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RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

THE RATIONAL USE OF DRUGS IN HYPERTENSION

Systematic literature review: full report

Consensus conference
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Abbreviations

ABP: ambulant blood pressure
ABPM: ambulant blood pressure monitoring
ACEI: angiotensin-converting-enzyme inhibitor
AE: adverse events
AH: arterial hypertension
AHT: arteriële hypertensie
ARB: angiotensin receptor blocker
ARR: absolute risk reduction
AT: active treatment
BB: beta-blocker
BP: blood pressure
CAD: coronary artery disease
CCB: calcium channel blockers
CHD: coronary heart disease
CI: confidence interval
CKD: chronic kidney disease
CO: crossover RCT
CV: cardiovascular
CVA: cerebrovascular accident
CVD: cardiovascular disease
DB: double blind
DBP: diastolic blood pressure
DM: diabetes mellitus
ESRD: end stage renal disease
GFR: glomerular filtration rate
GoR: grade of recommendation
HF: heart failure
HR: hazard ratio
HT: hypertensive/hypertension
HTA: hypertension artérielle
IDH: isolated diastolic hypertension
ISH: isolated systolic hypertension
IT: intensive treatment
ITT: intention-to-treat analysis
KDIGO: Kidney Disease: Improving Global Outcomes
LoE: level of evidence
MA: meta-analysis
MH: managed hypertension
MHT: managed hypertensions
MI: myocardial infarction
n: number of patients
NR: not reported
NS: not statistically significant

NT: no statistical test
NT: normotensive/normotension
OD: organ damage
OL: open label
PG: parallel group
PL: placebo
PO: primary outcome
RAAS: renin-angiotensin-aldosterone-system
RCT: randomized controlled trial
RR: relative risk
SB: single blind
SBP: systolic blood pressure
SDH: systolic and diastolic hypertension
SO: secondary outcome
ST: standard treatment
TIA: transient ischemic attack
Tx: treatment
Txt: treatment
WCH : white coat hypertension

1 Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Treatment of arterial hypertension' which will take place on the 5th of November 2015.

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
Précisions : ce consensus concerne l'HTA essentielle. Sujets non abordés : grossesse, syndrome métabolique, HTA de l'enfant
Verduidelijking: de consensus betreft de essentiële HTA. Onderwerpen die niet werden behandeld: zwangerschap, metabool syndroom, HTA bij kinderen

Question 1. Diagnostic
Quelles sont les techniques validées pour la mesure des chiffres de pression artérielle et quelles sont les normes et seuils diagnostiques pour ces techniques ?
Vraag 1. Diagnose
Welke technieken zijn gevalideerd voor het meten van de bloeddrukcijfers en wat zijn de diagnostische normen en drempels voor die technieken?

Question 2. Traitement non médicamenteux
Quelles sont les mesures non médicamenteuses (hygiène de vie, consommation de sel, poids…) à recommander en prévention et pour le traitement de l'hypertension artérielle ?
Vraag 2. Niet-medicamenteuze behandeling
Welke niet-medicamenteuze maatregelen (levenshygiëne, consumptie van zout, gewicht...) worden aanbevolen voor de preventie en de behandeling van arteriële hypertensie?

Question 3. Traitement médicamenteux : cibles thérapeutiques
Quelles sont les valeurs cibles d'un traitement médicamenteux pour : - Un adulte sans comorbidité ni complication de l'HTA - Un adulte avec complication (atteinte d'un organe cible) de l'HTA ? - Une personne âgée de plus de 60 ans ? - Un adulte présentant une des affections suivantes : diabète, insuffisance rénale, insuffisance cardiaque, ischémie coronarienne (angor et post-infarctus), affection cérébrovasculaire - Une personne âgée de plus de 80 ans ?
Vraag 3. Medicamenteuze behandeling: therapeutische streefwaarden
Wat zijn de streefwaarden van een medicamenteuze behandeling voor: - een volwassene zonder comorbiditeit of complicatie van HTA? - een volwassene met complicatie (aantasting van een doelwitorgaan) van HTA? - een persoon ouder dan 60 jaar?

- een volwassene die lijdt aan een van de volgende aandoeningen: diabetes, nierinsufficiëntie, hartinsufficiëntie, coronaire ischemie (angor en postinfarct), cerebrovasculaire aandoening?
- een persoon ouder dan 80 jaar?

Question 4. Traitement médicamenteux initial : choix chez un adulte de moins de 60 ans

Quel est le meilleur choix (efficacité/sécurité) pour un traitement initial d'une HTA, monothérapie versus autre monothérapie ou versus polythérapie, pour un traitement initial chez

- Un adulte sans comorbidité ni complication de l'HTA
- Un adulte avec complication (atteinte d'un organe cible) de l'HTA ?
- Un adulte présentant une des affections suivantes : diabète, insuffisance rénale, insuffisance cardiaque, ischémie coronarienne (angor et post-infarctus), affection cérébrovasculaire ?

Vraag 4. Initiële medicamenteuze behandeling: keuze bij een volwassene jonger dan 60 jaar

Wat is de beste keuze (doeltreffendheid/veiligheid) voor een initiële behandeling van HTA, monotherapie versus andere monotherapie of versus polytherapie, bij

- een volwassene zonder comorbiditeit of complicatie van HTA?
- een volwassene met complicatie (aantasting van een doelwitorgaan) van HTA?
- een volwassene die lijdt aan een van de volgende aandoeningen: diabetes, nierinsufficiëntie, hartinsufficiëntie, coronaire ischemie (angor en postinfarct), cerebrovasculaire aandoening?

Question 5. Traitement médicamenteux en cas d'échec de traitement(s) précédent(s) chez un adulte de moins de 60 ans ?

En cas de non atteinte des valeurs cibles déterminées pour un patient avec un traitement, quel est le meilleur choix de stratégie thérapeutique (efficacité, sécurité) pour l'ajout d'autres antihypertenseurs ?

Vraag 5. Medicamenteuze behandeling wanneer de vorige behandeling(en) niet aanslaat (aanslaan) bij een volwassene jonger dan 60 jaar?

Voor welke therapeutische strategie (doeltreffendheid, veiligheid) voor de toevoeging van andere antihypertensiva kan het best worden gekozen, wanneer de streefwaarden die voor de behandeling van een patiënt zijn vastgesteld, niet worden behaald?

Question 6. Traitement d'une HTA chez une personne âgée (60+)

Quel est le meilleur choix (efficacité/sécurité) pour un traitement médicamenteux initial d'une HTA, monothérapie versus autre monothérapie ou versus polythérapie, pour un traitement initial d'une HTA chez

- Une personne âgée de 60 à 79 ans ?
- Une personne âgée de 80 ans et plus ?

En cas de non atteinte des valeurs cibles déterminées pour un patient avec un traitement, quel est le meilleur choix de stratégie thérapeutique (efficacité, sécurité) pour l'ajout d'autres antihypertenseurs chez

- Une personne âgée de 60 à 79 ans ?
- Une personne âgée de 80 ans et plus ?

Vraag 6. Behandeling van HTA bij een oudere (60+)

Wat is de beste keuze (doeltreffendheid/veiligheid) voor een initiële medicamenteuze behandeling van HTA, monotherapie versus andere monotherapie of versus polytherapie, bij

- een persoon tussen 60 en 79 jaar?
- een persoon van 80 jaar en ouder?

Wanneer de streefwaarden die voor de behandeling van een patiënt zijn vastgesteld, niet worden behaald, voor welke therapeutische strategie (doeltreffendheid, veiligheid) kan dan het best worden gekozen voor de toevoeging van andere antihypertensiva bij
een persoon tussen 60 en 79 jaar?
een persoon van 80 jaar en ouder?

Question 7. Observance du traitement et aspects interdisciplinaires

Quelles sont les mesures efficaces (et efficientes) pour améliorer l'observance d'un traitement antihypertenseur ?
Une collaboration interdisciplinaire améliore-t-elle l'observance du traitement ?
Une collaboration interdisciplinaire améliore-t-elle l'état de santé du patient hypertendu, en termes de contrôle tensionnel et/ou de morbi-mortalité (et à quel coût) ?

Vraag 7. Therapietrouw en interdisciplinaire aspecten

Welke maatregelen zijn doeltreffend (en doelmatig) om de therapietrouw bij een behandeling met antihypertensiva te verbeteren?
Verbetert een interdisciplinaire samenwerking de therapietrouw?
Verbetert een interdisciplinaire samenwerking de gezondheidstoestand van een hypertensiepatiënt op het vlak van bloeddrukcontrole en/of morbi-mortaliteit (en tegen welke prijs)?

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 3,4,5,6 and 7

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

1.1.2.1 Populations

The following populations are to be evaluated.

People with arterial hypertension. This will usually be defined by the authors of the publication as a blood pressure ≥140/90 mmHg.

Trials involving normotensive patients, or trials with a mixed hypertensive/normotensive population will be excluded (in observational trials, exceptions will be allowed). Prespecified subgroup analyses of hypertensive patients in a mixed hypertensive/normotensive trial will be reported, if available.

Hypertensive populations of interest are:

- Adults with primary uncomplicated hypertension
- Elderly patients with hypertension (≥60y and ≥ 80y)
- Hypertensive patients with type 2 diabetes
- Hypertensive patients with heart failure
- Hypertensive patients with coronary artery disease (previous myocardial infarction or stable angina)
- Hypertensive patients with previous stroke
- Hypertensive patients with chronic kidney disease (as defined in the consensus conference on chronic kidney disease 2014[1])

Excluded from the literature search are: children, pregnant women, people with metabole syndrome, people with secondary hypertension.

1.1.2.2 Interventions

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

○ Diuretics	Thiazide-type diuretics - (Hydrochlorothiazide: only available as a combination) - (Altizide: only available as a combination) Thiazide-like diuretics - Chlortalidone - Indapamide Spironolactone

[1] Adults with chronic kidney disease (CKD), defined as a GFR < 60 ml/min and/or with signs of kidney damage, as defined by KDIGO.

Excluded from the literature search are:
- renal transplant patients
- patients with end stage renal failure (ESRD)
- patients on dialysis
- children

○ Beta-receptor blockers	Acebutolol Atenolol Betaxolol Bisoprolol Carvedilol Celiprolol Esmolol Labetalol Metoprolol Nebivolol Pindolol Propranolol
○ Calcium-channel blockers	Amlodipine Barnidipine Felodipine Isradipine Lacidipine Lercanidipine Nicardipine Nifedipine Nimodipine Nisoldipine Nitrendipine Verapamil Diltiazem
○ ACE inhibitors	Benazepril Captopril Cilazapril Enalapril Fosinopril Lisinopril Perindopril Quinapril Ramipril Zofenopril
○ Angiotensin-II receptor antagonists	Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan
○ Centrally acting antihypertensive drugs	Moxonidine
○ Renin inhibitors	Aliskiren

Table 1

The following product are excluded from the literature search:
Alpha blockers, loop diuretics, clonidine, methyldopa

1.1.2.3 Comparisons

The following comparisons are to be reported

- Threshold for treatment
    - At a certain blood pressure value, treatment versus no treatment or placebo

- Target for treatment
    - Treatment to reach a certain target blood pressure (strict control) versus treatment to reach another target blood pressure ("usual", less strict control)[2].

  Antihypertensive treatment: choice of drug

    Thiazide diuretics, beta blockers, calcium antagonists, ace-inhibitors, angiotensin II receptor blockers versus placebo and versus one another.

    No comparison within a class, except Thiazide-type and thiazide-like diuretics

    - Monotherapy versus combination therapy as initial antihypertensive treatment.
    - Increasing monotherapy versus adding a second drug if target blood pressure is not reached
    - Adding a specific drug to an existing treatment versus adding another drug to this existing treatment (no limit in the number of drugs)
    - Double RAAS inhibition does not need to be reported in detail (see also Consensus Conference on Chronic Kidney Disease 2014)

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
- Heart failure
- Kidney failure

[2] "Strict", "usual", "less strict": as defined by the authors of the study

1.1.2.5 Study criteria

Meta-analyses and systematic reviews

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

RCT's

- Double blind if feasible
- Duration: minimum 1 year.
- Minimum number of participants: 100. 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)
- Subgroup analyses will be reported if they are prespecified and address populations that are relevant to our research questions.

Observational studies (for questions about threshold and target blood pressure)

- Large cohort studies (>1000 participants)
- Because NICE 2011 also included post-hoc analyses of RCTs as evidence for threshold and target, we will do the same (we will consider them to be observational studies)

Other sources for safety and dosing

- 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.

Some publications will be excluded for practical reasons:

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

1.1.2.6 Guidelines

Only guidelines that report levels of evidence/recommendation are to be selected.
Only guidelines from 2010 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.

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

Table 1 gives an overview of the items assessed in this domain according to the Agree II score.(1)

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

Table 2: . Items assessed by the domain "Rigour of development" in AgreeII score.

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

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

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 EMB-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 to search for relevant publications, the following systematic reviews or meta-analyses were selected

Primary hypertension with or without risk factors, elderly patients

- National Clinical Guideline Centre (NICE). Hypertension. The clinical management of primary hypertension in adults. Clinical guideline 127. Methods, evidence, and recommendations, August 2011.
  http://www.nice.org.uk/guidance/cg127/evidence
- NHS Evidence – provided by NICE. Hypertension: Evidence update 32. March 2013..
  http://www.nice.org.uk/guidance/cg127/evidence
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama 2014;311:507-20, Feb 5. DOI: 10.1001/jama.2013.284427.

Hypertension and type 2 diabetes

- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama 2014;311:507-20, Feb 5. DOI: 10.1001/jama.2013.284427.

Hypertension and coronary disease

- Skinner J. S., Cooper A. Clinical evidence. Secondary prevention on ischaemic cardiac events. 2011 (search may 2010)
- Daskalopoulou SS, Rabi DM, Zarnke KB, et al. The 2015 canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015;31:549-68, May. DOI: 10.1016/j.cjca.2015.02.016. *+ previous editions.*
  (incomplete source material)

Hypertension and heart failure, hypertension and previous stroke

- Daskalopoulou SS, Rabi DM, Zarnke KB, et al. The 2015 canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015;31:549-68, May. DOI: 10.1016/j.cjca.2015.02.016. *+ previous editions.*
  (incomplete source material)

Hypertension and chronic kidney disease

- RIZIV-INAMI. The rational use of drugs in chronic kidney disease. Systematic literature review: full report. 2014 http://www.riziv.fgov.be/nl/publicaties/Paginas/consensusvergaderingen-juryrapport.aspx#.VajYu0Z8pYA

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 details of the search strategy can be found in appendix I

1.3 Selection procedure

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.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.

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 endpoint, across studies.

The GRADE system(2) 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 association (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

Table 3 Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed. The GRADE system has only been used in this literature review to assess RCT's, so the criteria specifically intended for observational studies (see table above) has 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

Table 4 GRADE system adapted by literature group

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

Study design

In this literature review RCT's and observational studies are included but GRADE was only applied to the RCT's.

Study quality

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

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

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

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

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

Consistency is judged by the literature group 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. In the NICE report, statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity(3)

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

- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCT's 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

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

The conclusions 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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4. GRADE working group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
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2 Critical reflections of the reading committee and the literature group

2.1.1 Comorbidity

Population selection criteria were diverse in the included studies. For some studies, patients with hypertension and a comorbid condition were required, while in other studies patients had to be free of clinically significant cardiovascular or non-cardiovascular disorders. Often one or several additional risk factors were required from a specified list of risk factors or co-morbid condition, with a resulting mixed "high risk" population with different risk factors (e.g. diabetes OR myocardial infarction OR stroke). When prespecified, subgroup analyses were often done on patients with and without diabetes, kidney disease, or depending on age.

There were few studies in patients with primary uncomplicated hypertension without comorbidities. Meta-analyses often pooled results from study populations with low cardiovascular risk together with patients with high cardiovascular risk (both primary prevention) and with patients with a history of events (secondary prevention). It is difficult to draw conclusions for the individual patient from these results.

It should also be noted that most of the time a hypertensive drug will be part of a polymedication scheme (most of the time several drugs will be used to achieve desired blood pressure). When starting a antihypertensive therapy, it is common that other medication will already be taken by the patient, or that he will end up taking more than just the antihypertensive drugs in his lifetime.

