of the Evidence (GRADE)
All-cause death	7 (21,435)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.941 (0.856–1.035)	5.1 per 100	4.8 per 100 (4.4–5.3)	++++ High
Cardiovascular death	5 (13,914)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.907 (0.686–1.199)	1.1 per 100	1.0 per 100 (0.7–1.3)	++++ High
Myocardial infarction	5 (15,929)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.606 (0.434– 0.847)	3.7 per 100	2.2 per 100 (1.6–3.1)	++++ High
Stroke	5 (16,322)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.762 (0.626–0.926)	3.6 per 100	2.7 per 100 (2.2–3.3)	++++ High
New cancer onset	3 (11,556)	No serious limitations	No inconsistency	Direct	No uncertainty	Unlikely	RR: 0.989 (0.851–1.151)	5.5 per 100	5.4 per 100 (4.7–6.3)	++++ High

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RR = relative risk.

Ref	Comparison	N/n	Outcomes	Result
ref*Savarese 2013 (67) Design: MA Search date: until January 2013 42.7% females; mean age 73.0 +/- 2.9 years; mean follow-up 3.5 +/- 1.5 years	Statins vs placebo	N= 7 n= 21435 (AFCAPS/TexCAPS 1998, ALLHAT-LLT 2002, ASCOT-LLA 2011, Bruckert 2003, CARDS 2006, JUPITER 2010, MEGA 2011)	**All-cause death**	RR: 0.941 (95% CI 0.856 to 1.035) NS Illustrative comparative risks (ICR): Placebo: 5.1/100 Statin: 4.8/100 (95% CI 4.4 to 5.3)
		N= 5 n= 13914 (AFCAPS/TexCAPS 1998, ASCOT-LLA 2011, Bruckert 2003, CARDS 2006, JUPITER 2010)	**Cardiovascular death**	RR: 0.907 (95% CI 0.686 to 1.199) NS ICR: Placebo: 1.1/100 Statin: 1.0/100 (95% CI 0.7 to 1.3)
		N= 5 n= 15929 (AFCAPS/TexCAPS 1998, ASCOT-LLA 2011, CARDS	**Myocardial infarction**	**RR: 0.606 (95% CI 0.434 to 0.847)** **SS in favour of statin** ICR:

		2006, JUPITER 2010, PROSPER 2002)		Placebo: 3.7/100 Statin: 2.2/100 (95% CI 1.6 to 3.1)
		N= 5 n= 16322 (ASCOT-LLA 2011, CARDS 2006, JUPITER 2010, MEGA 2011, PROSPER 2002)	**Stroke**	**RR: 0.762 (95% CI 0.626 to 0.926)** **SS in favour of statin** ICR: Placebo: 3.6/100 Statin: 2.7/100 (95% CI 2.2 to 3.3)
		N=3 n= 11556 (AFCAPS/TexCAPS 1998, ASCOT-LLA 2011, JUPITER 2010)	**New cancer onset**	RR: 0.989 (95% CI 0.851 to 1.151) NS ICR: Placebo: 5.5/100 Statin: 5.4/100 (95% CI 4.7 to 6.3)

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
AFCAPS/TexCAPS 1998(6) RCT Double-blinded	1416	Patients with average cholesterol levels and without prior CV disease Age: NA 25% females HTN: NA DM: 6% Smoking: 12% SUBGROUP ≥65y	5.2y	Lovastatin 20/40 mg vs placebo	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were randomized. No information on how many people were excluded in this step. *Trial was stopped prematurely. To be terminated when 320 participants had experienced* *primary outcome event. Stopped when 267 had done at 5.2 years*
ALLHAT-LLT 2002(8)	5707	Moderate hypercholesterolemia, HTN	4.8y	Pravastatin 40 mg vs placebo	ALLOCATION CONC: Adequate

RCT Double-blinded		Age: NA 49% females HTN: 100% DM: NA Smoking: NA SUBGROUP ≥65y			RANDO: Adequate BLINDING : no FOLLOW-UP: At the end of the trial, 84.8% of participants were known to be alive, 12.3% were confirmed dead, 0.5% were reported dead with confirmation pending, and 2.4% had unknown vital status. ITT:yes FUNDING: Methodological remarks: because of the modest cholesterol differential between pravastatin and usual care, ALLHAT-LLT lacked the power to discriminate between the expected reductions in mortality and CHD events and the null hypothesis.
ASCOT-LLA 2011(68) RCT Double-blinded	4445	HTN and at least 3 CV risk factors Age: 71y 20% females HTN: 100% DM: 27% Smoking: 24%	3.3y	Atorvastatin 10 mg vs placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : assessors: yes FOLLOW-UP: 99% ITT:yes Note: 4 week run-in FUNDING:Pfizer
Bruckert 2003(69) RCT Double-blinded	1229	Primary hypercholesterolemia Age: 75-76y 75% females HTN: 56% DM: 7% Smoking: 5%	1y	Fluvastatin 80 mg vs placebo	'not reported by Savarese 2013'
CARDS 2006(70)	1129	Type 2 DM and at least 1 other CV	3.9y	Atorvastatin 10	ALLOCATION CONC: Adequate

RCT Double-blinded		risk factor Age: 69y 31% females HTN: NA DM: 100% Smoking: 16% SUBGROUP ≥65y		mg vs placebo	RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate (triple blind part/pers/assess) FOLLOW-UP: 1% lost to follow up ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: excluded if during the baseline phase they had less than 80% compliance with placebo 12% excluded from baseline phase Trial stopped prematurely due to large beneficial treatment effect
JUPITER 2010(71) RCT Double-blinded	5695	CRP >2.0 mg/l Age: 74y 51% females HTN: 66% DM: NA Smoking: 8% SUBGROUP ≥65y	1.9y	Rosuvastatin 20 mg vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 100 % in efficacy analysis ITT: yes Stopped early with a median follow-up of 1.9 years. Run-in : 4-week run-in phase during which they received placebo. Only subjects who successfully completed the run-in phase were enrolled (19323 received run-in, of which 1521 excluded =7.8%) Primary endpoint event rate higher than predicted. Mortality higher than predicted (by comparison to other trials) Funding: High risk (funded by pharm industry)
MEGA 2011(72) RCT Open-label	1814	Hypercholesterolemic Japanese patients Age: NA 68% females	5y	Pravastatin 10/20 mg vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors

study		HTN: 52% DM: 21% Smoking: 14% SUBGROUP ≥65y			Inadequate; single blinded endpoint committee was blinded only because investigators stated that placebo-controlled trials are regarded with suspicion by Japanese participants FOLLOW-UP: 98 % in efficacy analysis ITT:yes FUNDING: low risk (funded by pharm industry)
PROSPER 2002(24) RCT Double-blinded	3239	Raised risk of CV disease because of smoking, HTN, or DM Age: 75y* 52% females* HTN: 62%* DM: 11%* Smoking: 27%* *Data from the published cohort of primary and secondary prevention patients Subgroup without established CVD	3.2y	Pravastatin 40 mg vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP: 25% did not complete trial (due to adverse event, death, refusal or lost) 13% refusal or lost to follow-up ITT:yes FUNDING: Bristol- Myers Squibb, USA

4.1.5.2 Summary and conclusions. Statin versus placebo in elderly patients without established cardiovascular disease

Statin versus placebo in elderly subjects without established cardiovascular disease			
Bibliography: Savarese 2013(67)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)***
All-cause death	21435 (7 studies) 1y-5.2y	RR: 0.94 (95% CI 0.86 to 1.04) NS	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK
Cardiovascular death	13914 (5 studies) 1.9y-5.2y	RR: 0.91 (95% CI 0.69 to 1.20) NS	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK
Myocardial infarction	15929 (5 studies) 1.9y-5.2y	**RR: 0.61 (95% CI 0.44 to 0.85)** **SS in favour of statin** ICR: Placebo: 3.7/100 Statin: 2.2/100 (95% CI 1.6 to 3.1)	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK
Stroke	16322 (5 studies) 1.9y-5y	**RR: 0.76 (95% CI 0.63 to 0.94)** **SS in favour of statin** ICR: Placebo: 3.6/100 Statin: 2.7/100 (95% CI 2.2 to 3.3)	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK
New cancer onset	11556 (3 studies) 1.9y-5.2y	RR: 0.99 (95% CI 0.85 to 1.15) NS	⊕⊕⊕⊕ **MODERATE** Study quality:OK Consistency:OK Directness:- duration somewhat short for this outcome Imprecision:OK

**GRADE as reported by Savarese 2013. New Cancer onset downgraded by farmaka to be consistent with total body of evidence regarding cancer risk.*

This is a well-conducted meta-analysis of RCTs that compare a statin to placebo in elderly patients without established cardiovascular disease. The mean age of included subjects was 73 +/- 2.9 years. The mean follow-up was 3.5 +/- 1.5 years.
The authors used the GRADE methodology to rate the quality of evidence.

In elderly patients without established cardiovascular disease, there is no statistically significant difference in all-cause death between statin and placebo.
GRADE: HIGH quality of evidence

In elderly patients without established cardiovascular disease, there is no statistically significant difference in cardiovascular death between statin and placebo.
GRADE: HIGH quality of evidence

In this population, statin treatment lowers the risk of myocardial infarction (RR: 0.61 (95% CI 0.44 to 0.85)).
GRADE: HIGH quality of evidence

In this population, statin treatment also lowers the risk of stroke (RR: 0.76 (95% CI 0.63 to 0.94)).
GRADE: HIGH quality of evidence

In elderly patients without established cardiovascular disease, there is no statistically significant difference in new onset cancer between statin treatment and placebo.
GRADE: MODERATE quality of evidence

4.1.6 Statin versus placebo in elderly patients with a history of coronary heart disease

4.1.6.1 Evidence tables

Meta-analysis: Statins for Secondary Prevention in Elderly Patients, A Hierarchical Bayesian Meta-Analysis

Inclusion criteria:
-randomized allocation to statin or placebo
-documented coronary heart disease at the time of randomization,
-≥50 elderly patients (defined as age ≥65 years),
-6 months of follow-up, and all-cause mortality, CHD mortality, nonfatal MI, need for revascularization, or stroke reported as an outcome measure
Search strategy: 5 electronic databases, the Internet, and conference proceedings to identify relevant trials. In addition, we obtained unpublished data for the elderly patient subgroups from 4 trials and for the secondary prevention subgroup from the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial.
Assessment of quality of included trials: yes. All qualifying studies were assessed for concealment of randomized assignment, completeness of follow-up, and intention-to-treat analysis. We recorded whether patients in the intervention and control groups were similar at the start of the study and treated equally except for the designated treatment
ITT analysis: unclear.("analyses were conducted on an intention-to-treat basis in 8 out of 9 RCTs.")
Other methodological remarks:

- We carried out this meta-analysis in accordance with standards set forth by the Quality of Reporting of Meta-Analyses of Randomised Controlled Trials (QUOROM) Statement.
- Data were analyzed with hierarchical Bayesian modeling: to account for all between-trial variations
- "We conducted Bayesian analyses adjusting for the proportion of patients with prior MI (including analyses with and without the HPS trial) and found that the treatment effects remained consistent. Finally, we conducted unadjusted non-Bayesian Frequentist analyses and again found that the treatment effects remained consistent."
- "The majority of the RCTs stratified randomization by age group, further reducing the risk of unbalanced randomization."

Table 1 Trial Characteristics

	Published Elderly Subgroups				Unpublished Elderly Subgroups				
	4S	CARE	LIPID	HPS	PLAC I	REGRESS	FLARE	LIPS	PROSPER
Year	1997	1998	2001	2002	1995	1995	1999	2002	2002
Mean follow-up, yrs	5.4*	5.0*	6.1	5.0	2.3	2.0	0.8	3.9*	3.2
No. of elderly	1,021	1,283	3,514	10,697	94	138	366	623	1,833
Age range, yrs	65–70	65–75	65–75	65–80	65–75	65–70	65–80	65–80	70–82
Mean age, yrs (SD)	66.8 (1.4)	69.0 (66,73)*	68.8 (2.7)	n/a	68.3 (2.6)	67.6 (1.5)	70.4 (3.7)	70.1 (3.9)	75.6 (3.4)
Inclusion criteria	MI >6 months or stable angina	MI 3–20 months	MI or unstable angina 3–36 months	Vascular disease or diabetes	Angiographic CAD or recent MI	Angiographic CAD	CAD requiring PCI	CAD requiring PCI	MI >6 months or stable angina
Study drug									
Drug	Simvastatin	Pravastatin	Pravastatin	Simvastatin	Pravastatin	Pravastatin	Fluvastatin	Fluvastatin	Pravastatin
Dose, mg/day	20-40	40	40	40	40	40	80	80	40
Nonstudy drugs									
Aspirin, %	35	82	79	63†	65	49	68	96	63
Beta-blockers, %	54	37	45	26†	18	74	57	54	33
Baseline characteristics									
Women, %	24	18	20	25†	39	0	23	22	42
Diabetes, %	5	19	10	29†	0	0	9	15	9
Smoking, %	18	12	6	14†	17	n/a	16	15	16
Hypertension, %	29	48	45	41†	57	27	38	43	46
Prior MI, %	83	100	60	41†	38	49	26	42	42
Mean baseline lipid levels, mmol/l§									
Total cholesterol	6.7	5.4	5.6	5.9†	6.0	5.8	5.5	5.1	5.7
LDL-C	4.9	3.6	3.9	3.4†	4.2	4.1	3.8	3.4	3.8
HDL-C	1.2	1.0	0.9	1.1†	1.1	0.9	1.1	1.0	1.2
Triglycerides	1.5	1.7	1.5	2.1†	1.9	1.6	1.5	1.6	1.6
Mean change in lipid levels, %									
Total cholesterol	−26	−20	−19	−20†	−19	−19	−23	−17	n/a
LDL-C	−36	−29	−28	−29†	−28	−27	−32	−24	−32‡
HDL-C	+7	+4	+7	+3†	+8	+9	+4	−1	+5‡
Triglycerides	−14	−12	−11	−14†	−10	−13	−5	−2	−12‡
Study quality									
Follow-up, %	100	>99	>99	>99	78	>99	95	99	89‡
Intention-to-treat	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Yes	Yes
Double-blind	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*Median (Q1, Q3). †Data from the published cohort of young and elderly patients. ‡Data from the published cohort of primary and secondary prevention patients. §To convert total cholesterol, LDL-C, and HDL-C from mmol/l to mg/dl, divide by 0.02586. To convert triglycerides from mmol/l to mg/dl, divide by 0.01129.

CAD = coronary artery disease; MI = myocardial infarction; LDL-C = low-density-lipoprotein cholesterol; HDL-C = high-density-lipoprotein cholesterol; n/a = not available; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Ref	Comparison	N/n	Outcomes	Result
ref* Afilalo 2008(73) Design: Hierarchical Bayesian Meta-Analysis Search date: Dec 2007 mean weighted follow-up period was 4.9 years (95,929 patient-years). age range of 65 to 82 years	Statin vs placebo	N= 9 n= 19569 (4S 1997, CARE 1998, LIPID 2001, HPS 2002, PLAC I 1995, REGRESS 1995, FLARE 1999, LIPS 2002, PROSPER 2002)	**All-Cause mortality**	**Statin:1531/9819 (15.59%)** **Placebo: 1827/9750 (18.74%)** **RR= 0.78 (95% Credible Interval 0.65 to 0.89)** **SS in favour of Statin** Statin therapy reduced the incidence of all-cause mortality by 22% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 28.
		N= 9 n= 19569 (4S 1997, CARE 1998, LIPID 2001, HPS 2002, PLAC I 1995, REGRESS 1995, FLARE 1999, LIPS 2002, PROSPER 2002)	**Coronary Heart Disease Mortality**	**Statin: 857/9819 (8.73%)** **Placebo:1102/9750 (11.30%)** **RR= 0.70 (95% Credible Interval 0.53 to 0.83)** **SS in favour of statin** Statin therapy reduced the incidence of coronary heart disease mortality by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 34.
		N= 8 n= 8872 (4S 1997, CARE 1998, LIPID 2001, PLAC I 1995, REGRESS 1995, FLARE 1999, LIPS 2002, PROSPER 2002)	**Nonfatal Myocardial Infarction**	**Statin: 357/4453 (8.02%)** **Placebo: 465/4419 (10.52%)** **RR= 0.74 (95% Credible Interval 0.60 to 0.89)** **SS in favour of statin** Statin therapy reduced the incidence of nonfatal myocardial infarction by 26% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 38.
		N= 7 n=8506 (4S 1997, CARE 1998, LIPID 2001, PLAC I 1995, REGRESS 1995, LIPS 2002, PROSPER 2002)	**Revascularization**	**Statin: 422/4274 (9.87%)** **Placebo:586/4232 (13.85%)** **RR= 0.70 (95% Credible interval 0.53 to 0.83)** **SS in favour of statin** Statin therapy reduced the need for revascularization (percutaneous coronary intervention or aortocoronary bypass surgery) by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 24.

		N= 5 n= 17421 (CARE 1998, LIPID 2001, HPS 2002, PLAC I 1995, PROSPER 2002)	**Stroke**	**Statin: 458/8723 (5.25%)** **Placebo:611/8698 (7.02%)** **RR= 0.75 (95% Credible interval 0.56 to 0.94)** **SS in favour of statin** Statin therapy reduced the incidence of stroke by 25% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 58.

RR= 5year pooled estimate

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
4S 1997(25, 74) RCT Double blind	No. of elderly: 1021	Inclusion criteria: MI > 6 months or stable angina Age range, yrs: 65-70 Mean age, yrs (SD): 66.8 (1.4) Nonstudy drugs - Aspirin, %:35 - Beta-blockers, %:54 Baseline characteristics: - Women, %:24 - Diabetes, %:5 - Smoking, %:18 - Hypertension, %:29 - Prior MI, %:83 Mean baseline lipid levels, mmol/ l - TC:6.7 - LDL-C:4.9 - HDL-C:1.2 - TG: 1.5	5.4y (Median (Q1, Q3))	Simvastatin 20-40mg/day vs placebo	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors unclear FOLLOW-UP: 100% note 2 week placebo run in FUNDING:Merck ITT:yes
CARE 1998(75) RCT	No. of elderly: 1283	Inclusion criteria: MI 3–20 months Age range, yrs:65-75 Mean age, yrs (SD): 69.0 (66.73)	5y (Median (Q1, Q3))	Pravastatin 40 mg/day vs placebo	ALLOCATION CONC: Adequate RANDO:

Double blind		Nonstudy drugs - Aspirin, %:82 - Beta-blockers, %:37 Baseline characteristics: - Women, %:18 - Diabetes, %:19 - Smoking, %:12 - Hypertension, %:48 - Prior MI, %:100 Mean baseline lipid levels, mmol/ l - TC: 5.4 - LDL-C:3.6 - HDL-C:1.0 - TG:1.7			Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: >99% ITT:yes FUNDING:?
LIPID 2001(76) RCT Double blind	No. of elderly: 3514	Inclusion criteria: MI or unstable angina 3–36 months Age range, yrs:65-75 Mean age, yrs (SD): 68.8 (2.7) Nonstudy drugs - Aspirin, %:79 - Beta-blockers, %:45 Baseline characteristics: - Women, %:20 - Diabetes, %:10 - Smoking, %:6 - Hypertension, %:45 - Prior MI, %:60 Mean baseline lipid levels, mmol/ l - TC:5.6 - LDL-C:3.9 - HDL-C:0.9 - TG:1.5	6.1y	Pravastatin 40 mg/day vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:?

HPS 2002(18) RCT Double blind	No. of elderly: 10697	Inclusion criteria: Vascular disease or diabetes Age range, yrs:65-80 Mean age, yrs (SD):n/a Nonstudy drugs* - Aspirin, %:63 - Beta-blockers, %:26 Baseline characteristics:* - Women, %:25 - Diabetes, %:29 - Smoking, %:14 - Hypertension, %:41 - Prior MI, %:41 Mean baseline lipid levels, mmol/ l* - TC:5.9 - LDL-C:3.4 - HDL-C:1.1 - TG:2.1 * Data from the published cohort of young and elderly patients	5.0y	Simvastatin 40 mg/day vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? 35% of patients were enrolled on the basis of noncoronary vascular disease and 1% on the basis of high-risk hypertension. There was a change in the protocol so that only patients whose total blood cholesterol was < 250 mg/dl could be randomized whilst patients with total blood cholesterol > 250 mg/dl who had already been enrolled in the study had to be re-evaluated and, if appropriate, pharmacologically treated. The DSMB and the SC agreed to stop randomization prematurely in late 1996 after the publication of CARE results
PLAC I 1995(61) RCT Double blind	No. of elderly: 94	Inclusion criteria: Angiographic CAD or recent MI Age range, yrs:65-75 Mean age, yrs (SD): 68.3 (2.6) Nonstudy drugs - Aspirin, %:65 - Beta-blockers, %:18 Baseline characteristics:	2.3y	Pravastatin 40 mg/day vs placebo	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : unclear FOLLOW-UP: 78% ITT: yes

		- Women, %:39 - Diabetes, %:0 - Smoking, %:17 - Hypertension, %:57 - Prior MI, %:38 Mean baseline lipid levels, mmol/ l - TC:6.0 - LDL-C:4.2 - HDL-C:1.1 - TG:1.9			
REGRESS 1995(64) RCT Double blind	No. of elderly: 138	Inclusion criteria: Angiographic CAD Age range, yrs:65-70 Mean age, yrs (SD): 67.6 (1.5) Nonstudy drugs - Aspirin, %:49 - Beta-blockers, %:74 Baseline characteristics: - Women, %:0 - Diabetes, %:0 - Smoking, %:n/a - Hypertension, %:27 - Prior MI, %:49 Mean baseline lipid levels, mmol/ l - TC:5.8 - LDL-C:4.1 - HDL-C:0.9 - TG:1.6	2.0y	Pravastatin 40 mg/day vs placebo	ALLOCATION CONC: Unclear RANDO: unclear. BLINDING : adequate FOLLOW-UP: >99% ITT: yes *Potential candidates receiving therapy with lipid-lowering agents or drugs that could significantly affect serum lipid levels had their drugs withdrawn (at least 12 weeks for patients receiving HMG-CoA reductase inhibitors, clofibrate, or their analogues and at least 6 weeks for patients receiving bile acid sequestrants, nicotinic acid, or other prohibited drugs*
FLARE 1999(58) RCT Double blind	No. of elderly: 366	Inclusion criteria: CAD requiring PCI Age range, yrs:65-80 Mean age, yrs (SD):70.4 (3.7) Nonstudy drugs - Aspirin, %:68 - Beta-blockers, %:57	0.8y	Fluvastatin 80 mg/day vs placebo	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : adequate

		Baseline characteristics: - Women, %:23 - Diabetes, %:9 - Smoking, %:16 - Hypertension, %:38 - Prior MI, %:26 Mean baseline lipid levels, mmol/ l - TC:5.5 - LDL-C:3.8 - HDL-C:1.1 - TG:1.5			FOLLOW-UP: 95% ITT: no
LIPS 2002(21) RCT Double blind	No. of elderly: 623	Inclusion criteria: CAD requiring PCI Age range, yrs:65-80 Mean age, yrs (SD): 70.1 (3.9) Nonstudy drugs - Aspirin, %:96 - Beta-blockers, %:54 Baseline characteristics: - Women, %:22 - Diabetes, %:15 - Smoking, %:15 - Hypertension, %:43 - Prior MI, %:42 Mean baseline lipid levels, mmol/ l - TC:5.1 - LDL-C:3.4 - HDL-C:1.0 - TG:1.6	3.9y (Median (Q1, Q3))	Fluvastatin 80 mg/day vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate, but see below FOLLOW-UP: >90% completed trial ITT:yes FUNDING:Novartis *"patients whose total cholesterol exceeded 7.2 mmol l^{-1} for 3 months or longer could discontinue study therapy at the investigator's discretion and receive an open-label statin or other lipid-lowering therapy. As a result, 10.7% of patients in the treatment arm and 24% in the placebo arm started taking other lipid-lowering medications (mainly statins) before their first major adverse cardiac event or completion of follow-up."* *"anecdotal evidence that many patients were aware of their total cholesterol levels as these had been tested by primary care physicians who were not involved in LIPS; as a result, these patients were no longer blinded to their*

					treatment allocation"
PROSPER 2002(24) RCT Double blind	No. of elderly: 1833	Inclusion criteria: MI > 6 months or stable angina Age range, yrs:70-82 Mean age, yrs (SD): 75.6 (3.4) Nonstudy drugs - Aspirin, %:63 - Beta-blockers, %:33 Baseline characteristics: - Women, %:42 - Diabetes, %:9 - Smoking, %:16 - Hypertension, %:46 - Prior MI, %:42 Mean baseline lipid levels, mmol/ l - TC:5.7 - LDL-C:3.8 - HDL-C:1.2 - TG:1.6	3.2y	Pravastatin 40 mg/day vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP: 25% did not complete trial (due to adverse event, death, refusal or lost) 13% refusal or lost to follow-up ITT:yes FUNDING: Bristol- Myers Squibb, USA. FOLLOW-UP: 89%* *Data from the published cohort of primary and secondary prevention patients

4.1.6.2 Summary and conclusions. Statin versus placebo in elderly patients with a history of coronary heart disease

Statin versus placebo in elderly patients with documented coronary heart disease			
Bibliography: Afilalo 2013(73)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	19569 (9 studies)	**RR= 0.78 (95% CrI 0.65 to 0.89)** **SS in favour of statin** The posterior median estimate of the number need to treat was 28	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear allocation concealment and randomization in 4/9 trials, unprespecified subgroups in half the trials Consistency: OK Directness: OK Imprecision: OK
Coronary heart disease mortality	19569 (9 studies)	**RR= 0.70 (95%CrI 0.53 to 0.83)** **SS in favour of statin** The posterior median estimate of the number need to treat was 34	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear allocation concealment and randomization in 4/9 trials, unprespecified subgroups in half the trials Consistency: OK Directness: OK Imprecision: OK
Nonfatal myocardial infarction	8872 (8 studies)	**RR= 0.74 (95%CrI 0.60 to 0.89)** **SS in favour of statin** The posterior median estimate of the number need to treat was 38	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear allocation concealment and randomization in 4/8 trials, unprespecified subgroups in half the trials Consistency: OK Directness: OK Imprecision: OK
Stroke	17421 (5 studies)	**RR= 0.75 (95%CrI 0.56 to 0.94)** **SS in favour of statin** The posterior median estimate of the number need to treat was 58	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK

This meta-analysis examined the effect of statin compared to placebo in elderly patients with established coronary heart disease. Data from 9 RCTs were included. The age range was 65 to 82 years. The mean age of this elderly population in the included trials however was relatively low: all trials reported a mean age of 70 years or less, except 1 trial (PROSPER 2002), in which the mean age was 75 years. We have not enough data on the very old (>80y).
The mean weighted follow-up was 4.9 years.

In elderly patients with known coronary heart disease, statins reduce all-cause mortality compared to placebo (RR= 0.78; 95% CrI 0.65 to 0.89).
GRADE: MODERATE quality of evidence

In this population, statins also reduce the risk of mortality due to coronary heart disease.

GRADE: MODERATE quality of evidence

In elderly patients with known coronary heart disease, statins reduce the risk of nonfatal myocardial infarction.
GRADE: MODERATE quality of evidence

Statins also reduce the risk of stroke in elderly patients with known coronary heart disease.
GRADE: HIGH quality of evidence

4.1.7 All-cause mortality in observational studies

4.1.7.1 Evidence tables

Allonen 2012(77)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
prospective cohort study median follow-up of 23 months	n= 1969	-Caucasian origin (purchase register of the Social Insurance Institution of Finland) -consecutive acute coronary syndrome (ACS) patients - mean age : 66y -female: 30.4%	Statin non user (n=94) Vs Statin regular user (n=1200)	Mortality	**HR:2.70 (95%CI 1.49 - 4.90)** **SS p=0.001**
*adjusted for ACS type, cerebrovascular attack, diabetes, age, 3-artery disease, and cancer					

Study limitations: The register was based on medication purchases, which naturally does not guarantee the actual consumption of the medication, but regular consecutive purchases logically reflect it. During the follow-up, authors did not measure total cholesterol, low density lipoprotein cholesterol, or high-density lipoprotein cholesterol levels, which would have reflected the impact ofstatin medication use.

Eindhoven-2012(78)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
prospective cohort study Median follow-up: 5.0 y The Netherlands (tertiary center)	n= 5647	-Mean age: 62 years - 73%: men -patients who underwent percutaneous coronary intervention (PCI) - Non-statin users were defined as those patients who did not use any statins one-month post-PCI.	Baseline statin user (n=4970) vs baseline non-statin user (n=677)	All cause mortality	**11% vs 28%** **HR: 0.49 (95%CI 0.40-0.59)** **SS**
*adjusted for age, sex, indication, prior MI, prior PCI, prior CABG, diabetes, hypertension, current smoking, family history of coronary disease, multivessel disease and the use of beta blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, nitrates, diuretics, digitalis and anticoagulants, statin dose					

Limitations:

-The reasons why 12 % of the patients did not receive a statin after the PCI procedure were unclear.

-As this study was originally not designed to evaluate statin therapy efficacy, hidden confounding could have been introduced.

- Referral cholesterol levels are not routinely measured anymore and LDL cholesterol values prior and after the PCI treatment were only available for approximately five percent of the patients. Therefore, no adjustments for LDL cholesterol levels in the analyses were done.

Makihara 2013(79)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
multicenter, hospital-based, prospective observational study median follow-up time: 2.0 y	n= 2822	- Japanese patients with first-ever ischemic stroke - Statin-users were defined as patients treated with statins at discharge	statin users (n = 993) vs nonusers (n =1829)	all cause mortality	**HR: 0.67 (95%CI: 0.50 to 0.89)** **SS p=0.006**
*adjusted for age, sex, smoking, hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease, chronic kidney disease, baseline NIH Stroke Scale score, antithrombotics or/and antihypertensives at discharge and LDL-cholesterol on admission.					

Limitations:

"Authors did not have information regarding compliance with statin use during the follow-up period, but non-compliance would have decreased the estimated effects of statin use. As this was an observational study, prescription of statins was determined by attending doctors, leading to confounding by indication. »

Palnum 2012(80)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: prospective population based cohort mean follow-up 2.7y	n=28 612	patients hospitalized for ischemic stroke in 2003 to 2006 from the entire Danish population	Statin use vs no statin use	Death	**HR: 0.45 (95%CI 0.42–0.48)** **SS in favour of statin use**
* Adjusted for patient characteristics (stroke severity, Charlson index, diabetes mellitus, atrial fibrillation, myocardial infarction, hypertension, former stroke, intermittent claudication, quality of in-hospital care, smoking, alcohol, type of residence, socioeconomic status, and civil status					

Cantu-Brito 2012(81)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Prospective cohort study Latin American cohort of the REACH registry	n= 1816	-Latin American stable outpatients (62.3% men, mean age 67 years) with symptomatic atherothrombosis (87.1%) or with multiple risk factors only (12.9%) -Hyperchol-esterolemia present in 60% and 73.9% respectively	Statin use at baseline Vs No statin use at baseline	4-year all cause mortality	**HR: 0.49** **(95%CI 0.362 to 0.678)** **SS p<0.001**
*adjusted for for baseline characteristics such as sex, DM, AF, past or current smoking habit, WHtR >60, and antiplatelet or anticoagulant therapy.					

The main limitations of this study are the reduced sample size and the lack of complete information for some characteristics at 4-year follow-up. Our study population is a very selected group at high cardiovascular risk that may not represent the whole Latin American population, especially the younger individuals in premorbid states. The main outcome events recorded during the follow-up were not centrally adjudicated, which may represent a flaw especially in assigning the category of death.

Kokkinos 2013(82)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
prospective cohort study median follow-up of 10y	n= 10043	dyslipidaemic veterans from Veterans Aff airs Medical Centers in Palo Alto, CA, and Washington DC, USA, -mean age 58,8 years	Statin use Vs no statin use	all-cause mortality	**18.5% vs 27.7%** **SS p<0.0001**
*adjusted for age, body-mass index, ethnic origin, sex, history of cardiovascular disease, cardiovascular drugs, and cardiovascular risk factors.					

Lipworth 2013(83)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: Prospective cohort study Enrolled from 2002 - 2009 Median follow-up 5.6y	67 385	Southeastern United states, self reported hypercholesterolaemia	statin use (self reported) versus no statin use	all-cause mortality	**HR : 0.86; 95% CI 0.77–0.95** **SS in favour of statin use**
*Age used as timescale in Cox proportional hazards models. All models adjusted for year of SCCS enrollment; marital status; education; income; health insurance; BMI; cigarette smoking; alcohol consumption; history of hypertension, MI/CABG, diabetes, and stroke; and for race and sex where appropriate					

4.1.7.2 Summary and conclusions. All-cause mortality in observational studies

We found several cohort studies that report all cause mortality in statin users versus non users.

Acute coronary syndrome

In a prospective cohort study by Allonen 2012(77), 1969 patients with acute coronary syndrome were followed for a median of 23 months after hospital discharge. Non-use of the prescribed statin was associated with a higher mortality rate compared to regular statin use (HR:2.70; 95%CI 1.49 - 4.90). No adjustments were made for important confounders (e.g. smoking, socio-economic …). Other prognostic factors may be related to noncompliance.

Percutaneous coronary intervention (PCI)

In a prospective cohort study by Eindhoven 2012(78), 5647 patients who underwent PCI were followed for a median of 5 years. Statin use was associated with a lower risk of all-cause mortality compared to non use (11% vs 28%; HR: 0.49; 95%CI 0.40-0.59).

Stroke patients

-In a prospective cohort study by Makihara 2013(79), 2822 patients with first-even ischemic stroke were followed for a median of 2 y. Statin use (defined as treatment with statins at discharge) was associated with a lower risk of all-cause mortality compared to no statin use (patients who were not prescribed statins at discharge) (HR: 0.67;95%CI: 0.50 to 0.89).
- In a Danish population-based prospective cohort study by Palnum 2012(80), 28 612 patients that were hospitalized for stroke were followed for a mean of 2.7 years. Statin use was associated with a lower risk of mortality compared to no statin use (HR: 0.45; 95%CI 0.42–0.48).