2.1.2 Race

Race sometimes has an impact on which therapeutic strategy should be preferred. This is seen with black populations, where for example NICE[1] recommendations make a distinction. Often the race of the study participants is described, and a few trials were done in one race exclusively, but generally population is mixed. It is to note that some of the large trials included in our literature review were done in Asian populations, which could also influence results. It not clear whether or not those results can simply be extrapolated to a Belgian population or if a measure of caution should be exerted.

2.1.3 Double RAAS inhibition

Because of information provided in the Consensus Conference on chronic kidney disease 2014, the Organizing Committee did not request a detailed report on double RAAS inhibition. Conclusion from the Consensus Conference on CKD in 2014 were that despite improvement in proteinuria, overwhelming evidence now demonstrates significant harm with dual therapy without any benefit in mortality or kidney function.

2.1.4 Treatment of resistant hypertension

Studies about adding a third or fourth drug to an existing regimen, or studies about treatment resistant hypertension do exist but they were found to be of short duration and to only report on intermittent outcomes such as blood pressure change. We did not find any that reported on hard endpoints, so we could not include any trial about this population.

2.1.5 Trials with a mixed hypertensive/normotensive population

Our literature search focuses on patients with hypertension, which is reflected in the search criteria of our Medline search. The systematic reviews (NICE[1] and JNC8[2]) that we used as a source for relevant RCTs have the same inclusion criteria we used: only RCTs with a 100% hypertensive population were eligible for inclusion. However, some interventions in specific subgroups (e.g. patients with heart failure, post-myocardial infarction, chronic kidney disease…) have not been studied in a 100% hypertensive population. The reason for this is that certain antihypertensive drugs are used for treating these conditions, irrespective of the initial blood pressure, because they have been found to improve survival or decrease morbidity. They are sometimes relevant for certain clinical questions/questions to the jury because these studies may provide indirect information on the choice of antihypertensive drug in a specific population. Some of the included guidelines base themselves on this indirect information to provide recommendations. In cases where information from these trials in non-100% hypertensive populations is of interest, they are briefly mentioned and main results laid out, but they are not analyzed in depth as they are outside the scope of this literature review.

The criteria for reporting those studies are as follows: RCTs in which a mixed hypertensive/normotensive population is studied, which examines a comparison of interest in a high risk subgroup of interest, and which reports information on the subgroup of hypertensive patients. This will not (and cannot) be a complete list, but may give an idea to the reader as to why guidelines choose a certain antihypertensive drug in a specific condition.

2.1.6 Heart failure

We found little to no studies in a hypertensive population with heart failure. Guidelines recommend certain drugs (ACE-inhibitors, angiotensin receptor blockers, beta-blockers, diuretics,…) for the treatment of hypertension in heart failure; these recommendations are based on:

- Studies in hypertensive populations without heart failure, that evaluate the outcome "incident heart failure" (e.g. studies in diuretics).
- Studies that evaluated these drugs in patients with heart failure, who did not necessarily have hypertension. Therefore, these are studies on drugs that improve the prognosis of heart failure (morbidity – mortality).

Treatment of heart failure is a complex issue that warrants its own in-depth research. Because this literature review is not an analysis on the treatment of heart failure but rather focusses on hypertension, discussing these studies would lead us too far.

2.2 Comparisons

2.2.1 Targets

We have included studies that evaluated target blood pressure in several different ways.

Some studies have directly compared two different target blood pressures by randomizing the participants to different targets (e.g. <140 mmHg vs <130 mmHg), regardless of the blood pressure that patients in the study actually achieved. Not only the choice of the target, but also the different treatment strategies used to reach this goal (choice of drug, intensification by adding different drugs or by increasing the dosage,…) can influence the outcomes.

Some studies have compared the risk associated with different blood pressure values that were actually achieved in the study. Those studies are often observational studies or post hoc analyses of

achieved blood pressures in RCTs. Observational studies are susceptible to selection bias and to other confounding factors. In the case of an RCT looking at the achieved blood pressure as an endpoint, rather than at the allocated treatment target, interpretation can also be misleading. This method neglects the principles of randomization and intention-to-treat analysis. The cohort with the lower achieved blood pressure may represent a population that is different at baseline (lower baseline blood pressure, better compliance, patients in whom the blood pressure is more easily reduced) than the cohort with the higher achieved blood pressure[4]. Furthermore, as the settings in studies do not always accurately represent the reality of clinical practice, it is difficult to extrapolate their reported results to all patients, and their clinical relevance is limited[5].
Some studies worked with a set target blood pressure, but compared risk associated with treatment versus no treatment. These cannot inform us about whether this blood pressure target is the ideal target, only whether this blood pressure target seems safe to achieve.

2.2.2 Note on head to head trials

From NICE 2011[1]:
"Most studies reported comparisons involving two or more drug classes in each treatment arm administered according to a stepped administration protocol. In such cases, an initial antihypertensive drug would be administered, followed by either:
• an increase in the dosage of the first drug, and/or
• the addition of a second drug if blood pressure targets were not reached using the first drug alone.
All results should therefore be interpreted as demonstrating the efficacy and tolerability of each drug only when used as the initial step in a wider antihypertensive drug treatment regimen."
The therapeutic arsenal against hypertension is vast, with several categories of drugs, and within these categories, different drugs. The possible combinations for head to head trials - pitting one drug against another - are numerous, even more so when two of them are compared. On top of that, there are relatively few of those trials. This leaves us with several head to head comparisons left unexplored.

2.3 Outcomes

The Organising Committee requested we report only relevant hard outcomes.
Hard outcomes are for example mortality, stroke or myocardial infarction. Intermediate outcomes are for example blood pressure lowering. Hard outcomes are typically less susceptible to be influenced by factors like lack of allocation concealment or inadequate randomization, or by the assessor. This is of importance since quite some studies were open label, or open label with blinded endpoint assessment.

2.3.1 Blood pressure measurements

There are many different blood pressure measurement techniques: office BP measurement (auscultatory or oscillometric techniques), home BP monitoring, ambulatory BP monitoring,… The used measurement technique can influence the measured BP values, and can be a source of heterogeneity between studies.
Most trials specified office BP measurements, although we do report some studies where home BP monitoring is used.

2.3.2 Composite outcomes

Many trials use composite outcomes to limit study population size or follow-up time. In a useful composite outcome, all components should have equal importance to the patient, and the expected effect of the intervention should be similar. It is important that this composite outcome is clearly defined in the protocol, and is not altered in the course of the trial[5].
There is a lot of heterogeneity of the composite outcomes in the studies used in this report. Their interpretation should be done with caution, taking into account the factors described above.

2.3.3 Adverse events

A lot of trials reported adverse effects, or withdrawal due to adverse effects. However the effects that were reported depended heavily on the comparison and were not the same across head to head comparison. Also, most trials worked with additional drugs or with a stepped regimen to achieve target blood pressure. The other drugs used (aside from the evaluated study drug) can have an effect on the reported adverse effects.

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 [6,7]. If the absolute risk reduction is very small, 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

- 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 Observational studies

To evaluate threshold and target blood pressure, we have included the results of observational studies.
An observational study cannot prove a causal link, it can merely establish an association between the treatment 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.

2.4.3 Post-hoc analyses

For certain populations, the available trials are of very poor quality: mostly post-hoc subgroup analyses. These post-hoc analysis do not guarantee that randomization is preserved and groups are big enough to draw conclusions. For these reasons, post-hoc analyses are reported as observational data in this report.

A few predefined subgroup analyses were found, but no correction was made for the use of multiple comparisons. Caution is warranted in the interpretation of these analyses, because the more subgroup analyses are performed, the bigger the chance that the result found is caused by accident[8,9].

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3 Guidelines

3.1 General information on selected guidelines

3.1.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 5. The NVDPA CV risk guideline was selected for its paragraph on patient adherence only.

Abbreviation	Guideline
CHEP Hypertension 2015(4)	The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension
Domus Medica Hypertension 2009(5) and update 2013(6)	Domus Medica - Richtlijn voor goede medische praktijkvoering: Hypertensie (herziening) 2009 en opvolgrapport 2013
ESH/ESC Hypertension 2013(7)	ESH/ESC Guidelines for the management of arterial hypertension - 2013
JNC-8 Hypertension 2014(8)	2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults - Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)
NICE Hypertension 2011(3)	NICE - The clinical management of primary hypertension in adults 2011 and Evidence update 2013
NVDPA CV risk 2012(9)	National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012.

Table 5: Selected guidelines and their abbreviations as used in this report.

Additionally, recommendations from the following guidelines are cited because the selected guidelines refer to these documents:

Abbreviation	Guideline
Domus Medica Heart failure 2011(10)	Domus Medica – Richtlijn voor goede medische praktijkvoering: Chronisch hartfalen - 2011
Domus Medica – CNI 2012(11)	Domus Medica – Richtlijn voor goede medische praktijkvoering: Chronische nierinsufficiëntie - 2012(11)
NICE CKD 2014(12)	NICE - Early identification and management of chronic kidney disease in adults in primary and secondary care

Table 6: Guidelines referred to by the selected guidelines

The selected guideline “NICE Hypertension 2011” refers to the guideline “NICE – Secondary prevention in primary and secondary care for patients following a myocardial infarction (2013) (NICE CG48)” in the section about treatment of hypertension in post-myocardial infarction. However, the NICE CG48 guideline refers back to the NICE Hypertension guideline for this section. Therefore, the NICE myocardial infarction guideline is not discussed separately in this document.

3.1.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Table 7 to Table 13.

CHEP Hypertension 2015(4)		
Grades of recommendation	No grades of recommendation. The CHEP does not use these terms because all CHEP recommendations are considered to be 'strong' in nature (ie, CHEP refrains from making 'weak' recommendations).	
Levels of evidence	A	Recommendations are based on randomized trials (or systematic reviews of trials) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes.
	B	Recommendations are based on randomized trials, systematic reviews or pre-specified subgroup analyses of randomized trials that have lower precision, or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes.
	C	Recommendations are based on trials that have lower levels of internal validity and/or precision, or trials reporting unvalidated surrogate outcomes, or results from non-randomized observational studies.
	D	Recommendations are based on expert opinion alone

Table 7: Grades of recommendation and Level of evidence of CHEP guidelines.

Domus Medica Hypertensie 2009(5) en opvolgrapport 2013(6); Domus Medica Heart failure 2011; Domus Medica CNI 2012		
Grades of recommendation	1	Strong recommendation; Benefits clearly outweigh harms or risks
	2	Weak recommendation; Balance between benefits and harms or risks OR uncertain balance between benefits and harms or risks; possibly balanced
Levels of evidence	A	RCT's without limitations or very convincing evidence from observational studies
	B	RCT's with limitations or strong evidence from observational studies
	C	Observational studies or case studies

Table 8: Grades of recommendation and Level of evidence of Domus Medica guidelines.

ESH/ESC Hypertension 2013(7)			
Grades of recommendation	Class	Definition	Suggested wording to use
	I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
	II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given	

		treatment or procedure.	
	IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
	IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
	III	Evidence 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	A	Data derived from multiple randomized clinical trials or meta-analyses.	
	B	Data derived from a single randomized clinical trial or large non-randomized studies.	
	C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.	

Table 9: Grades of recommendation and Level of evidence of ESH/ESC Hypertension guideline.

JNC-8 Hypertension 2014(8)		
Grades of recommendation	A	Strong Recommendation There is high certainty based on evidence that the net benefit is substantial.
	B	Moderate Recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.
	C	Weak Recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
	D	Recommendation against There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
	E	Expert Opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee 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 committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
	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 committee thought no recommendation should be made. Further research is recommended in this area.

Levels of evidence	High	Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect
	Moderate	RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed non–randomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses 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
	Low	RCTs with major limitations Non–randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses 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.

Table 10: Grades of recommendation and Level of evidence of JNC-8 Hypertension 2014 guideline.

NICE Hypertension 2011(3)		
No grades of recommendation		
Levels of evidence	High	Further research is very unlikely to change our confidence in the estimate of effect
	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
	Very low	Any estimate of effect is very uncertain

Table 11: Grades of recommendation and Level of evidence of NICE Hypertension 2011 guideline.

NVDPA CV risk 2012(9)		
Grades of recommendation	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for

		recommendation but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
Additional guidance/ Levels of evidence	CBR	Consensus-based recommendations: developed by the guidelines expert working group when a systematic review of the evidence found either an absence of direct evidence which answered the clinical question or poor quality evidence, which was deemed not to be strong enough to formulate an evidence-based recommendation.
	PP	Practice points: developed by the guidelines expert working group where a systematic review had not been conducted but there was a need to provide practical guidance to support the implementation of the evidence-based and/or consensus-based recommendations.

Table 12: Grades of recommendation and Level of evidence of NVDPA CV risk 2012 guideline.

NICE CKD 2014(12)		
Grades of recommendation	Interventions that must (or must not) be used	If there is a legal duty to apply the recommendation or occasionally if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Interventions that should (or should not) be used (strong recommendation) “offer”; “refer”; “advise”	For the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when they are confident that an intervention will not be of benefit for most patients.
	Interventions that could be used	An intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences.
Levels of evidence	High	Future research unlikely to change confidence in estimate of effect.
	Moderate	Further research likely to have an important impact on confidence in estimate of effect and may change the estimate.
	Low	Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate.
	Very Low	The estimate of effect is very uncertain.

Table 13: Grades of recommendation and Level of evidence of NICE CKD 2014 guideline.

3.1.3 Agree II score

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

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 14. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
CHEP Hypertension 2015(4)	6	5	6	6	6	6	4	7	**46**	**82%**
Domus Medica Hypertension 2009(5) and update 2013(6)	5	4	3	4	5	7	6	7	**41**	**73%**
ESH/ESC Hypertension 2013(7)	1	2	6	2	3	7	6	1	**28**	**50%**
JNC-8 Hypertension 2014(8)	7	7	6	6	5	7	7	1	**46**	**82%**
NICE Hypertension 2011(3)	7	7	7	5	7	5	4	5	**47**	**84%**
NVDPA CV risk 2012(9)	7	7	5	5	5	7	4	5	**45**	**80%**
Domus Medica Heart failure 2011(10)	5	4	3	4	5	7	7	7	**42**	**75%**
Domus Medica CNI 2012(11)	4	4	3	1	5	7	7	5	**36**	**64%**
NICE CKD 2014(12)	7	7	7	5	7	7	7	5	**52**	**93%**

Table 14: AGREE score of selected guidelines on item “Rigour of development”, see 1.1.2.6 for a description of the items.

3.1.4 Included populations – interventions – main outcomes

In Table 15 to Table 23, the populations, interventions and main outcomes considered in the selected guidelines are represented.

CHEP Hypertension 2015(4)	
Population	- Adults with hypertension
Interventions	- Assessment - Non-pharmacological interventions - Indications for drug therapy - Choice of therapy: initial therapy, combination therapy - Treatment BP target - Isolated systolic hypertension - Hypertension and comorbidity: ischemic heart disease, recent myocardial infarction, heart failure, stroke, chronic kidney disease, renovascular disease, diabetes
Outcomes	- Cardiovascular morbidity - Cardiovascular mortality - Total mortality - Health behaviour recommendations: BP - Patients with CKD: progressive renal impairment

Table 15: Included population, intervention and main outcomes of CHEP Hypertension guideline.

Domus Medica Hypertension 2009(5) and update 2013(6)	
Population	- Adult patients between 40 and 80 years of age, in response to a BP measurement (case finding) and/or in the context of follow-up of an elevated BP measurement
Interventions	- Case finding - Diagnosis

	- Assessment - Treatment thresholds and targets - Non-pharmacological treatment - Pharmacological treatment in hypertension without and with comorbidity (chronic kidney disease, coronary artery disease, heart failure, type 2 diabetes, post CVA/TIA) - Follow-up - Referral
Outcomes	- Not specified

Table 16: Included population, intervention and main outcomes of Domus Medica Hypertension guideline.

ESH/ESC Hypertension 2013(7)	
Population	- Adults >18y
Interventions	- Evidence favouring reduction of BP - When to initiate antihypertensive treatment, also in subgroups - Treatment targets - Choice of antihypertensive drugs - Monotherapy and combination therapy - Specific groups: elderly, diabetes, cerebrovascular disease, nefropathy, coronary heart disease, heart failure, adherence
Outcomes	- Not specified

Table 17: Included population, intervention and main outcomes of the ESH/ESC Hypertension 2013 guideline.

JNC-8 Hypertension 2014(8)	

Population	- adults aged 18 years or older with hypertension
	- prespecified subgroups:
	  o diabetes
	  o coronary artery disease
	  o peripheral artery disease
	  o heart failure
	  o previous stroke
	  o chronic kidney disease (CKD)
	  o proteinuria
	  o older adults
	  o men and women
	  o racial and ethnic groups
	  o smokers

Interventions	- Initiating antihypertensive pharmacologic therapy at a specific BP - Treatment with antihypertensive pharmacologic therapy to a specified BP goal - Comparison of various antihypertensive drugs or drug classes
Outcomes	- Overall mortality, cardiovascular disease (CVD)–related mortality, CKD-related mortality - Myocardial infarction, heart failure, hospitalization for heart failure, stroke - Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement),

	other revascularization (includes carotid, renal, and lower extremity revascularization) - End-stage renal disease (ESRD) (ie, kidney failure resulting in dialysis or transplantation), o doubling of creatinine level, halving of glomerular filtration rate (GFR).

Table 18: Included population, intervention and main outcomes of the JNC-8 Hypertension 2014 guideline.

NICE Hypertension 2011(3)	
Population	- Adults with hypertension (18 years and older). - Particular consideration will be given to the needs of black people of African and Caribbean descent and minority ethnic groups where these differ from the needs of the general population. - People aged 80 years or older.
Interventions	- Ambulatory monitoring. - Home blood pressure monitoring. - Blood pressure thresholds for intervention and targets for treatment. - First-line therapy options, for example angiotensin-converting enzyme inhibitors versus angiotension receptors blockers. - Calcium-channel blockers versus diuretics as preferred components in step two of the treatment algorithm, for example, combination therapy. - Adherence to medication. - Provision of appropriate information and support. - Resistant hypertension (that is, fourth-line therapy). - Response to blood pressure lowering drugs according to age and ethnicity

Outcomes	- Effectiveness
	  o Mortality from any cause
	  o Stroke (ischaemic or haemorrhagic)
	  o Myocardial infarction (MI) (including, where reported, silent MI)
	  o Heart failure
	  o New onset diabetes
	  o Vascular procedures (including both coronary and carotid artery procedures)
	  o Angina requiring hospitalisation
	  o Health-related quality of life (to use what is reported by trials)
	  o Major adverse cardiac and cerebrovascular events: fatal and non-fatal MI, fatal and non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation (AND DIFFERENT COMPOSITES OF THIS OUTCOME)
	  o BP lowering
	- Safety
	  o Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence)

	○ Angiooedema in black people of African and Caribbean descent

Table 19: Included population, intervention and main outcomes of the NICE Hypertension 2011 guideline.

NVDPA CV risk 2012(9)	
Population	The Guidelines for the Management of Absolute Cardiovascular Disease Risk make recommendations regarding the management of cardiovascular risk in Australian adults aged 45 years and over (35 years for Aboriginal and Torres Strait Islander peoples) who have no previous history of CVD
Interventions	- Assessment and review of CVD risk - Treatment: ○ Non-pharmacological ○ Pharmacotherapy (blood pressure-lowering, lipid-lowering, antiplatelet therapy) ○ People with diabetes, CKD - Monitoring of pharmacotherapy (maximizing benefits, patient adherence)
Outcomes	In principle, the primary outcome for each question was cardiovascular events (definition for CVD as for the Guidelines for the Assessment of Absolute Cardiovascular Disease Risk: "group term for all medical conditions affecting the heart or blood vessels (e.g. coronary heart disease, stroke,peripheral arterial disease, some types of kidney disease)"). The secondary outcome of interest was AR reduction, followed by surrogate outcomes such as individual risk factor reduction as specified in the questions (e.g. BP control).

Table 20: Included population, intervention and main outcomes of NVDPA CV risk guideline.

Domus Medica Heart failure 2011(10)	
Population	Adult patient with diagnosed or suspected chronic heart failure
Interventions	-Diagnosis and assessment of heart failure -Treatment of heart failure -Multidisciplinary revalidation and follow-up -Palliation
Outcomes	Not specified

Table 21: Included population, intervention and main outcomes of the Domus Medica Heart failure 2011 guideline.

Domus Medica CNI 2012(11)	
Population	- Adult patients (older than 18 years) with a chronic decreased renal function. Acute forms are not included.
Interventions	- Those aiming to slow down of progression of the disease. - Treatment of the symptomatology - The causal treatment is not considered
Outcomes	- Not described.

Table 22: Included population, intervention and main outcomes of Domus Medica CNI 2012 guideline.

NICE CKD 2014(12)	
Population	- Adults aged 18 and over. Specific consideration is given to older people, black and minority ethnic people and people at high risk of developing CKD
Interventions	- Measurement of kidney function and markers of kidney damage,

	frequency of monitoring, classification of CKD. - Non-pharmacological interventions: Diet, self-management support systems - Pharmacological therapy: renin-angiotensin-aldosterone system antagonists, antiplatelet and antithrombotic therapy, uric acid lowering therapy, vitamin D and bicarbonate supplementation
Outcomes	- Diagnostic: accuracy, bias, precision, sensitivity/specificity, area under curve - CKD progression, acute kidney injury - Mortality (all cause and cardiovascular) - Hospitalization - Side effects

Table 23: Included population, intervention and main outcomes of the NICE CKD 2014 guideline.

3.1.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 24 to Table 32.

CHEP Hypertension 2015(4)	
Development group	The CHEP Recommendations Task Force is a multidisciplinary panel of content and methodological experts comprised of 2 Co-Chairs, a Central Review Committee, and 14 subgroups. Each subgroup addresses a distinct content area in the field of hypertension
Target audience	Primary care and other health care providers

Table 24: Members of the development group and target audience of the CHEP Hypertension 2015 guideline.

Domus Medica Hypertension 2009(5) and update 2013(6)	
Development group	- Family physicians
Target audience	- Family physicians

Table 25: Members of the development group and target audience of the Domus Medica Hypertension 2009 and update 2013 guideline.

ESH/ESC Hypertension 2013(7)	
Development group	- Task Force (experts)
Target audience	- Physicians

Table 26: Members of the development group and target audience ESH/ESC Hypertension 2013 guideline.

JNC-8 Hypertension 2014(8)	
Development group	- The panel members appointed to JNC 8 were selected from more than 400 nominees based on expertise in hypertension (n = 14), primary care (n = 6), including geriatrics (n = 2), cardiology (n = 2), nephrology (n = 3), nursing (n = 1), pharmacology (n = 2), clinical trials (n = 6), evidence-based medicine (n = 3), epidemiology (n = 1), informatics (n = 4), and the development and Implementation of clinical guidelines in systems of care (n = 4).
Target audience	- Primary care providers

Table 27: Members of the development group and target audience of the JNC-8 Hypertension 2014 guideline.

NICE Hypertension 2011(3)

Development group	- A multidisciplinary Guideline Development Group comprising professional group members and consumer representatives of the main stakeholders developed this guideline. Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists.
Target audience	- Health professionals

Table 28: Members of the development group and target audience of the NICE Hypertension 2011 guideline.

NVDPA CV risk 2012(9)	
Development group	Multidisciplinary expert working group – 12 members including endocrinologists, cardiologists, nephrologists, general practitioners, geriatricians, a consumer and a PBAC representative.
Target audience	The Guidelines for the Management of Absolute CVD Risk are intended for use by general practitioners, Aboriginal health workers, other primary care health professionals and physicians. They are intended to provide health system policy makers with the best available evidence as a basis for population health policy

Table 29: Members of the development group and target audience of the NVDPA CV risk 2012 guideline.

Domus Medica Heart failure 2011(10)	
Development group	Family physicians and cardiologists
Target audience	Family physicians

Table 30: Members of the development group and target audience of the Domus Medica Heart failure 2011 guideline.

Domus Medica CNI 2012(11)	
Development group	Family physicians
Target audience	Family physicians

Table 31: Members of the development group and target audience of the Domus Medica CNI 2012 guideline.

NICE CKD 2014(12)	
Development group	Multidisciplinary, comprising professional group members and consumer representatives of the main stakeholders.
Target audience	Health care professionals and others.

Table 32: Members of the development group and target audience of the NICE CKD 2014 guideline.

3.1.6 Method of reporting of the recommendations and notes

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

Even though the NICE Hypertension 2011 guideline did not grade its recommendations, it does appraise and determine a level of evidence for the studies leading to the recommendations. For that reason, the recommendations of the NICE Hypertension 2011 guideline are also written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

3.2 Guidelines: Diagnosis (How is hypertension defined?)

3.2.1 CHEP hypertension 2015(4)

The CHEP Hypertension 2015 guideline defines different thresholds for diagnosis of hypertension, depending on the measurement technique:

Four approaches can be used to assess BP:

- **Office blood pressure measurement (OBPM): Measurement using electronic (oscillometric) upper arm devices is preferred over auscultation (Grade C) (unless specified otherwise, henceforth OBPM refers to electronic [oscillometric] measurement). When using mean OBPM, a systolic BP (SBP) ≥140 mmHg or a diastolic BP (DBP) ≥90 mmHg is high, and an SBP between 130-139 mmHg and/or a DBP between 85-89 mmHg is high-normal (Grade C).**
- **Ambulatory office blood pressure (AOBP): When using AOBP, a displayed mean SBP ≥135 mmHg or DBP ≥85 mmHg DBP is high (Grade D).**
- **Ambulatory blood pressure measurement (ABPM): Using ABPM, patients can be diagnosed as hypertensive if the mean awake SBP is ≥135 mmHg or the DBP is ≥85 mmHg or if the mean 24-hour SBP is ≥130 mmHg or the DBP is ≥80 mmHg (Grade C).**
- **Home blood pressure measurement (HBPM): Patients can be diagnosed as hypertensive if the mean SBP is ≥135 mmHg or the DBP is ≥85 mmHg (Grade C). If the OBPM is high and the mean home BP is <135/85 mm Hg, it is advisable to either repeat home monitoring to confirm the home BP is <135/85 mmHg or perform 24-hour ABPM to confirm that the mean 24-hour ABPM is <130/80 mmHg and the mean awake ABPM is <135/85 mmHg before diagnosing WCH (Grade D).**

Category	Systolic (mmHg)		Diastolic (mmHg)
High-normal	130-139 OBPM)	And/or	85-89 (OBPM)
High (hypertensive)	≥140 (OBPM) ≥135 (AOBP, ABPM, HBPM) ≥130 (ABPM24h)	And/or	≥90 (OBPM) ≥85 (AOBP, ABPM, HBPM) ≥80 (ABPM24h)

Table 33: Categories of blood pressure values as defined by CHEP Hypertension 2015. OBPM= Office blood pressure measurement; AOBP= Ambulatory office blood pressure; ABPM= Ambulatory blood pressure measurement; HBPM= Home blood pressure measurement; ABPM24h= 24-hour ambulatory blood pressure measurement

3.2.2 Domus Medica Hypertension 2009(5)

Category	Systolic (mmHg)		Diastolic (mmHg)
Hypertension	≥140	And/or	≥90
Severe hypertension	≥180	And/or	≥110
Isolated systolic hypertension	≥140	And	<90

Table 34: Categories of blood pressure values as defined by Domus Medica Hypertension 2009

3.2.3 ESH/ESC Hypertension 2013(7)

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	And	<80

Normal	120-129	And/or	80-84
High normal	130-139	And/or	85-89
Grade 1 hypertension	140-159	And/or	90-99
Grade 2 hypertension	160-179	And/or	100-109
Grade 3 hypertension	≥180	And/or	≥110
Isolated systolic hypertension	≥140	And	<90

Table 35: Categories of blood pressure values as defined by ESH/ESC Hypertension 2013

3.2.4 JNC-8 Hypertension 2014(8)

Note: definitions come from the JNC-7 guideline.

Category	Systolic (mmHg)		Diastolic (mmHg)
Hypertension	≥140	And/or	≥90

Table 36: Categories of blood pressure values as defined by JNC-8

3.2.5 NICE Hypertension 2011(3)

Note: definitions from the NICE 2004 Hypertension guideline.

Category	BP (mmHg)
Grade 1 hypertension	140-159/90-99
Grade 2 hypertension	≥160/100

Table 37: Categories of blood pressure values as defined by NICE Hypertension 2011

3.2.6 Summary

Different guidelines use slightly different definitions of hypertension and normal blood pressure, some choosing to utilize only two categories, others using up to seven different categories to cover the spectrum of blood pressure values. Most guidelines define hypertension as ≥140/90 mmHg, measured in office. With the exception of CHEP, no levels of evidence are provided for these definitions.

Definition of hypertension				
Guideline	**Category**	**Systolic (mmHg)**		**Diastolic (mmHg)**
CHEP	High-normal	130-139 (OBPM)	And/or	85-89 (OBPM)
	High (hypertensive)	≥140 (OBPM) ≥135 (AOBP, ABPM, HBPM) ≥130 (ABPM24h)	And/or	≥90 (OBPM) ≥85 (AOBP, ABPM, HBPM) ≥80 (ABPM24h)
Domus	Hypertension	≥140	And/or	≥90
	Severe hypertension	≥180	And/or	≥110
	Isolated systolic hypertension	≥140	And	<90
ESH/ESC	Optimal	<120	And	<80
	Normal	120-129	And/or	80-84
	High normal	130-139	And/or	85-89
	Grade 1 hypertension	140-159	And/or	90-99
	Grade 2 hypertension	160-179	And/or	100-109
	Grade 3 hypertension	≥180	And/or	≥110

	Isolated systolic hypertension	≥140	And	<90
JNC-8	Hypertension	≥140	And/or	≥90
NICE	Grade 1 hypertension	140-159	And/or	90-99
	Grade 2 hypertension	≥160	And/or	100

Table 38: Summary of categories of blood pressure values, as defined by selected guidelines. OBPM= Office blood pressure measurement; AOBP= Ambulatory office blood pressure; ABPM= Ambulatory blood pressure measurement; HBPM= Home blood pressure measurement; ABPM24h= 24-hour ambulatory blood pressure measurement

3.3 Guidelines: Threshold (when to start treatment)

3.3.1 Treatment threshold in adults with primary uncomplicated hypertension

3.3.1.1 CHEP Hypertension 2015(4)

Please note that treatment thresholds and targets refer to office BP measurement because the studies used to identify targets and evaluate treatment have largely used this mode of BP measurement.

Antihypertensive therapy should be prescribed for average DBP measurements of ≥100 mm Hg (Grade A) or average SBP measurements of ≥160 mm Hg (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.

3.3.1.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In persons with strongly elevated BP measurements, the family physician will start a treatment regardless of cardiovascular risk (immediately if systolic BP >180 mmHg, diastolic BP > 110 mmHg, or after several months if non-pharmacological advice proves ineffective with systolic BP >160 mmHg and diastolic BP >100 mmHg. (GRADE 1C)

For all other patients, the physician will first assess the cardiovascular risk (GRADE 1B):

- **In persons with a SCORE-risk of <5%: pharmacological treatment only when BP measurements are strongly elevated.**

Note: cardiovascular risk refers to the risk of cardiovascular death in the next ten years, based on the SCORE-model and adjusted to the circumstances in Belgium.

3.3.1.3 ESH/ESC Hypertension 2013(7)

Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes. (IA)

Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures. (IIaB)

Unless the necessary evidence is obtained it is not recommended to initiate antihypertensive drug therapy at high normal BP. (IIIA)

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

FIGURE 2 Initiation of lifestyle changes and antihypertensive drug treatment. Targets of treatment are also indicated. Colours are as in Figure 1. Consult Section 6.6 for evidence that, in patients with diabetes, the optimal DBP target is between 80 and 85 mmHg. In the high normal BP range, drug treatment should be considered in the presence of a raised out-of-office BP (masked hypertension). Consult section 4.2.4 for lack of evidence in favour of drug treatment in young individuals with isolated systolic hypertension.