High risk population

In a Latin-American prospective cohort study by Cantu-Brito 2012(81), 1816 patients with high cardiovascular risk were followed for 4 years. 87% had symptomatic atherothrombosis, 13% had multiple cardiovascular risk factors. Statin use at baseline was associated with a lower risk of 4-year all-cause mortality compared with no statin use at baseline (HR: 0.49; 95%CI 0.36 to 0.68).

Dyslipidaemia

-In a prospective cohort study by Kokkinos 2013(82) in 10 043 dyslipidaemic US veterans, followed for a median of 10 years, statin use was associated with a lower all-cause mortality rate compared to no statin use (18.5% vs 27.7%, p<0.0001).
- In a prospective cohort study by Lipworth 2013 in 67 358 patients with self-reported hypercholesterolaemia, followed a median of 5.6 years, statin use (self-reported) was associated with a lower risk of all-cause mortality compared to no statin use (self-reported), HR : 0.86; 95% CI 0.77–0.95.

Meta-analysis of observational studies and exploration of bias

Danaei 2012(84) published a meta-analysis of observational studies of statin use and mortality in primary prevention and in secondary prevention. When analyzing 4 studies in people with cardiovascular disease that compare incident users (new users) to non-users of a statin, the pooled,

multivariateadjusted mortality hazard ratio for statin use was 0.77 (95% CI 0.65 to 0.91). The hazard ration was 0.54 (95% CI: 0.45, 0.66) in 13 studies that compared prevalent users with nonusers.
In primary prevention, the pooled hazard ratio from 2 observational studies for incident users versus non-users was 0.80 (95%CI: 0.63, 1.02). Data for studies of prevalent users were not pooled (lack of data).
The author states that the inclusion of prevalent users induces bias.

Conclusion

In observational studies, statin use is associated with a lower mortality rate. The magnitude of the risk decrease cannot reliably be estimated, since correction for all confounders is difficult. There may be prognostic factors associated with not using a statin that also influence mortality.

4.1.8 Mortality rates in open-label follow-up of RCTs

Several placebo-controlled trials have reported post-trial follow-up results. After the trials, statin use in the treatment arms is found to be similar (when reported).

In the HPS study(85), 20 536 patients at high risk of vascular and non-vascular outcomes were allocated to either 40 mg simvastatin daily or placebo and followed in-trial for a mean of 5.3y. Post trial follow-up of surviving patients yielded a mean total duration of 11y follow-up. After trial, statin use in both treatment arms was similar.
Mortality
During the post-trial period, vascular mortality rates were similar in both treatment groups (1019 [11·5%] *vs* 1007 [11·6%]; RR 0·98 [95% CI 0·90–1·07]; p=0·71), so in-trial survival gains persisted (as stated by the authors, but no calculations on total follow-up provided).
During the post-trial period, non-vascular mortality rates were similar in both treatment groups (943 [10·6%] *vs* 942 [10·9%]; RR 0·97 [95% CI 0·89–1·06]; p=0·55),
Cancer
The incidence of a first diagnosis of any type of cancer(excluding, as prespecified, non-melanoma skin cancer) was similar throughout the in-trial and post-trial periods combined (1749 [17·0%] allocated simvastatin vs 1744 [17·0%] allocated placebo; RR 0·98 [0·92–1·05];p=0·60;

In the PROSPER trial(86), 5804 participants aged 70-82 years with either pre-existing vascular disease or increased risk of such disease because of smoking, hypertension or diabetes, were randomised to 40 mg pravastatin or matching placebo. In-trial follow-up was 3.2 years. Total mean follow up (+ post-trial follow up) was 8.6 years.
Mortality
All-cause mortality was not reduced in-trial, nor was it reduced in the total follow-up. Cardiovascular death was reduced in-trial, but not in the total follow-up

In the ALLHAT study(87), the authors conducted a randomized, controlled, multicenter trial, in which they assigned well-controlled hypertensive participants aged 55 years and older with moderate hypercholesterolemia to receive pravastatin (n=5170) or usual care (n=5185) for 4 to 8 years, when trial therapy was discontinued. After an average of 4.8 years of follow-up, there was no difference in the primary endpoint of all-cause mortality (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.89–1.11; P=.88)
Passive surveillance using national databases to ascertain deaths and hospitalizations continued for a total follow-up of 8 to 13 years to assess whether mortality and morbidity differences persisted or new differences developed. For the post-trial period, data are not available on treatments.
No significant differences appeared in mortality for pravastatin vs usual care (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.89-1.03)

The ASCOT-LLA trial(88) included 10305 hypertensive patients that were randomized into either atorvastatin 10 mg daily or placebo.
Within the first 2 years of post-trial (open-label phase), approximately two-thirds of patients previously assigned either atorvastatin or placebo were taking lipid-lowering treatment.
A median 11 years after initial randomization and 8 years after closure of LLA, during which

time most patients from both active and placebo treatment groups were taking statins,all-cause mortality (n = 520 and 460 in placebo and atorvastatin, respectively) remained significantly lower in those originally assigned atorvastatin (HR 0.86, CI 0.76–0.98, P = 0.02). CV deaths were fewer, but not significant (HR 0.89, CI 0.72–1.11, P = 0.32) and non-CV deaths were significantly lower (HR 0.85, CI 0.73–0.99, P = 0.03) in those formerly assigned atorvastatin attributed to a reduction in deaths due to infection and respiratory illness

4.2 Higher dose statin versus lower dose statin

4.2.1 Evidence tables. Mills 2011 meta-analysis. Intensive statin dose versus clinically common dose

Intensive statin dosing vs clinically common dose of statin

Meta-analysis: Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients

Inclusion criteria:
Any RCT evaluating a larger dose with a clinically common dose: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin for CVD therapeutic effects,
Studies had to be of 6 months duration, had to report on any of the following clinically important cardiovascular outcomes: All-cause mortality; CVD mortality; coronary heart disease (CHD) death plus non-fatal myocardial infarction (MI); fatal MI; non-fatal MI; strokes; and non-CVD deaths.
Search strategy:
MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, databases that included the full text of journals
In addition, searched the bibliographies of published systematic reviews and health technology assessments.
Finally, searched the own comprehensive rolling database of statin trials, updated monthly. Searches were not limited by language, sex, or age.
Assessment of quality of included trials:
yes: "Study evaluation included general methodological quality features, including sequence-generation, blinding, use of intent-to-treat analysis, % follow-up and allocation concealment."
ITT analysis: yes
Other methodological remarks:

- performed random-effects meta-analysis and a trial sequential analysis
- also conducted an optimal information size analysis to determine the strength of information for the meta-analysis on the primary outcome of CVD death and CHD plus non-fatal MI to determine the conservative number of patients required to provide an authoritative answer of therapeutic efficacy

Optimal information size:

- the authors note that the evidence for CHD plus non-fatal MI reduction is conclusive at the 80% power level

Ref	Comparison	N/n	Outcomes	Result
ref*Mills 2011(89) Design: MA Search date: 12/2010	Intensive statin dosing vs clinically common dose of statin	N= 9 n= 41760 (A-Z 2004, IDEAL 2005, PROVE-IT 2004, REVERSAL 2004, TNT 2005, Vascular basis. 2005, SAGE 2007, SEARCH 2008, Colivicchi 2010)	**All-cause mortality**	RR= 0.92 (95% CI 0.83 to 1.03) p=0.14 NS I^2=38%
		N=3 n= 8949 (A-Z 2004, PROVE-IT 2004, Colivicchi 2010)	**All-cause mortality** <u>Subgroup analysis: acute coronary syndrome</u>	**RR=0.75 (95% CI 0.61 to 0.91)** **P= 0.005** **SS in favour of intensive statin dosing** I^2=0%
		N= 7 n= 40793 (A-Z 2004, IDEAL 2005, PROVE-IT 2004, TNT 2005, SAGE 2007, SEARCH 2008, Colivicchi 2010)	**CVD mortality/CV deaths**	RR= 0.89 (95% CI 0.78 to 1.01) p=0.07 NS I^2= 34%
		N=3 n= 8949 (A-Z 2004, PROVE-IT 2004, Colivicchi 2010)	**CVD mortality/CV deaths** <u>Subgroup analysis: acute coronary syndrome</u>	**RR=0.74 (95% CI 0.59 to 0.94** **p=0.013** **SS in favour of intensive statin dosing** I^2=0% Note: "Applying a weighted event rate NNT for CVD death, we estimate that 119 (95% CI, 63–1364) patients should be treated to prevent one event per year."
		N= 2 n= 12957	Fatal MIs	RR= 0.75 (95% CI 0.41 to 1.35) p=0.34

		(SAGE 2007, SEARCH 2008)		NS
		N=4 n= 26342 (A-Z 2004, IDEAL 2005, SAGE 2007, SEARCH 2008)	Non-CVD deaths	RR= 0.97 (95% CI, 0.87 to 1.09) p=0.65 NS I^2=0%
		Subgroup N=1 n= 4497 (A-Z 2004)	Non-CVD deaths analysis: acute coronary syndrome	RR=0.98 (95% CI 0.54 to 1.08) p=0.96 NS
		N=1 n= 12064 (SEARCH 2008)	Fatal strokes	RR=0.85 (95% CI 0.59 to 1.20) NS
		N=5 n=32136 (IDEAL 2005, TNT 2005, SAGE 2007, SEARCH 2008, Colivicchi 2010)	Non-fatal MIs	**RR=0.82 (95% CI 0.76 to 0.90)** **p ≤ 0.0001** **SS in favour of the intensive statin dosing.** I^2=0%
		N=1 n=290 (Colivicchi 2010)	Non-fatal MIs Subgroup analysis: acute coronary syndrome	RR=0.55 (95% CI 0.28 to 1.07) p=0.08 NS
		N=9 n=31759 (A-Z 2004, IDEAL 2005, PROVE-IT 2004, REVERSAL 2004, Vascular basis. 2005, SAGE 2007, SEARCH 2008, Colivicchi 2010, Yu 2007)	Composite endpoint of CHD mortality plus non-fatal MI	**RR=0.90 (95% CI 0.84 to 0.96)** **p ≤ 0.0001** **SS in favour of the intensive statin dosing** I^2 =0% Note: Applying a weighted event rate number needed to treat (NNT), we estimate that patients receiving intensive statin dosing for secondary prevention have an NNT of 250 (95% CI, 162–735) to prevent a CHD or non-fatal MI per year.
		N=3 n= 8949 (A-Z 2004,	Composite endpoint of CHD mortality plus non-fatal MI Subgroup analysis: acute coronary syndrome	RR= 0.85 (95% CI 0.71 to 1.03) p = 0.10 NS

		PROVE-IT 2004, Colivicchi 2010)		I^2=32%
		N=10 n=41760 (A-Z 2004, IDEAL 2005, PROVE-IT 2004, REVERSAL 2004, TNT 2005, Vascular basis. 2005, SAGE 2007, SEARCH 2008, Colivicchi 2010, Yu 2007)	**Fatal and non-fatal strokes (excluding TIAs)**	**RR= 0.86 (95% CI 0.77 to 0.96)** **p =0.006** **SS in favour of the intensive statin dosing** I^2= 0%
		N=5 n=28109 (A-Z 2004, REVERSAL 2004, TNT 2005, SAGE 2007, SEARCH 2010)	**Risk of cancer**	RR=0.95 (95% CI 0.87 to 1.04) p=0.31 NS I^2= 0%
		N=6 n=39902 (A-Z 2004, IDEAL 2005, PROVE-IT 2004, TNT 2005, SEARCH 2008, Colivicchi 2010)	**Incidence of rhabdomyolysis**	RR= 1.70 (95% CI 0.56 to 5.19) p=0.34 NS I^2 =20%
		N=5 (A-Z 2004, IDEAL 2005, REVERSAL 2004, TNT 2005, SAGE 2007)	**Increased AST beyond normal**	**RR= 3.15 (95% CI 1.31 to 7.54)** **p=0.01** **SS in favour of intensive statin dosing** I^2 =53%
		N= 7 n= 37289 (A-Z 2004, IDEAL 2005, REVERSAL	**Increased ALT beyond normal**	**RR =1.57 (95% CI 1.29 to 1.91)** **p=0.002** **SS in favour of intensive statin dosing** I^2 = 93%

		2004, TNT 2005, SAGE 2007, SEARCH 2010, Colivicchi 2010)		
		N=4 n=21013 (A-Z 2004, PROVE-IT 2004, SEARCH 2008, Colivicchi 2010)	**Risk of CK beyond normal**	**RR=2.86 (95% CI, 2.02–4.04)** **p= ≤ 0.001** **SS in favour of intensive statin dosing,** *but article says: 'We did not find a significant increase in risk of CK beyond normal.'* Note: In one trial (A-Z 2004) with highdose simvastatin, CK increases in 10 times the upper limit of normal associated with myopathy were more common with simvastatin 80 mg than simvastatin 40 mg (nine vs. one) and in one trial (Colvicchi 2010) of atorvastatin 80 mg, CK increases in two times the normal limit associated with myopathy required discontinuation of the drug in two patients.

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
A-Z 2004(27) International, randomized, double-blind trial	4497	Patient status/condition at baseline: Acute coronary syndrome Age, mean, years: 61 Men, %: 76 Prior CHD, %: 100 Diabetes, %: 24 Hypertension, %: 50 Current smokers, %: 41 Baseline, mean mg/dL (change): LDL:111 (-37) HDL: 39 (-0.7)	2 y	Treatment comparisons (mg/day): S40–80 vs. S0–20 (40 mg/d of simvastatin for 1 month followed by 80 mg/d vs placebo for 4 months followed by 20 mg/d of simvastatin)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blinded FOLLOW-UP: adequate reporting 33% discontinued prematurely 3% lost to follow-up or follow-up too short for primary endpoints ITT:yes FUNDING: Merck note: lower start dose

					The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke.
IDEAL 2005(28) prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe	8888	Patient status/condition at baseline: CHD Age, mean, years:62 Men, %:81 Prior CHD, %: 100 Diabetes, %:12 Hypertension, %:33 Current smokers, %:21 Baseline, mean mg/dL (change): LDL:121 (-22) HDL:46 (-0.5)	4.8y	high dose of atorvastatin (80 mg/d), versus usual-dose simvastatin (20 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : endpoint-evaluation FOLLOW-UP: <1% lost to follow-up ITT:yes FUNDING: Pfizer note: no run-in Main Outcome Measure: Occurrence of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation
PROVE-IT 2004(29) RCT, double blind Noninferiority trial	4162	Patient status/condition at baseline: Acute coronary syndrome Age, mean, years:58 Men, %:78 Prior CHD, %: 100 Diabetes, %:18 Hypertension, %:50 Current smokers, %:37 Baseline, mean mg/dL (change): LDL:106 (-33) HDL:39 (0.65)	Follow-up lasted 18 to 36 months (mean, 2y)	40 mg of pravastatin daily (standard therapy) versus 80 mg of atorvastatin daily (intensive therapy)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blind FOLLOW-UP: - The rates of discontinuation of treatment because of an adverse event or the patient's preference or for other reasons were 21.4 percent in the pravastatin group and 22.8 percent in the atorvastatin group at one year (P=0.30) and 33.0 percent and 30.4 percent, respectively, at two years (P=0.11). - 0.2% lost to follow-up

					ITT:yes FUNDING: ? note: no run-in The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke
REVERSAL 2004(90) double blind RCT	654	Patient status/condition at baseline: Atherosclerotic Age, mean, years:56 Men, %: 72 Prior CHD, %: 100 Diabetes, %:19 Hypertension, %:69 Current smokers, %:26 Baseline, mean mg/dL (change): LDL:150 (-32) HDL:43 (0.7)	1.5y	Treatment comparisons (mg/day): A80 vs. P40	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blind FOLLOW-UP: “Adequate follow-up was reported in all trials” ITT: yes, for these endpoints FUNDING: Pfizer primary endpoint: coronary disease progression on intravascular ultrasound note: 2 week placebo run-in. 21% (176/833) of eligible participants did not meet criteria after run-in
TNT 2005(31) double blind RCT	10001	Patient status/condition at baseline: CHD Age, mean, years:61 Men, %:81 Prior CHD, %: 100 Diabetes, %:15 Hypertension, %:54 Current smokers, %:13	median 4.9y	10 mg atorvastatin versus 80 mg atorvastatin patients with LDL cholesterol levels	ALLOCATION CONC: unclear RANDO: unclear BLINDING : ‘double blind’, blinded assessors FOLLOW-UP: 35% excluded after run-in (mainly due to not meeting randomization criteria)

		Baseline, mean mg/dL (change): LDL:98 (-22) HDL:47 (0)		between 130 and 250 mg per deciliter (3.4 and 6.5 mmol per liter, respectively) and triglyceride levels of 600 mg per deciliter (6.8 mmol per liter) or less entered an eight-week run-in period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run-in phase (week 0), patients with a mean LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) (determined four weeks and two weeks before randomization) were randomly assigned to double-blind therapy with either 10 mg or 80 mg of atorvastatin per day.	3.6% of excluded run-in patients had ischemic event 3.6% of excluded run-in patients had adverse events <1% lost to follow-up ITT:yes FUNDING: Industry-funded note: washout period of one to eight weeks eight-week run-in period of open-label treatment with 10 mg of atorvastatin per day. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.
Vascular basis. 2005/Stone 2005(91) double blind RCT	199	Patient status/condition at baseline: CHD Age, mean, years: - Men, %:86 Prior CHD, %: 100 Diabetes, %:16 Hypertension, %:64 Current smokers, %:0 Baseline, mean mg/dL (change):	1y	Treatment comparisons (mg/day): 80 mg atorvastatin vs 5mg lovastatin (note: 1 other treatment arm Atorvastatin 80 mg + vit C and E)	ALLOCATION CONC: unclear RANDO: unclear BLINDING : 'double blind' FOLLOW-UP: 7% stopped early for reasons other than adverse events ITT: no

		LDL:148 (-33) HDL:45 (7.0)			FUNDING: NIH grant and unrestricted grant from Pfizer primary endpoint: ambulatory ECG ischemia note: no run-in
SAGE 2007(92) double blind RCT	893	Patient status/condition at baseline: CHD Age, mean, years:72 Men, %:69 Prior CHD, %: 100 Diabetes, %:23 Hypertension, %:65 Current smokers, %:6 Baseline, mean mg/dL (change): LDL:147 (-30) HDL:46 (11)	1y	Treatment comparisons (mg/day): A80 vs. P40	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors: yes FOLLOW-UP: 5% withdrawn due to lack of compliance or other reasons. 84% completed study ITT:yes no FUNDING: Pfizer primary endpoint: total duration of ischemia at month 12) note: washout period of 6 weeks no run-in
Yu 2007(93) double blind RCT	112	Patient status/condition at baseline: CHD Age, mean, years:66 Men, %:82 Prior CHD, %: 100 Diabetes, %:28 Hypertension, %:51 Current smokers, %:44 Baseline, mean mg/dL (change): LDL:116 (-39) HDL:50 (26)	0.5y	Treatment comparisons (mg/day): A80 vs. A10	ALLOCATION CONC: Adequate RANDO: unclear BLINDING : Participants/personnel/assessors yes FOLLOW-UP: 4% excluded from analysis due to raised CK or liver enzymes ITT:no

					FUNDING: Pfizer primary endpoint: carotid intimal-medial thickness note: 1 week washout phase
Colivicchi 2010(94) open label RCT	290	Patient status/condition at baseline: Acute coronary syndrome Age, mean, years:74 Men, %:52 Prior CHD, %: 100 Diabetes, %:71 Hypertension, %:89 Current smokers, %:- Baseline, mean mg/dL (change): LDL:126 (-64) HDL:40 (-)	1y	Treatment comparisons (mg/day): A80 vs. A20/40	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : assessors FOLLOW-UP: “Adequate follow-up was reported in all trials” ITT:yes FUNDING: ? Primary end point event (combination of cardiovascular death, non-fatal acute myocardial reinfarction and disabling stroke within 12 months of randomisation)
SEARCH 2010(30) RCT	12064	Patient status/condition at baseline: CHD Age, mean, years: - Men, %:83 Prior CHD, %: 100 Diabetes, %:- Hypertension, %:- Current smokers, %:- Baseline, mean mg/dL (change): LDL:97 (-14) HDL:39 (-)	6.7y	Treatment comparisons (mg/day): S80 vs. S20	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : yes FOLLOW-UP: 37% not eligible after run-in phase 2% lost to follow-up 30% stopping before end of study ITT:yes FUNDING: Merck

					The primary endpoint was major vascular events, defined as coronary death, myocardial infarction, stroke, or arterial revascularization a prerandomisation run-in phase of treatment with 20 mg simvastatin daily (and placebo vitamins)

Remarks:
Some inconsistencies between written results and forest plots as to included trials.

4.2.2 Summary and conclusions. Mills 2011 meta-analysis. Intensive statin dose versus clinically common dose

Higher dose statin versus moderater dose statin			
Bibliography: Meta-analysis: Mills 2011(89)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	41 760 (9 studies) 1y-6.7y	RR= 0.92 (95% CI 0.83 to 1.03) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 statin run-in in half the participants (2 trials) Consistency: OK Directness: OK, see study quality Imprecision: OK
CVD mortality	40 793 (7 studies) 1y-6.7y	RR= 0.89 (95% CI 0.78 to 1.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 statin run-in in half the participants (2 trials) Consistency: OK Directness: OK, see study quality Imprecision: OK
Composite endpoint of CHD mortality plus non-fatal MI	31 759 (9 studies) 1y-6.7y	**RR=0.90 (95% CI 0.84 to 0.96)** **SS in favour of the intensive statin dosing** NNT= 250(95%CI 162-735) (based on weighted event rate)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 statin run-in in 1/3 participants (2 trials) Consistency: OK Directness: OK, see study quality Imprecision: OK
Fatal and non-fatal strokes (excluding TIAs)	41 760 (10 studies) 6m-6.7y	**RR= 0.86 (95% CI 0.77 to 0.96)** **SS in favour of the intensive statin dosing**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 statin run-in in half the participants (2 trials) Consistency: OK Directness: OK, see study quality Imprecision: OK
Cancer	28 109 (5 studies) 1y-6.7y	RR=0.95 (95% CI 0.87 to 1.04) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 relatively short FU for this outcome Consistency: OK Directness: OK Imprecision: OK
Rhabdomyolysis	39 902 (6 studies) 1y-4.9y	RR= 1.70 (95% CI 0.56 to 5.19) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 statin run-in in 1/3 participants (2 trials) Consistency:OK Directness:OK Imprecision:-1

This meta-analysis compares high dose statin versus a lower dose statin for cardiovascular disease prevention. Participants in all included trials had a history of cardiovascular disease, mainly coronary heart disease.
The high dose statin was atorvastatin 80 mg in most trials, and simvastatin 40mg or 80 mg in 2 trials.
The lower dose statin was either simvastatin 20 mg, atorvastatin 10/20/40 mg, pravastatin 40 mg or lovastatin 5 mg.
Trial duration ranged from 6 months (1 smaller trial) to 6.7 years. Mean age ranged from 56y to 74y.

In this population, there is no statistically significant difference in all-cause mortality between high dose statin and lower dose statin, nor is there a statistically significant difference in mortality from cardiovascular disease.
GRADE: MODERATE quality of evidence

There is a lower risk of the composite endpoint of death from coronary heart disease or nonfatal myocardial infarction with higher dose statin. The authors calculate that 250 patients have to be treated with a high dose statin instead of a lower dose, to prevent 1 additional event (for a mean duration of 1 to 6.7 years).
GRADE: MODERATE quality of evidence

The risk of all stroke (fatal and nonfatal) is reduced with higher dose statin compared to lower dose statin.
GRADE: MODERATE quality of evidence

No significant difference in cancer rates is observed between both treatment groups
GRADE: MODERATE quality of evidence

No significant difference in rhabdomyolysis is found between treatment with higher dose statin compared to lower dose statin.
GRADE: LOW quality of evidence

4.2.3 Evidence tables. CTT 2012 Individual patient data meta-analysis

Statin versus control (22 trials) and statin high dose versus statin low dose (5 trials)

Meta-analysis of individual patient data

Inclusion criteria

- RCT
- Lipid modification therapy at least 1 treatment arm, no multiple interventions
- >= 2y scheduled duration
- Aim >= 1000 patients
- Results not known at time of protocol description (1995)

Search strategy "Potentially eligible studies are to be identified prospectively by a range of methods, including computer-aided literature searches, manual searches of journals, scrutiny of the reference lists of trials and review articles, scrutiny of abstracts and meeting proceedings, collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, and by inquiry among colleagues, collaborators, and manufacturers of lipid-modifying agents."

Note: no further information on the methods of the computer-aided literature search

Assessment of quality of included trials: no

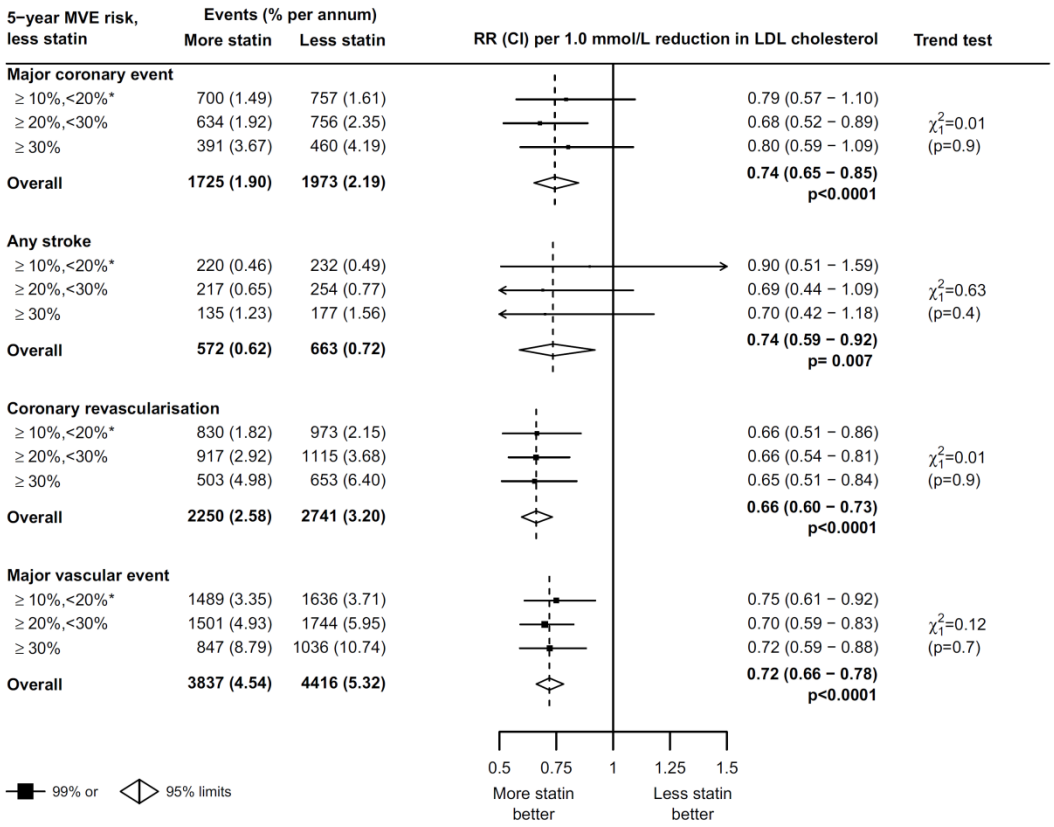
ITT analysis: yes

Other methodological remarks

- Risk modelling calculation with cox proportional hazards model
- No mention of analysis according to baseline risk in original protocol.
- Meta-analyses were weighted by the absolute LDL cholesterol difference in that trial at 1 year (mmol/l)
- Authors' note: Predicted risk compared well with observed risk for each trial, as well as within each 5-year risk group.
- Authors' note: Individual participant data were unavailable from only two eligible trials in 6331 higher-risk patients with pre-existing vascular disease (SPARCL36 and GREACE37)..

Ref	Comparison	N/n	Outcomes	Result	
CTT 2012 Design: MA Search date: (june 2011)	Statins high Vs Statins low	N= 5 n= 39 612		5-y MVE risk at baseline	RR (CI) per 1·0 mmol/L reduction in LDL cholesterol
			Major vascular event (major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations	≥10% to <20% ≥20% to <30% ≥30% Overall	**0.75 (0.61 – 0.92)** **0.70 (0.59 – 0.83)** **0.72 (0.59 – 0.88**) **0.72 (0.66 – 0.78) p<0.0001**
			Major coronary event (non-fatal myocardial infarction or coronary death)	≥10% to <20% ≥20% to <30% ≥30% Overall	0.79 (0.57 – 1.10) **0.68 (0.52 – 0.89)** 0.80 (0.59 – 1.09) **0.74 (0.65 – 0.85) p<0.0001**
			Any stroke	≥10% to <20% ≥20% to <30% ≥30% Overall	0.90 (0.51 – 1.59) 0.69 (0.44 – 1.09) 0.70 (0.42 – 1.18) **0.74 (0.59 – 0.92) p= 0.007**

Webfigure 6: Effects on major coronary events, strokes, coronary revascularisation procedures and major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk in the 5 trials of more vs less statin



*Includes 141 participants (48 from A to Z and 93 from SEARCH) with an estimated 5−year risk of MVE less than 10%.

* Characteristics of included studies: see below

statin high dose versus statin low dose (5 trials)					
A to Z 2004 International, randomized, double-blind trial	4497	Patients with acute coronary syndrome (ACS) Age, mean, years: 61 Men, %: 76 Prior CHD, %: 100 Diabetes, %: 24 Hypertension, %: 50 Current smokers, %: 41 Baseline, mean mg/dL (change): LDL:111 (-37) HDL: 39 (-0.7)	Follow-up was for at least 6 months and up to 24 months	40 mg/d of simvastatin for 1 month followed by 80 mg/d vs placebo for 4 months followed by 20 mg/d of simvastatin	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blinded FOLLOW-UP: adequate reporting 33% discontinued prematurely 3% lost to follow-up or follow-up too short for primary endpoints ITT:yes FUNDING: Merck note: lower start dose The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke.
IDEAL 2005 prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe	8888	Patients aged 80 years or younger with a history of acute MI Age, mean, years:62 Men, %:81 Prior CHD, %: 100 Diabetes, %:12 Hypertension, %:33 Current smokers, %:21 Baseline, mean mg/dL (change): LDL:121 (-22) HDL:46 (-0.5)	Median follow-up of 4.8 years	high dose of atorvastatin (80 mg/d), versus usual-dose simvastatin (20 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : endpoint-evaluation FOLLOW-UP: <1% lost to follow-up ITT:yes FUNDING: Pfizer note: no run-in Main Outcome Measure: Occurrence

					of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation
PROVE-IT 2004 RCT, Noninferiority trial	4162	Patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days Age, mean, years:58 Men, %:78 Prior CHD, %: 100 Diabetes, %:18 Hypertension, %:50 Current smokers, %:37 Baseline, mean mg/dL (change): LDL:106 (-33) HDL:39 (0.65)	Follow-up lasted 18 to 36 months (mean, 24)	40 mg of pravastatin daily (standard therapy) versus 80 mg of atorvastatin daily (intensive therapy)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : double blind FOLLOW-UP: - The rates of discontinuation of treatment because of an adverse event or the patient's preference or for other reasons were 21.4 percent in the pravastatin group and 22.8 percent in the atorvastatin group at one year (P=0.30) and 33.0 percent and 30.4 percent, respectively, at two years (P=0.11). - 0.2% lost to follow-up ITT:yes FUNDING: ? note: no run-in The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke

SEARCH 2010 double-blind randomised trial	12064	Men and women aged 18-80 years with a history of myocardial infarction, were either currently on or had clear indication for statin therapy, and had a total cholesterol concentration of at least 3·5 mmol/L if already on a statin or 4·5 mmol/L if not Age, mean, years: - Men, %:83 Prior CHD, %: 100 Diabetes, %:- Hypertension, %:- Current smokers, %:- Baseline, mean mg/dL (change): LDL:97 (-14) HDL:39 (-)	Mean follow-up of 6·7 (SD 1·5) years	80 mg simvastatin versus 20 mg simvastatin	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : yes FOLLOW-UP: 37% not eligible after run-in phase 2% lost to follow-up 30% stopping before end of study ITT:yes FUNDING: Merck The primary endpoint was major vascular events, defined as coronary death, myocardial infarction, stroke, or arterial revascularisation
TNT 2005 double blind RCT	10001	patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) Age, mean, years:61 Men, %:81 Prior CHD, %: 100 Diabetes, %:15 Hypertension, %:54 Current smokers, %:13 Baseline, mean mg/dL (change): LDL:98 (-22) HDL:47 (0)	median of 4.9 years.	10 mg atorvastatin versus 80 mg atorvastatin	ALLOCATION CONC: unclear RANDO: unclear BLINDING : 'double blind', blinded assessors FOLLOW-UP: 35% excluded after run-in (mainly due to not meeting randomization criteria) 3.6% of excluded run-in patients had ischemic event 3.6% of excluded run-in patients had adverse events <1% lost to follow-up ITT:yes FUNDING: Industry-funded

					note: washout period of one to eight weeks eight-week run-in period of open-label treatment with 10 mg of atorvastatin per day. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

4.2.4 Summary and conclusions: CTT 2012. Individual patient data meta-analysis

High dose statin versus lower dose statin in an overall population and in subgroups according to baseline risk			
Bibliography: Individual patient data meta-analysis: CTT 2012(4)			
Outcomes	**N° of participants (studies) Follow up**	**Results** RR (CI) per 1·0 mmol/L reduction in LDL	**Quality of the evidence (GRADE)**
Major vascular event: major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations	39 612 (5 studies)	HR= **0.72 (0.66 – 0.78)** **SS in favour of high dose** **SS in 3 highest 5-y MVE risk category subgroups (insufficient patients in 2 lowest risk groups)**	*Not applied*
Major coronary event: non-fatal myocardial infarction or coronary death	39 612 (5 studies)	**HR=0.74 (0.65 – 0.85)** **SS in favour of high dose** **SS in 5-y MVE risk group of ≥20% to <30%**	*Not applied*
Any stroke	39 612 (5 studies)	**HR= 0.74 (0.59 – 0.92)** **SS in favour of statin** NS in all 5y MVE risk groups	*Not applied*

<u>High dose statin versus low dose statin.</u>

Individual patient data from 5 trials were included. There were very few patients with a baseline risk of a major vascular event of less than 10%. All included patients had a history of cardiovascular disease.