3.3.1.4 JNC-8 Hypertension 2014(8)

In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90mmHg and treat to a goal DBP <90mmHg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140mmHg and treat to a goal SBP <140mmHg. (Expert Opinion – Grade E)

3.3.1.5 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people of any age with stage 2 hypertension. (Not graded)

3.3.1.6 Summary

Most guidelines agree that treatment should be initiated at a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure of ≥100 mmHg in adults with primary uncomplicated hypertension. The two guidelines that mention timing suggest that pharmacological treatment should be initiated after a period of several weeks with only non-pharmacological intervention. They also suggest to start pharmacological treatment immediately if BP values are ≥180/≥110 mmHg. JNC-8 has a threshold of SBP ≥140 mmHg and/or DBP ≥90 mmHg. ESH/ESC suggests to start pharmacological

treatment at this threshold only after several months of non-pharmacological intervention. No guideline recommends initiating treatment at BP values below 140/90 mmHg.

Threshold						
Primary uncomplicated hypertension						
	AGREE	**Systolic (mmHg)**		**Diastolic (mmHg)**	**Timing**	**GoR/LoE**
CHEP	82%	≥160		≥100	-	A
Domus	73%	>180		>110	immediately	1C
		160-179		100-109	After several weeks	1C
ESH/ESC	50%	≥180		≥110	immediately	IA
		160-179	**OR**	100-109	After several weeks	IA
		140-159		90-99	After several months	IIaB
		130-139		85-89	NOT recommended	IIIA
JNC-8	82%	≥140		≥90	-	E
NICE	84%	≥160		≥100	-	NG

Table 39: Summary of BP thresholds in primary uncomplicated hypertension in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.3.2 Treatment threshold in adult with hypertension, with or without additional cardiovascular risk factors

3.3.2.1 CHEP Hypertension 2015(4)

Antihypertensive therapy should be strongly considered if DBP readings average ≥90 mm Hg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors (Grade A).

Antihypertensive therapy should be strongly considered if SBP readings average≥ 140 mm Hg in the presence of macrovascular target organ damage (Grade C for 140-160 mm Hg; Grade A for > 160 mm Hg).

3.3.2.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In persons with strongly elevated BP measurements, the family physician will start a treatment regardless of cardiovascular risk (immediately if systolic >180 mmHg, diastolic > 110 mmHg, or after several months if non-pharmacological advice proves ineffective with systolic >160 mmHg and diastolic >100 mmHg. (GRADE 1C)

For all other patients, the physician will first assess the cardiovascular risk (GRADE 1B):

- **In high risk patients (SCORE >10%) and in patients with a history of cardiovascular disease or organ damage: initiate treatment swiftly and strive for strict BP control (<140/90 mmHg; for diabetes type 2 <130/80 mmHg;**

- **In persons with a SCORE-risk between 5 and 10%: the treatment will depend on the presence of several other factors, like family history (for a first degree relative with a cardiovascular event, female aged <65y, male <55y, the SCORE-risk is multiplied by 1,5), the degree of sedentarism and (abdominal) obesity;**
- **In persons with a SCORE-risk of <5%: pharmacological treatment only when BP measurements are strongly elevated.**

Note: cardiovascular risk refers to the risk of cardiovascular death in the next ten years, based on the SCORE-model and adjusted to the circumstances in Belgium.

3.3.2.3 ESH/ESC Hypertension 2013(7)

Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes. (IA)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range. (IB)

Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures. (IIaB)

Unless the necessary evidence is obtained it is not recommended to initiate antihypertensive drug therapy at high normal BP. (IIIA)

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

FIGURE 2 Initiation of lifestyle changes and antihypertensive drug treatment. Targets of treatment are also indicated. Colours are as in Figure 1. Consult Section 6.6 for evidence that, in patients with diabetes, the optimal DBP target is between 80 and 85 mmHg. In the high normal BP range, drug treatment should be considered in the presence of a raised out-of-office BP (masked hypertension). Consult section 4.2.4 for lack of evidence in favour of drug treatment in young individuals with isolated systolic hypertension.

3.3.2.4 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following (not graded):

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool(13).

3.3.2.5 Summary

The guidelines agree that the threshold to start pharmacological treatment in people with organ damage or CV risk factors is at or above an SBP of 140 and/or a DBP of 90 mmHg. The CHEP guideline specifies that for this threshold, the level of evidence is lower than for an SBP of 160 and above.

Thresholds						
Organ damage or CV risk factors						
	AGREE	**Systolic (mmHg)**	**GoR/ LoE**		**Diastolic (mmHg)**	**GoR/ LoE**
CHEP	82%	140-160	C	**OR**	≥90	A
		>160	A			
Domus*	73%	>140	1B		>90	1B
ESH/ESC	50%	≥140	IB		≥90	IB
NICE**	84%	≥140	NG		≥90	NG

Table 40: Summary of BP thresholds in patients with organ damage or cardiovascular risk factors in selected guidelines. *if SCORE is >10% **if 10y CV risk is >20% GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.3.3 Hypertension treatment threshold in elderly patients

3.3.3.1 Elderly patients ≥ 60 years

3.3.3.1.1 CHEP Hypertension 2015(4)

Antihypertensive therapy should be considered in all patients meeting indications 1-3 (see below), regardless of age (Grade B).

1) **Antihypertensive therapy should be prescribed for average DBP measurements of ≥100 mm Hg (Grade A) or average SBP measurements of ≥160 mm Hg (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors.**

2) **Antihypertensive therapy should be strongly considered if DBP readings average ≥90 mm Hg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors (Grade A).**

3) **Antihypertensive therapy should be strongly considered if SBP readings average≥ 140 mm Hg in the presence of macrovascular target organ damage (Grade C for 140-160 mm Hg; Grade A for > 160 mm Hg).**

Caution should be exercised in elderly patients who are frail. (not graded)

3.3.3.1.2 ESH/ESC Hypertension 2013(7)

In elderly hypertensive patients drug treatment is recommended when SBP is ≥160 mmHg.(IA)

Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated.(IIbC)

3.3.3.1.3 JNC-8 Hypertension 2014(8)

In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure at systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥90 mmHg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

3.3.3.2 Elderly patients ≥ 80 years

3.3.3.2.1.1 CHEP Hypertension 2015(4)

In the very elderly (aged ≥80 years) who do not have diabetes or target organ damage, the SBP threshold for initiating drug therapy is ≥160 mm Hg (Grade C).

3.3.3.3 Summary

The guidelines do not agree on the threshold for initiation of treatment for hypertension in elderly people. CHEP states that age does not play a role in choosing a threshold, only CV risk factors do. ESH/ESC states that for people ≥65 years old, the threshold is an SBP of ≥160 mmHg, but a lower threshold may be considered if treatment is well tolerated and if the patient is younger than 80 years. JNC-8 recommends a threshold of ≥150/90 mmHg for all patients aged 60 and above.

Thresholds						
Elderly						
	AGREE	**Systolic (mmHg)**		**Diastolic (mmHg)**		**GoR/ LoE**
CHEP	**82%**	≥160	**OR**	≥100	All patients, regardless of age/ no organ damage, no CV risk factors	B
		≥ 140		≥90	All patients, regardless of age/ in presence of organ damage or CV risk	B

					factors	
		≥160		-	≥80y without diabetes or organ damage	C
ESH/ESC	**50%**	≥160		-	≥65y	IA
		140-159		-	If well tolerated and <80y	IIbC
JNC-8	**82%**	≥150		≥90	≥60 y	A

Table 41: Summary of BP thresholds in the elderly in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.3.4 Hypertension treatment threshold in adults with type 2 diabetes

3.3.4.1 CHEP Hypertension 2015(4)

Persons with diabetes mellitus should be treated to attain SBP of < 130 mm Hg (Grade C) and DBP of < 80 mm Hg (Grade A) *(these target BP levels are the same as the BP treatment thresholds).*

3.3.4.2 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). (IB)

3.3.4.3 JNC-8 Hypertension 2014(8)

In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to a goal SBP <140 mmHg and goal DBP <90 mmHg. (Expert Opinion –Grade E)

3.3.4.4 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool(13)..

3.3.4.5 Summary

Most guidelines recommend a threshold of 140/90 mmHg in type 2 diabetics, with the exception of CHEP, which recommends a threshold of 130/80 mmHg.

Thresholds					
Type 2 diabetes					
	AGREE	**Systolic (mmHg)**		**Diastolic (mmHg)**	**GoR/ LoE**
CHEP	**82%**	130	**OR**	80	C
ESH/ESC	**50%**	140		90	IB

JNC-8	**84%**	140		90	E
NICE	**84%**	140		90	NG

Table 42: Summary of BP thresholds in type 2 diabetics in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.3.5 Hypertension treatment threshold in adults with chronic kidney disease

3.3.5.1 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). (IB)

3.3.5.2 JNC-8 Hypertension 2014(8)

In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to goal SBP <140 mmHg and goal DBP <90 mmHg. (Expert Opinion – Grade E)

3.3.5.3 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool (13)..

3.3.5.4 Summary

The guidelines agree on a threshold of 140/90 mmHg for initiation of hypertension treatment in patients with chronic kidney disease.

Thresholds					
Chronic kidney disease					
	AGREE	**Systolic (mmHg)**		**Diastolic (mmHg)**	**GoR/ LoE**
ESH/ESC	**50%**	140		90	IB
JNC-8	**84%**	140	**OR**	90	E
NICE	**84%**	140		90	NG

Table 43: Summary of BP thresholds in chronic kidney disease in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.3.6 Hypertension treatment threshold in adults with coronary disease

3.3.6.1 Adults with previous myocardial infarction

3.3.6.1.1 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). (IB)

3.3.6.1.2 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool (13)..

3.3.6.2 Adults with chronic stable angina

3.3.6.2.1 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). (IB)

3.3.6.2.2 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool(13)..

3.3.7 Hypertension treatment threshold in adults with heart failure

3.3.7.1 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). (IB)

3.3.7.2 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

Note: cardiovascular risk refers to risk of myocardial infarction or stroke in the next ten years, calculated with the QRISK2-tool(13)..

3.3.8 Hypertension treatment threshold in adults with previous stroke

3.3.8.1 ESH/ESC Hypertension 2013(7)

Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range (SBP 140–159 or DBP 90–99). IB

3.3.8.2 NICE Hypertension 2011(3)

Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:

- **target organ damage**
- **established cardiovascular disease**
- **renal disease**
- **diabetes**
- **a 10-year cardiovascular risk equivalent to 20% or greater.**

3.3.8.3 Summary

ESH/ESC and NICE recommend a threshold of 140/90 mmHg for initiation of hypertension treatment in patients with cardiovascular disease, without specifying between coronary heart disease, heart failure or previous stroke.

Thresholds					
Cardiovascular disease					
	AGREE	**Systolic (mmHg)**		**Diastolic (mmHg)**	**GoR/ LoE**
ESH/ESC	**50%**	140	**OR**	90	IB
NICE	**84%**	140		90	NG

Table 44: Summary of BP thresholds in cardiovascular disease in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4 Guidelines: Targets for treatment

3.4.1 Treatment target in adults with primary uncomplicated hypertension

3.4.1.1 CHEP Hypertension 2015(4)

The SBP treatment goal is a pressure level of < 140 mm Hg (Grade C). The DBP treatment goal is a pressure level of < 90 mm Hg (Grade A).

3.4.1.2 Domus Medica Hypertension 2009(5) and update 2013(6)

The target for treatment for hypertensive patients in middle age without comorbidities is <140/90 mmHg (conventional measurement technique) (GRADE 1B)

3.4.1.3 ESH/ESC Hypertension 2013(7)

A SBP goal <140 mmHg is recommended in patients at low–moderate CV risk (IB)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.1.4 JNC-8 Hypertension 2014(8)

In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90mmHg and treat to a goal DBP <90mmHg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140mmHg and treat to a goal SBP <140mmHg. (Expert Opinion – Grade E)

3.4.1.5 NICE hypertension 2011(3)

Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with treated hypertension.

3.4.1.6 Summary

In patients with primary uncomplicated hypertension, the treatment target is <140/90 mmHg in all guidelines.

Targets					
Primary uncomplicated hypertension					
	AGREE	**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	<140	C	<90	A
Domus	73%	<140	1B	<90	1B
ESH/ESC	50%	<140	IB	<90	IA
JNC-8	82%	<140	E	<90	A for ages 30-59
					E for ages 18-29

NICE	84%	<140	NG	<90	NG

Table 45: Summary of BP targets in primary uncomplicated hypertension in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.2 Treatment target in adult with hypertension, with our without additional risk factors

3.4.2.1 ESH/ESC Hypertension 2013(7)

A SBP goal <140 mmHg is recommended in patients at low–moderate CV risk (IB)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.2.2 Summary

The treatment BP target in patients with additional CV risk factors is only specified in one of the selected guidelines. This treatment target is <140/90 mmHg.

Targets					
Primary uncomplicated hypertension					
	AGREE	**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
ESH/ESC	50%	<140	IB	<90	IA

Table 46: Summary of BP targets in people with cardiovascular risk factors in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.3 Hypertension treatment target in elderly patients

3.4.3.1 Elderly patients > 60 years

3.4.3.1.1 ESH/ESC Hypertension 2013(7)

In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. (IA)

In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability. (IIbC)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.3.1.2 JNC-8 Hypertension 2014(8)

In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥90

mmHg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

In the general population aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140mmHg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

3.4.3.2 Elderly patients > 80 years

3.4.3.2.1 CHEP Hypertension 2015(4)

In the very elderly (age ≥80 years), the SBP target is <150 mm Hg (Grade C).

3.4.3.2.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In healthy people aged >80 years, without important comorbidities, we advise a target of 150/80 mmHg. In this vulnerable population the physician must compare the benefits and potentials harms of an antihypertensive treatment. (GRADE 2B)

3.4.3.2.3 ESH/ESC Hypertension 2013(7)

In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions (IB).

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.3.2.4 NICE hypertension 2011(3)

Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over with treated hypertension.

3.4.3.3 Summary

Most guidelines agree that for the very elderly (aged 80 or older), the treatment target is an SBP of <150 mmHg. For elderly (60/65y to 80y) people, treatment targets range from <150 to <140 mmHg in different guidelines. Most guidelines mention to take overall health and tolerability to treatment into account when deciding the treatment target in elderly people.

Target					
Elderly					
	AGREE	**Population**	**Systolic (mmHg)**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	≥80y	<150	-	C
Domus	73%	>80y and healthy without important comorbidities	150	80	2B
ESH/ESC	50%	Elderly <80y	150-140	-	IA

		Fit elderly <80y	<140		IIbC
		Fragile elderly	Adapted to individual tolerability		IIbC
		>80y in good physical and mental conditions	150-140		IB
JNC-8	82%	≥60y	<150	<90	A
NICE	84%	≥80y	<150	<90	NG

Table 47: Summary of BP targets in the elderly in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.4 Hypertension treatment target in adults with type 2 diabetes

3.4.4.1 CHEP Hypertension 2015(4)

Persons with diabetes mellitus should be treated to attain SBP of < 130 mm Hg (Grade C) and DBP of < 80 mm Hg (Grade A).

3.4.4.2 Domus Medica Hypertension 2009(5) and update 2013(6)

The target BP in diabetics without nephropathy is 130/80 mmHg; in case of diabetes with nephropathy: 125/75 mmHg (GRADE 1B)

3.4.4.3 ESH/ESC Hypertension 2013(7)

An SBP goal <140 mmHg is recommended in patients with diabetes (IA)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.4.4 JNC-8 Hypertension 2014(8)

In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to a goal SBP <140 mmHg and goal DBP <90 mmHg. (Expert Opinion –Grade E)

3.4.4.5 Summary

ESH/ESC and JNC-8 recommend a treatment SBP target of <140 mmHg in adults with type 2 diabetes, while CHEP and Domus Medica recommend lower treatment targets (<130 or 125 mmHg, depending on the presence or absence of nephropathy). Diastolic targets differ between guidelines as well, ranging from <90 to <80 mmHg or even 75 mmHg in the presence of nephropathy.

Targets						
Type 2 diabetes						
	AGREE		**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	-	<130	C	<80	A

Domus	73%	Without nephropathy	130	1B	80	1B
		With nephropathy	125	1B	75	1B
ESH/ESC	50%	-	<140	IA	-	-
JNC-8	82%	-	<140	E	<90	E

Table 48: Summary of BP targets in type 2 diabetics in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.5 Hypertension treatment target in adults with chronic kidney disease

3.4.5.1 CHEP Hypertension 2015(4)

For patients with nondiabetic chronic kidney disease, target BP is < 140/90 mm Hg (Grade B).

3.4.5.2 Domus Medica Hypertension 2009(5) and update 2013(6)

The target BP in case of kidney disease without proteinuria: 130/80 mmHg; in case of kidney disease with proteinuria: <125/75 mmHg (GRADE 1B)

3.4.5.3 ESH/ESC Hypertension 2013(7)

An SBP goal <140 mmHg should be considered in patients with diabetic or non-diabetic CKD. (IIaB) When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. (IIbB)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.5.4 JNC-8 Hypertension 2014(8)

In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to goal SBP <140 mmHg and goal DBP <90 mmHg. (Expert Opinion – Grade E)

3.4.5.5 Domus Medica CNI 2012(11)

In all patients with chronic renal failure, strive for an SBP between 120 and 139 mmHg and a DBP between 60 and 89 mmHg (Grade 1B).

3.4.5.6 NICE CKD 2014(12)

In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg. (not graded)

In people with CKD and diabetes, and also in people with an ACR of 70 mg/ mmol or more, aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg. (not graded)

3.4.5.7 Summary

In non-diabetic CKD patients without overt proteinuria, the guidelines agree on a treatment target of <140/90 mmHg, with the exception of Domus Medica Hypertension 2009, where the treatment target is 130/80.

In diabetic CKD patients, ESH/ESC recommends a treatment target of <140/85 mmHg, while NICE recommends a stricter target of <130/80 mmHg for this population.

In CKD patients with proteinuria, the treatment target differs between guidelines: SBP <130 to <125 mmHg and DBP from <90 to <75 mmHg.

Targets						
Chronic kidney disease						
	AGREE		**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	Non-diabetic	<140	B	<90	B
Domus	73%	Without proteinuria	130	1B	80	1B
		With proteinuria	<125	1B	<75	1B
ESH/ESC	50%	Non-diabetic	<140	IIaB	<90	IA
		Diabetic	<140	IIaB	<85	IA
		Overt proteinuria	<130	IIbB	<90	IA
JNC-8	82%	-	<140	E	<90	E
Domus CNI	64%	-	120-139	1B	60-89	1B
NICE CKD	93%	-	120-139	NG	<90	NG
		Diabetic or ACR of ≥70 mg/mmol	120-129	NG	<80	NG

Table 49: Summary of BP targets in chronic kidney disease in selected guidelines. ACR= Albumin/creatinine ratio. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.6 Hypertension treatment target in adults with coronary disease

3.4.6.1 Adults with previous myocardial infarction

3.4.6.2 Adults with chronic stable angina

3.4.6.2.1 CHEP Hypertension 2015(4)

Please note that the CHEP guideline uses the term “coronary artery disease” (CAD) and does not specify between previous myocardial infarction and chronic stable angina.

When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mm Hg because of concerns that myocardial ischemia might be exacerbated (Grade D).

3.4.6.2.2 ESH/ESC Hypertension 2013(7)

Please note that the CHEP guideline uses the term “coronary heart disease” (CHD) and does not specify between previous myocardial infarction and chronic stable angina.

A SBP goal <140 mmHg should be considered in patients with CHD. (IIaB)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.6.3 Summary

ESH/ESC recommends a treatment target of <140/90 mmHg in patients with coronary disease. CHEP warns against lowering DBP under 60 mmHg in this population.

Targets					
Coronary disease					
	AGREE	**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	-	-	Be cautious when DBP is ≤60 mm Hg	D
ESH/ESC	50%	<140	IIaB	<90	IA

Table 50: Summary of BP targets in coronary disease in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.4.7 Hypertension treatment target in adults with heart failure

None of the selected guidelines specified a treatment target for this population.

3.4.8 Hypertension treatment target in adults with previous stroke

3.4.8.1 CHEP Hypertension 2015(4)

After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently < 140/90 mm Hg (Grade C).

3.4.8.2 ESH/ESC Hypertension 2013(7)

A SBP goal <140 mmHg should be considered in patients with previous stroke or TIA. (IIaB)

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. (IA)

3.4.8.3 Summary

Both CHEP and ESH/ESC recommend a treatment target of <140/90 mmHg in patients with previous stroke.

Targets					
Previous stroke					
	AGREE	**Systolic (mmHg)**	**GoR/LoE**	**Diastolic (mmHg)**	**GoR/LoE**
CHEP	82%	<140	C	<90	C
ESH/ESC	50%	<140	IIaB	<90	IA

Table 51: Summary of BP targets in patients with previous stroke in selected guidelines. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded.

3.5 Guidelines: Antihypertensive treatment

3.5.1 Antihypertensive treatment in adults with primary uncomplicated hypertension

3.5.1.1 CHEP Hypertension 2015(4)

3.5.1.2 Recommendations for individuals with diastolic and/or systolic hypertension

Initial therapy should be monotherapy with a thiazide/ thiazide-like diuretic (Grade A), a beta-blocker (in patients younger than 60 years, Grade B), an ACE inhibitor (in nonblack patients, Grade B), a long-acting calcium channel blocker (CCB) (Grade B); or an ARB (Grade B). If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).

Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy (Grade B). Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB or beta-blocker (Grade B for the combination of thiazide/thiazide-like diuretic and a dihydropyridine CCB; Grade C for the combination of dihydropyridine CCB and ACE inhibitor; and Grade D for all other combinations). Caution should be exercised in combining a nondihydropyridine CCB and a beta-blocker (Grade D). The combination of an ACE inhibitor and an ARB is not recommended (Grade A).

Combination therapy using 2 first-line agents may also be considered as initial treatment of hypertension (Grade C) if SBP is 20 mm Hg greater than target or if DBP is 10 mm Hg greater than target. *However, caution should be exercised in patients in whom a decrease in BP from initial combination therapy is more likely to occur or in whom it would be poorly tolerated (eg, elderly patients).*

If BP is still not controlled with a combination of 2 or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added (Grade D).

Possible reasons for poor response to therapy (Supplemental Table S10) should be considered (Grade D).

Alpha-Blockers are not recommended as first-line agents for uncomplicated hypertension (Grade A); beta-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients 60 years of age or older (Grade A); and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients (Grade A). *However, these agents may be used in patients with certain comorbid conditions or in combination therapy.*

3.5.1.3 Recommendations for individuals with isolated systolic hypertension

Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic (Grade A), a long-acting dihydropyridine CCB (Grade A), or an ARB (Grade B). If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).

Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy (Grade B). Add-on drugs should be chosen from first-line options (Grade D).

If BP is still not controlled with a combination of 2 or more first-line agents, or there are adverse effects, other classes of drugs (such as alpha-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be added or substituted (Grade D).

Possible reasons for poor response to therapy should be considered (Grade D).

Alpha-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension (Grade A); and beta-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients aged ≥ 60 years (Grade A). *However, both agents may be used in patients with certain comorbid conditions or in combination therapy.*

3.5.1.4 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertension patients without comorbidity: the first choice is a thiazide(-like) diuretic in a low dose. Second options or possible associations with a diuretic are beta-blockers, ACE-I/ARBs or calcium antagonists (GRADE 1A)

ACE-I, calcium channel blockers and ARBs are being increasingly preferred above beta-blockers as a 2nd line treatment (update 2013) (NG)

To achieve the target BP, a combination of two or more antihypertensive medications is often necessary. Combining medications with different mechanisms of action achieves an additive blood pressure lowering effect (GRADE 1B).

3.5.1.5 ESH/ESC Hypertension 2013(7)

Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and

maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other. (IA)

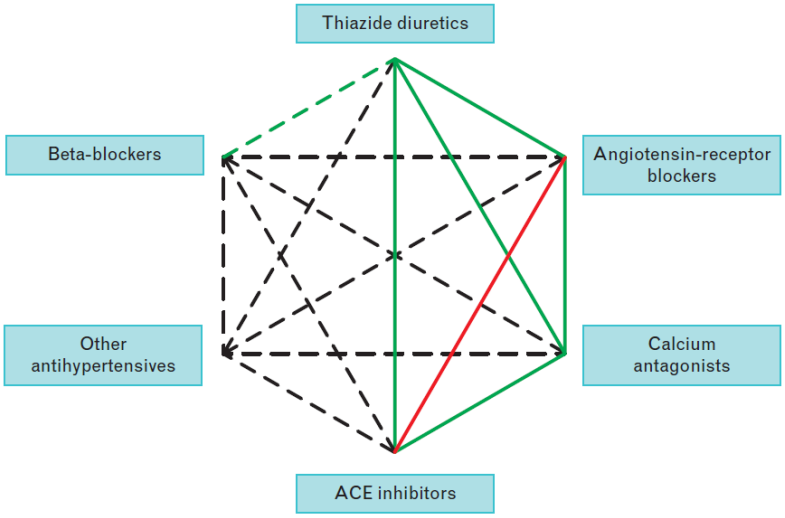
Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD. (IIaC)

Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk. (IIbC)

The combination of two antagonists of the RAS is not recommended and should be discouraged. (IIIA)

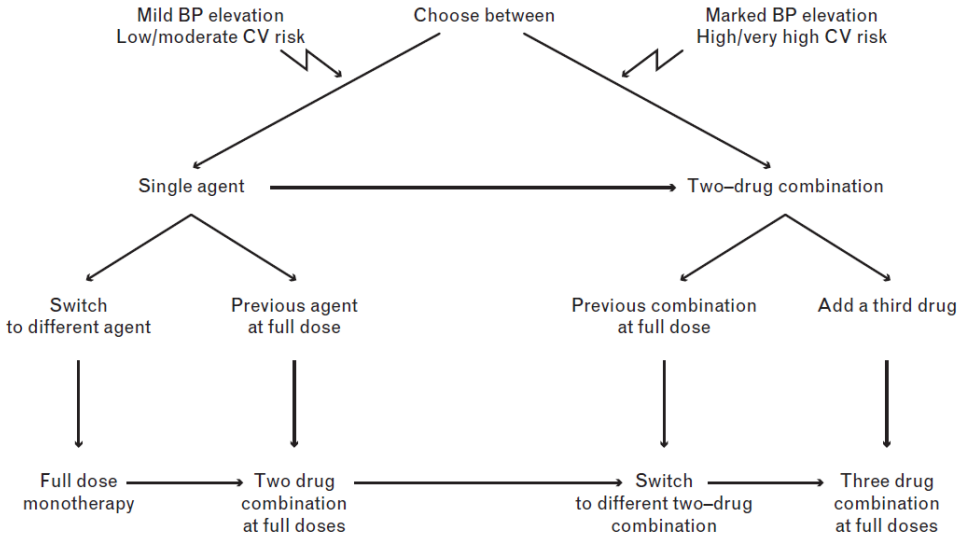
Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. (IIaC)

Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. (IIbB)



ACE = angiotensin-converting enzyme.

FIGURE 4 Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.



BP = blood pressure; CV = cardiovascular.

FIGURE 3 Monotherapy vs. drug combination strategies to achieve target BP. Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

3.5.1.6 JNC-8 Hypertension 2014(8)

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in previous recommendation (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list

provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion – Grade E)

3.5.1.7 NICE hypertension 2011(3)

Where possible, recommend treatment with drugs taken only once a day.

<u>Pharmacological interventions</u>
Prescribe non-proprietary drugs where these are appropriate and minimise cost.

Offer people with isolated systolic hypertension (systolic BP 160 mmHg or more) the same treatment as people with both raised systolic and diastolic blood pressure.

Offer people aged 80 years and over the same antihypertensive drug treatment as people aged 55–80 years, taking into account any comorbidities.

<u>Step 1 treatment</u>
Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB.

Do not combine an ACE inhibitor with an ARB to treat hypertension

Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.

If a diuretic is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5 mg–25.0 mg once daily) or indapamide (1.5mg slow release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.

For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide.

Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly:

- **those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists or**

- **women of child-bearing potential or**
- **people with evidence of increased sympathetic drive.**

If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes.

Step 2 treatment

If blood pressure is not controlled by Step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB .

If a CCB is not suitable for step 2 treatment, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.

For black people of African or Caribbean family origin, consider an ARB Step 3 treatment in preference to an ACE inhibitor, in combination with a CCB.

Before considering step 3 treatment, review medication to ensure step 2 treatment is at optimal or best tolerated doses.

Step 3 treatment

If treatment with three drugs is required, the combination of ACE inhibitor or angiotensin-II receptor blocker, calcium-channel blocker and thiazide-like diuretic should be used.

Step 4 treatment

Regard clinic blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.

For treatment of resistant hypertension at step 4:

- **Consider further diuretic therapy with low-dose spironolactone (25 mg once daily)**
- **Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l. If the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkaelemia.**

When using further diuretic therapy for resistant hypertension at step 4, monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter.

If further diuretic therapy for resistant hypertension at step 4 is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker

If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained.

3.5.1.8 Summary

As the initial treatment in patients with primary uncomplicated hypertension, CHEP, Domus Medica and ESH/ESC recommend to choose between the five main classes of antihypertensives (diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers), with a preference for a thiazide/thiazide-like diuretic as a first choice in two guidelines. JNC-8 recommends

only four classes, leaving out the beta-blockers. NICE recommends an ACE-inhibitor or angiotensin receptor blocker as a first choice in people under 55, and a calcium channel blocker (or thiazide if a calcium channel blocker is not suitable) for people over 55.

Two guidelines recommend to consider initiating with a combination of two drugs if the baseline blood pressure is very high.

Domus Medica recommends to either increase the dose of one drug, or to add another drug if the goal blood pressure is not reached within a month.

As the choice for the second drug, CHEP recommends any drug of the five main classes, while most guidelines favour combinations that do not feature a beta-blocker. NICE only recommends the combination of a calcium channel blocker with a RAS-blocker (either an ACE-inhibitor or an angiotensin receptor blocker).

If a three-drug treatment is needed, both JNC-8 and NICE recommend the combination of a calcium channel blocker, a thiazide and a ACE-inhibitor or angiotensin receptor blocker.

If a four-drug treatment is needed, NICE recommends to consider adding spironolactone to the CCB+thiazide+ACE-I/ARB- combination.

A combination of an ACE-inhibitor and a angiotensin receptor blocker is not recommended.

Two guidelines offer specific recommendations for people with isolated systolic hypertension. For this population, CHEP recommends to choose between thiazide/thiazide-like diuretics, calcium channel blockers and angiotensin receptor blockers for the initial treatment . NICE recommends an ACE-inhibitor or angiotensin receptor blocker as a first choice in people under 55, and a calcium channel blocker (or thiazide if CCB is not suitable) for people over 55.

If a two-drug treatment is needed in people with isolated systolic hypertension, CHEP recommends to choose between thiazide/thiazide-like diuretics, CCBs and ARBs, while NICE recommends the combination of a CCB with a RAS-blocker.

If a three-drug treatment is needed in people with isolated systolic hypertension, CHEP states that other classes (e.g. alpha-blockers, ACE-inhibitors, centrally acting agents or calcium channel blockers) may be added, while NICE recommends the combination of a CCB, a thiazide and a ACE-I or ARB.

If a four-drug treatment is needed in people with isolated systolic hypertension, NICE recommends to consider adding spironolactone to the CCB+thiazide+ACE-I/ARB- combination.