In this population, there is a statistically significant decrease* in major vascular events with high dose compared to a lower dose of statin. A statistically significant decrease in major vascular events is also observed in the 3 highest MVE risk categories.

GRADE: not applied

High dose statin results in a reduction of major coronary events compared to low dose statin. A statistically significant reduction in major coronary events was also observed in the subgroup of patients with a 5y MVE risk of ≥20% to <30%.

GRADE: not applied

High dose statin reduces the risk of stroke compared to low dose statin. In the different 5y MVE subgroups, the result was not statistically significant.

GRADE: not applied

**Reduction per 1.0 mmol/L reduction in LDL-cholesterol*

4.3 Statin versus fibrate

No studies found

4.4 Statin versus ezetimibe

No studies found

5 Evidence tables and conclusions: efficacy of other lipid-lowering drugs

5.1 Fibrate versus placebo

5.1.1 Evidence tables

Meta-analysis:
Inclusion criteria: prospective randomised controlled trials assessing the effects of fibrates on cardiovascular outcomes compared with placebo. The search was limited to randomised controlled trials with at least 100 patient- years of follow-up in each group, but without language restriction
Search strategy: a systematic review of the published work according to the PRISMA statement for the conduct of meta-analyses of intervention studies. Relevant studies were identifi ed by searching the following data sources: Medline via Ovid (from 1950 to March, 2010), Embase (from 1966 to March, 2010), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction),
Assessment of quality of included trials: yes, Study quality was judged by the proper conduct of randomisation, concealment of treatment allocation, similarity of treatment groups at baseline, the provision of a description of the eligibility criteria, completeness of follow-up, and use of intention-to-treat analysis, and was quantifi ed with the Jadad score. Potential publication bias was assessed with the Egger test and represented graphically with Begg funnel plots of the natural log of the RR versus its SE.
ITT analysis: yes
Other methodological remarks:
Summary estimates of RR ratios were obtained with a random effects model
The percentage of variability across studies attributable to heterogeneity beyond chance was estimated with the I^2 statistic
A cumulative meta-analysis was done to identify any trends in the effect of fibrates over time.
Funding National Health and Medical Research Council of Australia.

Ref	Comparison	N/n	Outcomes	Result
Jun_2010(95) Design: SR and MA Search date: march 2010 Age range :	Fibrates -clofi brate (N=7) -bezafibrate (N=4) -fenofibrate (N=3) -gemfibrozil (N=3) -etofibrate (N=1) versus Placebo	N= 5 n= 19944 (VA CO-OP Atherosclerosis 1973, VA-HIT 1999, Leader 2002, Field 2005, ACCORD 2010)	**Major cardiovascular outcomes**[1] (defined as a composite including both myocardial infarction and stroke)	**Fibrate: 1355/9975 (13.6%)** **Pla: 1515/9969 (15.2%)** **RR = 0.90(95% CI 0.82 to 1.00)** **SS in favor of treatment (fibrate) p =0.048**
		N= 16 n= 44667 (Newcastle-Tyne clofibrate trial 1971, IHD prevention clofibrate trial 1971, VA CO-OP Atherosclerosis 1973, Coronary Drug Project 1975, WHO CO-OP Trial 1978, Helsinki Heart 1987, Hanefeld et al 1991,BECAIT 1997,	**Coronary events** (myocardial infarction and coronary death)	**Fibrate 1871/21503 (8.4%)** **Pla: 2681/23164 (11.7%)** **RR = 0.87(95% CI 0.81 to 0.93)** **SS in favor of treatment (fibrate) p <0.0001**

46-68 years	Age range : 46-68 years	LOCAT 1997, SENDCAP 1998, VA-HIT 1999, BIP 2000, DAIS 2001, LEADER 2002, FIELD 2005, ACCORD 2010)		
		N= 16 n= 44813 (Newcastle-Tyne clofibrate trial 1971, IHD prevention clofibrate trial 1971, Acheson and Hutchinson 1972, VA CO-OP Atherosclerosis 1973, Coronary Drug Project 1975, WHO CO-OP Trial 1978, Helsinki Heart 1987, Hanefeld et al 1991, LOCAT 1997, VA-HIT 1999, BIP 2000, DAIS 2001, LEADER 2002, FIELD 2005, Emmerich et al 2009, ACCORD 2010)	**All-cause mortality**	RR = 0.87(95% CI 0.93 to 1.08) NS p=0.918
		N= 6 n= 22066 (VA CO-OP Atherosclerosis 1973, Coronary Drug Project 1975, Hanefeld et al 1991, LEADER 2001, FIELD 2005, ACCORD 2010)	**Cardiovascular death**	RR = 0.97(95% CI 0.88 to 1.07) p=0.587 NS
		N= 8 n= 27021 (Acheson and Hutchinson 1972, VA CO-OP Atherosclerosis 1973, Coronary Drug Project 1975, VA-HIT 1999, BIP 2000, LEADER 2001, FIELD 2005, ACCORD 2010)	**Total stroke**	RR = 1.03(95% CI 0.91 to 1.16 p=0.687 NS
		N= 4 n= 17413 (VA CO-OP Atherosclerosis 1973, LEADER 2002, FIELD 2005, ACCORD 2010)	**Total adverse events**	RR =1.21 (95% CI 0.91 to 1.61); p=0.19 NS

1)Authors noted some evidence of heterogeneity(I2=47•0%, Q=7•55, p=0•110) in the magnitude of the effect across the included studies, which was mostly attributable to the VA CO-OP Atherosclerosis study—a trial that specifically included individuals with preexisting cerebrovascular disease. A sensitivity analysis excluding the VA CO-OP Atherosclerosis study resulted in a similar estimate of effect of 12% RR reduction with a much reduced I2 value of 18・6%.

Formal statistical testing showed no evidence of publication bias for the outcome of major cardiovascular outcomes (Egger's test p=0・94; webappendix p 4), but we noted evidence of publication bias for the coronary outcome (Egger's test p=0・035; webappendix p 5). The conclusions were not changed after adjustment for publication bias with the trim and fi ll method34 (data not shown).

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Group of physicians of the Newcastle upon Tyne region (1971)(96) Randomised, multicentre; Great Britain	497	Secondary prevention Mean age: 53y Inclusion criteria: History of symptoms of IHD Excluded diabetics on OHG or insulin 80% men	5y	Clofibrate (1.5–2 g daily) vs Corn oil placebo	ALLOCATION CONC: Unclear RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP: described: yes COMPLETION RATE : 82.0/88.5 (treatment/placebo) ITT described :yes FUNDING: ? Jadad: 4
Research committee of Scottish society of physicians (1971)(97) Randomised, multicentre; Scotland	717	Secondary prevention Age 40–69 y; fi rst MI 8–16 w before trial, <24 m of angina or angina of >3 m, <2 y with ECG changes of angina but not of previous MI 83% men	6y	Clofibrate (1·6– 2 g daily) vs Olive oil placebo	ALLOCATION CONC: unclear RANDO: unclear DOUBLE BLINDING described : incomplete FOLLOW-UP: described: yes COMPLETION RATE: 79.99/81 (treatment/placebo) ITT described: no FUNDING:? Jadad=1
Acheson and Hutchinson (1972)(49) Randomised, unspecified number of centres; Great Britain	95	Secondary prevention History of focal cerebral vascular disease 68% men Excluded severe diabetics	8 y 8 m in treatment group; 7 y 7m in placebo group	Clofibrate (1–2 g daily) vs Corn oil then unspecified placebo	ALLOCATION CONC:unclear RANDO: inadequate DOUBLE BLINDING described : yes FOLLOW-UP: described:no COMPLETION RATE: NR (treatment/placebo) ITT described: no FUNDING:? Jadad=0
Veterans Administration Cooperative Study Group (1973) (98)	532	Secondary prevention Male veteran, cerebral I or TIA within 12 m	21·6 m in placebo group; 21·9	Clofibrate (2 g daily) vs Lactose	ALLOCATION CONC: unclear RANDO: unclear

Randomised, multicentre; USA		100% men 24% diabetics	m in treated group	placebo	DOUBLE BLINDING described : no FOLLOW-UP: described:yes COMPLETION RATE :73.9/78.4 (treatment/placebo) ITT described: yes FUNDING:? Jadad=1
Coronary Drug Project Research Group (1975)(99) Randomised, multicentre; USA	3892	Secondary prevention Male, age 30–64 y, verifi ed evidence of MI >3 m before entry, no recent worsening coronary disease or of other major illnesses 100% men	6.2 y	Clofibrate (1·8 g daily) vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP: described:yes COMPLETION RATE 92.6/92 (treatment/placebo) ITT described: yes FUNDING:? Jadad: 4
WHO-COOP committee of principal investigators (1978)(100) Randomised, multicentre; Scotland, Hungary, and Czech Republic	10627	Primary prevention Male, age 30–59 y (mean age :46), upper third level of cholesterol from 15 745 healthy men 100% men 0% diabetics	5.3y	Clofibrate (1·6 g daily) vs Olive oil placebo	ALLOCATION CONC: unclear RANDO: unclear DOUBLE BLINDING described : yes FOLLOW-UP: described:yes COMPLETION RATE 67.3/68.1 (treatment/placebo) ITT described: yes FUNDING:? Jadad: 2
Helsinki Heart Study (1987)(101) Randomised, multicentre; Finland	4081	Primary prevention Age 40–55 y (mean age :47), non-HDL cholesterol ≥5·2 mmol/L 100% men 3% diabetics	60·4 m	Gemfibrozil (1·2 g daily) vs Placebo	ALLOCATION CONC: unclear RANDO: adequate DOUBLE BLINDING described : yes FOLLOW-UP described:yes COMPLETION RATE 70.1 (overall)

					(treatment/placebo) ITT described: yes FUNDING:? Jadad: 4
Hanefeld (1991)(102) Randomised, multicentre; Germany	761	Primary prevention Male, age 30–55 y (mean age :46), newly diagnosed diabetes controlled by diet after 6 w of conventional diet 56% men	5y	Clofibrate (1·6 g daily) vs Placebo	ALLOCATION CONC: unclear RANDO: unclear DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 88.1/85.9 (treatment/placebo) ITT described: no FUNDING:? Jadad: 2
BECAIT (1997)(103) Randomised, multicentre; Sweden	81	Secondary prevention Male, age ≤45 y at fi rst MI, cholesterol ≥5·2 mmol/L and/or trig ≥1·6 mmol/L with angiographically evaluable coronary plaque after 3 m dietary intervention 100% men	5 y	Bezafibrate (600 mg daily) vs Placebo	ALLOCATION CONC: unclear RANDO: unclear DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE :81.0/79.5 (treatment/placebo) ITT described: no FUNDING:? Jadad=1 Trial designed to evaluate surrogate endpoints. The trial was not powered to examine clinical endpoints. SS less coronary events with fibrate compared to placebo.
LOCAT (1997)(104) Randomised,	395	Secondary prevention Male, age <70 y (mean age :60), CABG within 3–48 m, LVEF >35%,	2.7y	Gemfibrozil (1200 mg daily) vs Placebo	ALLOCATION CONC: unclear RANDO: Adequate

multicentre; Germany		BMI <30 kg/m2, SBP <160 mm Hg, DBP <95 mmHg, HDL <1·1 mmol/L, trig <4 mmol/L, LDL <4·5 mmol/L 100% men 0% diabetics			DOUBLE BLINDING described : yes FOLLOW-UP described:yes COMPLETION RATE: 94/94 (treatment/placebo) ITT described: no FUNDING:? Jadad: 2
SENDCAP (1998)(105) Randomised, multicentre; UK	164	Primary prevention Age 35–65 y (mean age: 51) , diet or OHG controlled type 2 DM, no history of cardiovascular disease with any of cholesterol ≥5·2 mmol/L, trig ≥1·8 mmol/L, HDL ≤1·1 mmol/L, total-to- HDL cholesterol ratio ≥4·7 71% men 100% diabetics no other lipid-lowering drugs	3–5 y (range)	Bezafibrate (600 mg daily) vs Placebo	ALLOCATION CONC: unclear RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 66.7/63.9 (treatment/placebo) ITT described: no FUNDING:? Jadad: 4 Trial designed to evaluate surrogate endpoints. The trial was not powered to examine clinical endpoints. SS less definite CHD event with fibrate compared to placebo.
VA-HIT (1999)(106) Randomised, multicentre; USA	2531	Secondary prevention Age <74 y (mean age: 64), history of CHD, absence of serious coexisting conditions, HDL ≤1·0 mmol/L, LDL ≤3·6mmol/L, trig ≤3.4mmol/L 100% men 25% diabetics	5·1 y (median)	Gemfibrozil (1200 mg daily) vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 97.6 (overall) (treatment/placebo) ITT described: yes FUNDING:? Jadad: 4
BIP (2000)(107)	3090	Secondary prevention	6·2 y	Bezafibrate	ALLOCATION CONC:

Randomised, multicentre; Israel		Age 45–74 y (mean age: 64), MI ≥6 m but <5 y and/or stable angina pectoris confirmed by investigations and lipid profi le of cholesterol 4·7–6·5 mmol/L, LDL ≤4·7 mmol/L (4·1 mmol/L if <50 y), HDL ≤1·2 mmol/L, trig ≤3·4 mmol/L 91% men 10% diabetics		(400 mg daily) vs Placebo	unclear RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 77/74 (treatment/placebo; patients alive at end of study on medication) ITT described: yes FUNDING:? Jadad: 4 The primary end point was fatal or nonfatal myocardial infarction or sudden death. (P=0.26). Total and noncardiac mortality rates were similar, and adverse events and cancer were equally distributed. NS findings for all clinical endpoints
DAIS (2001)(108) Randomised, multicentre; Canada, Finland, France, and Sweden	418	Primary/secondary prevention Age 40–65 y (mean age: 57), type 2 DM, lipid profile total cholesterol-to-HDL ratio of 4 plus either LDL 3·5–4·5 mmol/L, trig ≤5·2 mmol/L, or triglyceride 1·7–5·2 mmol/L and LDL ≤4·5 mmol/L 73% men 100% diabetics	3·3 y	Fenofibrate (200 mg daily) vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate DOUBLE BLINDING described : no FOLLOW-UP described: yes COMPLETION RATE :100 (treatment/placebo; 24 patients with imputed data) ITT described: yes FUNDING:? Jadad: 2 Trial designed to evaluate surrogate endpoints. The trial was not powered to

					examine clinical endpoints. NS findings for all clinical endpoints.
LEADER (2002)(109) Randomised, multicentre; UK	1568	Secondary prevention Men (mean age: 68) with lower extremity arterial disease 100% men 66% diabetics	4·6 y	Bezafibrate (400 mg daily) vs Placebo	ALLOCATION CONC: unclear RANDO: unclear DOUBLE BLINDING described : FOLLOW-UP described: yes COMPLETION RATE 19.2/22.4 (treatment/placebo) ITT described: yes FUNDING:? Jadad:2 coronary heart disease and stroke (Primary endpoint): NS Major coronary events: NS **Nonfatal coronary events: SS**
FIELD (2005)(110) Randomised, multicentre; Australia, New Zealand, and Finland	9795	Primary/secondary prevention Age 50–75 y (mean age: 62), type 2 DM according to WHO criteria +not on statin therapy 63% men 100% diabetics	5 y	Fenofibrate (200 mg daily) vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 98.5/99.1 (treatment/placebo) ITT described: yes FUNDING:? Jadad: 4 Coronary event (primary endpoint) HR= 0.89, 95% CI 0.75-1.05; p=0.16; NS **Non-fatal myocardial infarction HR= 0.76, 0.62-0.94; p=0.010; SS** Coronary heart disease mortality HR=1.19, 0.90-1.57; p=0.22 NS

					Total cardiovascular disease events HR=0.89, 0.80-0.99; p=0.035; SS **Coronary revascularisation HR=0.79, 0.68-0.93; p=0.003; SS** Total mortality (p=0.18) NS
Emmerich (2009)(111) Randomised, multicentre; Germany	296	Secondary prevention Age 18–78 y (mean age: 59), with type 2 DM and previous history of Retinopathy 31% men 100% diabetics	1y	Etofibrate (1000 mg daily) vs Placebo	ALLOCATION CONC: unclear RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 89 overall (treatment/placebo) ITT described: yes FUNDING:? Jadad=1
ACCORD (2010)(112) Randomised	5518	Primary/secondary prevention Type 2 DM with HbA1c ≥7·5%; age 40–79 y if clinical CV disease or age 55–79y (mean age: 62), if subclinical CV disease or ≥2 CV risk factors; and lipid profi le LDL 4·55–4·65 mmol/L, HDL <1·42 mmol/L (women and black people) or <1·29 mmol/L (others), and trig <8·5 mmol/L not on therapy or <4·5 mmol/L on therapy 69% men	4·7 y primary outcome, 5 y death	Fenofibrate (160 mg daily, adjusted as per renal function later in trial) vs Placebo (both treatment arms received simvastatin)	ALLOCATION CONC: Adequate RANDO: Adequate DOUBLE BLINDING described : yes FOLLOW-UP described: yes COMPLETION RATE 96.8/97.2 (treatment/placebo) ITT described: yes FUNDING:? Jadad: 4 This trial is discussed in detail in the chapter fibrate plus statin versus statin. No statistically significant difference was found between fenofibrate and placebo (in combination with simvastatin) on any endpoint.

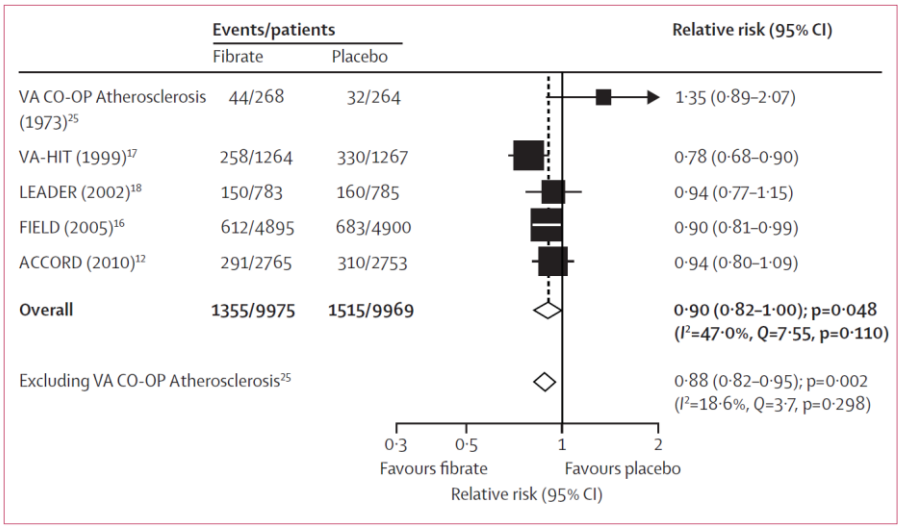


Figure 2: Effect of fibrates on risk of major cardiovascular outcomes

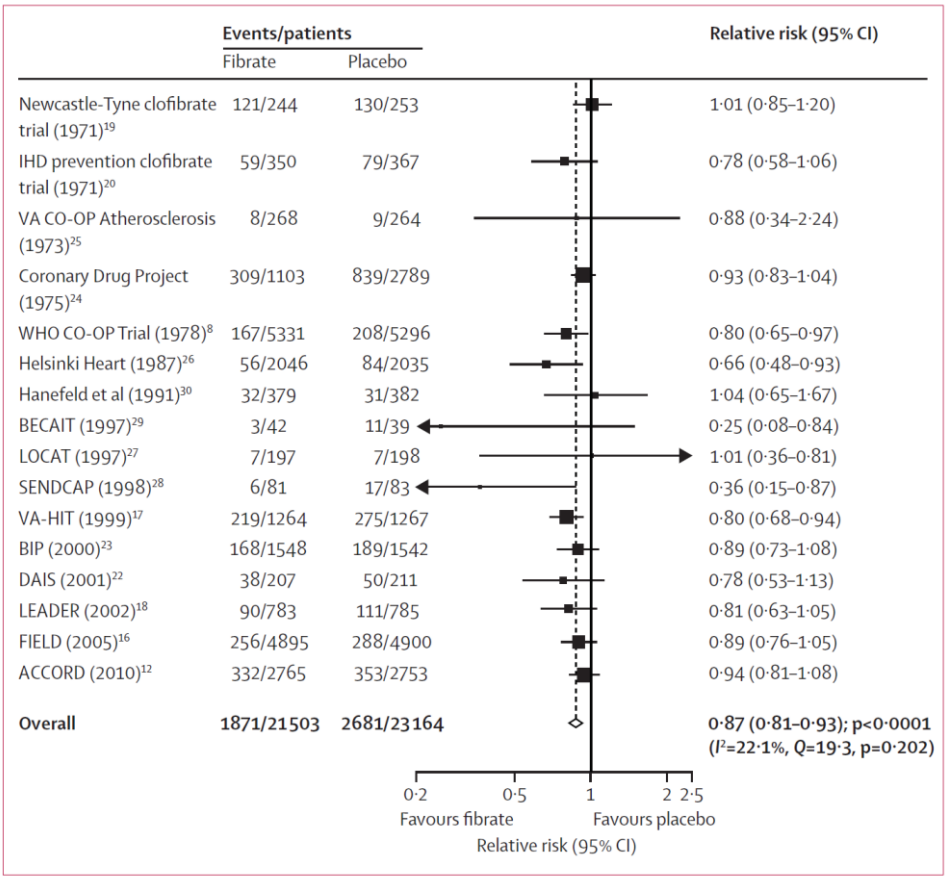


Figure 3: Effect of fibrates on the risk of coronary events

Author's conclusion (Jun 2010):
"Fibrates can reduce the risk of major cardiovascular events predominantly by prevention of coronary events, and might have a role in individuals at high risk of cardiovascular events and in those with combined dyslipidaemia. The findings contrast with the results of some of the individual trials that have reported no benefit. The magnitude of the proportional risk reduction is more modest than that achieved with other vascular preventive therapies targeting lipids, blood pressure, and coagulation, and the clinical relevance of the effect reported here will be debated."

5.1.2 Summary and conclusions. Fibrate versus placebo

Fibrate versus placebo			
Bibliography: Meta-analysis Jun 2010(95)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	44813 (16 studies)	RR = 0.87(95% CI 0.93 to 1.08) NS p=0.918	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision: OK
Cardiovascular death	22066 (6 studies)	RR = 0.97(95% CI 0.88 to 1.07) p=0.587 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision:OK
Major cardiovascular outcomes(including both myocardial infarction and stroke)	19944 (5 studies)	**Fibrate: 13.6%** **Pla: 15.2%** **RR = 0.90(95% CI 0.82 to 1.00)** **SS in favor of treatment (fibrate)** **p =0.048**	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision:OK
Coronary events (myocardial infarction and coronary death)	44667 (16 studies)	**Fibrate 8.4%** **Pla: 11.7%** **RR = 0.87(95% CI 0.81 to 0.93)** **SS in favor of treatment (fibrate)** **p <0.0001**	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision:OK
Total stroke	27021 (8 studies)	RR = 1.03(95% CI 0.91 to 1.16) p=0.687 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision:OK
Total adverse events	17413 (4 studies)	RR =1.21 (95% CI 0.91 to 1.61) p=0.19 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 low Jadad in half the trials Consistency: OK Directness:-1 +statin in some trials, clinical heterogeneity Imprecision:OK

A systematic review and meta-analysis pooled RCTs comparing a fibrate to placebo. Trials with fibrates that are not available in Belgium (clofibrate, gemfibrozil, etofibrate) were also included. Statistical heterogeneity was considered acceptably low for most endpoints. However, clinically, the trials were very diverse: high risk populations (clinical cardiovascular disease or type 2 diabetes) and low risk populations(primary prevention) were pooled together; the quality of included trials was

mixed, with low quality trials also included. No mention was made by the authors whether other lipid-lowering drugs were allowed in the trials.

Compared to placebo, fibrates do not have a statistically significant effect on all-cause mortality or cardiovascular death.
GRADE: LOW quality of evidence

Compared to placebo, fibrates reduce the risk of major cardiovascular outcomes. However, the result is only borderline significant.
GRADE: LOW quality of evidence

Fibrates reduce the risk of coronary events compared to placebo.
GRADE: LOW quality of evidence

Fibrates have no statistically significant effect on total stroke rate compared to placebo.
GRADE: LOW quality of evidence

No statistically significant difference in total adverse events is observed.
GRADE: LOW quality of evidence

When considering only the trials that examine fibrates versus placebo that are available in Belgium, conclusions are the same (BECAIT 1997(103), SENDCAP 1998(105), BIP 2000(107), LEADER 2002(109), DAIS 2001(108), FIELD 2005(110)):

- No statistically significant difference in mortality rates (all-cause or cardiovascular) is shown in any trial.
- coronary events : significantly less coronary events in 2/3 trials that examined surrogate endpoints as primary outcome.
- Significantly less nonfatal MI in 2/3 trials that examine clinical endpoints.

GRADE classification remains LOW.

5.2 Ezetimibe versus placebo

No trials met our inclusion criteria.

5.3 Statin plus fibrate versus statin

5.3.1 Evidence tables. Simvastatin plus fenofibrate versus simvastatin in patients with type 2 diabetes

Study details	n/Population	Comparison	Outcomes		Methodological
Ginsberg-2010-1246 (112) = ACCORD Lipid trial Design: RCT DB 77 clinical sites organized into seven networks in the United States and Canada . Duration of follow-up (mean): 4.7 years	n= 5518 Mean age: 62 -Previous CV event: 36.5% -AHT: 140±18mmHg/ 74±11mmHg Total CHOL: 175±37mg/dl LDL: 100±30mg/dl HDL: 38±8mg/dl -Smoking (current): 14.6% -BMI: 32.3 - duration of diabetes: median 9y <u>Inclusion</u> type 2 diabetes, HbA1c ≥ 7.5% If clinical CV disease: 40-79y ; if subclinical CVdisease or ≥2 CV risk factors: 55 to 79 years.	fenofibrate (start 160mg/d and if necessary adjusted according GFR) + simvastatin (average dose : 22,3mg) Vs placebo + simvastatin (average dose : 22,4mg)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: participants prescribed masked medication at most recent visit: Fenofibrate: 77.3% Placebo: 81.3% Lost-to follow-up: 1.01% Drop-out and Exclusions: 1.99 % • Described: yes • Balanced across groups: yes ITT:Yes SELECTIVE REPORTING: no
			Major fatal or nonfatal cardiovascular event (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (PO)	FF + simva : 291/2765 (2.24%/year) Pla + simva: 310/2753 (2.41%/year) HR: 0.92 (0.79 – 1.08) NS ; p=0.32	
			Death from any cause	FF + simva: 203/2765 (1.47 %/year) Pla + simva: 221/2753 (1.61% /year) HR: 0.91 (0.75 – 1.10) NS ; p=0.33	
			Death from cardiovascular cause	FF + simva: 99/2765 (0.72%/year) Pla + simva: 114/2753 (0.83%/year) HR: 0.86 (0.66 – 1.12) NS ; p=0.33	
			Major coronary disease event (fatal coronary event, nonfatal myocardial infarction, or unstable angina)	FF + simva: 332/2765 (2.58%/year) Pla + simva: 353/2753 (2.79%/year) HR: 0.92 (0.79 – 1.07) NS ; p=0.26	
			Stroke	FF + simva: 51/2765 (0.38%/year) Pla + simva: 48/2753 (0.36% /year) HR: 1.05 (0.71 – 1.56) NS ; p=0.80	

	LDL cholesterol level of 60 to 180 mg/dl, HDL cholesterol < 55 mg/dl for women and blacks or below 50 mg per deciliter (1.29 mmol per liter) for all other groups, and a triglyceride level below 750 mg per deciliter (8.5 mmol per liter) if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy. <u>Exclusion</u> included the use of a medication known to interact with statins or fibrate; history of pancreatitis, myositis/myopathy, or gallbladder disease; or refusal to discontinue any current lipid-altering treatment.		**Nonfatal myocardial infarction**	FF + simva: 173/2765 (1.32%/year) Pla + simva: 186/2753 (1.44%/year) HR: 0.91 (0.74 – 1.12) NS ; p=0.39	Other important methodological remarks : Open-label simvastatin therapy began at the randomization visit, and the masked administration of either fenofibrate or placebo began 1 month later. -Because of a rise in serum creatinine levels in some patients while receiving 160mg of fenofibrate, starting in 2004, the dose of fenofibrate was adjusted according to the eGFR with the use of the abbreviated MDRD equation At the last clinic visit,15.9% in the fenofibrate group and 7.0% in the placebo group were receiving a reduced dose - The dose of simvastatin was modified over time in response to changing guidelines Sponsor: National Heart, Lung, and Blood Institute,the National Institute of Diabetes and Digestive and Kidney
			Fatal or nonfatal congestive heart failure	FF + simva :120/2765 (0.90% /year) Pla + simva: 143/2753 (1.09% /year) HR: 0.82 (0.65 – 1.05) NS ; p=0.10	
			Safety		
			Drug discontinuation due to decrease in the estimated GFR	FF + simva : 66/2765 (2.4%) Pla + simva: 30/2753 (1.1%)	
			Hemodialysis and end-stage renal disease	FF + simva : 75/2765 Pla + simva: 77/2753 NS	

					Diseases, the National Institute on Aging, the National Eye Institute, the Centers for Disease Control and Prevention, and General Clinical Research Centers at many sites. Fenofibrate and matching placebo were donated by Abbott Laboratories; simvastatin was donated by Merck. The drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript.

In the ACCORD study, all patients were randomly assigned to receive either intensive glycemic control (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a glycated hemoglobin level of 7.0 to 7.9%). A subgroup of patients in the ACCORD study were also enrolled in the ACCORD Lipid trial and underwent randomization, in a 2-by-2 factorial design, to receive simvastatin plus either fenofibrate or placebo

5.3.2 Summary and conclusions: Simvastatin plus fenofibrate versus simvastatin in patients with type 2 diabetes

Simvastatin plus fenofibrate versus simvastatin plus placebo in patients with type 2 diabetes			
Bibliography: Ginsberg 2010-ACCORD-Lipid(112)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	5 518 (1study) mean 4.7y	1.47 %/y vs 1.61% /y HR: 0.91 (95%CI 0.75 – 1.10) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:-1 protocol change and simvastatin dose lower than current guidelines Imprecision: OK
Death from cardiovascular cause	5 518 (1study) mean 4.7y	0.72%/y vs 0.83%/y HR: 0.86 (95%CI 0.66 – 1.12) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:-1 protocol change and simvastatin dose lower than current guidelines Imprecision: OK
Major fatal or nonfatal CV event (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (PO)	5 518 (1study) mean 4.7y	2.24%/y vs 2.41%/y HR: 0.92 (95%CI 0.79 – 1.08) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:-1 protocol change and simvastatin dose lower than current guidelines Imprecision: OK
Major coronary disease event (fatal coronary event, nonfatal myocardial infarction, or unstable angina)	5 518 (1study) mean 4.7y	2.58%/y vs 2.79%/y HR: 0.92 (95%CI 0.79 – 1.07) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:-1 protocol change and simvastatin dose lower than current guidelines Imprecision: OK
Stroke	5 518 (1study) mean 4.7y	0.38%/y vs 0.36% /y) HR: 1.05 (95%CI 0.71 – 1.56) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:-1 protocol change and simvastatin dose lower than current guidelines Imprecision: OK

In this double blind RCT, simvastatin (average 22.3mg/d) plus fenofibrate 160mg/d was compared to simvastatin plus placebo in patients with type 2 diabetes. 1/3 of the included patients had a previous cardiovascular event. The mean age of the participant was 62y. Participants had type 2 diabetes for a mean duration of 9 years.

Follow-up in the trial was a mean of 4.7 years.

The dose of simvastatin was modified during the trial in response to changing guidelines.

There is no statistically significant difference in all-cause mortality between simvastatin plus fenofibrate and simvastatin-only, nor is there a statistically significant difference in rates of death from cardiovascular cause.
GRADE: MODERATE quality of evidence

The primary endpoint of this trial was a composite of major fatal or nonfatal cardiovascular events (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). No statistically significant difference between combination therapy and simvastatin monotherapy was found.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in major coronary disease events (fatal coronary event, nonfatal myocardial infarction, or unstable angina) between both treatments.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in the rate of stroke between both treatments.
GRADE: MODERATE quality of evidence

Adverse events were not reported in much detail.

5.4 Statin plus ezetimibe versus statin

No trials met our inclusion criteria for efficacy.

5.4.1 Evidence tables. Ezetimibe: all-cause mortality in observational studies

Patel 2013(113)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
retrospective cohort study USA (2005-2008)	n= 3827	-Patients with dyslipidemia diagnosis - Mid-America Cardiology Patient Database	Statin + Ezetimibe (n=918) Vs Statin (n=2909)	All-cause mortality	OR: 1.067 (95%CI: 0.713 to 1.598)
*adjusted for patient characteristics, selected cardiovascular diseases and risk factors, and medications					

Remarks: Authors noted "Though this study indicates a lack of clinical efficacy for ezetimibe, it does face several limitations. Despite the large sample size, the data only comes from one group of cardiologists at one medical center and is retrospective."