Treatment choice						
Primary uncomplicated hypertension						
Diastolic and/or systolic hypertension						
	Initial treatment	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**	**Three-drug treatment**	**GoR/LoE**

CHEP	Th or Th-l	A	Add a drug from another class, either thiazide, BB, CCB, ACE-I or ARB	Th+CCB (B) CCB+ACE-I (C) All other combinations (D)	Not specified	/
	BB	B				
	ACE-I	B				
	ARB	B				
	CCB	B				
	Consider combination if SBP≥20 mmHg or DBP≥10 mmHg above target	C	ACE-I+ARB NOT recommended	A		
	BB not as initial treatment ≥60y	A				
Domus	First choice: Th/Th-l; Other options are BB, ACE-I, ARB or CCB	1A	Preference for: ACE-I, ARB or CCB rather than BB	NG	Not specified	/
ESH/ESC	diuretics, ACE-I, ARB, CCB or BB	IA	Preferred combinations:	IIaC	Not specified	/
			Th+ ARB or ACE-I			
			Th+ CCB			
			CCB+ ARB or ACE-I			
	Markedly high baseline BP: 2 drugs	IIbC	Combination 2 RAS antagonists not recommended	IIIA		
JNC-8	Th, CCB, ACE-I, ARB Alone or in combination	B	Add a drug from another class: Th, CCB, ACE-I or ARB	E	CCB+ Th+ ACE-I or ARB	E
	If goal BP not reached within a month of treatment, increase dose intial drug or add second drug	E				
NICE	<55y: ACE-I or ARB >55 y: CCB, or thiazide if CCB is not suitable	NG	CCB+ ACE-I or ARB	NG	CCB+ thiazide+ ACE-I or ARB	NG
	Do not combine ACE-I and ARB	NG			Step 4: consider adding spironolactone	NG
Isolated systolic hypertension						
	Initial treatment	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**	**Three-drug treatment**	**GoR/LoE**
CHEP	Th/Th-l	A	Add a drug from first-line options	D	Other classes (e.g. alpha-	D
	CCB	A				

	ARB	B			blockers, ACE-I, centrally acting agenst or CCBs may be added	
NICE	Same treatment as raised systolic/diastolic BP: <55y: ACE-I or ARB >55 y: CCB, or thiazide if CCB is not suitable	NG	Same treatment as raised systolic/diastolic BP: CCB+ ACE-I or ARB	NG	Same treatment as raised systolic/diastolic BP: CCB+ thiazide+ ACE-I or ARB	NG
					Step 4: consider adding spironolactone	NG

Table 52: Summary of recommended antihypertensive treatment choice in diastolic and/or systolic primary uncomplicated hypertension and in isolated hypertension. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.2 Antihypertensive treatment in adults with hypertension, with or without additional risk factors

3.5.2.1 ESH/ESC Hypertension 2013(7)

Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk. (IIbC)

3.5.2.2 Summary

Only the ESH/ESC Hypertension 2013 guideline mentions treatment choice in patients with high cardiovascular risk. In these patients, initiation with a two-drug combination may be considered.

Treatment choice			
Additional cardiovascular risk factors			
	Population	**Initial treatment**	**GoR/LoE**
ESH/ESC	High CV risk	Two-drug combination	IIbC

Table 53: Summary of recommended antihypertensive treatment in people with high CV risk. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2.

3.5.3 Antihypertensive treatment in elderly patients

3.5.3.1 Elderly patients > 60 years

3.5.3.1.1 CHEP Hypertension 2015(4)

Beta-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients 60 years of age or older (Grade A).

3.5.3.2 Elderly patients > 80 years

3.5.3.2.1 Domus Medica Hypertension 2009(5) and update 2013(6)

Possible pharmacological treatments are low-dose thiazide diuretics, combined with ACE-I if BP is insufficiently controlle (GRADE 2B)

3.5.3.2.2 ESH/ESC Hypertension 2013(7)

In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. (IC)
Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian. (IIaC)

All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension.(IA)

3.5.3.3 Summary

In the elderly, ESH/ESC recommends all hypertensive agents as initial treatment, while CHEP does not recommend a beta-blocker.

In the very elderly (>80y), Domus Medica recommends a thiazide diuretic as an initial treatment and the combination with an ACE-inhibitor if additional treatment is needed. ESH/ESC recommends the continuation of well-tolerated treatment in this population.

In elderly people with isolated hypertension, ESH/ESC prefers initiation with diuretics or calcium channel blockers.

In the frail elderly, the treatment choice is based on monitoring the clinical effect.

Treatment choice					
Elderly					
	Population	**Initial treatment**	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**
CHEP	≥60y	BB not recommended	A	Not specified	-
Domus	>80y	Thiazide	2B	Th+ ACE-I	2B
ESH/ESC	Frail elderly	Decision based on monitoring clinical effect	IC	Not specified	-
	>80y	Continuation of well-tolerated treatment	IIaC		
	elderly	All hypertensive agents recommended	IA		
	Elderly+ isolated hypertension	Diuretics or CCB preferred	IA		

Table 54: Summary of recommended antihypertensive treatment choice in the elderly. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; BB= beta-blocker; ACE-I= ACE-inhibitor.

3.5.4 Antihypertensive treatment in adults with type 2 diabetes

3.5.4.1 CHEP Hypertension 2015(4)

Combination therapy using 2 first line agents may also be considered as initial treatment of hypertension (Grade B) if SBP is 20 mm Hg greater than target or if DBP is 10 mm Hg greater than

target. *However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (eg, elderly patients and patients with autonomic neuropathy).*

For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy (Grade A).

For persons with diabetes and hypertension not included in other recommendations in this section, appropriate choices include (in alphabetical order): ACE inhibitors (Grade A), ARBs (Grade B), dihydropyridine CCBs (Grade A), and thiazide/thiazide-like diuretics (Grade A).

If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic (Grade A).

3.5.4.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertension patients with type 2 diabetes mellitus: in diabetes patients with nephropathy the preferential choice is an ACE-I or an angiotensin-2-antagonist (GRADE 1A).

3.5.4.3 ESH/ESC Hypertension 2013(7)

All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. (IA)

It is recommended that individual drug choice takes comorbidities into account. (IC)

Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes. (IIIB)

3.5.4.4 JNC-8 Hypertension 2014(8)

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

3.5.4.5 Summary

In patients with type 2 diabetes, all five classes are recommended as an initial treatment by ESH/ESC, and all classes except beta-blockers by CHEP and JNC-8. CHEP prefers a calcium channel blocker as the second agent if an ACE-inhibitor is the initial treatment.

In diabetic patients with cardiovascular risk, one guideline prefers to initiate with an ACE-inhibitor or an angiotensin receptor blocker.

In diabetic patients with nephropathy, three guidelines prefer to initiate with an ACE-I or an ARB.

Treatment choice					
Type 2 diabetes					
	Population	**Initial treatment**	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**
CHEP	-	ACE-I	A	If ACE-I is initial treatment, preference for combination with CCB	A
		ARB	B		
		CCB	A		
		Th/Th-I	A		
	DM II +CV risk	ACE-I or ARB	A		
Domus	DM II +nephropathy	ACE-I or ARB first choice	1A	-	-
ESH/ESC	-	All classes	IA	-	-
JNC-8	-	Th/Th-I, CCB, ACE-I or ARB	B	-	-

Table 55: Summary of recommended antihypertensive treatment choice in type 2 diabetics. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-I: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.5 Antihypertensive treatment in adults with chronic kidney disease

3.5.5.1 CHEP Hypertension 2015(4)

For patients with hypertension and proteinuric chronic kidney disease (urinary protein > 500 mg per 24 hours or albumin to creatinine ratio > 30 mg/mmol), initial therapy should be an ACE inhibitor (Grade A) or an ARB if there is intolerance to ACE inhibitors (Grade B).

Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy (Grade D). For patients with chronic kidney disease and volume overload, loop diuretics are an alternative (Grade D).

In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels (Grade D).

The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease (Grade B)

3.5.5.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertensive patients with non-diabetic kidney disease: in nephropathy without proteinuria, it is best to initiate with the standard treatment, namely a diuretic. In nephropathy with proteinuria, it is best to start with an ACE-inhibitor or to add this to a diuretic (GRADE 1A)

3.5.5.3 ESH/ESC Hypertension 2013(7)

RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. (IA)

Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. (IA)

Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. (IIIA)

Aldosterone antagonists cannot be recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia. (IIIC)

3.5.5.4 JNC-8 Hypertension 2014(8)

In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

3.5.5.5 Domus Medica CNI 2012(11)

Initiate treatment with an ACE-I in diabetics with a corrected albuminuria of more than 2,5 mg/mmol in men and more than 3,5 mg/mmol in women, regardless of the presence of hypertension or the stage of chronic renal failure (GRADE 2B);

In non-diabetics with chronic renal failure and a corrected proteinuria of more than 30 mg/mmol (GRADE 2B); in non-diabetics with chronic renal failure and a corrected proteinuria of more than 100 mg/mmol, regardless of the presence of hypertension or cardiovascular disease (GRADE 1B).

There are no reasons to differ from the treatment guided by the cardiovascular algorithm (GRADE 1A).

3.5.5.6 NICE CKD 2014(12)

Offer a low-cost renin–angiotensin system antagonist to people with CKD and:

- **diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)**
- **hypertension and an ACR of 30 mg/mmol or more (ACR category A3)**
- **an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease)**

Do not offer a combination of renin–angiotensin system antagonists to people with CKD.

Follow the treatment recommendations in Hypertension (NICE guideline CG127) for people with CKD, hypertension and an ACR of less than 30 mg/ mmol (ACR categories A1 and A2), if they do not have diabetes

In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase.

Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre.

When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked.

Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required.

Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued.

Following the introduction or dose increase of renin–angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%.

If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin–angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%.

If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more: investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs) if no other cause for the deterioration in renal function is found, stop the renin–angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required.

3.5.5.7 Summary

In non-diabetic patients with chronic kidney disease and without overt proteinuria, Domus Medica and NICE CKD agree that the standard treatment for hypertension can be followed.

In CKD patients with proteinuria, initiation with an ACE-inhibitor or angiotensin receptor blocker is recommended. Additional drugs can be diuretics (thiazide or thiazide-like or loop diuretics when there is volume overload) or other hypertensive drugs.

In diabetic CKD patients with albuminuria, an ACE-inhibitor or angiotensin receptor blocker as the initial treatment is recommended.

Treatment choice					
Chronic kidney disease					
	Population	**Initial treatment**	**GoR/LoE**	**Two-drug**	**GoR/LoE**

				treatment	
CHEP	proteinuria ACR >30 mg/mmol	ACE-I	A	Th-(l)	D
		ARB if intolerance for ACE-I	B		
	+Volume overload			Loop diurectics	D
				Other antihypertensive agents	D
Domus Hypertension	No proteinuria	Diuretic (standard treatment)	1A	-	-
	Proteinuria	ACE-I	1A	-	-
ESH/ESC	Microalbuminuria or overt proteinuria	ACE-I or ARB	IA	Other antihypertensive agents	IA
JNC-8		ACE-I or ARB	B	-	-
Domus CNI	Diabetic+ albuminuria	ACE-I	2B	-	-
	Proteinuria >30 mg/mmol	ACE-I	1B	-	-
		Treatment guided by cardiovascular algorithm	1A	-	-
NICE CKD	ACR >30 mg/mmol	ACE-I or ARB	NG	-	-
	Diabetic+ ACR >3mg/mmol	ACE-I or ARB	NG	-	-
	ACR <30mg/mmol and non-diabetic	Follow recommendations of Hypertension guideline	NG	-	-

Table 56: Summary of recommended antihypertensive treatment choice in people with chronic kidney disease. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

ACR= Albumin/creatinine ratio

NOT RECOMMENDED			
	Population	Drug	**GoR/LoE**
CHEP	No proteinuria	ACE-I+ARB	IIIA
ESH/ESC		ACE-I+ARB	IIA
	CKD	Aldosterone antagonists	IIC
NICE CKD	CKD	ACE-I +ARB	NG
	Serum potassium concentration > 5.0 mmol/L	ACE-I or ARB	NG

Table 57: Summary of not recommended antihypertensive drugs in people with chronic kidney disease. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. NG= not graded. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.6 Antihypertensive treatment in adults with coronary disease

3.5.6.1 Adults with previous myocardial infarction

3.5.6.1.1 CHEP Hypertension 2015(4)

Note: CHEP Hypertension 2015 makes following recommendations about patients with "recent myocardial infarction".

Initial therapy should include a b-blocker and an ACE inhibitor (Grade A).

An ARB can be used if the patient is intolerant of an ACE inhibitor (Grade A in patients with left ventricular systolic dysfunction).

CCBs may be used in patients after myocardial infarction when b-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when heart failure is present, evidenced by pulmonary congestion on examination or radiography (Grade D).

3.5.6.1.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertensive patients with coronary artery disease (angina and post-myocardial infarction): initial therapy with a beta blocker, regardless of BP values; as a second option or as a combination in angina a calcium antagonist is recommended. An ACE-inhibitor/sartan is recommended when beta-blockers are not tolerated, or as a combination after myocardial infarction (GRADE 1B)

3.5.6.1.3 ESH/ESC Hypertension 2013(7)

In hypertensive patients with a recent myocardial infarction beta-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but beta-blockers and calcium antagonists are to be preferred, for symptomatic reasons (angina). (IA)

3.5.6.1.4 Summary

In patients with a previous myocardial infarction, the first choice is a beta-blocker. CHEP recommends a combination of an ACE-inhibitor and a beta-blocker. Domus Medica recommends a calcium channel blocker, and an ACE-inhibitor or an angiotensin receptor blocker as additional treatment.

Treatment choice					
Previous myocardial infarction					
	Population	**Initial treatment**	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**
CHEP		BB + ACE-I	A	-	-
	if intolerant for ACE-I	ARB	A	-	-
	if contra-indication for BB and no heart failure	CCB	D	-	-

Domus Hypertension		BB	1B	CCB, ACE-I, ARB	1B
	If intolerant for BB	ACE-I/ARB	1B		
ESH/ESC	Recent myocardial infarction	BB	IA	-	-
	All other CHD	BB, CCB	IA	-	-
		All other hypertensive agents	IA	-	-

Table 58: Summary of recommended antihypertensive treatment choice in people with previous myocardial infarction. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.6.2 Adults with chronic stable angina

3.5.6.2.1 CHEP Hypertension 2015(4)

Note: CHEP Hypertension 2015 makes following recommendations about patients with "coronary artery disease".

An ACE inhibitor or ARB is recommended for most patients with hypertension and CAD (Grade A).

For patients with stable angina, beta-blockers are preferred as initial therapy (Grade B). CCBs may also be used (Grade B).

Short-acting nifedipine should not be used (Grade D).

For patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended (Grade B).

In high-risk patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazidelike diuretic in selected patients (Grade A).

3.5.6.2.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertensive patients with coronary artery disease (angina and post-myocardial infarction): initial therapy with a beta blocker, regardless of BP values; as a second option or as a combination in angina a calcium antagonist is recommended. An ACE-inhibitor/sartan is recommended when beta-blockers are not tolerated, or as a combination after myocardial infarction (GRADE 1B)

3.5.6.2.3 ESH/ESC Hypertension 2013(7)

In hypertensive patients with a recent myocardial infarction beta-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but beta-blockers and calcium antagonists are to be preferred, for symptomatic reasons (angina). (IA)

3.5.6.2.4 Summary

In people with stable angina, a beta-blocker is recommended as a first choice by CHEP, Domus Medica and ESH/ESC. For ESH/ESC calcium channel blockers are also a valid first choice. As a second choice and/or as a second agent, calcium channel blockers, ACE-inhibitors and angiotensin receptor blockers are recommended. ESH/ESC mentions that all antihypertensive drugs can be used in patients with stable angina.

Treatment choice					
Stable angina					
	Population	**Initial treatment**	**GoR/LoE**	**Two-drug treatment**	**GoR/LoE**
CHEP	CAD	ACE-I or ARB	A	individualized	A
	Stable angina	BB (first choice)	B		
		CCB	B		
Domus Hypertension		BB	1B	CCB, ACE-I, ARB	1B
	If intolerant for BB	ACE-I/ARB	1B		
ESH/ESC	CHD	BB, CCB (preference)	IA	-	-
		All antihypertensive drugs can be used	IA	-	-

Table 59: Summary of recommended antihypertensive treatment choice in people with stable angina. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

NOT RECOMMENDED			
	Population	Drug	**GoR/LoE**
CHEP	Stable angina	Short-acting nifedipine	D
	CAD without systolic heart failure	ACE-I+ ARB	B

Table 60: Summary of not recommended antihypertensive drugs in people with coronary artery disease. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.7 Antihypertensive treatment in adults with heart failure

3.5.7.1 CHEP Hypertension 2015(4)

In patients with systolic dysfunction (ejection fraction < 40%), ACE inhibitors (Grade A) and beta-blockers (Grade A) are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial infarction, increased B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association class II-IV symptoms (Grade A). Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB therapy. Other diuretics are recommended as additional therapy if needed (Grade B for thiazide/thiazide-like diuretics for BP control, Grade D for loop diuretics for volume control).
Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those found to be effective in trials unless adverse effects become manifest (Grade B).

An ARB is recommended if ACE inhibitors are not tolerated (Grade A).

A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated (Grade B).

For hypertensive patients whose BP is not controlled, an ARB may be combined with ACE inhibitor therapy and other antihypertensive drug treatment (Grade A). Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function (Grade C). Additional therapies may also include dihydropyridine CCBs (Grade C).

3.5.7.2 Domus Medica Hypertension 2009(5) and update 2013(6); Domus Medica Heart failure 2011(10)

The following recommendation comes from the Domus Medica Hypertension 2009 guideline:

In hypertensive patients with heart failure: diuretics and ACE-inhibitors/angiotensin receptor blockers. After acute myocardial infarction with heart failure: ACE-inhibitor/sartan (GRADE 1A).

In the evidence update in 2013, this recommendation is discarded. For recommendations on treatment of hypertension in chronic heart failure patients, the update refers to the Domus Medica Heart failure 2011 guideline.

The following recommendations are from the Domus Medica Heart failure 2011 guideline:

> **<u>Heart failure with preserved and decreased ejection fraction</u>**
> **Initial therapy: diuretics (loop diuretics, thiazide) (GRADE 1C)**
>
> *Start with a low dose and increase until clinical improvement of fluid retention occurs. Consider addition of spironolactone.*
>
> **<u>Heart failure with decreased ejection fraction</u>**
> **Start ACE-inhibitor as soon as possible after diuretics (GRADE 1A), in a low dose, and increase dose gradually (GRADE 1C)**
>
> *Target dose: enalapril 20 mg, ramipril 10 mg, captopril 150 mg, lisinopril 20 mg, perindopril 4 mg.*
>
> **Add a beta blocker (metoprolol SR/XL, bisoprolol, carvedilol or nebivolol) (GRADE 1A) in a low dose in clinically stable patients or when half of the target dose of the ACE-inhibitor has been reached during two weeks, and increase until target dose, or if not tolerated, until the maximum tolerable dose is reached (GRADE 1c)**
>
> *Target dose: metoprolol SR/XL 200 mg 1x/day, bisoprolol 10 mg 1x/day, carvedilol 50 mg 2x/day, nebivolol 10 mg 1x/day or 5 mg 2x/day.*
>
> **If cough occurs: replace ACE-inhibitor with an angiotensin-2-receptor blocker (GRADE 1A).**

Target dose: valsartan (2 x 160/day), candesartan (1 x 32 mg/day) and losartan (1x 150 mg/day).

If the combination of an ACE-inhibitor/beta-blocker (or angiotensin-2 receptor blocker) is insufficient, add spironolactone carefully in NYHA-class 3 and 4 (dose:12,5 to 50 mg/day, unless in case of contra-indications and renal insufficiency) (GRADE 1A)

If there is still fluid retention despite base therapy, add loop diuretics and if necessary, a thiazide, modulated (GRADE 1A) and if necessary, add digoxin in a next step, if atrial fibrillation is not present.(GRADE 1A) It is not necessary to measure serum digoxin concentration, unless there is a suspicion of intoxication or of insufficient adherence to therapy. Avoid drugs and (herbal) preparations that have a known detrimental effect on heart failure (GRADE 1A).

3.5.7.3 ESH/ESC Hypertension 2013(7)

Diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe LV dysfunction to reduce mortality and hospitalization. (IA)

In patients with heart failure and preserved EF, there is no evidence that antihypertensive therapy per se or any particular drug, is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with beta-blockers, etc.) should also be considered. (IIaC)

3.5.7.4 Summary

The choice of antihypertensive treatment in patients with heart failure is complex: it is not always specified whether the treatment applies to patients with heart failure AND hypertension or heart failure with or without hypertension and whether need for additional treatment pertains to lowering of blood pressure or to relief of fluid retention symptoms.

In heart failure with preserved ejection fraction, Domus Medica recommends starting with diuretics and to consider adding spironolactone if fluid retention symptoms remain. ESH/ESC recommends treatment guided by relief of symptoms.

In heart failure with decreased ejection fraction, CHEP recommends initial treatment with an ACE-inhibitor and a beta-blocker, and to add a thiazide or thiazide-like diuretic if needed. In systolic dysfunction AND a recent CV hospitalization, myocardial infarction, increased BNP/pro-BNP level or in NYHA II-IV, an aldosterone agonist may be added. If hypertension is not controlled with previous treatment, a combination of an ACE-inhibitor and an angiotensin receptor blocker or another antihypertensive drug may be considered.

In the Domus Medica guideline, the first drug of choice is a diuretic, followed by the initiation of an ACE-inhibitor and a beta-blocker. If fluid retention symptoms are insufficiently controlled, spironolactone, a higher dose of diuretics, or digoxin may be added.

The ESH/ESC guideline does not provide a set order of initiating medication, and states that diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers and/or spironolactone may be considered.

Treatment choice					
Heart failure					
	Population	**Initial treatment**	**GoR/LoE**	**Additional treatment**	**GoR/LoE**
CHEP	Systolic dysfunction	ACE-I and BB	A	Th-(I)	B
	If ACE-I not tolerated	ARB	A		
	Systolic dysfunction+ • recent CV hospitalization • AMI • increased BNP or pro-BNP level • NYHA II-IV			Aldosterone antagonists	A
	Hypertension not controlled with above treatment			ACE-I + ARB or other antihypertensive drug treatment (e.g. CCB)	A
Domus Heart failure	Preserved and decreased ejection fraction	Diuretics (loop diuretics, thiazide)	1C	spironolactone	1C
	Decreased ejection fraction	Add ACE-I	1A		
		Add BB	1A		
	Cough	Replace ACE-I with ARB	1A		
	NYHA III – IV and insufficient effect (on fluid retention) with ACE-I + BB	Add spironolactone	1A	Loop diuretics, thiazide, digoxin	1A
ESH/ESC		Diuretics, BB, ACE-I, ARB and/or spironolactone	IA		
	Preserved ejection fraction	Treatment guided by relief of symptoms	IIaC		

Table 61: Summary of recommended antihypertensive treatment in people with heart failure. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.5.8 Antihypertensive treatment in adults with previous stroke

3.5.8.1 CHEP Hypertension 2015(4)

Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A).

Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred (Grade B).

For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended (Grade B).

3.5.8.2 Domus Medica Hypertension 2009(5) and update 2013(6)

In hypertensive patients post CVA/TIA: standard treatment (GRADE 2B)

3.5.8.3 ESH/ESC Hypertension 2013(7)

All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced (IA).

3.5.8.4 Summary

In patients with previous stroke, CHEP recommends initial treatment with a combination of an ACE-inhibitors and a thiazide or thiazide-like diuretic, while the Domus Medica guideline recommends the standard treatment. The ESH/ESC-guideline recommends all drug regimens, provided that BP is effectively reduced.

Treatment choice		
Previous stroke		
	Initial treatment	**GoR/LoE**
CHEP	ACE-I+ Th-(l)	B
Domus hypertension	Standard treatment	2B
ESH/ESC	All drug regimens	IA
NOT RECOMMENDED		
CHEP	ACE-I+ ARB	B

Table 62: Summary of recommended antihypertensive treatment in people with previous stroke. GoR= Grade of recommendation; LoE= level of evidence; for meaning of GoR/LoE see section 3.1.2. Th= Thiazide; Th-l: Thiazide-like diuretic; BB= beta-blocker; CCB= calcium channel blocker; ACE-I= ACE-inhibitor; ARB= angiotensin receptor blocker.

3.6 Guidelines: adherence

3.6.1 CHEP Hypertension 2015(4)

Adherence to an antihypertensive prescription can be improved using a multipronged approach. See Table 63.

Strategies to improve patient adherence
Assist your patient by - Tailoring pill-taking to fit patients' daily habits (Grade D) - Simplifying medication regimens to once-daily dosing (Grade D) - Replacing multiple pill antihypertensive combinations with single pill combinations (Grade C) - Using unit-of-use packaging (of several medications to be taken together) (Grade D) - Using a multidisciplinary team approach to improve adherence to an antihypertensive prescription (Grade B)
Assist your patient in getting more involved in their treatment by - Encouraging greater patient responsibility/autonomy in monitoring their blood pressure and adjusting their prescriptions (Grade C)

- Educating patients and their families about their disease and treatment regimens (Grade C)
Improve your management in the office and beyond by - Assessing adherence to pharmacological and nonpharmacological therapy at every visit (Grade D) - Encouraging adherence with therapy by out-of-office contact (either by phone or mail), particularly during the first 3 months of therapy (Grade D) - Coordinating with pharmacists and work-site health care givers to improve monitoring of adherence with pharmacological and lifestyle modification prescriptions (Grade D) - Utilizing electronic medication compliance aids (Grade D)

Table 63: Strategies to improve patient adherence.

3.6.2 ESH/ESC Hypertension 2013(7)

Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. (IIbB)

3.6.3 NICE hypertension 2011(3)

Provide appropriate guidance and materials about the benefits of drugs and the unwanted side effects sometimes experienced in order to help people make informed choices.

People vary in their attitudes to their hypertension and their experience of treatment. It may be helpful to provide details of patient organisations that provide useful forums to share views and information.

Provide an annual review of care to monitor blood pressure, provide people with support and discuss their lifestyle, symptoms and medication.

Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated with non-adherence if a specific need is identified. Target the intervention to the need. Interventions might include:

- **suggesting that patients record their medicine-taking**
- **encouraging patients to monitor their condition**
- **simplifying the dosing regimen**
- **using alternative packaging for the medicine using a multi-compartment medicines system.**

3.6.4 NVDPA CV risk 2012(9)

One recent Cochrane review (72 trials) assessed different interventions to improve BP control in hypertensive adults in a primary care, outpatient or community setting.

Organisational interventions (nine trials) to enable regular review in tandem with a rigorous stepped-care approach to antihypertensive drug treatment were found to be the most effective, but this finding was dominated by findings from a single large trial – the Hypertension Detection and

Follow-Up study. Self-monitoring (18 trials) was associated with a reduction in SBP (2.5 mmHg) and DBP (1.8 mmHg) and may be a useful adjunct strategy. Other interventions assessed in this systematic review did not produce clear results. Educational interventions directed at physicians (10 trials) did not change BP control, but education for patients (20 trials) may have a modest effect although heterogeneity was noted. Use of health care professionals such as nurses and pharmacists (12 trials) demonstrated generally favourable but heterogeneous results. Lastly, reminders (postal, computer or telephone) improved follow-up and control of patients, but produced heterogeneous results in terms of BP reduction.

Another Cochrane review (38 trials) specific to BP lowering therapy in an ambulatory setting suggested that simplifying dosing regimens was the most consistently effective intervention (seven out of nine studies). Motivational strategies (e.g. financial incentives or reminder packages/aids) and complex interventions involving more than one technique were less consistent. Effects were generally modest and patient education alone was largely ineffective. Further, in a systematic review of 11 trials investigating the effects of home BP monitoring on medication adherence, six of the 11 trials reported a statistically significant improvement in medication adherence; 84% of these were complex interventions using home BP monitoring in combination with other adherence-enhancing strategies such as patient counselling by nurses, pharmacists or telephone-linked systems, patient education and the use of timed medication reminders. Two moderate quality reviews of simplifying doses by using fixed dose combinations to improve adherence for raised BP reported improved compliance with combination treatment (24% decrease risk of non-compliance in one review).

3.6.5 Summary

Four guidelines mention strategies for improving patient adherence. Three guidelines make formal recommendations, while NVDPA CV risk 2012 describes the literature it found on this subject without making a recommendation.

All of them comment on simplifying the dosing regimen (e.g. by using combination pills), even though the evidence supporting interventions to increase adherence is inconclusive. For this reason, NICE only recommends this intervention to overcome practical problems if a specific need is identified.

4 Evidence tables and conclusions

4.1 Threshold (when to start treatment): evidence tables and conclusions

4.1.1 Primary uncomplicated hypertension with or without additional risk factors

4.1.1.1 Clinical evidence profile: Treatment vs no treatment in mild hypertension in patients without previous cardiovascular disease.

Meta-analysis:

Inclusion criteria: RCT's, ≥ 1y, primary prevention population, SBP 140-159 or DBP 90-99 mmHg and no evidence of cardiovascular disease at baseline. >80% of patients in a trial had to have mild hypertension as defined above. Treatment with antihypertensive drugs either as monotherapy or with the addition of other drugs in a stepped care approach. Control: placebo or no antihypertensive treatment.
Search strategy: DARE and Cochrane database searched for related reviews and meta-analyses. The following electronic databases were searched for primary studies:
CENTRAL (2013, Issue 9), MEDLINE (1946 to October 2013), EMBASE (1974 to October 2013), ClinicalTrials.gov (all dates to October 2013), and reference lists of articles. Electronic databases were searched using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to hypertension. Other sources: a) Reference lists of all papers and relevant reviews identified b) Authors of relevant papers were contacted regarding any further published or unpublished work c) Authors of trials reporting incomplete information were contacted to provide the missing information
Assessment of quality of included trials: yes: Risk of bias was also assessed independently by 2 reviewers using the risk of bias tool and the following criteria: sequence generation, allocation concealment, blinding, Incomplete outcome data, selective reporting or other biases. Disagreements between independent reviewers arising in any of the stages above were resolved by a third reviewer.
ITT analysis: yes/no Unclear; not reported
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Diao 2012 (14) Design: SR+ MA Search date: (October 2013) N=4 n= 8912	Antihypertensive therapy vs. no antihypertensive therapy	N= 4 n= 8912 (ANBP, MRC, SHEP, VA-NHLBI)	Total mortality (PO)	AH: 77/4481 No AH: 90/4431 RR: 0.85 (95% CI 0.63 to 1.15) NS
		N= 3 n= 7080 (MRC, SHEP, VA-NHLBI)	Total cardiovascular events (total stroke, total MI and total congestive heart failure) (PO)	AH: 81/3523 No AH: 84/3557 RR 0.97 (95% CI 0.72 to 1.32) NS
		N= 3 n= 7080 (MRC, SHEP, VA-NHLBI)	Total stroke (fatal and nonfatal)	AH:10/3523 No AH: 20/3557 RR: 0.51 (95% CI 0.24 to 1.08) NS
		N= 3 n= 7080 (MRC, SHEP, VA-NHLBI)	Total coronary heart disease (fatal and non-fatal myocardial infarction, sudden death)	AH: 71/3523 No AH: 64/3557 RR: 1.12 (95% CI 0.80 to 1.57) NS

		N= 1 n= 17354 (MRC) Note:Withdrawals due to adverse effects (WDAEs) was only available from all patients in the MRC trials and not from the subgroup of patients with mild hypertension. Assuming that withdrawals due to adverse effects would be similar in the participants with mild hypertension and those with moderate to severe hypertension, we have calculated this value for the whole trial.	Withdrawals due to adverse drug effects	**AH: 980/8700** **No AH: 203/8654** **RR 4.80 (95%CI 4.14 to 5.17)** **ARR: 8.9%** **SS**

Table 64

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
ANBP, 1980(15) RCT, SB, placebo-controlled *Individual subject data*	3931	Adults, ages 30 to 69 years DBPs ≥ 95 or < 110 if SBP < 200 mmHg	4 years	Chlorothiazide 500mg once or twice daily, methyldopa, propranolol, or pindolol added as 2nd-order treatment, and hydralazine or clonidine added as 3rd-order treatment. Control: placebo	ALLOCATION CONC: Inadequate RANDO: Unclear "patients randomly allocated, with stratification by age and sex" Not enough detail to know how this was done. BLINDING : Participants Inadequate: Trial was single blind so investigators physicians caring for the patient were not blinded as to treatment allocation FOLLOW-UP: NOTE: high risk of attrition bias: All components from the composite outcome were terminating events, without complementary mortality survey. All analyses regarding these separated components are subject to a censoring bias.
MRC, 1985(16) RCT, SB, placebo-controlled *Individual subject data*	17354	Adults, ages 35 to 64 years, SBPs < 200 and DBPs 90-109 mmHg	Mean 5.5 years	Bendrofluazide 10 mg daily (71% mono), Propranolol 80-240 mg daily (78% mono), methyldopa added if required. Control: placebo	ALLOCATION CONC: Unclear: not described RANDO: Adequate BLINDING : Participants Inadequate: Trial was single blind so investigators physicians caring for the patient were not blinded as to treatment allocation FOLLOW-UP:

					NOTE: high risk of attrition bias: Myocardial infarction and stroke were reasons for terminating the study follow-up, except for death flagging. This induces a censoring attrition bias, limited to the occurrence non-fatal events myocardial infarction or stroke.
SHEP, 1991(17) RCT, DB, placebo controlled *Individual subject data*	4736	Adults, ages ≥ 60 years, SBPs 160-219 and DBPs of < 90 mmHg	Mean 4.5 years	Chlorthalidone 12.5-25 mg (69%), Step 2. atenolol 25-50 mg (23%) or reserpine 0.05-0.1 mg. Identical placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/Investigators Adequate FOLLOW-UP: NICE: no ITT in 1 study, attrition >20% in two studies
VA-NHLBI, 1978(18) RCT, DB, placebo-controlled *No individual subject data*	1012	Ambulatory patients, with mean age 37.5 years, range (21-50 years). 25% patients were African-Americans. Male (100%). Baseline mean DBP was 93.3 mmHg. The inclusion criteria was DBP 85-105 mmHg. *<20% of patients had moderately elevated blood pressure*	2 years	CHTD 50 mg, 100 mg, (53% CHTD alone). Reserpine 0.25 mg. Control: placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants/Investigators Adequate FOLLOW-UP:

Table 65 Characteristics of included studies

Author's conclusions:

Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs. Treatment caused 9% of patients to discontinue treatment due to adverse effects. More RCTs are needed in this prevalent population to know whether the benefits of treatment exceed the harms.