5.4.2 Summary and conclusions: Ezetimibe: all-cause mortality in observational studies

A retrospective cohort study by Patel 2013(113) in the USA in 3827 patients from a Cardiology patient database compared the use of a statin + ezetimibe to a statin only. No statistically significant difference in all-cause mortality was observed between the two treatments. (OR: 1.07; 95%CI 0.71 to 1.60).
GRADE: LOW quality of evidence

6 Evidence tables and conclusions: Safety of statins

6.1 Naci 2013 network meta-analysis. Individual statin vs placebo/control and active-comparator.

6.1.1 Evidence tables

Meta-analysis: Comparative Tolerability and Harms of Individual Statins - A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized, Controlled Trials

Inclusion criteria: open-label and double-blind randomized, controlled trials comparing one statin with another at any dose or with control(placebo, diet, or usual care) for adults with, or at risk of developing, cardiovascular disease. We included trials of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin if they had >50 participants per trial arm and lasted >4 weeks based on prespecified inclusion and exclusion criteria.
We included trials that reported tolerability (number of participants who discontinued the study medication because of adverse events), elevations in hepatic transaminases (number of participants with clinically meaningful elevations in either alanine aminotransferase or aspartate aminotransferase, 3× baseline values as commonly defined by trial investigators), elevations in creatine kinase (CK; number of participants with clinically meaningful increases in baseline CK levels as defined by trial investigators, ranging from 3× to 10× higher than baseline concentrations), myalgia (number of individuals with muscle pain, as defined by trial investigators), myopathy (number of participants with 10× baseline CK levels associated with muscle symptoms), and rhabdomyolysis (number of participants with severe muscle damage, as diagnosed by trial investigators). In addition, we were interested in the incidence of cancer and diabetes mellitus (as defined by trial investigators), so trials reporting these outcomes were also eligible for inclusion. Both fixed dose and titration designs were included. As per our protocol, we excluded trials conducted in patients with renal insufficiency
Search strategy: Search strategy was based on a publicly available protocol previously developed by the study authors to evaluate the comparative clinical benefits of tatins. We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify studies published between January 1, 1985, and March 10, 2013. To identify the relevant literature, we developed a search strategy using the search terms atorvastatin, fluvastatin, imvastatin, lovastatin, pravastatin, rosuvastatin, cholesterol, cardiovascular disease, and hydroxymethylglutaryl-coenzyme A reductase inhibitors/therapeutic use. Our updated search in MEDLINE adopted Cochrane Collaboration's sensitivity and precision- maximizing strategy. We searched for pitavastatin trials post hoc separately because our protocol did not include pitavastatin (protocol finalization coincided with the Food and Drug Administration approval of this agent). We also performed manual searches using the authors' files and reference lists from original communications and review articles to cross-check references. Two researchers (B.T., H.T.) independently performed abstract, title, and full-text screening. A third researcher approved study selection (H.N.).
Assessment of quality of included trials: yes ("We also extracted information on the methodological quality of included studies. In particular, information was collected on blinding, random sequence generation, allocation concealment, indications of incomplete outcome data, indications of selective reporting (possible for trials with published protocols), and industry sponsorship. One researcher extracted data (H.N.) and another independently checked for accuracy (B.T.).")
ITT analysis: no
Other methodological remarks: The overall methodological quality of included trials was moderate. Older trials had lower methodological quality with inadequate sequence generation and treatment allocation concealment. A large number of trials did not report details about randomization procedures and allocation concealment. Only 11 trials had high methodological quality on all 6 items.

Discontinuation because of adverse events

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 Average follow-up 68w	Statin vs control (placebo or no statin)	n= 76 462	OR= 0.95 (95%CI 0.83 to 1.08) NS *I*2= 21.9%	n=131 503	**Atorvastatin at >20 and ≤40 mg/d** **OR=2.72 (95% CrI 1.46 to 5,09)** **SS** **Atorvastatin at >40 mg/d** **OR =1.69 (95% CrI 1.18 to 2.44)** **SS.** Other comparisons: NS
	Statin vs statin		**Simva vs atorva** **OR=0.61 (95%CI 0.42 to 0.89)** **SS** *I*2= 71.9% **Simva vs rosuva** **OR=.49 (95%CI, 0.27 to 0.88)** **SS** *I*2=0.0%	n=151 823	**Atorva vs Simva** **OR=1.34 (95% CrI 1.06 to 1.69)** **SS** **Atorva vs prava** **OR= 1.46 (95% CrI 1.10 to 1.92)** **SS** Other comparisons: NS

Myalgia

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 Average follow-up 68w	Statin vs control	n= 43 531	OR= 1.07 (95%CI 0.89 to 1.29) NS *I*2=22.1%	n=99433?	NS for all comparisons
	Statin vs statin		**Simva vs atorva** **OR= 0.56 (95% CI 0.42 to 0.75)** **SS (participants randomized to simvastatin had lower odds of experiencing myalgia compared with those receiving atorvastatin)** ***I*2=0.0%**	n=84 391	Simva vs atorva OR= 0.78 (95%CrI 0.55 to 1.13) NS Other comparisons: also NS

Myopathy

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	NR	NR	NR	Atorva vs control OR= 1.21 (95% CrI 0.25 to 4.95) NS Prava vs control OR= 1.06 (95% CrI 0.18 to 4.81) NS Rosuva vs control OR= 0.91; (95% CrI 0.12 to 4.43) NS Simva vs control OR= 1.23 (95% CrI 0.29 to 4.21) NS
	Statin vs statin	NR	NR	NR	NS *("There was no evidence of potential differences between individual statins in terms of myopathy outcomes (results not shown).")*

Rhabdomyolysis

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	NR	NR	NR	Atorvastatin OR= 1.33 (95% CrI 0.31 to 6.92) NS Pravastatin OR= 0.20 (95% CrI, 0.00 to 11.15) NS Rosuvastatin OR= 0.19 (95% CrI 0.00 to 9.22) NS Simvastatin OR= 2.03 (95% CrI 0.40 to 14.81) NS

	Statin vs statin	NR	NR	NR	NS *("There were no statistically detectable differences between individual statins in terms of rhabdomyolysis.")*

Transaminase elevations

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	122665	**OR=1.51 (95% CI 1.24 to 1.84)** **SS** *I*2= 52.3%	165534	Atorva **OR= 2.55 (95% CrI 1.71 to 3.74)** **SS** Fluva **OR= 5.18 (95% CrI 1.89 to 15.55)** **SS** Simvastatin at ≤10 mg/d **OR= 0.41 (95% CrI 0.18 to 0.85)** **SS** Atorvastatin at >20 and ≤40 mg/d **OR= 2.42 (95% CrI 1.10 to 5.55)** **SS** Atorvastatin at >40 mg/d **OR= 5.25 (95% CrI 3.89 to 7.24)** **SS** Fluvastatin at >40 mg/d **OR= 4.16 (95% CrI 1.60 to 14.36)** **SS** Simvastatin at >40 mg/d **OR= 2.83 (95% CrI 1.47 to 5.87)**

					SS
	Statin vs statin	NR	Prava vs atorva **OR= 0.27 (95% CI 0.10 to 0.74)** **SS** I2=61.3%		Prava vs atorva **OR= 0.39 (95% CrI 0.24 to 0.65)** **SS** Rosu vs atorva **OR= 0.63 (95% CrI 0.42 to 0.94)** **SS** Simva vs atorva **OR= 0.45 (95% CrI 0.28 to 0.73)** **SS** Fluva vs prava **OR= 5.19 (95% CrI 1.75 to 16.73)** **SS** Fluva vs rosu **OR= 3.25 (95% CrI 1.08 to 10.50)** **SS** Fluva vs simva **OR= 4.50 (95% CrI 1.49 to 14.19)** **SS**

CK elevations

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	101324	OR= 1.13 (95% CI 0.85 to 1.51) NS I2= 20.4%	127571 137980?	Pitava **OR= 3.63 (95% CrI 1.10 to 14.10)** **SS** Simva > 40mg/d **OR= 4.14 (95% CrI 1.08 to 16.24)** **SS**
	Statin vs statin	NR	NR	NR	Individuals randomized to fluvastatin had significantly lower odds of experiencing CK elevations compared with all other statins, except for lovastatin (see table 2 in Naci 2013).

Cancer

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	100523	OR, 0.96; 95% CI 0.91–1.02 NS I2= 0.0%	105450	NS
	Statin vs statin	NR	NR	NR	NS (see table 3)

Diabetes mellitus

Ref	Comparison	N/n direct	Result direct comparison	N/n MTM	Result indirect comparison (MTM)
ref*Naci_2013_44 Design: MTM Search date: march 2013 N=135 n=246 955 average follow-up 68w	Statin vs control	113698	Statins as a class **OR= 1.09 (95% CI 1.02 to 1.16)** **SS** I2= 2.8% Rosuva **OR= 1.16 (95% CI 1.02 to 1.31)** **SS** I2= 0.0%	NR	NS (the drug-level network meta-analysis did not achieve statistical significance for any of the individual statins as a result of wider 95% CrIs (rosuvastatin had a similar effect size estimate in both pairwise and network meta-analyses)
	Statin vs statin	NR	NR	NR	NS (there were no statistically detectable differences between individual statins in terms of diabetes mellitus incidence)

Remarks:

- There was limited information on both myopathy and rhabdomyolysis outcomes.

6.1.2 Summary and conclusions. Naci 2013 network meta-analysis. Individual statin vs placebo/control and active-comparator.

This network meta-analysis collected all the trials that compare a statin to placebo or no treatment, or to another statin. Trials that were longer than 4 weeks were included. The aim of this analysis was to explore adverse events.
We could not perform a GRADE assessment of these endpoints because of lack of information. The overall methodological quality of included trials was reported by the authors as being moderate.

To fully interpret the results of a mixed-treatment meta-analysis, results from direct comparisons as well as the results from indirect comparisons should be reported. Information on direct comparisons however was missing for a lot of the endpoints.

Statin versus placebo			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants Follow up**	**Results**	**Quality of the evidence (GRADE)**
Myalgia	43 531 (direct) 99 433 (indirect) mean 68w	Direct comparison OR= 1.07 (95%CI 0.89 to 1.29) NS Indirect comparison NS for all comparisons	*not applied*
Myopathy	NR	Direct comparison Not reported Indirect comparison NS for all comparisons	*not applied*
Rhabdomyolysis	NR	Direct comparison Not reported Indirect comparison NS for all comparisons	*not applied*

The network meta-analysis by Naci 2013 compared statins versus placebo for muscle-related outcomes. No statistically significant differences were found for myalgia, myopathy or rhabdomyolysis
GRADE: not applied

Statin versus statin			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Myalgia	84 391 (indirect)	**Simva vs atorva** Direct comparison **OR= 0.56 (95% CI 0.42 to 0.75)** **SS in favour of simvastatin** Indirect comparison OR= 0.78 (95%CrI 0.55 to 1.13) NS **Other comparisons:** also NS	*not applied*
Myopathy		Direct comparison Not reported Indirect comparison NS for all comparisons	*not applied*
Rhabdomyolysis		Direct comparison Not reported Indirect comparison NS for all comparisons	*not applied*

The network meta-analysis by Naci 2013 compared statins versus other statins for muscle-related outcomes. Simvastatin was found to have a lower risk of myalgia than atorvastatin in the direct comparison, but not in the indirect comparison. All other comparisons were not statistically significantly different.
No statistically significant differences were found for myopathy and rhabdomyolysis.
GRADE: not applied

Statin versus placebo			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cancer	100 523 (direct) 105 450 (indirect) mean 68w	Direct comparison OR, 0.96; 95% CI0.91–1.02 NS Indirect comparisons NS for all comparisons	*not applied*

The network meta-analysis by Naci 2013 compared statins versus placebo for the outcome cancer. No statistically significant difference was found.
GRADE: not applied

Statin versus statin			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cancer	NR	Direct comparison Not reported Indirect comparisons NS for all comparisons	*not applied*

The network meta-analysis by Naci 2013 compared statins versus other statins for the outcome cancer. No statistically significant differences were found between different statins.
GRADE: not applied

Note:
The network meta-analysis by Naci 2013 comparing statins to placebo and other statins, also examined transaminase elevations and CK elevations. In the direct comparison, statins had a higher risk of transaminase elevations than placebo (**OR=1.51; 95% CI 1.24 to 1.84).**
In the direct comparison, there was no statistically significant difference in CK elevations between statins and placebo.

Statins versus placebo			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants Follow up**	**Results**	**Quality of the evidence (GRADE)**
Diabetes mellitus	113 698 (direct) mean 68w	Direct comparison Statins as a class **OR= 1.09 (95% CI 1.02 to 1.16)** **SS** Rosuvastatin **OR= 1.16 (95% CI 1.02 to 1.31)** **SS** Indirect comparison NS for all comparisons (individual statins)	*not applied*

The network meta-analysis by Naci 2013 compared statins versus placebo for the outcome diabetes mellitus. People taking statins had a higher risk of developing diabetes. In the direct comparison, this difference was only statistically significant for rosuvastatin. In the indirect comparisons, no statistically significant differences were found.
GRADE: not applied

Statin versus statin			
Bibliography: Mixed treatment meta-analysis: Naci_2013(114)			
Outcomes	**N° of participants Follow up**	**Results**	**Quality of the evidence (GRADE)**
diabetes mellitus	NR	Direct comparison Not reported Indirect comparison NS for all comparisons	*not applied*

The network meta-analysis by Naci 2013 compared statins versus other statins for the endpoint diabetes mellitus. No statistically significant differences were found between different statins. .
GRADE: not applied

6.2 Intracerebral hemorrhage or hemorrhagic stroke

6.2.1 Evidence tables

Meta-analysis:

Inclusion criteria: randomized trials (regardless of language, publication status, and sample size) that included data on the frequency of intracerebral hemorrhage and statin exposure.

"Most studies defined intracerebral hemorrhage as intraparenchymal brain hemorrhage confirmed by neuroimaging or autopsy. however, we also included studies that defined intracerebral hemorrhage using International Classification of Disease diagnosis codes (which havebeen shown to be accurate for this end point)"

Excluded articles that aggregated statins with other lipid-lowering classes (although we contacted authors to inquire whether a separate analysis of statins was available).

Excluded studies focused solely on intracranial hemorrhage after intravenous or intra-arterial thrombolysis for acute ischemic stroke.

Observational studies also searched and included but not reported here.

Search strategy: "We used a multistep approach to find studies. First, we searched 17 electronic bibliographic databases from inception until June 1, 2011: Cardiosource Clinical Trials, Cochrane Central Register of Controlled Trials, Cochrane Health Technology Assessment Database, Database of Abstracts of Reviews of Effects, European Medicines Agency Web site, Excerpta Medica, Healthstar, International Standard Randomized Controlled Trial Number Register, Medline, NIH www.ClinicalTrials.gov, OVID Full Text Journals, PreMedline, Stroke Trials Registry, UpToDate Online, US Food and Drug Administration Web site, Web of Science With Conference Proceedings, and What's What Online. We adapted search terms to each database and updated the search during the analysis phase using automated e-mail alerts (Table I in the online-only Data Supplement)."

"Second, we used the "find similar" and "find citing articles" functions in bibliographic databases to locate related articles. Third, we manually screened bibliographies of statin product monographs, review articles, eligible primary studies, treatment guidelines, and previous meta-analyses. Fourth, we reviewed abstract proceedings of cardiology, neurology, and endocrinology meetings that had not yet been indexed in bibliographic databases. Finally, we contacted authors of studies that reported rates of statin exposure and intracerebral hemorrhage in their publications but did not report an exposure-outcome association; we successfully obtained these data in >90% of cases."

Assessment of quality of included trials: yes ("We used the Jadad scale to measure methodological quality for randomized trials with points recorded for randomized sequence generation, blinding, and description of withdrawals and dropouts, we also recorded loss to follow-up and requested such data from authors when it was not available.5 We used the Downs and Black6 scale to measure methodological quality for observational studies, again requesting clarification from authors for missing details. The scale includes items on quality of reporting, external validity, internal validity, and statistical power. We also reviewed design articles and secondary reports to supplement our measurement of methodological quality. We converted the Downs-Black and Jadad scales to a common unweighted fraction ranging from 0 to 1.0 for use in meta-regression.")

ITT analysis: yes (no definition given of performed ITT: "For randomized trials, we recorded the number of events and patients at risk in each arm using an intention-to-treat framework and computed risk ratios (RRs) for each study, which were subsequently pooled.")

Other methodological remarks:

- We performed a DerSimonian-Laird random-effects meta-analysis to pool effect estimates across studies. We reported summary effects as RRs with 95% CIs. We assessed heterogeneity using the I2 statistic. Descriptive statistics were expressed as medians with interquartile ranges (IQRs).
- We tested for publication bias by inspecting funnel plots and performing Begg and Mazumdar rank correlation tests for each of the 3 major study designs.
- We prespecified several additional analyses to assess the robustness of our results and to explore potential sources of heterogeneity.

Ref	Comparison	N/n	Outcomes	Result
ref*Hackam 2011 Design: Collaborative Systematic Review and Meta-Analysis Search date: 06/2011 median follow-up per trial of 3.9 years	Statin vs placebo	N= 23 n= 526518 patient-years (4D 2005, ACAPS 1994, AFCAPS/TexCAPS 1998, ALERT 2003, ALLHAT 2002, ASCOT 2003, ASPEN 2006, AURORA 2009, Bone 2007, CARE 1996, CLAPT 1999, CORONA 2007, GISSI-HF 2008, GISSI-P 2000, GREACE 2002, HPS 2002, JUPITER 2008, LIPID 1998, MEGA 2006, MIRACL 2001, PROSPER 1995, SPARCL 2006, SSSS 1994)	**Intracerebral hemorrhage**	RR= 1.10 (95% CI 0.86 to 1.42) NS
		N= ?(Not specified by Hackam 2011)	**Total stroke**	**RR= 0.85 (95% CI 0.78 to 0.93)** **SS in favour of statin.** I^2=40%
		N= ? (Not specified by Hackam 2011)	**Ischemic stroke**	**RR= 0.83 (95% CI 0.75 to 0.92)** **SS in favour of statin.** I^2=37%

* Characteristics of included studies: see below

Remarks:
Sensitivity analyses “In meta-regression of all 42 studies, we found no association between effect size and study region (P ・ 0.23), patient prevention status (P ・ 0.36), history of cerebrovascular disease (P ・ 0.09), methodological quality (P ・ 0.27), or study epoch (P ・ 0.80).”
“Among 11 studies (including SPARCL) exclusively enrolling patients with cerebrovascular disease, we found no evidence that statins selectively increased the risk of intracerebral hemorrhage (RR,1.03; 95% CI, 0.82–1.30; Figure 4).” **Note: of these 11 studies, 10 were observational studies.**

Ref + design (bv. Dubbel blinde rct)	n	Population	Duration	Comparison	Methodology
4D (DeutscheDiabetes-Dialyse-Studie) 2005(5) RT	1255	Subjects with type 2 diabetes mellitus receiving maintenance hemodialysis	4.0 years	20 mg of atorvastatin per day or matching placebo.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP:30% discontinued before end of study (6% medical reasons, 10% wish of patient,…) ITT:yes note: 4 week run-in placebo FUNDING: Pfizer Jadad Score: 5
ACAPS (Asymptomatic Carotid Artery Progression Study) 1994(33) RT	919	Asymptomatic patients with subclinical atherosclerosis and dyslipidemia	2.8 years	20 mg lovastatin vs placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors Carers and patients were blinded FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: 3- to 4-week run-in period during which they were given lovastatin placebo and open-labeled warfarin (1 mg/dL). “One purpose of the run-in phase was to identify and exclude participants who took <80% of their pills” (randomization after run-in) “Of the 960 persons returning for the baseline visit, only 4% (n=41) failed to qualify for randomization. The majority (33 of the 41) failed the run-in because of adherence problems.” Jadad Score: 4

AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) 1998(6) RT	6605	Patients with normal or mildly elevated total and LDL cholesterol, low HDL cholesterol, and no clinically evident atherosclerotic disease	5.2 years	Lovastatin 20/40 mg vs placebo	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: no dropouts reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Run-in: Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were randomized. No information on how many people were excluded in this step. *Trial was stopped prematurely. To be terminated when 320 participants had experienced* *primary outcome event. Stopped when 267 had done at 5.2 years* Jadad Score: 4
ALERT (Air Force/Texas Coronary Atherosclerosis Prevention) 2003(7) RT	2102	Patients with renal transplants, stable graft function, receiving cyclosporine	6.7 years (Extended follow-up)	Fluvastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate ITT:yes FUNDING:Novartis we doubled study-medication dose after around 2 years. This rise in dose of fluvastatin from 40 to 80 mg daily was predicted to reduce LDL-cholesterol concentrations by an additional 6%. Jadad Score: 4
ALLHAT(Antihypertensive	10355	Patients with	4.8 years	Pravastatin vs placebo	ALLOCATION CONC:

and Lipid-Lowering Treatment to Prevent Heart Attack Trial) 2002(8) RT		hypertension and at least 1 other risk factor for coronary heart disease			Adequate RANDO: Adequate BLINDING : no FOLLOW-UP: At the end of the trial, 84.8% of participants were known to be alive, 12.3% were confirmed dead, 0.5% were reported dead with confirmation pending, and 2.4% had unknown vital status. ITT:yes FUNDING: Methodological remarks: because of the modest cholesterol differential between pravastatin and usual care, ALLHAT-LLT lacked the power to discriminate between the expected reductions in mortality and CHD events and the null hypothesis. Jadad Score: 3
ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) 2003(10) RT	10305	Hypertensive patients with at least 3 other cardiovascular risk factors	3.3 years	Atorvastatin vs placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : assessors: yes FOLLOW-UP: 99% ITT:yes Note: 4 week run-in FUNDING:Pfizer Jadad Score:5
ASPEN (Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-	2410	Mainly primary prevention patients with type 2 diabetes mellitus	4.0 years	10 mg atorvastatin Vs placebo;	ALLOCATION CONC: unclear RANDO: unclear

Dependent Diabetes Mellitus) 2006(11) RT					BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: 22% drop outs reported ITT:yes FUNDING: unclear risk (funded by pharm industry) Jadad Score: 4
AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) 2009(12) RT	2776	Patients receiving maintenance hemodialysis	3.8 years	Rosuvastatin vs placebo	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Participants/personnel/assessors not described FOLLOW-UP: no patients lost ITT:yes) FUNDING:AstraZeneca Jadad Score: 4
Bone 2007(34) RT	626	Postmenopausal women with mild hypercholesterolemia	1.0 years	Atorvastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Unclear;states double blind but only reports that the participants were blinded to intervention FOLLOW-UP: 5% dropped out ITT:yes FUNDING: unclear risk (funded by pharm industry)

					Jadad Score: 5
CARE (Cholesterol and Recurrent Events) 1996(14) RT	4159	Patients with myocardial infarction	5.0 years	Pravastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? Jadad Score: 4
CLAPT (Cholesterol Lowering Atherosclerosis PTCA trial) 1999(115) RT	226	Men scheduled to undergo elective coronary angioplasty	2.0 years	Lovastatin vs placebo	Jadad Score: 2
CORONA (Controlled Rosuvastatin in Multinational Trial in Heart Failure) 2007(15) RT	5011	Chronic ischemic heart failure	2.7 years	rosuvastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel:Adequate Assessors: unclear FOLLOW-UP: ? ITT:yes note: 2-4 week placebo run-in FUNDING:AstraZeneca Jadad Score: 5
GISSI-HF (Gruppo Italiano per lo Studio della	4574	Chronic heart failure (regardless of cause)	3.9 years	rosuvastatin vs placebo	ALLOCATION CONC: Adequate

Sopravvivenza nell'Infarto Miocardico–Heart Failure) 2008(16) RT					RANDO: Adequate BLINDING : Participants/personnel/assessors FOLLOW-UP: ITT:yes FUNDING: Società Prodotti Antibiotici (SPA; Italy), Pfizer, Sigma Tau, and AstraZeneca. Jadad-score 5
GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevention) 2000(17) RT	4271	Patients with recent acute myocardial infarction	2.0 years	atorvastatin vs placebo	ALLOCATION CONC: inadequate RANDO: ? BLINDING : inadequate FOLLOW-UP: ? ITT:yes/no ('author's definition') FUNDING: Methodological remarks:GISSI-P was started in 1993 and its story was crossed by the publication of the results of similarly designed clinical trials. The publication of 4S results in 1994 prompted the Data Safety and Monitoring Board (DSMB) and the Steering Committee (SC) ; decreased statistical power due to its premature stopping Jadad-score 2
GREACE (Greek Atorvastatin and Coronary-Heart-Disease Evaluation) 2002(116) RT	1600	Patients with established CAD	3.0 years	Atorvastatin vs placebo	Jadad Score:3
HPS (Heart Protection	20536	Patients with coronary	5.0 years	simvastatin vs placebo	ALLOCATION CONC:

Study) 2002(18) RT		disease, other occlusive vascular disease, or diabetes mellitus			Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? There was a change in the protocol so that only patients whose total blood cholesterol was < 250 mg/dl could be randomized whilst patients with total blood cholesterol > 250 mg/dl who had already been enrolled in the study had to be re-evaluated and, if appropriate, pharmacologically treated. The DSMB and the SC agreed to stop randomization prematurely in late 1996 after the publication of CARE results. Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity. Jadad Score: 5
JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) 2008(19) RT	17802	Asymptomatic patients with elevated C-reactive protein	1.9 years	rosuvastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/ assessors Adequate FOLLOW-UP: drop outs unclear ITT: yes FUNDING: High risk (funded by pharm industry) Other remarks: Stopped early with a follow-up of 1.9 years. Jadad Score:4
LIPID (Long-Term	9014	Patients with coronary	6.1 years	Pravastatin vs placebo	ALLOCATION CONC:

Intervention With Pravastatin in Ischaemic Disease) 1998(60) RT		artery disease			Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: >99% ITT:yes FUNDING:? Jadad Score:4
MEGA (Primary Prevention of Cardiovascular Disease With Pravastatin in Japan) 2006(22) RT	7832	Asymptomatic patients with hypercholesterolemia	5.3 years	Pravastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors Inadequate; single blinded endpoint committee was blinded only because investigators stated that placebo-controlled trials are regarded with suspicion by Japanese participants FOLLOW-UP: 98 % in efficacy analysis ITT:yes FUNDING: low risk (funded by pharm industry) Jadad Score:3
MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering) 2001(117) RT	3086	Patients with recent acute coronary syndrome	0.3 years	Not specified by Hackam 2011	Jadad Score: 4
PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) 1995(26) RT	5804	Elderly patients with vascular disease or risk factors for vascular disease	3.2 years	pravastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate FOLLOW-UP: 25% did not complete trial (due to adverse event, death, refusal or lost) 13% refusal or lost to follow-up

					ITT:yes FUNDING: Bristol- Myers Squibb, USA Jadad Score:5
SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) 2006(54) RT	4731	Patients with a history of stroke or TIA	4.9 years	atorvastatin vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/personnel/assessors? Adequate FOLLOW-UP: ITT:yes FUNDING:? Jadad Score: 4
SSSS (Scandinavian Simvastatin Survival Study) 1994(25) RT	4444	Patients with coronary artery disease	5.4 years	Not speci fied by Hackam 2011	ALLOCATION CONC: /unclear RANDO: unclear BLINDING : Participants/personnel/assessors unclear FOLLOW-UP: note 2 week placebo run in FUNDING:Merck Jadad Score:5

6.2.2 Summary and conclusions. Intracerebral hemorrhage or hemorrhagic stroke

Statins versus placebo and intracerebral hemorrhage			
Bibliography: Hackam 2011(118)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Intracerebral hemorrhage	526518 patient-years (23 studies) Median 3.9y	RR= 1.10 (95% CI 0.86 to 1.42) NS	⨁⨁⨁⊖ **MODERATE** Study quality: OK, high jadad Consistency: OK Directness: -1 clinical heterogeneity Imprecision: OK

This meta-analysis included all RCTs comparing statin to placebo that report the endpoint 'intracerebral hemorrhage'. The populations of the selected RCTs were clinically heterogenous: some trials included patients without clinically apparent cardiovascular disease, whilst other trials included patients with CV disease, or only type-2 diabetic patients. Median duration of trials was 3.7 y and ranged from 4 months to 6.7 years.

In this clinically heterogenous population, no statistically significant difference in intracerebral hemorrhage was found between statin treatment and placebo.
GRADE: MODERATE quality of evidence

The authors also included observational studies for some calculations. These results are not reported here, but do not alter the conclusion.

When we compare this result to the endpoint 'haemorrhagic stroke' in the meta-analyses from the previous chapters, we find some discrepancy.

Taylor 2013(32) found no statistically significant difference in haemorrhagic stroke between statin treatment and placebo, in patients without a history of cardiovascular disease. Only 2 trials were included.
GRADE: LOW quality of evidence

Manktelow 2009(48) compared statins versus placebo in patients with a history of stroke or TIA. In this population, treatment with statins results in a higher risk of hemorrhagic stroke compared to placebo. Data from 2 RCTs were included.
GRADE: MODERATE quality of evidence

Note: Hackam 2011(118) found no statistically significant difference between statin and placebo in patients with cerebrovascular disease. This conclusion was based on 10 observational studies + 1 RCT.

6.3 New onset type-2 diabetes

6.3.1 Evidence tables

Sattar 2010(119)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
SR + MA of RCTs Design: MA Search date: (jan-2009)	N= 13 n= 91 140	Non-diabetic at baseline Stable individuals (no organ transplants, no haemodialysis)	Statin Vs No statin	New diabetes (during a mean of 4y)	**OR: 1.09** **95%CI: 1.02-1.17** NNH = 255 (for 4y treatment)
*Metaregression of baseline age (risk of incident diabetes > in older) , baseline BMI, change in LDL-cholesterol					

Wang 2012(120)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retro-spective cohort (Taiwan National Health Insurance beneficiaries)	n= 42060	- Individuals without endocrine disorders and naive to systemic steroid. - Men age ≥45 years and women age ≥55 years during 2000 to 2003 who continuously received statins ≥30 days during 2000 to 2003 and those naive to statins before 2004 were identified - Mean age: 63 +/- 9 - Female: 4199 (50%) for statin group, 16500 (49%) for control group Excluded: - Follow-up < 30 days - presence of ICD-9 codes of diabetes - exposure to antidiabetic medication - MI - received revascularization before the entry	Statin (n=8412) vs control (n=33648)	Diabetes	**2.4% vs 2.1%** **HR: 1.15 (95% CI 1.08 to 1.22)** **p<0.001** **SS in favour of control**
			Statin (n=8412) vs control (n=33648)	Major adverse cardiovascular events (MACE, the composite of myocardial infarction and ischemic stroke)	**HR: 0.91 (95% CI 0.84 to 0.99)** **p=0.031** **SS in favour of statins.**
			Statin (n=8412) vs control (n=33648)	in-hospital mortality	**HR: 0.61 (95% CI 0.55 to 0.67)** **p<0.001** **SS in favour of statins.**
			Statin (n=8412) vs control (n=33648)	Risk for MI	**HR: 0.82 (95% 0.68 to 0.98)** **p=0.028** **SS in favour of statins**
			Statin (n=8412) vs control (n=33648)	Ischemic strokes	HR: 0.94 (95% CI 0.86 to 1.03) p=0.176 NS
Adjusted for age, sex, hypertension, CHD, stroke, chronic kidney disease, hemodialysis, and Charlson index.					

Zaharan 2012(121)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective cohort (national pharmacy claims database)	n = 1 235 671	-Irish primary care population on any medication - *new* statin users were identified (vs non-users) - study overepresented by females, socio-economically deprived and elderly patients	- statin (n= 239 628) vs no statin (n= 996 043)	New onset treated diabetes	Full cohort: **RR: 1.20** **95%CI: 1.17-1.23**
			Atorvastatin vs no statin (total n=120307)	New onset treated diabetes	**HR: 1.25 (95% CI 1.21 to 1.28)** **p<0.0001** **SS in favour of statin**
			Pravastatin vs no statin (total n=41899)	New onset treated diabetes	HR: 1.02 (95% CI 0.98 to 1.06) NS
			Rosuvastatin vs no statin (total n=19888)	New onset treated diabetes	**HR: 1.42 (95% CI 1.33 to 1.52)** **p<0.0001** **SS in favour of statin**
			Simvastatin vs no statin (total n=11458)	New onset treated diabetes	**HR 1.14 (95% CI 1.06 to 1.23)** **p = 0.0005** **SS in favour of statins**
			Fluvastatin vs no statin (total n= 3125)	New onset treated diabetes	HR: 1.09 (95% CI 0.95 to 1.24) NS
*adjusted for gender, age, prescription of oral corticosteroids, antipsychotics, antihypertensives, medication for ischaemic heart disease, anti-obesity and other lipid modifying agents.					

Remark: There were statistically significant overall dose and duration effects for all statins, excepting fluvastatin, which only demonstrated a duration effect.

Preiss 2011(122)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
SR + MA of RCTs Search date: (update april 2011)	N= 5 n= 32 752	Non diabetics: 3/5 trials (n= 25 853) patients with stable coronary heart disease; 2/5 trials patients following recent ACS	High dose statin vs moderate dose statin	New diabetes	**RR: 1.12** **95%CI:** **1.04-1.22** 2 additional cases in the intensive dose group per 1000 patient years NNH =498 (compared to moderate dose statin)

Ko 2013(123)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
propensity score–matched cohort, Ontario Myocardial Infarction Database (OMID)	n= 17080	- patients with myocardial Infarction - >65 years old - Age: 77.79y +/- 7.19 - Female: 7912 (46.3%) - 17% had prior heart failure - mean Charlson comorbidity score: 0.63 +/- 1.04. - hospitalized in Ontario, Canada, from april 1, 2004 to march 31, 2010. Excluded: - patients with diabetes mellitus - patients who were not prescribed statin medications	Moderate-dose statin therapy vs Intensive-dose statin therapy	New development of diabetes mellitus after hospital discharge.	1y: 2.3% vs 2.6% 2y: 5.5% vs 6.1% 3y: 8.1% vs 8.9% 4y: 10.7% vs 11.7% 5y: 13.0% vs 13.6% p=0.19 NS
			Moderate-dose statin therapy vs Intensive-dose statin therapy	Rate of death or ACS	**5y: 46.5% vs 44.8%** **p=0.044** **SS in favour of intensive dose statin therapy.**
			Moderate-dose statin therapy) vs Intensive-dose statin therapy	Rate of ACS	**5y: 23.5% vs 22.2%** **p=0.039** **SS in favour of intensive dose statin therapy.**
			Moderate-dose statin therapy vs Intensive-dose statin therapy	Death rate	5y: 34.8% vs 34.8% p=0.89 NS
*Adjusted for several known factors for diabetes mellitus development, such as age, hypertension, and hyperlipidemia (unable to adjust for several risk factors in the propensity model, such as smoking, obesity, diet, and physician activity levels.)					

Carter 2013(124)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective cohort (population based, Ontario, Drug benefit database)	n = 471 250	- age 66 or older; mean age 73y - 54.1% women - no diabetes at baseline - new statin users - 48.3% receiving statin in primary prevention; 51.7% in secondary prevention started treatment with a statin from 1 August 1997 to 31 March 2010.	Atorvastatin vs pravastatin	Incident diabetes	**HR: 1.22** **95%CI: 1.15-1.29** (31 vs 23 events per 1000 person years)
			Rosuvastatinvs pravastatin	Incident diabetes	**HR: 1.18** **95%CI: 1.10-1.26** (34 vs 23 events per 1000 person years) The risk associated with rosuvastatin could depend on dose and duration of treatment.
			Simvastatin vs pravastatin	Incident diabetes	**HR: 1.10** **95%CI: 1.04-1.17** (26 vs 23 events per 1000 person years)
			Fluvastatin vs pravastatin	Incident diabetes	HR: 0.95 95%CI: 0.81-1.11
			moderate dose vs low dose		HR: 1.22 (95%CI 1.19 to 1.26)
			High dose vs low dose		HR: 1.30 (95%CI 1.20 to 1.40)
*adjusted for age, sex, year of cohort entry, recent acute coronary syndrome, chronic coronary artery disease, Charlson score, previous use of diuretic (thiazide), nitroglycerin, angiotensin receptor blocker, β blocker, hormones and analogues. (but: not adjusted for weight, ethnicity, family history)					

6.3.2 Summary and conclusions. New onset type 2 diabetes.

6.3.2.1 Statin versus placebo

Information from RCTs

Sattar 2010(119) is a systematic review and meta-analysis of RCTs comparing a statin to placebo that examined the outcome of new onset diabetes. There is a higher risk of new diabetes with statins compared to placebo (OR 1.09; 95% CI 1.02-1.17, NNH=225 for 4years of treatment).

In the previous chapters, Taylor 2013(32) found similar results in a population without a history of cardiovascular disease. Naci 2013(114), a network meta-analysis, also found a higher risk of diabetes with statins compared to placebo in the direct comparison.

Information from observational studies

We found 2 retrospective cohort studies (Wang 2012(120) and Zaharan 2012(121)), both from health insurance databases (1 study in Taiwan, 1 study in Ireland).
Both find that statin use is associated with a higher risk of new onset diabetes.
The Taiwanese cohort study(120) calculated a hazard ratio of 1.15 (95% CI 1.08 to 1.22) for the association of statin and type 2 diabetes.

The Irish cohort study(121) calculated data for the individual statins and found that atorvastatin, simvastatin and rosuvastatin were associated with a higher rate of new onset diabetes. The authors also describe an overall dose and duration effect for all statins, except fluvastatin (which only de only demonstrated a duration effect).

Using observational data in a specific statistical method of emulating the design and analysis of a hypothetical RCT of statins, Danaei 2013(125)also found an increased risk of type 2 diabetes (HR: 1.14; 95%CI 1.10-1.19).

6.3.2.2 High dose statin versus lower dose statin

Information from RCTs

A meta-analysis of RCTs by Preiss 2011(122) compared a high dose statin versus a moderate dose statin for the outcome of new onset diabetes. The population of the included trials all had a history of coronary heart disease.
Patients taking a high dose statin have a higher risk of developing diabetes compared to patients who take a lower dose (RR: 1.12; 95%CI:1.04-1.22). 498 patients have to be treated with a high dose statin compared to a moderate dose to cause 1 extra case of diabetes.

Information from observational studies

A Canadian propensity-score matched cohort study by Ko 2013(123)included 17080 elderly patients with myocardial infarction and compared intensive-dose statin use to moderate-dose statin. There was no statistically significant difference in new onset diabetes up to 5 years between both dosages.

A Canadian retrospective cohort study by Carter 2013(124) compared different statins to pravastatin for the outcome new onset diabetes. It found that atorvastatin, rosuvastatin and simvastatin but not fluvastatin were associated with a higher rate of incident diabetes compared to pravastatin. The risk associated with rosuvastatin could depend on dose and duration of treatment.
Moderate dose statin use (HR: 1.22 (95%CI 1.19 to 1.26) and high dose statin use (HR: 1.30; 95%CI 1.20 to 1.40) was associated with a higher risk of incident diabetes compared to low dose statin use.

6.3.2.3 Conclusion: statin use and the risk of type 2 diabetes

Evidence from both RCTs and observational studies point to an increased risk of diabetes with statin use. There is evidence of a dose-response relationship.

GRADE: MODERATE quality of evidence

6.4 Musculoskelettal problems

6.4.1 Evidence tables

Nichols 2007(126)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results* per 1000 person-years**
Cohort retrospective study Mean follow-up was approximately the same among all groups (36.3-41.5 months), ranging from 1 to 108 months.	n= 32225 (diabetics= 10247 and non diabetics= 21978) matched to an equal number of health plan members based on age group, diabete diagnosis and year of health plan enrollment.	-mean age: 59y -community-based clinical practice, comparing patients who had newly initiated statin treatment with patients who were not receiving statin treatment. -Statin initiators were older, had higher body mass index (BMI) and blood pressure, high-risk lipid profiles, more comorbidities, and were more likely to be taking other pharmaceutical agents.	Statins (lovastatin or simvastatin) initiators Vs No statin exposure	Myalgia	Diabetics 18.0 (95%CI: 16.4 to 19.6) Vs 15.8 (95%CI: 14.3 to 17.4) NS (P=0.055)
					Non Diabetics **20.0 (95%CI: 18.8 to 21.3)** **Vs** **10.8 (95%CI: 9.9 to 11.8)** **SS (P<0.001)**
				Mild Myositis	**Diabetics** **4.7 (95%CI: 3.9 to 5.6)** **Vs** **1.7 (95%CI: 1.3 to 2.3)** **SS (P<0.001)**
					Non Diabetics **4.5 (95%CI: 3.9 to 5.2)** **Vs** **0.8 (95%CI: 0.6 to 1.1)** **SS (P<0.001)**
				Severe Myositis	Diabetics 0.4 (95%CI: 0.2 to 0.7) Vs 0.3 (95%CI: 0.1 to 0.5) NS (P=0.359)

					Non Diabetics **0.8 (95%CI: 0.6 to 1.1)** **Vs** **0.2 (95%CI: 0.1 to 0.4)** **SS (P<0.001)**
				Rhabdomyolysis	Diabetics 0.1 (95%CI: 0.1 to 0.3) Vs 0.2 (95%CI: 0.1 to 0.5) NS (P=0.425)
					Non Diabetics 0.2 (95%CI: 0.1 to 0.4) Vs 0.2 (95%CI: 0.1 to 0.4) NS (P=0.999)
				Any myopathic event	**Diabetics** **24.2 (95%CI: 22.4 to 26.2)** **Vs** **18.9 (95%CI: 17.3 to 20.7)** **SS (P<0.001)**
					Non Diabetics **26.8 (95%CI: 25.4 to 28.2)** **Vs** **12.6 (95%CI: 11.6 to 13.7)** **SS (P<0.001)**
*Prevalence rate/1000 person-years adjusted for covariates (age, sex, blood pressure, height, weight, comorbidities, smoking, drugs known to increase the risk for myopathy: fibrates, corticosteroids, and calcium channel blockers)					

Authors defined 4 levels of myopathy. In accordance with the ACC, AHA, and NHLBI clinical advisory and published research, myopathy is defined as any muscle complaint, and myalgia as muscle complaints without CK elevation. The ACC, AHA, and NHLBI define myositis as muscle symptoms with CK elevations. Authors created 2 categories of myositis: mild myositis (CK levels 1 ×-3 × ULN) and severe myositis (CK levels 3 ×-10 × ULN). Rhabdomyolysis was defined as CK levels >10× ULN, consistent with ACC, AHA, and NHLBI definitions.

To identify myalgia, it was assumed that CK tests in the normal range (16-206 U/L) performed during permanent or temporary discontinuation of statin treatment according to dispense records, were triggered by muscle complaints and were therefore defined as myalgia.

Hippisley-Cox 2010(127)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Prospective open cohort study using routinely collected data. England and Wales	n= 2 004 692 (225 922 (10.7%) were new users of statins)	-mean age: 50.5 years -primary care patients -Compared with non-users of statins, new users tended to be older and were more likely to be men and to have comorbidities such as atrial fibrillation, cardiovascular disease, peripheral vascular disease, treated hypertension, diabetes, and chronic kidney disease -They were also more likely to have results recorded on computer for liver function tests and CK concentrations	Simvastatin vs No Statin	Myopathy	Women **HR : 3.03 (95%CI : 2.35 to 3.91)**
					Men **HR : 6.14 (95%CI : 5.09 to 7.40)**
			Atorvastatin Vs No Statin	Myopathy	Women **HR : 2.90 (95%CI : 2.09 to 4.01)**
					Men **HR : 6.68 (95%CI : 5.32 to 8.39)**
			Fluvastatin Vs No Statin	Myopathy	Women Insufficient data
					Men **HR : 4.79 (95%CI : 2.12 to 10.80)**
			Pravastatin Vs No Statin	Myopathy	Women **HR : 2.64 (95%CI : 1.29 to 5.39)**
					Men **HR : 4.84 (95%CI : 2.86 to 8.17)**
			Rosuvastatin Vs No Statin	Myopathy	Women **HR : 5.41 (95%CI : 2.64 to 11.07)**
					Men **HR : 4.21 (95%CI : 1.87 to 9.48)**
* Hazard Ratio adjusted -in women for age3, age3ln(age), bmi, ethnicity, type 1 diabetes, type 2 diabetes, treated hypertension, liver, hypothyroidism, corticosteroids -in men for age3, age3ln(age), bmi, ethnicity, type 2 diabetes, corticosteroids					

Moderate or serious myopathic event for our study was defined as a diagnosis of myopathy or rhabdomyolysis or a raised creatine kinase concentration of four or more times the upper limit of normal, as this represents an event where treatment is likely to be discontinued.

Mansi 2013(128)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Retrospective Cohort Analysis -Data extracted from Military health Care system 4-year follow-up USA	n= 58977	-mean age : 49y -%male: 47% -Patients classified into 2 groups: statin users (patients with at least 1 dispensed statin prescription of a 3-month supply in Fiscal Year 2004) and nonusers (patients who received a prescription for any medication (but not a statin) and did not receive a statin prescription during the 4 years of follow-up) -mean age of the statin users were significantly older than the nonusers, and their Charlson comorbidity score was higher than that of the nonusers.	statin users vs nonusers	All osteoarthritis, other arthropathies	**OR: 1.26 (95%CI 1.19-1.33)** **SS p<0.0001**
				Dorsopathies, rheumatism, chondropathies	**OR: 1.20 (95%CI 1.12-1.27)** **SS p<0.0001**
				Dislocations, sprains, strains	OR: 1.04 (95%CI 0.99-1.10) NS p=0.1178
*adjusted for age, sex and Charlson comorbidity index					

Although authors adjusted for these factors (age, sex and Charlson comorbidity index), other unknown confounders can contribute to the differences. Oncological diseases and several musculoskeletal diseases occur more frequently in older populations. In addition, other potential confounders, such as smoking, alcohol abuse, obesity and polypharmacy, are not directly represented in the Charlson comorbidity index.The follow-up period in our study (4 years) may not be long enough to demonstrate all oncological and osteoarthritic changes Authors also did not account for the different types of statins used and the likelihood of presence of drug-drug interaction as a contributing factor for the increased incidence of our outcomes

6.4.2 Summary and conclusions: musculoskeletal problems

Information from RCTs

Different meta-analyses of RCTs have reported muscle-related endpoints (see also chapter efficacy).

-The meta-analysis by Taylor 2013(32) in primary prevention found no statistically significant difference between statins and placebo in myalgia or muscle pain, nor in rhabdomyolysis.

-The network meta-analysis by Naci 2013(114) compared statins versus placebo for muscle-related outcomes. No statistically significant differences were found for myalgia, myopathy or rhabdomyolysis.

Information from observational studies

-A retrospective cohort study in the USA by Nichols 2007(126) in 32 225 health plan members compared the initiation of a statin (lovastatin or stimvastatin) to no statin exposure. The mean follow-up was 3 years.
In non-diabetics, statin use was associated with a higher prevalence rate of **myalgia** compared to no use (20.0/1000 person-years ; 95%CI: 18.8 to 21.3) vs 10.8/1000 person-years ; 95%CI: 9.9 to 11.8). Myalgia was defined as a temporary discontinuation of statin treatment in the database records, combined with a normal CK test.
Statin use was associated with an increased prevalence rate of **mild myositis and severe myositis** in non-diabetics, and with increased prevalence rate of mild myositis in diabetics (e.g. for non-diabetics: mild myositis 4.5/1000 person-years ; 95%CI: 3.9 to 5.2 with statin use vs 0.8/1000 person-years ; 95%CI: 0.6 to 1.1 without statin and severe myositis 0.8/1000 person-years ; 95%CI: 0.6 to 1.1 vs 0.2/1000 person-years ; 95%CI: 0.1 to 0.4).
No statistically significant association between statin use and **rhabdomyolysis** was found.
Statin use was associated with a higher prevalence of **any myopathic event** (all previous endpoints combined), in both diabetics and non-diabetics (Diabetics 24.2/1000 person-years; 95%CI: 22.4 to 26.2 with statin use vs 18.9/1000 person-years 95%CI: 17.3 to 20.7 without statin use. Non-diabetics 26.8/1000 person-years ; 95%CI: 25.4 to 28.2 with statin use vs 12.6/1000 person-years without statin use ; 95%CI: 11.6 to 13.7).

-In a UK prospective open cohort study by Hippisley-Cox 2010(127), the association between individual statins and myopathy (moderate or serious) was examined. 2 004 692, of which 225 922 new statin users were follow for a maximum of 6 years.
Moderate or serious myopathic event was defined as a diagnosis of myopathy or rhabdomyolysis or a raised creatine kinase concentration of four or more times the upper limit of normal.
The use of each individual statin was associated with increased risk of myopathy in both men and women. (example: simvastatin use in men vs no statin use: HR : 6.14; 95%CI : 5.09 to 7.40).

-A retrospective cohort analysis in the USA in 58 977 patients by Mansi 2013(128) studied the association between statin use and musculoskeletal outcomes. Follow-up was 4 years.

They found statin use to be associated with a diagnosis of osteoarthritis and other arthropathies (**OR: 1.26; 95%CI 1.19-1.33)**. Statin use was also associated with a diagnosis of dorsopathies, rheumatism and chondropathies (**OR: 1.20; 95%CI 1.12-1.27)**. No association was found with dislocations, sprains and strains.

Conclusion

Statin use is associated with myopathy (myalgia, myositis). This association is not found in RCTs, which may be explained by the exclusion of patients with risk factors for myopathy, inadequate reporting and other methodological problems.
The association is found in observational studies. However, in the studies reported here, the outcomes are retrieved from medical records. If patients do not visit their doctor with minor symptoms, or if coding and retrieving the information is difficult, a bias in the results will be introduced.
For rhabdomyolysis, no statistically significant association was found in these observational studies, possibly due to sample size.

GRADE: LOW quality of evidence

6.5 Cognition

6.5.1 Evidence tables

Richardson 2013 (rct + cohort)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR Search date: Till October 2012	RCT N= 1 n= 20536 (HPS 2002)	CHD prevention (primary or secondary)	Statin vs placebo	Dementia	RR: 1.00 (95% CI 0.61 to 1.64) NS
	MA of cohort studies N=10 n=4360137 (Rea 2005, Zandi 2005, Szwast 2007, Wolozin 2007, Smeeth 2009, Hippisley – Cox and Coupland 2010, Beydoun 2011, Parikh 2011, Ancelin 2012, Bettermann 2012) Weaknesses in cohort studies arose from poor representativeness of the cohorts (11 of 26), inadequate follow-up (11 of 26), and limited comparability (8 of 26), most often due to failure to control for level of education.	Mainly community based	Statin vs placebo	Dementia	**RR: 0.87 (95% CI 0.82 to 0.92)** **SS in favour of statin**

	Cohort at lowest risk of bias N= 1 n=1560 (Beydoun 2011)	Community (USA)	Statin vs placebo	Dementia	**RR: 0.41 (95% CI 0.18 to 0.92)** **SS in favour of statin**
	Pooled analysis of cohort studies N=10 n=759553 (Rea 2005, Zandi 2005, Arvanitakis 2008, Smeeth 2009, Sparks 2008, Haag 2009, Li 2010, Beydoun 2011, Ancelin 2012, Bettermann 2012)	Mainly community based	Statin vs placebo	Alzheimers disease	**RR: 0.79 (95% CI 0.63 to 0.99)** **SS in favour of statin**
	Pooled analysis of cohort studies at the lowest risk of bias N=3 n=11584 (Beydoun 2011, Li 2010, Haag 2009)	Mainly community based	Statin vs placebo	Alzheimers disease	**RR: 0.57 (95% CI 0.42 to 0.77)** **SS in favour of statin**
	RCT N=1 n=20536	CHD prevention (primary or secondary)	Statin vs placebo	Mild cognitive impairment	RR: 0.98 (95% CI 0.93 to 1.03) NS
	Meta-analysis of cohort studies N=4 n=4019 (Yaffe 2002, Cramer 2008, Sparks 2008, Beydoun 2011)	Mainly community based	Statin vs placebo	Mild cognitive impairment or cognitive impairment without dementia	**RR: 0.66 (95% CI 0.51 to 0.86)** **SS in favour of statin**

	Cohort with lowest risk of bias N=1 n= 1308 (Beydoun 2011)	Not reported in Richardson: , Study design, patient characteristics, and reported outcomes are provided for cohort studies in Tables 8, 9, and 12 of Supplement 2.	Statins vs placebo	Mild cognitive impairment or cognitive impairment without dementia	RR=0.71 (95% CI 0.33 to 1.52) NS

*adjusted as follows: **Rea 2005**: age, sex, education, baseline modified Mini-Mental State Examination, cardiovascular disease, cerebrovascular disease, alcohol use; **Zandi 2005**: age, sex, education, number of ApoE4 alleles, hypertension, diabetes mellitus; **Szwast 2007**: age, sex, education, ApoE4; **Wolozin 2007**: age, cardiovascular disease, hypertension, diabetes mellitus, Charlson Index (a measure of chronic disease); **Smeeth 2008**: age, sex, likelihood of statin use, date of statin initiation, new diagnoses or drug therapies; **Hippisley-Cox and Coupland 2010**: age, cardiovascular disease, cerebrovascular disease, diabetes mellitus, depression, use of tricyclic antidepressants or selective serotonin reuptake inhibitors, body mass index; **Beydoun 2011**: age, sex, race, education, cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, body mass index, blood pressure, smoking status; **Parikh 2011**: medical comorbid conditions defined by the Centers for Medicare & Medicaid Services Hierarchical Condition Categories risk-adjustment model; **Ancelin 2012**: age, location, education; **Bettermann 2012**: age, sex, race, education, ApoE4, cardiovascular disease, cerebrovascular disease, baseline mild cognitive impairment, treatment group, location; **Sparks 2008**: age, sex, education, ApoE4; **Haag 2009**: age, sex, education, ApoE4, cardiovascular disease, cerebrovascular disease, diabetes mellitus, other lipid-lowering agents, smoking status, blood pressure, body mass index, total cholesterol; **Li 2010**: age, cohort, sex, race, education, ApoE4, baseline Cognitive Abilities Screening Instrument, cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, other lipid-lowering agents, smoking status, body mass index; **Yaffe 2002**: age, education, treatment group, coronary artery bypass grafting, total cholesterol, smoking status; **Cramer 2008**: education, ApoE4, cerebrovascular disease, diabetes mellitus, smoking status.
No confounders reported for Arvanitakis 2008.

- For most RCTs, insufficient information was available to judge risk of bias resulting from sequence generation (10 of 19), allocation concealment (10 of 19), or selective outcome reporting (15 of 19).

6.5.2 Summary and conclusions: cognition

A systematic review by Richardson 2013(129) searched all RCTs and observational studies on statins and cognitive function (dementia, Alzheimer disease and cognitive impairment).

They found 1 RCT (HPS 2002) that compared statins to placebo and reporting on the outcome **dementia**. No significant difference was found between statin and placebo (1.00; 95% CI 0.61 to 1.64).
10 observational studies found that statins were associated with a decreased risk for dementia (RR: 0.87; 95% CI 0.82 to 0.92).
GRADE: MODERATE quality of evidence

For **Alzheimer disease**, a pooled analysis of 10 cohort studies found that statins were associated with a decreased risk (RR: 0.57; 95% CI 0.42 to 0.77).
GRADE: LOW quality of evidence

1 RCT (HPS 2002) that reported on **mild cognitive impairment** was found. No significant difference in the incidence of mild cognitive impairment was observed between statin treatment and placebo (RR: 0.98; 95% CI 0.93 to 1.03).
A meta-analysis of 4 cohort studies showed that statin therapy was associated with a decreased risk for mild cognitive impairment or cognitive impairment without dementia. (RR: 0.66; 95% CI 0.51 to 0.86)
GRADE: MODERATE quality of evidence

*This systematic review also discussed evidence from RCTs and observational studies on **cognitive performance**. No worsening of cognitive performance was found with statins compared to placebo.This was the case in patients with cognitive impairment as well as in patients with normal cognition at baseline.*
GRADE: MODERATE to LOW quality of evidence

After the search date of this systematic review, another observational study was published (Steenland 2013(130)). This longitudinal follow-up of >5000 research volunteers tested cognitive performance in statin users versus non users. Statin use was associated with slower worsening of cognitive tests.

6.6 Cataract

6.6.1 Evidence tables

Hippisley-Cox 2010(127)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Prospective open cohort study using routinely collected data. England and Wales	n= 2 004 692 (225 922 (10.7%) were new users of statins)	-mean age: 50.5 years -primary care patients -Compared with non-users of statins, new users tended to be older and were more likely to be men and to have comorbidities such as atrial fibrillation, cardiovascular disease, peripheral vascular disease, treated hypertension, diabetes, and chronic kidney disease -They were also more likely to have results recorded on computer for liver function tests and CK concentrations	Simvastatin vs No Statin	Cataract	Women **HR : 1.30 (95%CI : 1.25 to 1.36)**
					Men **HR : 1.31 (95%CI : 1.25 to 1.38)**
			Atorvastatin Vs No Statin	Cataract	Women **HR : 1.30 (95%CI : 1.22 to 1.37)**
					Men **HR : 1.32 (95%CI : 1.24 to 1.41)**
			Fluvastatin Vs No Statin	Cataract	Women **HR : 1.26 (95%CI : 1.05 to 1.52)**
					Men **HR : 1.16 (95%CI : 0.95 to 1.42)**
			Pravastatin Vs No Statin	Cataract	Women **HR : 1.40 (95%CI : 1.24 to 1.57)**
					Men **HR : 1.31 (95%CI : 1.15 to 1.50)**
			Rosuvastatin Vs No Statin	Cataract	Women **HR : 1.25 (95%CI : 1.04 to 1.51)**
					Men **HR : 1.56 (95%CI : 1.28 to 1.90)**
* Hazard Ratio adjusted -in women for age3, age3ln(age), ln(bmi), bmi0.5, ethnicity, smoking, cardiovascular disease, type 1 diabetes, type 2 diabetes, rheumatoid arthritis, atrial fibrillation, corticosteroids; -in men for age3, age3ln(age), bmi−2, bmi−1, Townsend score, ethnicity, smoking, cardiovascular disease, type 1 diabetes, type 2 diabetes, atrial fibrillation, corticosteroids					

Leuschen 2013(131)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
Cohort retrospective study (propensity score-matched cohort) USA using retrospective data from October 1, 2003, to March 1, 2010.	n= 46249	-aged 30 to 85 years old (mean age 57y) - enrolled in Tricare Prime or Plus in the San AntonioMulti-Market Area, and - had at least 1 outpatient visit during the baseline period and 1 outpatient visit during the follow-up period. -statin users were patients who received and filled a statin medication prescription for at least 90 days -Nonusers were patients who did not receive a statin at any time throughout the study	Statins users (n=6972) Vs Nonusers (n=6972) After propensity score matching	All cataract	**OR: 1.09 (95%CI 1.02-1.17)** **SS p=0.01** **In favor of nonusers**
			Statins users (n=6113) Vs Nonusers (n=27400) Among Patients With No Charlson Comorbidities	All cataract	***OR: 1.25 (95%CI 1.14-1.38)** **SS p<0.001** **In favor of nonusers** ****OR: 1.20 (95%CI 1.06-1.35)** **SS p=0.003** **In favor of nonusers**
*adjusted for age, sex, obesity, smoking, alcohol use, illicit drug use, glaucoma at baseline, vision defects/blindness, number of all admissions during baseline, number of all outpatient visits during baseline, and use of different classes of medications (Beta Blocker, Diuretic, Calcium channel blocker…) ** Adjusted for all the above covariates and mean low-density lipoprotein cholesterol.					

Klein 2006(132)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
observational longitudinal population-based study USA	n= 1299	-95% non-Hispanic white people -mean age: 63.2y	Statin use vs no statin use	Five-year Incidence of nuclear cataract	**OR: 0.60** **(95%CI 0.39-0.93)** **SS in favor of statin use**
*adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking, and diabetes					

Remarks: Small sample size

Tan 2007(133)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
cohort study (1992-2004)	n= 3654	-elderly Australian population -mean age: 64y	Statin use vs no statin use	Any cataract	**MultivariateHR:** **0.52(95%CI 0.29-0.93)** **P=0.028** **SS in favor of statin use**
* Additionally adjusted for gender, total cholesterol, high-density lipoprotein cholesterol, smoking, obesity, and diabetes					

Remarks:
Because participants without gradable photographs for all cataract types were excluded, the analyses of any cataract were based on a reduced number of participants and should be interpreted cautiously.

6.6.2 Summary and conclusions: cataract

There is conflicting evidence concerning statin use and the risk of cataract.

A meta-analysis by Kostis 2013(134) combined observational studies and RCTs that report on statin use and the risk of cataract (only abstract available). It found that statin use is associated with a decreased risk of cataract (OR 0.81; 95%CI 0.71-0.93).

Our own literature search yielded the following studies:

In a UK prospective open cohort study by Hippisley-Cox 2010(127), the association between individual statins and cataract was examined. 2 004 692 patients, of which 225 922 new statin users were follow for a maximum of 6 years.
The use of each individual statin was associated with increased risk of cataract in both men and women. (example: simvastatin use in men vs no statin use: HR 1.30; 95%CI 1.25-1.36).
(This study was not included in Kostis 2013)

A retrospective cohort study by Leuschen 2013(131) in the USA compared statin us to no statin use for the outcome cataract. In a propensity-score matched cohort of 6 972 pairs of users and nonusers, followed for 7 years, statin use was associated with a higher risk of cataract (OR: 1.09; 95%CI 1.02-1.17).
(This study was not included in Kostis 2013)

In a prospective cohort by Klein 2006(132) of 1 299 patients in the USA, with a maximum follow-up of 7 years, Statin use was associated with a decreased risk of nuclear cataract (OR: 0.60; 95%CI 0.39-0.93).
(This study was included in Kostis 2013)

In an Australian population-based cohort study of 3 654 participants by Tan 2007(133), statin use was associated with a decreased risk of cataract (HR: 0.52; 95%CI 0.29-0.93).
(This study was included in Kostis 2013)

Conclusion

The evidence concerning statin use and cataract is conflicting.
GRADE: VERY LOW quality of evidence

6.7 Cancer

6.7.1 Evidence tables: site-specific cancer

6.7.1.1 Evicence tables: Bladder cancer

Zhang 2013(135)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR +MA Search date: (January 1966 – October 2012)	Subtotal RCT N= 3 n= 25977 (Clearfield 2001, Strandberg 2004, HPS 2005)	Adult study participants (18 years or older) Bladder cancer incidence reported	Statin vs control (placebo or no statins)	Bladder cancer	RR: 0.83 (95% CI 0.63 to 1.10) NS
	Subtotal Cohort studies N=5 (Sato 2006, Farwell 2008, Friedman 2008, Haukka 2010, Jacobs 2011)	Adult study participants (18 years or older) Bladder cancer incidence reported	Statin vs control (placebo or no statins)	Bladder cancer	RR: 1.11 (95% CI 0.91 to 1.35) NS
	Overall N=13 (Clearfield 2001, Strandberg 2004, HPS 2005, Sato 2006, Farwell 2008, Friedman 2008, Haukka 2010, Jacobs 2011, Graaf 2004, Kaye 2004, Coogan 2007, Vinogradova 2011, Kuo 2012)	Adult study participants (18 years or older) Bladder cancer incidence reported	Statin vs control (placebo or no statins)	Bladder cancer	Rr: 1.07 (95% CI 0.95 to 1.21) NS
*Adjusted for confounders: - Cohort studies: Sato 2006: Age, sex					

Farwell 2008: Age, diabetes mellitus, elevated cholesterol, cardiovascular disease, hypertension, alcohol use, smoking, weight, thyroid disease, renal failure, chest pain, mental illness, lung disease, gastro-intestinal disease.
Friedman 2008: state of residence
Haukka 2010: age, follow-up period
Jacobs 2011: age, sex, diabetes mellitus, BMI, NSAID use, education, elevated cholesterol, hypertension, heart disease, smoking, frequency of physician visits.

- Case-control studies:

Graaf 2004: age, diabetes mellitus, NSAID use, comorbidity score, use of diuretics, use of calcium channel blockers, use of angiotensin-converting enzyme inhibitors, use of other lipid-lowering drugs, use of hormones, prior hospitalization.
Kaye 2004: age, BMI, smoking
Coogan 2007: age, race, BMI, education, religion, alcohol use, use of hormones
Vinogradova 2011: age, BMI, NSAID use, cardiovascular disease, hypertension, arthritis, smoking, use of Cox2-inhibitors, aspirin use.
Kuo 2012: diabetes mellitus, NSAID use, hypertension, use of other lipid-lowering drugs, prior hospitalization.

Remarks:

- Inclusion criteria were as follows: an original study comparing statin treatment with an inactive control (placebo or no statins), adult study participants (18 years or older), bladder cancer incidence reported, and follow-up over 1 year.
- Studies reporting different measures of RR like risk ratio, rate ratio, hazard ratio (HR), and odds ratio (OR) were included in the meta-analysis. In practice, these measures of effect yield a similar estimate of RR, since the absolute risk of bladder cancer is low.

Quality assessment results

Figure 2 illustrates our opinion about each item of bias risk for included RCTs, and most of the items were at ‘‘low risk’’ based on Cochrane handbook, suggesting a reasonable good quality of RCTs. Table 2 summarizes the quality scores of cohort studies and case–control studies. The Newcastle–Ottawa Scale scores for the included studies ranged from 5 to 8, with a median 6, and 7 studies (70 %) were deemed to be of a high quality (≥6). The median scores for the three categories were 3 for selection, 1.5 for comparability, and 2 for ascertainment of exposure/outcome. Lower quality scores tended to arise from the method of ascertainment of exposure/outcome.

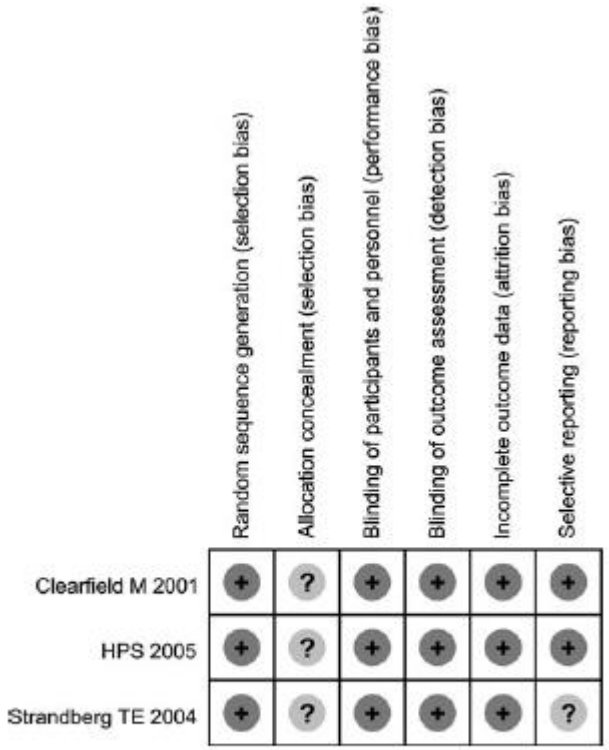


Fig. 2 Methodological quality of included randomized controlled trials: review authors' opinion on each item of bias risk based on Cochrane handbook. "+", "−," or "?" reflected low risk of bias, high risk of bias, and uncertain of bias, respectively

Table 2 Methodological quality of included cohort studies and case–control studies based on the Newcastle–Ottawa Scale

Case–control studies	Selection	Comparability	Exposure	Total score
Graaf [16]	☆☆☆	☆☆	☆☆	7
Kaye [17]	☆☆☆☆	☆☆	☆☆	8
Coogan [20]	☆☆	☆☆	☆	5
Vinogradova [26]	☆☆☆	☆	☆☆	6
Kuo [24]	☆☆☆	☆☆	☆☆	7
Cohort studies	**Selection**	**Comparability**	**Outcome**	**Total score**
Sato [27]	☆	☆	☆☆☆	5
Farwell [21]	☆☆	☆	☆☆	5
Friedman [25]	☆☆☆☆	☆	☆	6
Haukka [22]	☆☆☆☆	☆	☆☆	7
Jacobs [23]	☆☆	☆☆	☆☆☆	7

6.7.1.2 Evicence tables: Breast cancer

Undela 2012(136)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: MA of observational studies Search date: (from January 1966 up to January 2012) Follow-Up: 2-15 years	All studies (case-control + cohort) N= 24 (of which 3 were excluded due to their large CIs and no effect on the final combined estimated RR /) n=2440988 (Cohort: n=2042439/Case-control: n=398549)	Female subjects, 14 studies population based, 10 studies hospital-based	Statin use vs no statin use	Breast cancer	RR:0.99 (95%CI 0.94 to 1.04) NS
	N= 10(case-control + cohort)		Long-term statin use	Breast cancer	RR: 1.03 (95% CI 0.96 to 1.11) NS
*All studies were controlled for potential confounding factors (at least for age) by matching or adjustments. n≥8 confounders: N=8 n≤7 confounders: N=16					

Comments:

- We included all articles irrespective of publication length; that is we did not exclude articles published as short reports or conference abstracts, even though the critical appraisal of such publications is limited
- Studies reporting different measures of RR like risk ratio, rate ratio, hazard ratio (HR), and odds ratio (OR) were included in the meta-analysis. In practice, these measures of effect yield a similar estimate of RR, since the absolute risk of breast cancer is low.
- Data extraction and quality assessment: Two investigators (K.U. and V.S.) independently reviewed the primary studies to assess the appropriateness for inclusion in the present meta-analysis and data were extracted. The following information was assayed from each study: (i) first author's last name, year of publication, and country of the population studied; (ii) study design; (iii) number of female subjects and number of breast cancer cases; (iv) RR estimates and 95 % CIs; (v) definition of statin exposure and breast cancer assessment; (vi) control for potential confounding factors by matching or adjustments, if applicable. We extracted the RR estimates that reflected the greatest degree of control for potential confounding factors.

Table 1 Studies included in the meta-analysis

Author, year[a] (country)[b]	Study period (years)	All female subjects	BC cases	Description of exposure/ reference[e]	Study quality	
					Definition of statin use	Number of variables adjusted[f]
Lovastatin study groups, 1993 (US, Canada & Finland) [12][c]	NR	241	3	a	Self-reported	1
Blais et al. 2000 (Canada) [10][d]	6 (1988–1994)	715	NR	b	NR	1, 9, 10, 13, 22
Beck et al. 2003 (Canada) [13][c]	8 (1989–1997)	67,472	879	e	Database	1
Cauley et al. 2003 (US) [11][c]	15 (1986–2001)	7,528	240	d	Medical records	1–4
Graaf et al. 2004 (Netherlands) [14][d]	3 (1995–1998)	9,182	NR	c	NR	1–3,6–9,11–13
Kaye and Jick 2004 (UK) [15][d]	12 (1990–2002)	8,091	236	d	Medical records	1, 14, 15
Boudreau et al. 2004 (US) [17][d]	2 (1997–1999)	1,982	231	g	Medical records	1, 5
Friis et al. 2005 (Denmark) [16][c]	13 (1989–2002)	171,937	3,141	e	Database	1, 5, 28, 29
Eliassen et al. 2005 (US) [19][c]	12 (1988–2000)	75,828	1,624	d	Self-reported	1, 3, 14, 17, 21, 23–25
Kochhar et al. 2005 (US) [20][d]	6 (1998–2004)	40,421	4,771	d	Database	1, 11, 15, 21
Cauley et al. 2006 (US) [21][c]	11 (1993–2004)	156,351	4,383	d	Medical records	1, 2, 14, 15, 17, 21, 24, 26–28
Dumasia et al 2006 (US) [22][d]	10 (1995–2005)	1,042	NR	d	Self-reported	NR
Boudreau et al. 2007 (US) [24][c]	14 (1990–2004)	92,888	2,707	g	Database	1, 3, 9, 11, 14
Setoguchi et al. 2007 (US) [29][c]	9 (1994–2003)	19991	227	d	Medical records	1–3, 11, 20, 17, 29, 30
Coogan et al. 2007 (US) [25][d]	14 (1991–2005)	2,355	69	c	Self-reported	1, 3, 14, 18–21
Friedman et al. 2008 (US) [30][c]	9 (1994–2003)	NR	1,706	e	Medical records	35
Smeeth et al. 2008 (UK) [26][c]	11 (1995–2006)	364,854	3,204	d	Medical records	1–11, 22, 31, 32, 37–40
Pocobelli et al. 2008 (US) [31][d]	6 (1995–2001)	8,620	607	g	Self-reported	1, 3, 14, 17, 18, 25, 27, 31, 35
Eaton et al. 2009 (US) [27][d]	3 (2005–2008)	189	NR	d	Self-reported	1
Haukka et al. 2010 (Finland) [32][c]	9 (1996–2005)	6,046	583	d	Database	1, 33
Hippisley et al. 2010 (England & Wales) [28][c]	6 (2002–2008)	1,014,197	9,823	d	Medical records	NR
Woditschka et al. 2010 (US) [33][d]	10 (1997–2007)	247,348	NR	d	Medical records	3, 36
Jacobs et al. 2011 (US) [23][c]	10 (1997–2007)	65,106	2,489	f	Self-reported	1–3, 13–15, 20, 24, 27, 34
Vinogradova et al. 2011 (UK) [34][d]	10 (1998–2008)	78,604	7,708	e	Medical records	1, 2, 14, 15, 30, 37–40

NR not reported, *BC* breast cancer

[a] Publication year, [b] country of study conducted, [c] cohort studies, [d] case–control studies

[e] a, systematic use of lovastatin versus SEER data; b, any use of statins versus use of bile acid-binding resins; c, regular use of statins versus no use of statins; d, current use of statins versus no current use of statins; e, any use of statins versus no use of statins; f, current use of cholesterol-lowering drugs versus never use of cholesterol-lowering drugs; g, ever use of statins versus no use of statins

[f] 1 age, 2 use of nonsteroidal anti-inflammatory drugs, 3 use of hormones, 4 use of cardiovascular drugs, 5 use of antihypertensive drugs, 6 use of diuretics, 7 use of angiotensin-converting enzyme inhibitors, 8 use of calcium channel blockers, 9 use of other lipid-lowering therapy, 10 use of fibric acids, 11 diabetes mellitus, 12 prior hospitalization, 13 comorbidity score, 14 body mass index, 15 smoking, 16 body weight, 17 family history of breast cancer, 18 education, 19 religion, 20 race, 21 alcohol consumption, 22 previous neoplasms, 23 height, 24 physical activity, 25 menopausal status, 26 hysterectomy, 27 mammogram, 28 percentage of calories from fat, 29 health service utilization, 30 arthritis, 31 calendar year, 32 propensity score, 33 follow-up period, 34 history of elevated cholesterol, 35 state of residence, 36 use of oral contraceptives, 37 cardiovascular disease, 38 hypertension, 39 use of Cox2-inhibitors, 40 use of aspirin

6.7.1.3 Evicence tables: Colorectal cancer

Liu 2013(137)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: MA of RCTs and observational studies Search date: last update on July 30, 2013	Subtotal RCT N=11 n=95984	Both primary and secondary prevention	Statin use vs control	Colorectal cancer	RR: 0.96 (95% CI 0.85 to 1.08) NS
	Subtotal Cohort N=13 n=7538633	Mainly population-based	Statin use vs control	Colorectal cancer	**RR: 0.93 (95% CI 0.87 to 0.99) SS**
	Overall (RCT + Cohort + Case-control) N= 42 n= 7908674		Statin use vs control	Colorectal cancer	**RR: 0.90 (95% CI 0.86 to 0.95) SS**
	Subtotal RCT N=6 n=52590	Both primary and secondary prevention	Long-term statin use (≥ 5y)	Colorectal cancer	RR: 0.91 (95% CI 0.78 to 1.07) NS
	Subtotal Cohort N=7 n=4756550	Mainly population-based	Long-term statin use (≥ 5y)	Colorectal cancer	RR: 0.98 (95% CI 0.90 to 1.07) NS
	Overall (RCT + Cohort + Case-control) N=20 n=5021294		Long-term statin use (≥ 5y)	Colorectal cancer	RR: 0.96 (95% CI 0.90 to 1.03) NS
*adjusted for confounding variables (see screenshot below).					

Table 3 Descriptive characteristics of randomized control study included in the meta-analysis

Study	Study location	Statin type	Dosage of statin use	All participants	Statin users (*n*)	CRC cases	Exposure period	Period of follow-up (year)
Shepherd (WOSCP) [39]	Scotland	Pravastatin	40 mg daily	6,595	3,302	61	1989–1991	Mean 4.9
Sacks (CARE) [40]	USA	Pravastatin	40 mg daily	4,159	2,081	33	1989–1991	Median 5.0
Downs (AFCAPS) [41]	USA	Lovastatin	20–40 mg daily	6,605	3,304	45	1991–1993	Mean 5.2
(LIPID) [43]	Australia	Pravastatin	40 mg daily	9,014	4,512	146	1990–1992	Mean 6.0
(HPS) [44]	United Kingdom	Simvastatin	40 mg daily	20,536	10,269	145	1994–1997	Median 5.0
(ALLHAT-LLT) [42]	USA	Pravastatin	40 mg daily	10,355	5,170	84	1994–2002	Mean 4.8
Shepherd (PROSPER) [45]	United Kingdom	Pravastatin	40 mg daily	5,804	2,839	110	1997–1999	Mean 3.2
Colhoun (CARDS) [46]	UK and Ireland	Atorvastatin	10 mg daily	2,838	1,428	50	1997–2001	Median 3.9
Strandberg (4S) [47]	Nordic counties†	Simvastatin	20 mg daily	4,444	2,221	57	1988–1989	Median 10.4
Nakamura (MEGA) [48]	Japan	Pravastatin	10–20 mg daily	7,832	3,866	123	1994–1999	Mean 5.3
Ridker et al. [49]	In 26 countries	Rosuvastatin	20 mg daily	17,802	8,901	705	2003–2006	Median 1.9

WOSCP West of Scotland Coronary Prevention Study Group, *CARE* Cholesterol and Recurrent Events Trial investigators, *AFCAPS* Air Force/Texas Coronary Atherosclerosis Prevention Study, *LIPID* long-term intervention with pravastatin in ischemic disease, *HPS* heart protection study, *ALLHAT-LLT* antihypertensive and lipid-lowering treatment to prevent heart attack trial, *PROSPER, CARDS*, *4S* Scandinavian Simvastatin Survival Study, *MEGA* Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese

† Denmark, Finland, Iceland, Norway, and Sweden

Table 2 Descriptive characteristics of cohort studies included in the meta-analysis

Study	Study location	Cohort size	Statin type	Definition f statin use	Exposure period	Period of follow-up (year)	Patient population source and setting	Adjustment variables*
Friis et al. [26]	Denmark	334,754	Any statin	≥2 prescriptions	1989–2002	Mean 3.3 range 0–14 years	Prescription Database of North Jutland County and the Danish Cancer Registry; population-based	1, 2, 10, 30, 37
Jacobs et al. [27]	USA	132,136	L, P, S, F	Current use	1997–2001	Mean 5 years	Cancer Prevention Study II (CPS-II) Nutrition Cohort; population-based	1–3, 10, 16, 24, 28–33
Setoguchi et al. [28]	USA	31,723	Any statin	≥3 prescriptions	1994–2003	Mean 2.9 years	Pharmaceutical Assistance Contract for the Elderly in Pennsylvania; population-based	1–22
Farwell et al. [29]	USA	62,842	A, F, L, P, S	≥2 prescriptions	1997–2005	Median 5.0, range 2.0–7.2 years	Veterans Affairs (VA) administrative and clinical databases; population-based	1, 7, 10, 16, 24, 25, 27, 28, 33,
Flick et al. [30]	USA	69,115	Any statin	Used ≥100 days	2002–2003	Median 2.8, Max 3.5 years	California Men's Health Study (CMHS) cohort; population-based	1, 10, 16, 18, 24–27, 29, 31, 33
Singh et al. [31]	Canada	35,739	Any statin	≥2 prescriptions	1995–2005	Regular: median 3, range 1–5 years; Long-term: median 7, range 5–9 years	Manitoba Health and Healthy Living (MHHL) Population Registry; population-based	1, 2, 10, 16, 18
Haukka et al. [32]	Finland	944,962	Any statin	≥1 prescriptions	1996–2005	Mean 8.8 years	Social Insurance Institution (SII) and Finnish Cancer Registry (FCR); population-based	1, 2, 45
Friedman et al. [33]	USA	4,222,660	Any statin	≥1 prescriptions	1994–2003	Median 4.91, range 1 day–9.42 years	Kaiser Permanente Medical Care Program in northern California (KPMCP); population-based	2, 51
Hippisley et al. [34]	England & Wales	1,014,197	A, S, F, P, R	≥1 prescriptions	2002–2008	>5 years	Egton Medical Information System (EMIS); population-based	1, 2, 7, 18, 24, 25
Jacobs et al. [35]	USA	133,255	L, P, S, F	Current use	1997–2007	>5 years	Cancer Prevention Study II Nutrition Cohort	1, 2, 3, 7, 10, 24, 25, 28–30, 32, 33
Lee et al. [36]	USA	131,922	Any statin	Current use	1990–2006	>1,688,745 person-years	Nurses' Health Study and Health Professionals Follow-up Study; population-based	1, 2, 10, 16, 24–27, 31, 51, 52
Simon et al. [37]	USA	159,219	Any statin	Current use	2005–2010	Mean 10.7, Max 15.6 years	Women's Health Initiative (WHI); population-based	2, 3, 10, 19, 24–29, 32, 36, 43, 53
Clancy et al. [38]	Italy	266,109	Any statin	≥1 prescriptions	2003–2010	841,680 person-years	Emilia-Romagna Region (RER) health care database; population-based	1, 2, 4, 9–11, 16, 21

CRC colorectal cancer; Statin type: *A* atorvastatin, *C* cerivastatin, *F* fluvastatin, *P* pravastatin, *R* rosuvastatin, S simvastatin, *L* lovastatin

* Adjusted for same variables as Table 1

Adjustment variables: 1, age; 2, sex; 3, race; 4, inflammatory bowel disease; 5, benign mammary dysplasia; 6, arthritis; 7, diabetes; 8, use of gastroprotective drugs; 9, estrogen use; 10, use of nonsteroidal anti-inflammatory drugs; 11, obesity; 12, tobacco abuse; 13, mammography; 14, gynecologic examination; 15, Papanicolaou smear; 16, colonoscopy; 17, stool occult blood; 18, comorbidity score; 19, number of physician visits; 20, distinct generic medicines taken; 21, prior hospitalizations; 22, prior nursing home stay; 23, precinct of residence; 24, body mass index; 25, smoking status; 26, family history of colorectal cancer; 27, alcohol use; 28, education; 29, physical activity level; 30, hormone replacement therapy; 31, red meat consumption; 32, history of heart attack; 33, hypercholesterolemia; 34, ethnic group; 35, sports participation; 36, level of vegetable consumption; 37, use of cardiovascular drugs; 38, use of glucocorticosteroids; 39, use of immunomodulators; 40, use of 5-aminosalicylic acids; 41, use of diuretics; 42, use of angiotensin-converting enzyme inhibitors; 43, use of calcium channel blockers; 44, other lipid-lowering therapy; 45, duration of follow-up; 46, history of neoplasia; 47, diabetic nephropathy; 48, colorectal evaluation; 49, cholecystectomy; 50, sulfonylurea prescription; 51, calendar year; 52, total energy intake; 53, hypertension; 54, Cox2-inhibitors; 55, metformin use

CRC colorectal cancer; Statin type: *A* atorvastatin, *C* cerivastatin, *F* fluvastatin, *P* pravastatin, *R* rosuvastatin, *S* simvastatin, *L* lovastatin

6.7.1.4 Evicence tables: Gastric cancer

Singh 2013(138)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: a systematic review and MA of observational studies (mainly case-control) Search date: Up to dec 2012	Observational studies N= 8 n= NR	Asian (11, 12) and Western (13, 14, 26-29)	Statin use vs control	Gastric cancer	**Adjusted OR: 0.65 (95% CI 0.45 to 0.93)** **SS in favour of statin use**
	RCTs (post-hoc MA and individual RCT)	Europe/Japan, primary and secondary prevention	Statin use vs control	Gastric cancer	Adjusted OR: 0.83 (95% CI 0.66 to 1.05) NS
*adjusted for see table 1 below.					

Table 1. Characteristics of included studies assessing the risk of gastric cancer (GC) with statin use

Study	Study design	Location/setting	Time Period	Exposure ascertainment	Outcome assessment	All subjects		On statins		Not on Statins		Confounding variables adjusted for[a]
						GC	Total	GC	Total	GC	Total	
Observational studies												
Chiu et al. [11]	C–C	Taiwan; Population-based	2005–2008	National Pharmacy Database	Medical diagnostic codes	337	1685	56	354	281	1331	1,2,6,7,10, 13
Huakka et al. [28]	Nested C–C	Finland; Population-based	1996–2005	National Pharmacy Database	Record linkage, with Finnish Cancer Registry	1667	944 962	770	472 481	897	472 481	1,2,14
Kaye et al. [13]	C–C	UK; Population-based	1990–2002	National Pharmacy Database	Medical diagnostic codes	39	18 088	4	3244	35	14 844	1,2,4,5,10, 14
Graaf et al. [27]	Nested C–C	Netherlands; Population-based	1985–2008	PHARMO Record Linkage	Hospital discharge records	104	20 105	NR	1444	NR	18 661	1,2,8,9,10, 12,14
Vinogradova et al.[14]	Nested C–C	UK; Population-based	1998–2008	National Pharmacy Database	Medical diagnostic codes	1992	10 271	322	1685	1670	8586	1,2,4,5,8,1112,13,14
Lee et al. [12]	C–C	South Korea; Hospital-based	1999–2008	Pharmacy dispensing records	Medical diagnostic codes	983	1966	99	466	884	1500	1,2,8
Friedman et al.[26]	Cohort	USA; Population-based	1994–2003	Pharmacy dispensing records	Kaiser Permanente Cancer Registry	137	4 222 660	NR	361 849	NR	3 860 811	8,13
Marelli et al. [29]	Nested C–C	USA; Population-based	1991–2009	Pharmacy dispensing records	Electronic Medical Record review	31	91 714	13	45 857	18	45 857	1,2,3,4,5
Randomized, controlled trials (RCTs)												
Cholesterol Treatment Trialists' (CTT) [25]	22 RCTs (*post-hoc*)	Europe/USA /Australia; Hospital-based	–	Individual drug dispension	Adverse event reporting by investigators	192	134 537	92	67 258	100	67 279	Variable
Matshushita et al. [30]	Three clinical trials (individual. patient data)	Japan; Hospital-based	–	Individual drug dispension	Adverse event reporting by investigators	95	13 724	43	7375	52	6349	Variable
Sato et al. [31]	RCT (*post-hoc*)	Japan; Hospital-based	1991–1995	Individual drug dispension	–	4	263	3	179	1	84	1,2,5

[a]1, age, 2, sex, 3, race, 4, BMI, 5, smoking/alcohol, 6, *H. pylori*, 7, peptic ulcers, 8, other medications (aspirin/NSAIDs), 9, other lipid lowering agents, 10, healthcare utilization, 11, socioeconomic status, 12, comorbidities, 13, calender year, 14=region.

C–C, case–control; CTT, cholesterol treatment trialists' Collaboration; RCT, randomized, controlled trials; NR, not reported.

Table 2. Newcastle–Ottawa scale for assessment of quality of included studies—case–control studies (each asterisk represents if individual criterion within the subsection were fulfilled)

Quality assessment criteria	Acceptable(*)	Chiu et al. [11]	Huakka et al. [28]	Kaye et al. [13]	Graaf et al. [27]	Vinogradova et al. [14]	Lee et al. [12]	Marelli et al. [29]
Selection								
Is the case definition adequate?	Yes, with independent validation	–	–	–	–	–	*	–
Representativeness of cases?	Consecutive or obviously representative series of cases	*	*	*	*	*	–	*
Selection of controls?	Community controls	*	*	*	*	*	–	*
Definition of controls?	No history of gastric cancer (GC)	*	*	*	*	*	*	*
Comparability								
Study controls for age/gender	Yes	*	*	*	*	*	*	*
Study controls for at least three additional factors	Race, smoking, body mass index (BMI), history of *Helicobacter pylori*, diet, other medication use (aspirin/NSAIDs), alcohol use, healthcare utilization	*	–	*	–	*	–	*
Exposure								
Ascertainment of exposure?	Secure record, structured interview by a healthcare practitioner, blind to case–control status	*	*	*	*	*	*	*
Same method of ascertainment of cases/controls?	Yes	*	*	*	*	*	*	*
Non-response rate?	Same for both the groups	*	*	*	*	*	–	–
Overall quality score (maximum = 9)		8	7	8	7	8	5	7

NSAIDs, Non-steroidal anti-inflammatory drugs.

Table 3. Newcastle–Ottawa scale for assessment of quality of included studies—cohort studies (each asterisk represents if individual criterion within the subsection were fulfilled)

Quality assessment criteria	Acceptable(*)	Friedman et al. [26]
Selection		
Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*
Ascertainment of exposure?	Secured records, structured interview	*
Demonstration that outcome of interest was not present at the start of the study?	Only incident cases of gastric cancer (GC)	*
Comparability		
Study controls for age/sex?	Yes	–
Study controls for at least 3 additional risk factors?	Race, smoking, body mass index (BMI), history of *Helicobacter pylori*, diet, other medication use (aspirin/NSAIDs),alcohol use, healthcare utilization	–
Outcome		
Assessment of outcome?	Independent blind assessment, record linkage	*
Was follow-up long enough for outcome to occur?	Follow-up >3 years	*
Adequacy of follow-up of cohorts?	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	–
Overall quality score (maximum = 9)		6

NSAIDs, non-steroidal anti-inflammatory drugs.

6.7.1.5 Evicence tables: Liver cancer

Singh 2013(139)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR & MA of observational studies and RCTs Search date: May 2012	N= 7 (observational) n= 1 791 199	Asian & Western (see also table 2 below)	Statin use vs control	Liver Cancer	**OR: 0.60 (95% CI 0.49 to 0.73)** **p=0.01** **SS in favour of statins**
	N= 3 (RCT) n= 148 524	Asian & Western (see also table 2 below)	Statin use vs control	Liver Cancer	RR: 0.95 (95% CI 0.62 to 1.45) p=0.86 NS
*adjusted for see table 1 below:					

Table 1. Characteristics and Quality of Included Studies Assessing the Risk of HCC With Statin Use

Study	Design	Location	Setting	Time period	Total no. of subjects	No. of HCC cases	Variables adjusted for[a]	Study quality[b]		
Observational studies								Selection	Comparability	Outcome/exposure
Chiu et al, 2011[11]	Case-control	Taiwan	Population based	2005–2008	2332	1166	1–7, 10	***	**	**
El-Serag et al, 2009[13]	Case-control	United States	Population based	2001–2002	6515	1303	1–6, 9	***	**	***
Tsan et al, 2012[12]	Cohort	Taiwan	Population based	1997–2008	33,413	1021	1, 2, 5, 7, 11	***	**	***
Friis et al, 2005[14]	Cohort	Denmark	Population based	1989–2002	334,754	171	1, 2, 9, 15	****	*	***
Marelli et al, 2011[23]	Cohort	United States	Population based	1991–2009	91,714	105	1, 2, 8, 12, 13, 14	****	**	***
Friedman et al, 2008[24]	Cohort	United States	Population based	1994–2003	361,859	42	15	****	—	**
Khurana et al, 2005 (abstract)[25]	Case-control	United States	Population based	1997–2002	480,306	409	1, 3	*	*	—
RCTs								Randomized	Double-blind	Withdrawals/dropouts
Matsushita et al, 2010[26]	RCT	Japan	Individual patient data analysis of trials	2010	13,724	12	NR	N/A	N/A	N/A
CTT, 2012[27]	RCT	Europe, Australia, North America	Individual patient data analysis of RCT	2012	134,537	68	NR	N/A	N/A	N/A
Sato et al, 2006[28]	RCT	Japan	Secondary analysis of RCT	1991–1995	263	1	1, 2, 13	1	1	—

N/A, not applicable.
[a]1, age; 2, sex; 3, HBV; 4, HCV; 5, cirrhosis; 6, alcoholic liver disease; 7, diabetes mellitus; 8, race; 9, other medications (aspirin/nonsteroidal anti-inflammatory medications, angiotensin-converting enzymes inhibitors); 10, other lipid-lowering agents; 11, socioeconomic status; 12, body mass index; 13, smoking; 14, comorbidities; 15, calendar year.
[b]Study quality assessment of observational studies was performed using the Newcastle–Ottawa scale; each asterisk represents if an individual criterion within the subsection was fulfilled. For RCTs, study quality was assessed using the Jadad scale.

Table 2. Comparison of Reported Baseline Risk Factors for HCC and Analysis of Potential Confounders in Included Studies

Study	Age (y)		Sex (% male)		Diabetes (% total)		Cirrhosis (% total)		HBV/HCV (% total)		Alcoholic liver disease or alcohol use (% total)		Angiotensin-converting enzyme inhibitor/nonsteroidal anti-inflammatory drug/aspirin (% total)		Nonstatin lipid-lowering drug (% total)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Chiu et al[11]	66.1	65.9	68.9	68.9	40.8[a]	34.1	39.4[a]	4.9	23.9[a]/25.1[a]	5.3/3.5	5.8[a]	2.5[a]	10.5/55.9[a]/6.9	11.3/61.7/6.9	2.2[a]	3.9
El-Serag et al[13]	72	72	99	99	100	100	28.2[a]	1.6	1.9[a]/14.7[a]	0.2/1.8	16.5[a]	1.2	64[a]/21.2/44.6[a]	67.4/20.6/47.9	4.1	3.9
Tsan et al[12]	34.7	46.3	57.1	58.3	61.9[a]	23.1	11.6	10.6	100/0	100/0	8.9	6.9	52.6[a]/NR/54.6[a]	13.8/NR/14.1	7.8	1.2
Friis et al[14]	60.7	46.6[a]	57	50	NR		NR		NR		NR		NR/NR/80[a]	NR/NR/48	NR	
Marelli et al[23]	64.2	64.2	52.2	52.6	16.1	15.8	NR		0.06	0.07	NR		—/28.4/19.4	—/28.2/19.6	NR	
Friedman et al[24b]	NR		NR		NR		NR		NR		NR		NR		NR	
Khurana et al (abstract)[25]	61.1		91.7		NR		NR		NR/2.9		NR		NR		NR	
Matsushita et al[26]	57.9	57.1	52.6	50.5	19.7	21.5	NR		NR		NR		NR		NR	
CTT[27]	63		71		NR		NR		NR		NR		NR		NR	
Sato et al[28]	NR		81.7		NR		NR		NR		NR		NR		NR	

NOTE. For case-control study design, case refers to patients with HCC and control refers to patients without HCC; for cohort study design, case refers to statin users and control refers to statin nonusers.
NR, not reported.
[a]$P < .05$, cases vs controls.
[b]Separate analyses of male and female subjects.

6.7.1.6 Evicence tables: Lung cancer

Deng 2013 (140)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR + MA of RCTs and observational studies Search date: From inception to September 2013	N= 15 (observational) n= 4 853 561	Europe, USA, Asia	Statin use vs control	Lung cancer	RR*: 0.89 (95% CI 0.77 to 1.04) NS
	N=8 (RCT) n=65 012	Europe, USA, Australia; primary and secondary prevention	Statin use vs control	Lung cancer	RR*: 0.95 (95% CI 0.85 to 1.06) p= 0.483 NS
	N= 6 (observational among elderly people) n=64 328	Europe, USA, Australia; primary and secondary prevention	Statin use vs control	Lung cancer	RR*: 1.03 (95% CI 0.96 to 1.11) p=0.759 NS
*unclear reporting for adjustment. Not all studies were adjusted for smoking					

Remarks:

- Reported RR's (see *) are "random", not "fixed". (p.684 in Deng 2013)
- We evaluated the methodological quality of all randomized controlled trials (RCTs) by using Jadad scoring system. Studies would be regarded as good methodological quality with scores not less than three points. Besides, we used a subgroup analysis to evaluate some influencing factors for the effect of statins on lung cancer risk.

Table 3 Assessment of methodological quality of RCTs by using Jadad scoring system

Study	Randomization	Allocation concealment	Blinding (observer)	Blinding (patient)	Adequate follow-up	Jadad score
WOSCOPS (44)	*		*	*	*	4
4S (45)	*		*	*	*	4
LIPS (46)	*	*	*	*	*	5
ALLHAT (47)	*	*			*	3
HPS (48)	*	*	*	*	*	5
LIPID (49)	*	*	*	*	*	5
PROSPER (50)	*	*	*	*	*	5
AFCAPS (51)	*	*	*	*	*	5
Each asterisk "*" means one point of the Jadad scoring system.						

6.7.1.7 Evicence tables: Esophageal cancer

Singh 2013 (141)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR & MA of RCTs and observational studies Search date: August 2012	N= 13 (7 case-control, 5 cohort and 1 post hoc analysis of 22 RCT's) n= 1 132 969	General population	Statin intake vs no statin intake	Esophageal cancer	**Adjusted OR: 0.72 (95% CI 0.60 to 0.86)** **SS in favour of statins**
	High quality observational studies: N=7 n=110 039	General population	Statin intake vs no statin intake	Esophageal cancer	**Adjusted OR: 0.70 (95% CI 0.56 to 0.88)** **SS in favour of statins**
	N= 5 n= 2 125	Patients known to have Barret's esophagus	Statin intake vs no statin intake	Esophageal cancer	**Adjusted OR: 0.59 (95% CI 0.45 to 0. 78)** **SS in favour of statins** **NNT= 389**
*adjusted for see table 1 below.					

Table 1. Characteristics of Included Studies Assessing the Risk of EC With Statin Use

Study	Design	Location	Setting	Time period	Exposure assessment	Total subjects	EC cases	Variables[a]	Study quality (NOS)[b]			
									Selection	Comparability	Outcome/ exposure	Overall quality score (maximum, 9)
Studies on patients with BE												
Nguyen et al[44]	C-C	United States	Population based	2000–2004	Pharmacy	812	116	1–3, 6, 10	***	**	***	8
Kastelein et al[16]	Cohort	The Netherlands	Hospital based	2003–2010	Patient interview	570	38[c]	1, 2, 6, 8, 9	****	**	***	9
Kantor et al[18]	Cohort	United States	Hospital based	1983–2009	Patient interview	411	56	1, 2, 5, 6	***	**	***	8
Beales et al[17]	C-C	United Kingdom	Hospital based	NR	Patient interview	255	85	1, 2, 4–6, 11, 12	****	**	***	9
Altawil et al[39]	Cohort	United States	Hospital based	2004–2010	EMR	77	17[d]	NR	***	**	***	8
Studies on all patients with EC												
Kaye and Jick[36]	C-C	United Kingdom	Population based	1990–2002	Pharmacy	18,088	100	NR	***	*	**	6
Vinogradova et al[19]	C-C	United Kingdom	Population based	1998–2008	Pharmacy	16,200	3159	1, 2, 4, 5, 6, 7, 10	***	**	***	8
Bhutta et al[34]	C-C	United Kingdom	Population based	2000–2008	Pharmacy	21,475	4242	1, 2, 4–7, 11	**	**	**	6
Marelli et al[38]	Cohort	United States	Population based	1990–2009	EMR	91,714	73	1–3, 5, 6	****	**	***	9
Friedman et al[35]	Cohort	United States	Population based	1994–2003	Pharmacy	361,859	68	NR	****	—	***	7
Khurana et al[37]	C-C	United States	Population based	1998–2004	NR	484,226	659	1, 5, 7, 12	*	*	**	4
Lai et al[41]	C-C	Asia	Population based	2000–2009	NR	2745	549	1, 2, 6, 12	***	*	*	5
CTT[40]	Post-hoc analysis of RCTs	Europe, Australia, North America	Hospital based	2012[e]	Variable	134,537	123	1, 2, 4, 5, 10	N/A	N/A	N/A	N/A

C-C, case-control; CTT, Cholesterol Treatment Trialists'; DM, diabetes mellitus; EMR, electronic medical record; N/A, Not applicable; NR, not reported; NOS, Newcastle−Ottawa Score.
[a]Studies were adjusted for the following variables: 1, age; 2, sex; 3, race; 4, body mass index; 5, smoking; 6, NSAIDs/aspirin; 7, DM; 8, BE length; 9, BE histology; 10, other comorbidities; 11, other medications; 12, alcohol use.
[b]Study quality assessment of observational studies performed using the Newcastle−Ottawa Scale (each asterisk represents whether individual criterion within the subsection were fulfilled).
[c]EAC or HGD (in patients with Barrett's).
[d]All dysplasia or EAC.
[e]Year of publication.

6.7.1.8 Evicence tables: Pancreatic cancer

Cui 2012(142)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR + MA of RCTs and observational studies Search date: Up to August 2011	N= 16 (3 RCT's, 5 cohort en 8 case-control) n= 1 692 863	General population or cardiovascular risk factors	Statin use vs control	Pancreatic cancer	RR: 0.89 (95% CI 0.74 to 1.07) NS
	N= 3 (RCT's) n=7118	Coronary heart disease (N=2) or postmenopausal women without CV disease	Statin use vs control	Pancreatic cancer	RR= 0.99 (95% CI 0.44 to 2.21) NS
	N=5 (Cohort) n= not reported	Variable population, maily database	Statin use vs control	Pancreatic cancer	RR: 1.05 (95% CI 0.93 to 1.19) NS
	N=8 n=not reported	Long-term follow-up	Statin use vs control	Pancreatic cancer	RR=0.94 (95% CI 0.81 to 1.08) NS
	N=5 n=not reported	Long-term statin use	Statin use vs control	Pancreatic cancer	RR= 0.97 (95% CI 0.76 to 1.23) NS
*adjusted for different confounders					

Quality assessment by authors:

"The quality of included RCTs was assessed based on Cochrane handbook, by recording seven items of bias risk: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (follow-up < 4 years). Each of the seven items is scored as ''low risk,'' ''unclear risk,'' or ''high risk.''

Meanwhile, the included cohort and case–control studies were assessed based on the Newcastle-Ottawa Scale for quality of non-randomized studies in meta-analyses. The Newcastle-Ottawa Scale contains eight items that are categorized three categories: selection (three items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). A ''star'' presents a ''high-quality'' choice of individual study."

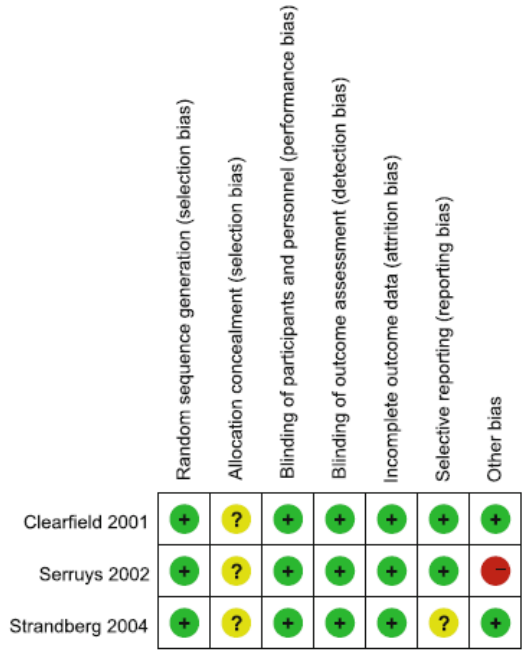


Fig. 2 Methodological quality of included randomized controlled trials: review authors' opinion on each item of bias risk based on Cochrane handbook. "Other bias" means follow-up <4 years

Table 2 Methodological quality of included cohort studies and case–control studies based on the Newcastle–Ottawa Scale

Cohort studies	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur[a]	Adequacy of follow-up of cohorts	
Sato et al. [37]	–	–	☆	–	☆	☆	☆	☆	5
Friedman et al. [16]	☆	☆	☆	☆	☆	☆	–	–	6
Haukka et al. [36]	☆	☆	☆	☆	☆	☆	–	☆	7
Jacobs et al. [34]	☆	☆	–	–	☆ ☆	☆	☆	☆	7
Marelli et al. [35]	☆	☆	☆	☆	☆ ☆	☆	☆	☆	9

Case–control studies	Selection				Comparability	Exposure			Total score
	Adequate definition of cases	Represen-tativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate[b]	
Graaf et al. [38]	–	☆	☆	☆	☆ ☆	☆	☆	–	7
Kaye and Jick [13]	☆	☆	☆	☆	☆ ☆	☆	☆	–	8
Dorais et al. [41]	☆	–	–	–	☆	☆	–	–	3
Khurana et al. [12]	–	☆	☆	–	☆ ☆	–	☆	–	5
Coogan et al. [39]	–	☆	–	☆	☆ ☆	–	☆	–	5
Bradley et al. [14]	☆	–	☆	☆	☆ ☆	☆	☆	–	7
Chiu et al. [15]	–	☆	–	☆	☆ ☆	☆	☆	–	6
Pugh et al. [40]	☆	–	–	–	☆ ☆	☆	–	–	4

[a] Follow-up >4 years

[b] Same rate for both groups

6.7.1.9 Evicence tables: Prostate cancer

Bansal 2012(143)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: MA of observational studies Search date: February 2012	N= 27 (15 cohort and 12 case-control studies) n =1 893 571	Male subjects	Statin use vs control	Prostate cancer	**RR: 0.93 (95% CI 0.87 to 0.99)** **p=0.03** **SS in favour of statin use**
	N=11 (7 cohort and 4 case-control studies) n=273 798	Male subjects Long-term statin use (study definition varied >2.85 y to >10y)	Statin use vs control	Prostate cancer	RR: 0.94 (95% CI 0.84 to 1.05) p=0.31 NS
	N=15 (cohort) n=1 812 005	Male subjects	Statin use vs control	Prostate cancer	RR: 0.93 (95% CI 0.87 to 1.01) p=0.09 NS
*adjusted for different variables, see Table 1 below.					

The pooled RR of the studies that were able to either control for PSA levels by comprehensive PSA screening of the entire population or adjusted for PSA testing was 0.91 (95% CI 0.81–1.02, p=0.13)
Note: only pubmed searched.

Table 1. Studies included in the meta-analysis.

Author, Year* (Country)†	Study period (years)	All male subjects	PCa cases	Description of exposure‖	Definition of statin use¶	Number of variables adjusted#
Lovastatin study groups, 1993 (U.S., Canada & Finland) [11]‡	NR	504	5	a	A	1
Blais *et al.*, 2000 (Canada) [15]§	6 (1988–1994)	858	78	b	NR	1, 27, 31, 33, 34
Graaf *et al.*, 2004 (Netherlands) [16]§	3 (1995–1998)	9,785	186	c	NR	1, 3, 5, 11–13, 27, 29–31
Kaye and Jick, 2004 (U.K.) [12]§	12 (1990–2002)	8,020	569	d	B	1, 4, 19, 32
Friis *et al.*, 2005 (Denmark) [9]‡	13 (1989–2002)	168,133	1407	e	C	1, 5, 28, 29
Shannon *et al.*, 2005 (U.S.) [17]§	7 (1997–2004)	302	100	e	C	1–5, 25, 27
Platz *et al.*, 2006 (U.S.) [10]‡	12 (1990–2002)	34,989	2,579	d	A	1, 3, 4, 8, 10, 19–26
Sato *et al.*, 2006 (Japan) [13]‡	14 (1991–2005)	215	2	f	A	1
Flick *et al.*, 2007 (U.S.) [8]‡	2 (2002–2004)	69,047	888	g	B	1–3
Murtola *et al.*, 2007 (Finland) [14]§	7 (1995–2002)	49,446	24,723	g	C	1, 11–17
Boudreau *et al.*, 2008 (U.S.) [25]‡	2 (1990–2005)	83,372	2,532	g	C	1, 3, 5, 7, 27
Friedman *et al.*, 2008 (U.S.) [34]‡	9 (1994–2003)	NR	1,706	e	B	35
Smeeth *et al.*, 2008 (U.K.) [35]‡	11 (1995–2006)	364,675	3,525	d	B	1, 3, 9, 11–14, 27, 28, 35–38
Agalliu *et al.*, 2008 (U.S.) [37]§	13 (2002–2005)	1,943	1,001	d	A	1, 2, 4, 8, 19
Breau *et al.*, 2010 (U.S.) [26]‡	17 (1990–2007)	2,447	224	d	A	1, 3, 5, 9, 39–41
Haukka *et al.*, 2010 (Finland) [30]‡	9 (1996–2005)	10,928	1051	d	C	1, 42
Hippisley *et al.*, 2010 (England & Wales) [36]‡	6 (2002–2008)	990,495	7,129	d	B	NR
Murtola *et al.*, 2010 (Finland) [5]‡	8 (1996–2004)	23,208	1,594	d	C	1, 8, 10, 12–17, 24, 35
Coogan *et al.*, 2010 (U.S.) [31]§	6 (1992–2008)	3,374	1,367	e	A	2, 4–6, 18, 19, 32, 43, 44
Loeb *et al.*, 2010 (U.S.) [27]§	6 (2003–2009)	1,351	1,351	e	B	45
Farwell *et al.*, 2011 (England) [6]‡	10 (1997–2007)	55,875	546	h	B	1, 3, 7–9, 18, 19, 39, 46–52
Tan *et al.*, 2011 (Ohio) [28]‡	10 (2000–2010)	4,204	1,797	g	B	1, 2, 4, 53, 54
Jacobs *et al.*, 2011 (U.S.) [38]‡	10 (1997–2007)	3,913	NR	i	A	1–10, 18
Chang *et al.*, 2011 (Taiwan) [32]§	3 (2005–2008)	1,940	388	g	C	3, 5, 9, 27, 32, 39, 55, 56
Fowke *et al.*, 2011 (U.S.) [33]§	8 (2002–2010)	2,148	1029	g	A	1–4, 9, 8–10, 24, 45, 54, 55
Mondul *et al.*, 2011 (Maryland) [29]§	13 (1993–2006)	2,399	683	d	A	1, 2, 4, 10, 13, 19, 24
Marcella *et al.*, 2011 (New Jersey) [7]§	3 (1997–2000)	767	387	g	B	1, 2, 4, 6, 13, 57, 58

PCa, Prostate cancer; NR, Not reported.
*Publication year;
†Country of study conducted;
‡Cohort studies;
§Case-control studies.
‖a, systematic use of lovastatin *vs.* SEER data; b, any use of statin *vs.* use of bile acid-binding resins; c, use of statins *vs.* no use of statins; d, current use of statins *vs.* no current use of statins; e, any use of statins *vs.* no use of statins; f, systematic use of statins *vs.* general population; g, ever use of statins *vs.* no use of statins; h, use of statins *vs.* use of anti-hypertensives; i, current use of cholesterol-lowering drugs *vs.* never use of cholesterol-lowering drugs.
¶A, self-reported; B, medical records; C, prescription database.
#1, age; 2, race; 3, diabetes mellitus; 4, BMI; 5, NSAID use; 6, education; 7, elevated cholesterol; 8, history of PSA testing; 9, cardiovascular disease; 10, family history of prostate cancer; 11, use of diuretics; 12, use of calcium channel blockers; 13, use of angiotensin-converting enzyme inhibitors; 14, use of angiotensin receptor blockers; 15, use of metformin; 16, use of sulfonylureas; 17, use of insulin; 18, alcohol use; 19, smoking; 20, height; 21, major ancestry; 22, vasectomy; 23, vigorous physical activity; 24, aspirin use; 25, total energy intake; 26, intakes of calcium, fructose, a-linolenic acid, tomato sauce, red meat, fish, supplemental zinc, and high intake of vitamin E; 27, use of other lipid-lowering drugs; 28, use of cardiovascular drugs; 29, use of hormones; 30, prior hospitalisation; 31, chronic disease score; 32, frequency of physician visits; 33, previous neoplasm; 34, use of fibric acids; 35, calendar period of PSA screening; 36, propensity score; 37, cancer; 38, dementia; 39, hypertension; 40, use of 5-α reductase inhibitors; 41, use of α-blockers; 42, follow-up period; 43, study center; 44, interview year; 45, clinical stage and biopsy gleason score; 46, weight; 47, thyroid disease; 48, renal failure; 49, chest pain; 50, mental illness; 51, lung disease; 52, gastro-intestinal disease; 53,number of cores taken; 54, prostate volume; 55, benign prostatic hyperplasia; 56, matching variables.
doi:10.1371/journal.pone.0046691.t001

Chan 2012 1781 (144)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
Design: prospective cohort followed between 2000 and 2008	n= 5069	-Community dwelling, ambulatory men who were age 65 or older and living in 6 geographic regions of the United States in 2000 to 2002 -Excluded: self-reported history of PCa or any patient with missing statin data	Statin use (any use in the previous two weeks) vs control	Prostate cancer	Age and site adjusted OR = 1.24 (95% CI 0.98 to 1.57) p=0.07 NS
	n=4120		Statin use (any use in the previous two weeks) vs control	Prostate cancer	Multivariate*OR=1.07 (95% CI 0.82 to 1.40) p=0.63 NS
*adjusted for age, study site, race, body mass index, marital status, family history of prostate cancer, marital status, comorbid conditions, physical activity, and smoking history					

6.7.1.10 Evicence tables: Renal cancer

Zhang 2013 1625 (145)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: MA of observational studies and randomized trials Search date: Oct 2012	N= 12 (2 RCT's, 5 cohort and 5 case-control)	European, USA, Asian	Statin use vs control	Renal/Kidney cancer	RR = 0.92 (95% CI 0.71 to 1.19) p<0.001 NS
	N=2 (RCT's)	UK, USA	Statin use vs control	Renal/Kidney cancer	RR=1.01 (95% CI 0.57 to 1.79) p=0.509 NS
	N=5 (cohort)	USA, UK, Japan	Statin use vs control	Renal/Kidney cancer	RR= 1.07 (95% CI 0.96 to 1.20) p=0.217 NS
	N= 6		Long-term statin use	Renal/Kidney cancer	RR = 1.01 (95% CI 0.83 to 1.22) p=0.753 NS
*adjusted for different confounders, see table 1.					

Table 1. Study characteristics

Author	Year	Country	Study design	Study period	Treated n/N or cases n/N	Contros n/N	Description of Exposure	Statin type	Confounders for adjustment
Chiu HF	2012	Taiwan	case-control	2005-2009	38/177	143/708	a	A, F, L, P, R, S	7, 10, 12, 17, 22
Wei Liu	2012	USA	cohort	1990-2008	66/22,208	211/78,722	a	NR	4, 7, 8, 9, 10, 18, 22
Jacobs EJ	2011	USA	cohort	1997-2007	140/331,955 person-years	241/710,184 person-years	d	L, P, S, F	1, 2, 4, 6, 7, 8, 10, 18, 19, 20, 21, 22
Hippisley-Cox J	2010	England & Wales	cohort	2002–2008	NR/225,922	NR/1,778,770	b	A, F, P, R, S	1, 2, 3, 4, 7, 8, 16, 22
Khurana V	2008	USA	case-control	1998-2004	432/1,446	164,009/482,287	b	NR	1, 2, 4, 8, 11
Friedman GD	2008	USA	cohort	1994-2003	135/361,859	NR/NR	a	A, C, F, L, P, R, S	8, 23
Coogan PF	2007	USA	case-control	1991-2005	16/226	190/3,900	c	NR	1, 4, 5, 6, 9, 11, 16
Sato S	2006	Japan	cohort	1991-1995	0/179	1/84	e	P	1, 2
HPS	2005	UK	RCT	1994-1997	23/10,269	22/10,267	c	S	Randomization
Kaye JA	2004	UK	case-control	1990–2002	3/39	15/14,844	b	NR	1, 4, 8
Graaf MR	2004	Netherlands	case-control	1995–1998	NR/101	986/16,976	c	A, C, F, P, S	1, 3, 7, 10, 12, 13, 14, 15, 16, 17
Clearfield M	2001	USA	RCT	NR	0/499	1/498	b	L	Randomization

NR= Not Reported;

HPS = Heart Protection Study Collaborative Group;

Treated n/N = No. of cases in the treated group, for cohort studies; cases n/N = No. of exposed in the cases, for case–control studies;

Description of exposure: a = any use of statins versus no use of statins; b = current use of statins versus no current use of statins; c = regular use of statins versus no use of statins; d = current use of cholesterol-lowering drugs versus never use of cholesterol-lowering drugs; e = systematic use of statins versus general population;

Statin type: A= Atorvastatin, C = Cerivastatin, F= Fluvastatin, L = Lovastatin, P= Pravastatin, R= Rosuvastatin, S= Simvastatin;

Confounders for adjustment: 1 = age; 2 = sex; 3 = comorbidity score; 4 = body mass index; 5 = religion; 6 = education; 7 = NSAID use; 8 = smoking; 9 = alcohol use; 10 = diabetes mellitus; 11 = race; 12 = use of other lipid-lowering drugs; 13 = use of calcium channel blockers; 14 = use of angiotensin-converting enzyme inhibitors; 15 = use of diuretics; 16 = use of hormones; 17 = hospitalizations; 18 = physical activity; 19 = frequency of physician visits; 20 = cholesterol; 21 = heart disease; 22 = hypertension; 23 = state of residence

6.7.1.11 Evicence tables: Skin cancer

Li 2013 1544 (146)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR + MA of RCTs and meta-analyses Search date: June 2013	N= 24 (17 studies were post-hoc analyses or RCTs, 5 were case–control studies, and 2 were cohort studies) n= 414 627	Europe, USA, Asia, New Zealand	Statin use	Melanoma skin cancer	RR=0.94 (95% CI 0.85 to 1.04) p=0.07 NS
	N=8		Long-term statin use	Melanoma skin cancer	RR= 0.93 (95% CI 0.73 to 1.18) NS
	N=14 (12 studies were post-hoc analyses or RCTs, 1 was case–control study and 1 was cohort study) n= 103 260		Statin use	Non-melanoma skin cancer	RR=1.03 (95% CI 0.90-1.19) (= Random effect model) NS
*adjusted *("even though the included studies had acceptable quality, detailed information of confounding factors was not provided (such as family history, skin color and sun exposure). To minimize the risk of misleading conclusions led by the lack of confounder control, we extracted adjusted RRs for different confounding factors whenever available.)*					

Quality assessment. The criteria adapted from the Cochrane handbook for systematic reviews of interventions (Higgins et al, 2011) and the validated Newcastle–Ottawa scale (NOS) (Wells et al, 2000) were used to assess the methodological quality of RCTs, case–control and cohort studies, respectively.

Sahi 2012(147)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: cohort patients with listed purchases of statins during 1994–2007 FU until dec 2009 Mean length of follow-up 9.2 .	n= 454 937	Finland population	Statin use vs no statin use	Merkel cell carcinoma	SIR 1.25 (95% CI 0.93 to 1.65) NS
		Finland population Ages <60 years	Statin use vs no statin use	Merkel cell carcinoma	SIR= 3.16 (95% CI 0.65 to 9.23) NS
		Finland population Ages 60–74 years	Statin use vs no statin use	Merkel cell carcinoma	**SIR=1.94 (95% CI 1.23 to 2.90)** **SS**
		Finland population Ages ≥ 75 years	Statin use vs no statin use	Merkel cell carcinoma	SIR= 0.89 (95% CI 0.57 to 1.31) NS
		Finland population	Statin use vs no statin use	Merkel cell carcinoma at each 5 year step when moving towards older age groups	**RR=0.79 (95% CI 0.67 to 0.92)** **SS** *["The relative risk of MCC decreased significantly, 0.79 fold (95% CI 0.67–0.92), at each 5 year step when moving towards older age groups."]*
*no reported adjustment for possible confounders					

"There was no significant variation in SIR related to length of follow-up or gender."

standardized incidence ratio (SIR): the observed number of cases was divided by the expected number.

6.7.1.12 Evicence tables: Hematological cancer

Bonovas 2007(148)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design:SR + MA of RCTs and observational studies Search date: (dec 2006)	N= 14 (six RCTs, seven case–control and one cohort study)		Statin use vs no statin use		
	RCTs N=6 n=46 852	mean age 61 y, mean FU 6.1y		Haematological malignancies	RR = 0.92 (95% CI 0.72, 1.16) NS
	Observational N= 8 (7 case-control, 1 cohort) n= 365 201	Europe, Canada, USA, Japan		Haematological malignancies	RR = 0.83, (95% CI 0.53, 1.29) NS high heterogeneity between the studies, but not explored
*adjusted for : see below					

Randomized, double-blind, placebo-controlled trials included in the meta-analysis

Study	Agent	No. of subjects	Duration (years)	Incident haematological malignancies			Reported outcome
				Statin group	Placebo group	RR (95% CI)	
4S [24]*	Simvastatin	4444	Median: 10.4	17 of 2221	19 of 2223	0.90 (0.47, 1.72)	Incident haematological malignancies
ALERT [25]	Fluvastatin	2094	Mean: 5.1	11 of 1045	18 of 1049	0.61 (0.29, 1.29)	Incident haematological malignancies
HPS [26]	Simvastatin	20536	Mean: 5.0	64 of 10 269	52 of 10 267	1.23 (0.85, 1.77)	Incident haematological malignancies
LIPID [27]	Pravastatin	9014	Mean: 8.0	37 of 4512	52 of 4502	0.71 (0.47, 1.08)	Incident lymphomas and leukaemias
AFCAPS [28]	Lovastatin	6605	Mean: 5.2	12 of 3304	11 of 3301	1.09 (0.48, 2.47)	Incident lymphomas
CARE [29]	Pravastatin	4159	Mean: 4.8	8 of 2081	10 of 2078	0.80 (0.32, 2.02)	Incident lymphomas and leukaemias

*RR, Relative risk (risk ratio); CI, confidence interval. *Numbers in parentheses, reference citation.*

Observational studies:

Study	Study location	Study design	All subjects	HM cases	RR (95% CI)	Control for potential confounders*	Type of HM studied
Fortuny *et al.* 2006 [30]†	Czech Rep., France, Germany, Ireland, Italy and Spain	C-C	4568	2362	0.61 (0.45, 0.84)	1–3	Incident lymphoma
Iwata *et al.* 2006 [31]	Japan	C-C	1100	221	2.24 (1.37, 3.66)	1, 2, 4–6	Incident lymphoma and myeloma
Landgren *et al.* 2006 [32]	USA	C-C	870	179	0.4 (0.2, 0.8)	1, 7–9	Incident myeloma
Friis *et al.* 2005 [33]	Denmark	Cohort	334 754	1626	0.88 (0.60, 1.29)	1, 2, 10–13	Incident haematological malignancies
Graaf *et al.* 2004 [34]	The Netherlands	C-C	20105	93	0.28 (0.06, 1.30)	1, 2, 12–22	Incident lymphoma
Zhang *et al.* 2004 [35]	USA	C-C	1318	601	0.5 (0.4, 0.8)	1, 9, 23, 24	Incident non-Hodgkin lymphoma
Blais *et al.* 2000 [36]	Canada	C-C	264	24	2.17 (0.38, 12.36)	1, 2, 4, 18, 25, 26	Incident lymphoma
Traversa *et al.* 1998 [37]	Italy	C-C	2222	202	1.5 (0.8, 2.6)	1, 2	Incident leukaemia

*HM, Haematological malignancy; RR, relative risk; CI, confidence interval. *1, age; 2, gender; 3, country; 4, year of visit; 5, serological status for antihepatitis B surface antigens; 6, serological status for antihepatitis C virus antibodies; 7, race; 8, education; 9, body mass index; 10, calendar period; 11, use of cardiovascular drugs; 12, use of nonsteroidal anti-inflammatory drugs; 13, use of hormone replacement therapy; 14, geographical region; 15, duration of follow-up; 16, diabetes mellitus; 17, prior hospitalizations; 18, chronic disease score; 19, chronic use of diuretics; 20, chronic use of angiotensin-converting enzyme inhibitors; 21, chronic use of calcium channel blockers; 22, use of other lipid-lowering therapy; 23, menopausal status; 24, family history of non-Hodgkin lymphoma in first-degree relatives; 25, previous neoplasm; 26, use of fibric acids. †Numbers in parentheses, reference citation.*

Jacobs 2011(149)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: prospective cohort 1997-2007	n= 133 255	Population based (Cancer Prevention Study II Nutrition)	Current use of cholesterol-lowering drugs for five or more years	Non-Hodgkin Lymphoma	**RR: 0.74 (95%CI 0.62 to 0.89)** **SS in favour of statin use**
*adjusted for : Adjusted for age, sex, race, education, smoking, BMI, physical activity level, nonsteroidal anti-inflammatory drug use, hormone therapy, history of elevated cholesterol, heart disease, diabetes, and hypertension.					

6.7.2 Summary and conclusions: site-specific cancers

6.7.2.1 Bladder cancer

A systematic review and meta-analysis (Zhang 2013(135)) searched all RCTs and observational studies that reported on the incidence of bladder cancer.

A pooled analysis of 3 RCTs found no statistically significant difference between statin use and placebo for bladder cancer (RR: 0.83; 95% CI 0.63 to 1.10).

A pooled analysis of 5 cohort studies also found no statistically significant difference (RR: 1.11; 95% CI 0.91 to 1.35).
Pooling RCTs, cohort studies and case-control studies also resulted in no statistically significant difference in bladder cancer between statin use an no statin use.

The authors did an extensive quality assessment of the included studies.

GRADE: MODERATE quality of evidence

6.7.2.2 Breast cancer

A systematic review and meta-analysis of observational studies (cohort and case-control) examined the association between statin use and breast cancer (Undela 2012(136).
The pooled result of 24 studies showed no statistically significant association between statin use and breast cancer.
The pooled result of 10 studies of long term statin use showed no statistically significant difference in the incidence of breast cancer between statin use and no statin use RR: 1.03; 95% CI 0.96 to 1.11).

G*RADE: LOW quality of evidence*

6.7.2.3 Colon cancer

Liu 2013(137) did a systematic review and meta-analysis on RCTs and observational studies that reported colorectal cancer.
The pooled results of 11 RCTs finds no statistically significant difference in the incidence of colon cancer between statin use and placebo (RR: 0.96; 95% CI 0.85 to 1.08).
The pooled result of 13 cohort studies finds that statin use is associated with a lower incidence of colon cancer (RR: 0.93; 95% CI 0.87 to 0.99).
Pooling the results of RCTs, cohort studies and case-control studies also shows an association between statin use and a lower incidence of colon cancer.

When long-term statin use (≥ 5y) is compared to no statin use, there is no statistically significant difference in the incidence of colon cancer. This result is consistent between the pooled analysis of RCTs, the pooled analysis of cohort studies and the pooled analysis of RCTs and observational studies.

We conclude that statins do not increase the risk of colon cancer.
GRADE: *LOW quality of evidence*

6.7.2.4 Gastric cancer

Singh 2013(138) conducted a systematic review and meta-analysis of RCTs and observational studies concerning statin use and the risk of gastric cancer.
In a pooled analysis of observational studies (mainly case-control studies), statins are associated with a lower incidence of gastric cancer (OR: 0.65; 95% CI 0.45 to 0.93).
When considering evidence from RCTs (3 post hoc analyses: both meta-analyses and individual RCTs), no statistically significant difference in gastric cancer incidence is found between statin use and no statin use (OR: 0.83; 95% CI 0.66 to 1.05).

Statins do not seem to increase the risk of gastric cancer.
GRADE: LOW quality of evidence
The evidence for a lower risk of gastric cancer with statin use is weak.

Note: a more recent systematic review and meta-analysis (Wu 2013(150)) that did not report any quality assessment, updated these results by replacing 1 Taiwanese case-control study by a more recent version. They find the same results as Singh 2013.

6.7.2.5 Liver cancer

A systematic review and meta-analysis of observational studies and RCTs by Singh 2013(139)compared statins to no statin use for the outcome liver cancer.
A pooled analysis of 7 observational studies (both cohort and case-control) finds an association between statin use and al lower incidence of liver cancer compared to no use (OR: 0.60; 95% CI 0.49 to 0.73).
Information from RCTs (2 individual patient data meta-analyses and 1 RCT) finds no statistically significant difference in the incidence of liver cancer between statin use and placebo (RR: 0.95; 95% CI 0.62 to 1.45).

Statin use is not associated with an increased risk of liver cancer. The evidence of a decreased risk with statin use is weak
GRADE: LOW quality of evidence

6.7.2.6 Lung cancer

A systematic review and meta-analysis by Deng 2013(140) searched all observational studies (cohort and case-control) and RCTs that reported the outcome lung cancer.
No statistically significant difference in lung cancer incidence is found between statin use and no statin use. This result is found in a pooled analysis of 8 RCTs (RR: 0.95; 95% CI 0.85 to 1.06)and in a pooled analysis of 15 observational studies (RR: 0.89; 95% CI 0.77 to 1.04).

A pooled analysis of 6 observational studies among elderly people also found no statistically significant difference in lung cancer incidence between statin us and no statin use.

Statin use does not seem to influence the risk of lung cancer
GRADE: LOW quality of evidence

6.7.2.7 Esophageal cancer

A systematic review and meta-analysis by Singh 2013(141) looked at all RCTs and observational studies that reported esophageal cancer. 13 trials were included, representing 1 132 969 patients.

In a meta-analysis of all included trials (N=13, of which 1 was a post-hoc analysis of 22 RCTs), statin use was associated with a lower risk of esophageal cancer (Adjusted OR: 0.72 (95% CI 0.60 to 0.86).

This association was also found when performing a meta-analysis of 7 high-quality observational studies and in a meta-analysis of 5 studies in patients with Barret's esophagus.

Note: in the post-hoc analysis of 22 RCTs that was included, the risk of esophageal cancer was not significantly different between statin use and control.

GRADE: LOW quality of evidence

6.7.2.8 Pancreatic cancer

A systematic review and meta-analysis (Cui 2012(142)) searched for all RCTS and observational studies that report the outcome pancreatic cancer. 16 studies were included (3 RCTs, 5 cohortstudies and 8 case-controlstudies), representing 1 692 863 patients.
A meta-analysis of all studies combined, found no association between statin use and pancreatic cancer. In a meta-analysis of the 5 cohortstudies, also no association was found.
A meta-analysis of the 3 RCTs also found no statistically significant difference in pancreatic cancer risk between statin use and control.
GRADE: LOW quality of evidence

6.7.2.9 Prostate cancer

A systematic review and meta-analysis (Bansal 2012(143)) searched for all observational studies that examine the association between statin use and prostate cancer. 15 cohort and 12 case-control studies were found, representing 1 893 571 patients.

A meta-analysis of 27 studies found a statistically significant inverse association between statin use and prostate cancer. The result verged on borderline statistical significance (RR: 0.93; 95% CI 0.87 to 0.99).
When only studies with long-term statin use were pooled (N=11), no association between statin use and prostate cancer was found (RR: 0.94; 95% CI 0.84 to 1.05).
When only cohort studies were pooled, no statistically significant association between statin use and prostate cancer was found (RR: 0.93; 95% CI 0.87 to 1.01).

When considering only trials that control for PSA levels, there is also no statistically significant association found.

One additional prospective cohort study of 5069 patients (Chan 2012(144)) was published after the search date of the meta-analysis by Bansal 2012.

In this study, statin use was not associated with prostate cancer (OR=1.07; 95% CI 0.82 to 1.40).

We conclude that there is no association between statin use and prostate cancer.
GRADE: LOW quality of evidence

6.7.2.10 Renal cancer

A systematic review and meta-analysis by Zhang 2013(145) searched for all RCTs and observational studies that report on statin use and renal cancer.
In a pooled analysis of all studies (2 RCT's, 5 cohort and 5 case-control), no association is found between statin use and renal cancer.
No association was found among RCTs (RR= 1.01; 95% CI 0.57, 1.79) and among cohort studies (RR= 1.07, 95%CI 0.96 to 1.20).

GRADE: LOW quality of evidence

6.7.2.11 Skin cancer

A systematic review and meta-analysis by Li 2013(146) searched for all RCTs and observational studies that report on statin use and skin cancer.
In a pooled analysis of 24 studies (17 RCTs or post-hoc analyses, 5 case-control, 2 cohort), no statistically significant association is found between statin use and melanoma skin cancer (RR=0.94; 95% CI 0.85 to 1.04).
When pooling 8 studies on long term statin use, there is also no statistically significant association observed (RR= 0.93; 95% CI 0.73 to 1.18).
In a pooled analysis of 14 studies (12 RCTs or post-hoc analyses,1 case-control and 1 cohort), no association between statin use and non-melanoma skin cancer was found (RR=1.03; 95% CI 0.90-1.19).
GRADE: LOW quality of evidence

A Finnish cohort study (Sahi 2012(147)) that was published after the search date of Li 2013 followed 454 937 statin users for a mean of 9.2 years and compared them to the general population for the incidence of Merkel cell carcinoma (MCC).

No statistically significant association was found between statin use and MCC, when compared to the incidence rate in the general population (SIR 1.25; 95% CI 0.93 to 1.65) . A statistically significant

association between statin use and increased incidence of MCC was found in the age group 60-74y (SIR 1.94; 95% CI 1.23 to 2.90).
The authors report that "The relative risk of MCC decreased significantly, 0.79 fold (95% CI 0.67–0.92), at each 5 year step when moving towards older age groups." The authors conclude that the risk of MCC among statin users was elevated up to the age of 70 and decreased significantly together with increasing age.

Because of methodological problems (e.g. lack of correcting for possible confounders, low event rates), these results are to be interpreted with caution.

GRADE: VERY LOW quality of evidence

6.7.2.12 Hematological cancer

A systematic review and meta-analysis by Bonovas 2007(148) searched for all RCTs and observational studies that report on statin use and hematological cancer.
When pooling the results of 6 RCTs of 46 852 patients with an average of 6.1 years of follow-up, no statistically significant difference in haematological malignancies is found between statin use and no statin use (RR = 0.92 95% CI0.72, 1.16).
When pooling the results of 8 observational studies (7 case-control, 1 cohort), no association is found between statin use and haematological malignancies.
GRADE: VERY LOW quality of evidence

The following study appeared after the search date of Bonovas 2007.
A US population based cohort study by Jacobs 2011 (149) in 133 255 participants compared the use of cholesterol-lowering drugs to no use for the outcome Non-Hodgkin lymphoma. An inverse association was found between current use of cholesterol-lowering drugs for five or more years and the risk of non-Hodgkin Lymphoma (RR: 0.74; 95%CI 0.62 to 0.89).
GRADE: LOW quality of evidence

6.7.3 Total cancer

Information from RCTs

Different meta-analyses of RCTs have reported on the risk of cancer.

-In the meta-analysis by Taylor 2013(32), no statistically significant difference between statins and placebo is observed in the incidence of cancer.
-Savarese 2013(67) found that, In elderly patients without established cardiovascular disease, there is no statistically significant difference in new onset cancer between statin treatment and placebo.

The CTT collaboration published a meta-analysis of individual patient data from 22 placebo-controlled RCTs (and 5 RCTs of high dose statin versus lower dose, not reported here) to evaluate the risk of cancer(151).
The rate ratio of cancer with statins compared to placebo is 1.00 (95% CI 0.96-1.05).
The rate ratio of cancer mortality is 1.00 (95% CI 0.93–1.08) with statin use compared to placebo.

Information from observational studies.

2 recent, large, well conducted cohort studies also found no statistically significant association between statin use and cancer:

- A US population based cohort study by Jacobs 2011 (149) in 133 255 participants compared the use of cholesterol-lowering drugs to no use. No association was found between current use ≥5y of cholesterol-lowering drugs and overall cancer incidence (RR 0.97; 95% CI 0.92–1.03).

-Marelli 2011(152) conducted a retrospective cohort analysis of 45,857 matched pairs on the incidence of cancer in older adults who have and who have not used statins. No association was found between statin use and cancer incidence (HR 1.04; 95% CI 0.99 - 1.09).

Conclusion

Statins do not influence the risk of cancer.
GRADE: LOW to MODERATE quality of evidence

7 Evidence tables and conclusions: safety of other lipid lowering drugs

7.1 Fibrates and risk of myopathy

7.1.1 Evidence tables

Enger 2010(153)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
Design: retrospective cohort study Study period of January 1, 2004, to June 30, 2007	n= 584,784	-cohort of new users of statins (86.9%) fibrates (12.5%) or both (0.6%), using claims data from a large United States health insurer -The fibrate initiators and combination initiators were somewhat younger, were more likely to be male, and had a higher proportion with histories of diabetes than the statin initiators. .	Statins only n=484345	Rhabdomyolysis	IR: 3.30 per 100,000 Patient-Years 95%CI: 1.93 to 5.30
				Myopathy	IR: 1.76 per 100,000 Patient-Years 95%CI: 0.83 to 3.32
			Fenofibrate only n=32769	Rhabdomyolysis	IR: 2.78 per 100,000 Patient-Years 95%CI: 0.25 to 12.97 (vs statins only: Adjusted IRR*: 0.85 95%CI: 0.11 to 6.49)
				Myopathy	IR: 0.00 per 100,000 Patient-Years 95%CI: 0.00 to 6.86
			Statins and fenofibrate n=36319	Rhabdomyolysis	IR: 15.00 per 100,000 Patient-Years 95%CI: 5.02 to 35.67 **(vs statins only: Adjusted IRR*: 3.75 95%CI: 1.23 to 11.40**)
				Myopathy	IR: 3.75 per 100,000 Patient-Years 95%CI: 0.34 to 17.48 (vs statins only: Crude IRR: 2.13 95%CI: 0.27 to 17.05)
* Adjusted for age, gender, hypertension, and number of co-morbidities					

Remarks:

-This study focused only on outcomes associated with inpatient hospital care.

-Authors did not match treatment groups, so there may be unmeasured confounders that are associated with the reason for being prescribed a combination of treatments and the risk for the adverse event.

7.1.2 Summary and conclusions. Fibrates and risk of myopathy

A retrospective cohort study by Enger 2010(153) studied 584 784 patients on statins, fibrate or combination therapy of a statin + a fibrate. Follow-up was 3 years.
Compared to statin use only, the combination of fenofibrate and a statin was associated with a higher risk of rhabdomyolysis (IRR (incidence rate ratio) 3.75; 95%CI: 1.23 to 11.40). No adjustment was made for important risk factors for rhabdomyolysis.
For myopathy, no statistically significant difference was found between statin + fenofibrate compared to a statin only.

GRADE: VERY LOW quality of evidence

7.2 Fibrates and cancer risk

7.2.1 Evidence tables

Bonovas 2012(154)					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
SR and MA of RCTs Search date: (jan-2012)	N= 17 n= 44 929 Average follow-up was 5.2 years. (min. 2y)	-mean age 55 y - Coronary Artery Disease: (n=8) -Diabetes Type 2 (n=4) - Lower Extremity Arterial Disease (n=1) - Peripheral arteriopathy (n=1) - Non-Insulin-Dependent Diabetes Mellitus (n=1) -Dyslipidemia (n=1) - High-cholesterol Population (n=1)	Fibrates Vs placebo	Cancer incidence (n=10)	RR: 1.02 (95%CI 0.92-1.12)
				Cancer mortality (n=16)	RR: 1.06 (95%CI 0.92-1.22)

Some limitations (as remarked by the authors):

- The trials included in this meta-analysis were not designed to specifically analyze the relationship between fibrates and cancer risk. They have assessed cancer outcomes as secondary (safety) endpoints. Thus, problems in cancer detection and reporting may exist.

-The search was restricted to published studies and authors did not seek for unpublished/original data.

- a main issue remaining beyond control is cancer latency. As the exposure and followup times only lasted for nearly five years, estimates of cancer risk resulting from longer exposure to fibrates are not possible.

Thus, the results should be interpreted with caution.

7.2.2 Summary and conclusions: Fibrates and cancer risk

A systematic review and meta-analysis by Bonovas 2012(154) pooled 17 RCTs of 44 929 participants that compare fibrates to placebo. Average follow-up was 5 years.
No statistically significant difference in cancer incidence or cancer mortality is found. (RR: 1.02; 95%CI 0.92-1.12) and 1.06; 95%CI 0.92-1.22 respectively).

GRADE: LOW quality of evidence

7.3 Statin + ezetimibe versus statin, adverse events

7.3.1 Evidence tables

Ezetimibe +atorvastatin coadministration versus placebo + atorvastatin (4:1) in patients with primary hypercholesterolaemia

Study details	n/Population	Comparison	Outcomes		Methodological
Ballantyne_2004_1424 (155) Design: RCT DB multinational, extension study Duration of follow-up: 12 month	n= 246 Of the 576 patients who completed the 12-week base study,246 patients were randomised into the 12-month extension study. <u>Inclusion</u> Men and women ≥18 years of age were screened for primary hypercholesterolemia, defined as calculated LDL-C7 of 145 to 250 mg/dL, inclusive, and triglyceride levels ≤350 mg/dL. <u>Included population</u> -Mean age: 58 -CHD: 12% -Peripheral vascular disease: 2.5% -Hypertension: 42% (ATV); 34% (EZE+ATV) -Diabetes: 2% (ATV); 7% (EZE+ATV)	EZE 10 mg + ATV (10, 20, 40 or 80 mg, uptitrated to target LDL) Vs placebo + ATV (10, 20, 40 or 80 mg, uptitrated to target LDL) dietary advice to all patients.	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : unclear Remarks: no description of randomization, allocation concealment or blinding FOLLOW-UP (completed 12 months: 83% (EZE+ATV) 87% (ATV) Lost-to follow-up: Not detailed Drop-out and Exclusions: Not detailed • Described: no • Balanced across groups: yes, according to authors ITT: yes
			Safety		
			All adverse events (treatment emergent)	EZE+ATV: 142/201 (71%) ATV: 30/45(67%) NT	
			Treatment-related adverse events	EZE+ATV: 45/201 (22%) ATV: 12/45(27%) NT 'similar'	
			Serious adverse events	EZE+ATV: 17/201 (8%) ATV: 5/45 (11%) NT	
			Discontinuations due to adverse events	EZE+ATV: 19/201 (9%) ATV: 3/45 (7%) NT 'similar'	
			Treatment-related liver function tests ≥3· ULN* ALT and/or AST	EZE+ATV: 0 ATV: 0 NT	
			CK ≥10· ULN	EZE+ATV: 0 ATV: 0 NT	

	-Smoking: 9% (ATV); 13% (EZE+ATV) -BMI:NR <u>Exclusion</u> - congestive heart failure (NYHA class III or IV heart failure); uncontrolled cardiac arrhythmias; myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; uncontrolled or newly diagnosed (<1m) diabetes mellitus; unstable endocrine or metabolic diseases; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; known coagulopathy.				SELECTIVE REPORTING: unclear Other important methodological remarks extension study: The low enrolment into the extension study was due to the late availability of the extension protocol. Sponsor: Schering-Plough Research Institute, Kenilworth, NJ, and Merck/Schering-Plough Pharmaceuticals, North Wales, PA

7.3.2 Summary and conclusions. Statin + ezetimibe versus statin adverse events

Ezetimibe 10 mg plus atorvastatine (uptitrated to target LDL) versus placebo plus atorvastatine (uptitrated to target LDL) in patients with primary hypercholesterolaemia.			
Bibliography: Ballantyne 2004(155)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Treatment-related adverse events	246 (1 study) 12 m	22% vs 27% 'similar'; NT	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear description Consistency:NA Directness:-1 unknown dosage of atorvastatin Imprecision:NA
Discontinuations due to adverse events	246 (1 study) 12 m	9% vs 7% 'similar'; NT	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear description Consistency:NA Directness:-1 unknown dosage of atorvastatin Imprecision:NA

This RCT is a 12 month extension of an initial 12-week trial comparing ezetimibe 10 mg + atorvastatin to atorvastatin + placebo in patients with primary hypercholesterolaemia. Atorvastatin was started at a dose of 10 mg and was uptitrated to a target LDL. We have no information on the actual mean dose that was given to the participants. The mean age of the participants was 58 years. 12% had a history of coronary heart disease.

No information on hard efficacy endpoints was provided.
GRADE: not applicable

The number of treatment-related adverse events is 22% with the combination of ezetimibe + atorvastatin and 27% with atorvastatin monotherapy. The authors describe this as 'similar', but no statistical test was provided.
GRADE: LOW quality of evidence

Discontinuation due to adverse events was 9% with combination therapy and 7 % with atorvastatin monotherapy. Again, no statistical test is provided.
GRADE: LOW quality of evidence

8 Adverse events

8.1 Statins

- Muscle toxicity[1]: dose-dependent adverse event. Myalgia occurs in 5 to 10% of patients treated, and myopathy occurs in 0.1%; this can even lead to rhabdomyolysis causing renal failure. This risk is increased when used concomitantly with certain other drugs. Hypothyroidism is a predisposing factor for rhabdomyolysis: it may be useful to evaluate thyroid function before starting statins.
- Moderate rise in transaminases, rarely hepatitis.
- Polyneuritis, peripheral neuropathy.
- Statins in high doses: increased incidence of type 2 diabetes, but this does not outweigh the benefit in people at high cardiovascular risk[2].
- Rarely, tendinopathy, mainly affecting the Achilles tendon, sometimes with tendon rupture[3]
- Pancreatitis.
- Possible interference with steroid synthesis: use during pregnancy and when breastfeeding is not recommended.
- According to one study (Prosper 2002) statins give rise to an increased risk of cancer; this has not been confirmed by other studies and meta-analyses.

- *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*

- *1. Folia Farmacotherapeutica, Sept. 2011.*
- *2. Folia Farmacotherapeutica, Feb. 2011.*
- *3. Folia Farmacotherapeutica, Jun. 2010; La Revue Prescrire; 2010; 30:29-30.*

8.2 Fibrates

- Gastrointestinal symptoms are common, mainly when starting treatment. Moderate liver disorders, rise in transaminases and rarely hepatitis. Gallstone formation, pancreatitis.
- Myalgia with raised serum creatine kinase (CK) levels, mainly when used concomitantly with a statin or in cases of renal impairment. Rhabdomyolysis is possible. Hypothyroidism is a predisposing factor for rhabdomyolysis: evaluation of thyroid function may be useful before starting fibrates.
- Venous thrombosis and pulmonary embolism.
- Artefactual rise in serum creatinine.
- Rise in homocysteine levels.
- Hypoglycaemia.
- Exanthemata, rash, photosensitivity.
- Headache, vertigo, fatigue, visual disorders, insomnia, altered taste.
- Thrombocytopenia, anaemia, leukopenia.
- Acute and chronic renal impairment.
- Peripheral neuropathy[1]
- Erectile dysfunction.
- Due to the possible interference with steroid synthesis, lipid-lowering agents should preferably not be used during pregnancy or when breastfeeding.

- *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*

- *La Revue Prescrire, December 2012/Volume 32 No. 350 (Supplément Interactions médicamenteuses), p144, p542.*
- *1. La Revue Prescrire, April 2013/Volume 33, No. 354, p275.*

8.3 Ezetimibe

- Headache.
- Gastrointestinal symptoms (abdominal pain, diarrhoea).
- Rise in liver enzymes.
- Myalgia and rhabdomyolysis have been reported, both when combined with a statin and when not combined with a statin.
- Hypersensitivity reactions: skin eruptions, angio-oedema.
- Arthralgia.
- Gallstones, cholecystitis, acute pancreatitis.
- Thrombocytopenia
- A carcinogenic effect is suspected and is still being investigated.
- Due to the possible interference with steroid synthesis, lipid-lowering agents should preferably not be used during pregnancy or when breastfeeding.
    - *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
    - *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, p 1308.*
    - *La Revue Prescrire, December 2012/Volume 32 No. 350 (Supplément Interactions médicamenteuses), p 146.*

8.4 Anion exchangers

- Very common gastrointestinal symptoms (nausea, constipation).
- Deficiencies of fat soluble vitamins, folic acid and iron when taking high doses for long periods.
- Anaemia.
- Binding of certain drugs to the anion exchanger, e.g. digitalis glycosides, vitamin K antagonists, fibrates and statins. Separate administration is recommended in these cases.
- Due to the possible interference with steroid synthesis, lipid-lowering agents should preferably not be used during pregnancy or when breastfeeding.

- *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
- *La Revue Prescrire, December 2012/Volume 32 No. 350 (Supplément Interactions médicamenteuses), p 542.*

8.5 Nicotinic acid and acipimox

- Vasodilatation, hot flushes: very common. Palpitations, tachycardia, oedema
- Headache and dizziness: common.
- Itching, cutaneous eruptions when starting treatment; hyperpigmentation.
- Common gastrointestinal symptoms (diarrhoea, nausea, vomiting, anorexia). Gastroduodenal ulcer.
- Hepatotoxicity. Rise in liver enzymes, uric acid and plasma glucose: common.
- Anaphylaxis, even after the first dose: rare.
- Muscle cramps, myalgia, myopathy.
- Antabuse effect.

- Due to the possible interference with steroid synthesis, lipid-lowering agents should preferably not be used during pregnancy or when breastfeeding.
- A speciality based on the combination **of nicotinic acid + laropiprant has been withdrawn from sale worldwide following a recommendation from the** *Committee for Medicinal Products for Human Use* (CHMP). This recommendation was made following new data from a large study (HPS2-THRIVE, not yet published) in which the combination of **nicotinic acid** + laropiprant together with a statin did not result in a significant reduction in the number of major cardiovascular events as compared with a statin alone; furthermore, an increased incidence of serious non-fatal adverse events was seen in patients treated with this combination. The CHMP therefore decided that the risk-benefit ratio of the combination of **nicotinic acid** + laropiprant is unfavourable [1]

- *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 2512-2515.*
- *La Revue Prescrire, December 2012/Volume 32 No. 350 (Supplément Interactions médicamenteuses), p147.*

1. *Folia Pharmacotherapeutica March 2013*

8.6 Omega 3 fatty acids

- Dyspepsia and gastrointestinal symptoms, moderate rise in liver enzymes.
- Rare: skin problems.
- Antithrombotic effect: bleeding in patients who also take platelet aggregation inhibitors.

- *Belgian Centre for Pharmacotherapeutic Information (consulted on 08/10/2013)*
- *La Revue Prescrire, December 2012/Volume 32 No. 350 (Supplément Interactions médicamenteuses), p 146.*

Appendix 1. Excluded publications after reading full text

Reference	*Reason for exclusion*
Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. The American journal of medicine. 2009.	*older search date than Jun 2010 and no quality assessment*
Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. Journal of the National Cancer Institute. 2011.	*population too specific*
Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM : monthly journal of the Association of Physicians. 2012.	*a more recent MTM explores these comparisons*
Alexandre L, Clark AB, Cheong E, Lewis MP, Hart AR. Systematic review: potential preventive effects of statins against oesophageal adenocarcinoma. Alimentary pharmacology & therapeutics. 2012.	*more recent systematic review included (Singh_2013)*
Amarenco P, Goldstein LB, Sillesen H, Benavente O, Zweifler RM, Callahan A, 3rd, et al. Coronary heart disease risk in patients with stroke or transient ischemic attack and no known coronary heart disease: findings from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke; a journal of cerebral circulatio 2010.	*not original RCT. exploratory analysis*
Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke; a journal of cerebral circulatio 2004.	*more recent MA available (Manktelow 2009)*
Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluatio Health technology assessment. 2008.	*all intermediary endpoints and duration <1y*
Bangalore S, Fayyad R, Laskey R, Demicco D, Deedwania P, Kostis JB, et al. Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial. European heart journal. 2013.	*not original RCT. non-prespecified analysis*
Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut. 2010.	*design*
Berard E, Bongard V, Dallongeville J, Arveiler D, Ruidavets JB, Ferrieres J. Cancer mortality according to lipid-lowering drugs and lipoproteins in a general populatio Current medical research and opinio 2011.	*methodology: comparison*
Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Associatio 2012.	*methodological: secondary analysis from RCT*
Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. Expert opinion on drug safety. 2010.	*not a systematic review*
Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to Moderate Muscular Symptoms with High-Dosage Statin Therapy in Hyperlipidemic Patients —The PRIMO Study. Cardiovascular Drugs and Therapy. 2005.	*no non-statin control group*
Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. Journal of cardiovascular pharmacology. 2011.	*methodo search and subgroup of no specific interest*
Cenedella RJ. Cholesterol and cataracts. Survey of ophthalmology. 1996.	*not a cohort study*
Chan DK, O'Rourke F, Shen Q, Mak JC, Hung WT. Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins. Acta neurologica Scandinavica. 2011.	*another MA adressing this question already included. no quality appraisal, includes also 2 placebo-controlled trials*
Chang CH, Kusama M, Ono S, Sugiyama Y, Orii T, Akazawa M. Assessment of statin-associated muscle toxicity in Japan: a cohort study conducted using claims database and laboratory informatio BMJ ope 2013.	*no control group*
Chodick G, Heymann AD, Flash S, Kokia E, Shalev V. Persistence with statins and incident cataract: a population-based historical cohort study. Annals of epidemiology. 2010.	*no statin-free control group*

Choi HD, Shin WG. Safety and efficacy of statin treatment alone and in combination with fibrates in patients with dyslipidemia: a meta-analysis. Current medical research and opinio 2013.	*unclear search. not available in belgian libraries*
Collier DJ, Poulter NR, Dahlof B, Sever PS, Wedel H, Buch J, et al. Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm. Journal of hypertensio 2011.	*post hoc analysis*
Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, et al. Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting. Journal of clinical lipidology. 2013.	*no non statin control group*
Danaei G, Rodriguez LA, Cantero OF, Logan R, Hernan MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. Statistical methods in medical research. 2013.	*statistical method*
Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. American journal of epidemiology. 2012.	*statistical methods*
De Caterina R, Scarano M, Marfisi R, Lucisano G, Palma F, Tatasciore A, et al. Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. Journal of the American College of Cardiology. 2010.	*data on statins difficult to extract. this endpoint is also reported in more recent MAs*
de Lorgeril M, Salen P, Abramson J, Dodin S, Hamazaki T, Kostucki W, et al. Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. Archives of internal medicine. 2010.	*comment, no RCT*
Desai P, Chlebowski R, Cauley JA, Manson JE, Wu C, Martin LW, et al. Prospective analysis of association between statin use and breast cancer risk in the women's health initiative. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013.	*not available in belgian libraries*
Dong YH, Lin JW, Wu LC, Chen CY, Chang CH, Chen KY, et al. Examining the association between statins and lung cancer incidence in patients with type 2 diabetes mellitus. Journal of the Formosan Medical Association = Taiwan yi zhi. 2013.	*population*
Fong DS, Poon KY. Recent statin use and cataract surgery. American journal of ophthalmology. 2012.	*case control*
Fu JH, Mok V, Lam W, Wong A, Chu W, Xiong Y, et al. Effects of statins on progression of subclinical brain infarct. Cerebrovascular diseases (Basel, Switzerland). 2010.	*nonclinical endpoints*
Gao Y, Cao J, Lu XC, Liu XF, Ma C, Fan L. [Comparison on the effects of clopidogrel, statins combination in treating coronary artery disease among the elderly patients: a retrospective cohort study]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2012.	*language*
Geng Q, Ren J, Chen H, Lee C, Liang W. Adverse events following statin-fenofibrate therapy versus statin alone: a meta-analysis of randomized controlled trials. Clinical and experimental pharmacology & physiology. 2013.	*not available in belgian libraries*
Geng Q, Ren J, Chen H, Lee C, Liang W. Adverse events of statin-fenofibric acid versus statin monotherapy: a meta-analysis of randomized controlled trials. Current medical research and opinio 2013.	*not available in belgian libraries*
Goldstein MR, Mascitelli L, Pezzetta F, Haan MN, Cramer C, Kalbfleisch J, et al. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology. 2009.	*is a comment on a cohort trial*
Gray SL, Aragaki AK, LaMonte MJ, Cochrane BB, Kooperberg C, Robinson JG, et al. Statins, angiotensin-converting enzyme inhibitors, and physical performance in older wome Journal of the American Geriatrics Society. 2012.	*endpoints*
Greve AM, Gerdts E, Boman K, Gohlke-Baerwolf C, Rossebo AB, Nienaber CA, et al. Prognostic importance of atrial fibrillation in asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. International journal of cardiology. 2013.	*not a research question*
Guo J, Meng F, Ma N, Li C, Ding Z, Wang H, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. The American journal of cardiology. 2012.	*inadequate search. included trials too short, too small or open label*
Hackam DG, Austin PC, Huang A, Juurlink DN, Mamdani MM, Paterson JM, et al. Statins and intracerebral hemorrhage: a retrospective cohort study. Archives of neurology. 2012.	*endpoint*

Hamilton-Craig I, Kostner K, Colquhoun D, Woodhouse S. At sea with SEAS: the first clinical endpoint trial for ezetimibe, treatment of patients with mild to moderate aortic stenosis, ends with mixed results and more controversy. Heart, lung & circulatio 2009.	*not original publication*
Hebert PR, Evans D, Schneider WR, Rodriquez-Paz E, Hennekens CH. The need for increased utilization of statins after occlusive stroke. Journal of cardiovascular pharmacology and therapeutics. 2011.	*not a systematic review*
Jonathan E, Derrick B, Emma L, Sarah P, John D, Jane A, et al. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. Lancet. 2011.	*this subgroup analysis is not a research questio*
Josan K, Majumdar systematic review, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008.	*newer trials included in more recent MA (Mills 2011)*
Joy TR, Hegele RA. Narrative review: statin-related myopathy. Annals of internal medicine. 2009.	*not a systematic review*
Kalavrouziotis D, Buth KJ, Cox JL, Baskett RJ. Should all patients be treated with an angiotensin-converting enzyme inhibitor after coronary artery bypass graft surgery? The impact of angiotensin-converting enzyme inhibitors, statins, and beta-blockers after coronary artery bypass graft surgery. American heart journal. 2011.	*statin not focus of study*
Kang S, Liu Y, Liu XB. Effects of aggressive statin therapy on patients with coronary saphenous vein bypass grafts: a systematic review and meta-analysis of randomized, controlled trials. Clinical therapeutics. 2013.	*subgroup too specific*
Kizer JR, Madias C, Wilner B, Vaughan CJ, Mushlin AI, Trushin P, et al. Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. The American journal of cardiology. 2010.	*inadequate search dates; not a specific research question*
Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus me Journal of the American College of Cardiology. 2012.	*not a subgroup of interest*
Koton S, Molshatzki N, Bornstein NM, Tanne D. Low cholesterol, statins and outcomes in patients with first-ever acute ischemic stroke. Cerebrovascular diseases (Basel, Switzerland). 2012.	*too small for relevant endpoint*
Lai SW, Liao KF, Lin CL, Sung FC, Cheng YH. Statins use and female lung cancer risk in Taiwa The Libyan journal of medicine. 2012.	*methodology*
Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis. 2011.	*all trials included in Jun; subgroup of no specific interest*
Li L, Ambegaonkar BM, Reckless JP, Jick S. Association of a reduction in low-density lipoprotein cholesterol with incident cardiovascular and cerebrovascular events among people with type 2 diabetes mellitus. European journal of preventive cardiology. 2013.	*population*
Liao YC, Hsieh YC, Hung CY, Huang JL, Lin CH, Wang KY, et al. Statin therapy reduces the risk of ventricular arrhythmias, sudden cardiac death, and mortality in heart failure patients: a nationwide population-based cohort study. International journal of cardiology. 2013.	*population*
Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. Vascular health and risk management. 2010.	*more recent high quality systematic review available (Richardson 2013)*
Lonardo A, Loria P. Potential for statins in the chemoprevention and management of hepatocellular carcinoma. Journal of gastroenterology and hepatology. 2012.	*not a systematic review*
Loomba RS, Arora R. Prevention of cardiovascular disease utilizing fibrates--a pooled meta-analysis. American journal of therapeutics. 2010.	*methodology not appropriate*
Lustman A, Nakar S, Cohen AD, Vinker S. Statin use and incident prostate cancer risk: does the statin brand matter? A population-based cohort study. Prostate cancer and prostatic diseases. 2013.	*not available in belgian libraries*
Lutski M, Shalev V, Porath A, Chodick G. Continuation with statin therapy and the risk of primary cancer: a population-based study. Preventing chronic disease. 2012.	*no statin-free control group*

Ma T, Chang MH, Tien L, Liou YS, Jong GP. The long-term effect of statins on the risk of new-onset diabetes mellitus in elderly Taiwanese patients with hypertension and dyslipidaemia: a retrospective longitudinal cohort study. Drugs & aging. 2012.	*not available in Belgian libraries*
McCullough PA, Ahmed AB, Zughaib MT, Glanz ED, Di Loreto MJ. Treatment of hypertriglyceridemia with fibric acid derivatives: impact on lipid subfractions and translation into a reduction in cardiovascular events. Reviews in cardiovascular medicine. 2011.	*not a systematic review*
McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. The Cochrane database of systematic reviews. 2009.	*more recent MA richardson 2013*
McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Cochrane review on 'Statins for the treatment of dementia'. International journal of geriatric psychiatry. 2013.	*not a reseach population*
McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke; a journal of cerebral circulatio 2012.	*unclear inclusion criteria (duration). combining placebo and low dose statin trials.*
Meza V, Ganduglia C, Ciapponi A. Combined therapy with statins and fibrates for people with dyslipidaemia. Cochrane Database of Systematic Reviews. 2008.	*protocol*
Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM : monthly journal of the Association of Physicians. 2011.	*a more recent MTM (NACI 2013) adresses this question*
Minder CM, Blaha MJ, Horne A, Michos ED, Kaul S, Blumenthal RS. Evidence-based use of statins for primary prevention of cardiovascular disease. The American journal of medicine. 2012.	*not a systematic review*
Mondul AM, Caffo B, Platz EA. Minimal detection bias in the inverse association between statin drug use and advanced prostate cancer risk: a simulation study. Cancer epidemiology. 2011.	*desing*
Mood GR, Bavry AA, Roukoz H, Bhatt DL. Meta-analysis of the role of statin therapy in reducing myocardial infarction following elective percutaneous coronary interventio The American journal of cardiology. 2007.	*search question too specific, duration of included trials*
Mora S, Wenger NK, Demicco DA, Breazna A, Boekholdt SM, Arsenault BJ, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulatio 2012.	*risk factor analysis*
Moreno G, Mangione CM. Management of cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: 2002-2012 literature review. Journal of the American Geriatrics Society. 2013.	*inadequate search*
Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. Journal of the American College of Cardiology. 2009.	*analysis not prespecified*
Naci H, Brugts JJ, Fleurence R, Ades AE. Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. QJM : monthly journal of the Association of Physicians. 2013.	*endpoint available in more recent MA. inclusion criteria differ from ours (duration > 4wks)*
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Appendix 2. Some results from individual RCTs

As an illustration of how baseline risk influences absolute risk reduction and NNT, we have added individual results from some of the trials that are included in different meta-analyses.
They are roughly arranged from lower risk to higher risk.

Ref	n	Population	Duration	Comparison	Outcomes	Results
AFCAPS/TexCAPS 1998(6) Remarks: *Trial was stopped prematurely. To be terminated when 320 participants had experienced primary outcome event. Stopped when 267 had done at 5.2 years*	6606	participants in Texas, USA; "Average" TC and LDL-C levels and below-average HDL-C levels TC, [180-264mg/dL];LDL-C, [130-190 mg/dL]; HDL-C,≤ [45mg/dL]for men or ≤ [47 mg/dL] for women; and triglycerides, ≤ [400 mg/dL] mean age 58; None with any clinical evidence of CVD 22% hypertension 13% current smoker 3.5% diabetes	mean 5.2y Remarks: *Trial was stopped prematurely. To be terminated when 320 participants had experienced primary outcome event. Stopped when 267 had done at 5.2 years*	20-40mg lovastatin vs placebo	**Acute major coronary events defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death (primary endpoint)**	3.5% vs 5.5% at a mean of 5.2y *rate: 0.68/100py vs 1.09/100py* **RR 0.63 (95%CI 0.50-0.79); SS** **NNT for a mean of 5.2 years : 49** *(based on crude rates)* **NNT per personyear: 244** *(based on rate/100py)*
					MI (fatal and nonfatal)	1.7% vs 2.9% at a mean of 5.2y *rate: 0.33/100py vs 0.56/100py* **RR 0.60 (95%CI 0.43-0.83); SS** **NNT for a mean of 5.2 years: 84** (*based on crude rates)* **NNT per personyear: 434** *(based on rate/100py)*
					Fatal cardiovascular events	0.10/100py vs 0.14/100py NT
					Total mortality	0.46/100py vs 0.44/100py NT 'similar'

WOSCOPS(26)	6595	men with hypercholesterolaemia (LDL-C≥ 155 mg/dl) based in Scotland mean age 55 (44% current smoker) <u>< 10% with clinical evidence of CVD</u>	mean 4.9y	40 mg pravastatin vs placebo	**Nonfatal MI or death from CHD (primary endpoint)**	5.5% vs 7.9% at 5 years **RRR 31(95%CI 17 to 43); SS** **NNT for 5 years: 42**
					Fatal or nonfatal stroke	1.6% vs 1.6% at 5 years RRR 11(-33 to 40) NS
					Death from all cardiovascular causes	1.6% vs 2.3% at 5 years **RRR= 32(95%CI 3 to 53)** **NNT for 5 years = 143**
					Death from any cause	3.2% at 5 years vs 4.1% at 5 years RRR: 22(0 to 40) p=0.051; NS

JUPITER 2008(19)	17802	LDL-C<130 mg/dl hs-CRP ≥2.0 mg/l >50 years None with any clinical evidence of CVD	median 1.9y Remarks: *Stopped early with a follow-up of 1.9 years.* *Primary endpoint event rate higher than predicted.*	20 mg rosuvastatin vs placebo	**Myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes (primary endpoint)**	1.60% vs 2.82% at a median of 1.9y *rate: 0.77/100py vs 1.36/100py* **HR: 0.56 (95%CI 0.46 to 0.69); SS** **NNT for 2 years: 95** *(On the basis of Kaplan–Meier estimates)*
					Any myocardial infarction	0.35% vs 0.76% at a median of 1.9y *rate 0.17/100 py vs 0.37 /100 py* **HR: 0.46 (95%CI 0.30 to 0.70); SS** **NNT for a median of 1.9y: 241** *(based on crude rades)* **NNT per personyear : 500** *(based on rate/100py)*
					Myocardial infarction, stroke, or confirmed death from cardiovascular causes	0.93% vs 1.76% at a median of 1.9y *rate 0.45/100py vs 0.85/100py* **HR= 0.53 (95% CI 0.40 to 0.69)** **NNT for a median of 1.9y: 120** *(based on crude rates)* **NNT per personyear: 250** *(based on rate/100py)*
					Any stroke	0.37% vs 0.72% at a median of 1.9y *rate: 0.18/100py vs 0.34/100py* **HR: 0.52 (95%CI 0.34-0.79); SS** **NNT for a median of 1.9y: 287** *(based on crude rates)* **NNT per personyear: 625** *(based on rate/100py)*
					Any death	2.22% vs 2.77% at a median of 1.9y *rate: 1.00/100py vs 1.25/100py* **HR: 0.80 (95% CI 0.67-0.97); SS** **NNT for a median of 1.9y= 182** *(based on crude rates)* **NNT per personyear: 400** *(based on rate/100py)*

ASCOT-LLA 2003(10)	10305	Hypertensive patients (aged 40–79 years) with at least three other cardiovascular risk factors* with non-fasting total cholesterol concentrations 6·5 mmol/L or less 10% previous stroke or TIA 5% peripheral vascular disease **left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, or premature family history of CHD.*	median of 3·3 y	10 mg atorvastatin vs placebo	**Non-fatal MI* plus fatal CHD (primary endpoint)**	1.9% vs 3.0% at a median of 3.3 years *rate 0.60/100py vs 0.94/100py* **HR 0.64(95%CI 0.50 to 0.83); SS** **NNT for a median of 3.3 years: 90** *(based on crude rates)* **NNT per personyear: 294** *(based on rate/100 py)*
					Fatal and nonfatal stroke	1.7% vs 2.4% at a median of 3.3 years *rate 0.54/100py vs 0.74/100py* **HR 0.73(95%CI 0.56-0.96); SS** **NNT for a median of 3.3y: 143** *(based on crude rates)* **NNT per personyear: 500** *(based on rate/100py)*
					Cardiovascular mortality	1.4% vs 1.6% at a median of 3.3 years *rate 0.44/100py vs 0.49/100py* HR 0.90 (95%CI 0.66-1.23) NS
					All-cause mortality	3.6% vs 4.1% at a median of 3.3y *rate 1.11/100py vs 1.28/100py* HR 0.87 (95%CI 0.71 – 1.06) NS

PROSPER 2002(24)	5804	Elderly patients with a history of, or risk factors for, vascular disease (Raised risk of CV disease because of smoking, HTN, or DM) 70-82y	mean 3.2y	40 mg pravastatin vs placebo	**Coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke (Primary endpoint)**	**<u>all patients</u>** 14.1% vs 16.2% at a mean of 3.2y **HR= 0·85 (95% CI 0·74–0·97); SS** **NNT for a mean of 3.2y =48** *(based on crude rates)* **<u>subgroup previous vascular disease</u>** 17.4% vs 21.7% at a mean of 3.2y **HR 0.78(95%CI 0.66-0.93); SS** **NNT for a mean of 3.2y =23** *(based on crude rates)* **<u>subgroup no previous vascular disease</u>** 11.4% vs 12.1% at a mean of 3.2y HR= 0.94(95%CI 0.77-1.15) NS
					Coronary heart disease death or non-fatal myocardial infarction	10.1 % vs 12.2% at a mean of 3.2y **HR= 0.81 (95%CI 0.69-0.94); SS** **NNT for a mean of 3.2y =48** *(based on crude rates)*
					Fatal or non-fatal stroke	4.7% vs 4.5% at a mean of 3.2y HR 1.03 (95%CI 0.81-1.31) NS
					Vascular death	4.7% vs 5.4% at a mean of 3.2y HR 0.85 (95%CI 0.67-1.07) NS
					All cause death	10.3% vs 10.5% at a mean of 3.2y HR 0.97 (95%CI 0.83-1.14) NS

SSSS 1994(25)	4444	Patients with angina pectoris or previous myocardial infarction and serum cholesterol 5·5-8·0 mmol/L on a lipid-lowering diet *(= 212mg/dl to 308mg/dl)* age 35-70y 26% hypertension 25% smokers	median 5.4y	20 mg simvastatin vs placebo	**major coronary events: coronary death nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest(secondary endpoint)**	19% vs 28% at a median of 5.4y **RR 0.66 (95%CI 0.59-0.75); SS** **NNT for a median of 5.4y: 11** *(based on crude rates)*
					All cardiovascular death (secondary endpoint)	6.1% vs 9.3% at a median of 5.4y **RR 0.62(95%CI 0.52-0.80); SS** **NNT for a median of 5.4y: 31** *(based on crude rates)*
					All death (primary endpoint)	8.2% vs 11.5% at a median of 5.4y **RR 0.70 (95% CI 0.58-0.85); SS** **NNT for a median of 5.4y: 30** *(based on crude rates)*

LIPID 1998(60)	9014	The patients had a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg per deciliter	mean 6.1y	40mg pravastatin vs placebo	**Death due to CHD or nonfatal MI**	12.3% vs 15.9% at a mean of 6.1y **RRR 24 (95%CI 15-32)** **NNT for a mean of 6.1y: 28** *(based on crude rates)*
					Any MI	7.4% vs 10.3% at a mean of 6.1y **RRR 29(95%CI 18-38); SS** **NNT for a mean of 6.1y: 34** *(based on crude rates)*
					Any stroke	3.7% vs 4.5% at a mean of 6.1y RRR 19 (95%CI 0-34), p=0.048 **NNT for a mean of 6.1y: 125** *(based on crude rates)*
					Death due to coronary heart disease (primary endpoint)	6.4% vs 8.3% at a mean of 6.1y RRR 24 (95%CI 12-35); SS **NNT for a mean of 6.1y:53** *(based on crude rates)*
					Death due to cardiovascular disease	7.3% vs 9.6% at a mean of 6.1y RRR 25(95%CI 13-35); SS **NNT for a mean of 6.1y: 43** *(based on crude rates)*
					Death from any cause	11.0% vs 14.1% at a mean of 6.1y RRR 22(95%CI 13-31); SS **NNT for a mean of 6.1y: 32** *(based on crude rates)*

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