4.1.1.2 *Summary and conclusions: Treatment vs no treatment in mild hypertension in patients without previous cardiovascular disease.*

Antihypertensive therapy versus no antihypertensive therapy for mild hypertension in primary prevention			
Bibliography: meta-analysis Diao 2012(14) (included 4 RCTs: ANBP 1980(15), MRC 1985(16), SHEP 1991(17), VA-NHLBI 1978(18)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	8912 (4 studies) 2-5.5y	RR: 0.85 (95% CI 0.63 to 1.15) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 high risk of bias due to blinding issues and incomplete outcome reporting Consistency:ok Directness:ok Imprecision:-1. More RCTs needed
Total cardiovascular events (total stroke, total MI and total congestive heart failure)	7080 (3 studies) 2-5.5y	RR 0.97 (95% CI 0.72 to 1.32) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:- -2 high risk of bias due to blinding issues and incomplete outcome reporting Consistency:OK Directness:OK Imprecision: -1. More RCTs needed: wide CI
Total stroke (fatal and nonfatal)	7080 (3 studies) 2-5.5y	RR: 0.51 (95% CI 0.24 to 1.08) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:- -2 high risk of bias due to blinding issues and incomplete outcome reporting Consistency:OK Directness:OK Imprecision: -1. More RCTs needed: wide CI
Total coronary heart disease (fatal and non-fatal myocardial infarction, sudden death)	7080 (3 studies) 2-5.5y	RR: 1.12 (95% CI 0.80 to 1.57) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:- -2 high risk of bias due to blinding issues and incomplete outcome reporting Consistency:OK Directness:OK Imprecision: -1. More RCTs needed: wide CI
Withdrawals due to adverse drug effects	17354 (1 study) 5.5y	**RR 4.80 (95%CI 4.14 to 5.17)** **SS**	⨁⨁⊖⊖ **LOW*** Study quality:-1 incomplete outcome data Consistency:NA Directness:-1. Population and treatment Imprecision:OK

Table 66

** the Cochrane authors rated this as moderate quality of evidence*

We found 1 Cochrane systematic review of 4 RCTs about treating mild hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg) in participants who did not have cardiovascular disease at baseline. 3 RCT's included relatively younger patients, while 1 RCT included patients > 60y. Duration of follow up varied between 2 and 5.5 years. The analyses are based on individual patient data from 3 RCTs and of general data from 1 RCT.

The paucity of data and methodological problems within the RCTs limits our confidence in the results. On top of that, these are mainly older trials, with older type antihypertensive drugs.

The Cochrane authors conclude that more RCTs are needed to know whether treatment benefits exceed the harms. Our reading committee advises that a large international trial with long-term follow up may be better.

Treatment of mild hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg) did not result in a statistically significant difference in cardiovascular event rates between treated and untreated groups.
GRADE: VERY LOW quality of evidence

Treatment of mild hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg) did not result in a statistically significant difference in stroke rates between treated and untreated groups.
GRADE: VERY LOW quality of evidence

Treatment of mild hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg) did not result in a statistically significant difference in coronary heart disease rate between treated and untreated groups.
GRADE: VERY LOW quality of evidence

Treatment of mild hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg) resulted in a statistically significant increase of withdrawals due to adverse drug effects in treated patients, compared to untreated patients. These results are based on the results of 1 large RCT, which included also patients with moderate and severe hypertension.
GRADE: LOW quality of evidence

Additional information could be found in observational studies.

4.1.1.3 Observational data: Treatment threshold in adults with or without additional risk factors

Study details and results for SRs/MAs assessing the risk of developing clinical outcomes at different BP thresholds.								
Reference	**N**	**Population**	**BP measurement method**	**Follow-up**	**Study design**	**Outcomes**	**BP values at baseline (groups / thresholds); mmHg**	**Best BP threshold (authors' conclusions)**
Asayama et al., 2009(19) MA of data from 4 cohort studies	4571	General population (HT and NT)	Clinic	Mean 9.5 years	Prognostic: Risk (HR) of developing clinical outcomes	Stroke; death from stroke	Optimal: <120/ <80 Normal: 120-129/80-84 High normal: 130-139/85-89 Grade 1 (mild) HT: 140-159/ 90-99 Grade 2 (moderate) HT: 160-179/ 100-109 Grade 3 (severe) HT: ≥180/110	Untreated groups: risk (HR) of first stroke increased linearly with BP. Treated people with optimal BP had higher risk of stroke than untreated people with optimal BP.
Law et al., 2009(20) SR/MA of 108 RCTs	248445	HT and NT People of any age, disease status, pre-Treatment BP and use of other drugs 3 categories: no history of CVD, coronary heart	Clinic	Mean 3.5 years	BP difference trials designed to achieve a difference in BP between randomised groups	CHD events; stroke	10mm SBP increments from 120 – 180 mmHg	note: - results standardized to a blood pressure reduction of 10 mmHg systolic or 5mmHg diastolic, but in-trial reductions were usually lower) - BP treatment reduced risk of CVD and stroke, regardless of patients' pre-treatment BP (as low as 110 SBP and 70 DBP; mmHg). Lowering BP by 10mmHg SBP or 5mmHg

		disease, previous stroke						DBP reduced CVD events by around 25%, heart failure (by about 25%) and stroke (by about 33%). Authors concluded that BP lowering drugs should be offered to anyone at high risk (whatever the reason for high risk, e.g. age, cardiovascular disease event) not just to people with high BP, because a given BP reduction lowers the risk of coronary heart disease and stroke by a constant proportion irrespective of pre-treatment BP.
Fagard et al., 2007(21) SR/MA of 7 studies	11502	General population, primary care and secondary care (HT and NT)	Clinic and ABPM (to give diagnoses)	Mean 8 years	Risk of developing events in people diagnosed as NT, WCH, MH or sustained HT	CV events	NT: normal BP clinic and ABPM; mean BP 121.8/75.6 and 119.7/72.6 respectively WCH: clinic HT, normal ABPM; mean BP 148.2/86.2 and 125.6/74.9 respectively MH: normal clinic, ABPM HT; mean BP 129.9/78.6 and 141.1/83.2 respectively Sustained HT: clinic HT and ABPM HT; mean BP 157.7/88.5 and 152.4/85.7 HT diagnosis - cut off BP	NS difference between WCH and NT for incidence of CV events; worse CV events in MH and sustained HT

							Clinic: 140/90 mmHg ABPM: 135/85 mmHg (except 1 study 135/83mmHg)	

Table 67

Prognostic studies							
Study details and results for prognostic studies assessing the risk of developing clinical outcomes at different BP thresholds							
Reference	**N**	**Population**	**Follow-up**	**Study design**	**Outcomes**	**BP values at baseline (groups / thresholds); mmHg**	**Best BP threshold (authors' conclusions)**
Clinic BP measurements							
Arima et al., 2006(22) Sub-analysis of RCT (PROGRESS)	6105	HT and NT (Cerebrovascular disease)	Mean 3.9 years	Risk of developing events in people with different baseline BP values	Stroke, CV events	SBP values <120 (median 114) 120-139 (median 130) 140-159 (median 149) ≥160 (median 169)	The benefits of treatment were comparable for patients who were or were not HT at baseline, for baseline BP levels extending down to 115/75mmHg.
Arima et al., 2009(23) Cohort (HISAYAMA)	1621	General population (HT and NT)	32 years	Risk of developing events in people with different baseline BP values (grouped)	Stroke	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Grade 1 HT: 140-159 /90-99 Grade 2 HT: 160-179 /100-109 Grade 3 HT: ≥180 /110	Age-adjusted incidence of total stroke rose progressively with higher BP in both genders

Assmann et al., 2005(24) Cohort (PROCAM)	5389	General population (HT and NT)	10 years	Risk of developing events in people with different baseline BP values (grouped)	Major coronary event	NT: ≤140 /90 New HT: SBP >159 and/or DBP>94 Adequately treated HT: <160 /95 Inadequately treated HT: ≥160/95	In all HT men, including those receiving "adequate" antihypertensive Tx, the 10-year risk of CHD was at least doubled.
Barengo et al., 2009 and 2009(25),(26) Cohort	41895 (study 1) 47610 (study 2)	General population (HT and NT)	Median 20 years	Risk of developing events in people with different baseline BP values (grouped)	Study 1: Mortality (all cause and CV) Study 2: stroke (fatal or non-fatal)	NT:<160/95 and no Tx HT (≥160 SBP or 95 DBP or Tx in last 7 days); treated and controlled (<160/95mmHg) HT: Tx and not controlled HT and aware (HT diagnosis or current Tx) but untreated HT but unaware	In men, all-cause and cardiovascular mortality were significantly higher in all hypertensive groups compared with the normotensive group. In women, the mortality in those whose hypertension was controlled was not significantly different from the normotensive group, suggesting that these women benefitted from achieving normal BP, although the uncontrolled, untreated and unaware groups had higher mortality. The risk of stroke was significantly higher in men and women in all hypertensive groups compared with the normotensive group. It may be higher in treated than untreated patients if they have had hypertension longer and it is more severe (also unaware were significantly younger so had lower risk).
Carlsson et al., 2009(27) Cohort study	2280	General population (HT and NT)	26 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	NT/optimal: <130 / <85 Pre-HT: 130-139 and/or 85- 89 DBP High: 140 - 159 and/or 90-94 DBP Very high: ≥160 and/or DBP ≥95	Risk of Events increased with increasing BP; Very high blood pressure (≥160/95mmHg) is an independent risk factor for all-cause and CV mortality in men and women.

Gudmundsson et al., 2005(28) Cohort study	3246	General population (HT and NT)	Up to 20 years (mean 13.6 for men and 14.4 for women)	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	NT/high-NT:<140 /<90 Mild-moderate HT: 140-179 /90-109 Severe HT: ≥180 /≥110	Patients treated for HT whose BP is not controlled have a higher risk of mortality than those whose BP is controlled. (Note: Tx target <160/<95mmHg; treatment not as aggressive as it would be today; number controlled to <140/90mmHg was less than half those labelled "controlled" in this study.)
Ishikawa et al., 2008(29) Cohort (JMS)	11103	General population (HT and NT)	Mean 10.7 years	Risk of developing events in people with different baseline BP values (grouped)	Stroke	NT: <140/90, no treatment HT: treated (receiving Tx, irrespective of current BP) C: Controlled (<140/90) U: Uncontrolled (≥140 and/or DBP ≥90) HT: untreated (≥140 /90 without Tx) M: Mild (SBP 140-159 or DBP 90-99) MS: Moderate-severe (SBP ≥160 and/or DBP ≥100)	Risk of stroke higher among HT vs. NT patients, and treated vs. non-treated HT, even when BP controlled to <140/90mmHg Untreated HT might have had a shorter duration of HT (and therefore lower risk of stroke) or have WCH (also lower risk).
Kagiyama et al., 2008(30) Cohort	639	General population (HT and NT) but elderly (80 years)	4 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality and CV mortality	SBP values NT: <140 Mild HT: 140-159 moderate-severe HT: >160	No association between total mortality and SBP in the very elderly overall (however increased risk with increase BP), but there was an association in those with CVD or on Tx.

Kokubo et al., 2008(31) Cohort (SUITA)	5494	General population (HT and NT)	Mean 11.7	Risk of developing events in people with different baseline BP values (grouped)	CV events (MI or Stroke)	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Stage 1 HT: 140-159 /90-99 Stage 2/3 HT: ≥160 /≥100 Very few people in stage 3 so combined into 'stage 2' values	Normal and high normal BP were a risk factor for the incidence of stroke and MI in men compared with optimal BP, as well as hypertension stage 1 or more. In women, the risk was seen at hypertension stages but not at normal/high normal BP (although numbers of events were lower in women).
Kono et al., 2005(32) Case-control	708	HT (with vs. without CV event)	n/a as case-control study	Risk of developing events in people with different baseline BP values (grouped)	CV events	SBP values NT: <140 Mild HT: 140-159 moderate-severe HT: >160	Positive relationship between BP status and risk of cardiovascular events
Kshirsagar et al., 2006(33) Cohort (ARIC)	8960	General population (HT and NT)	Mean 11.6 years	Risk of developing events in people with different baseline BP values (grouped)	CVD	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89	Normal BP and high normal BP were associated with a greater risk of incident cardiovascular disease compared with optimal BP. The risk was also higher for black people of African and Caribbean descent, older people (55-64 compared with 45-54), those with diabetes, high BMI, raised LDL cholesterol or renal insufficiency.
Obara et al., 2007(34) Post-hoc analysis (cohort)	1798	General population (HT and NT)	10,300 person-years	Risk of developing events in people with different baseline BP values (grouped)	Onset of or death due to circulatory disease (stroke, angina, MI, cardiac death)	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Grade 1 HT: 140-159 /90-99 Grade 2 HT: 160-179	In a relatively old cohort (mean age 60 years), risk of cardiovascular disease increased in higher BP groups

						/100-109 Grade 3 HT: ≥180 /110	
Okayama et al., 2006(35) Cohort (NIPPON DATA 80)	4244	General population (HT and NT)	19 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	SBP values Group 1: <120 Group 2: 120-139 Group 3: 140-159 Group 4: 160-179 Group 5: >179 DBP values Group 1: <80 Group 2: 80-84 Group 3: 85-89 Group 4: 90-99 Group 5: >99	Increased BP associated with cardiovascular disease mortality at all ages
Sairenchi et al., 2005(36) Cohort	97153	General population (HT and NT)	Mean 8.7 years (men), 8.9 years (women)	Risk of developing events in people with different baseline BP values (grouped)	Mortality	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Stage 1 HT: 140-159 /90-99 Stage 2/3 HT: ≥160 /≥100	Impact of SBP and DBP on cardiovascular disease around 2 times larger among middle-aged than elderly subjects (men and women); generally an increase in risk with increase BP values
Sleight et al., 2009(37) Post-hoc analysis of RCT (ONTARGET)	25558	People with atherosclerotic disease or diabetes with end organ damage (High risk)	Mean 56 months	Risk of developing events in people classed into baseline BP quartiles	CV events (CV death, MI, Stroke, HF)	SBP values (quartiles) ≤130 mmHg 130-142 mmHg 142-154 mmHg >154 mmHg	No relationship found between SBP reduction and risk of MI, congestive heart failure and cardiovascular death. Avoid excessive SBP reduction (below 130mmHg) in older sicker high-risk patients For the primary outcome, there is a J-shaped pattern (nadir 130mmHg) in the relationship between on-treatment SBP (deciles) and adjusted risk of events; this was also true for cardiovascular mortality

							(nadir 130mmHg) and MI (126mmHg) but not for stroke.
Haider et al., 2003(38) Cohort (Framingham heart study subset)	2040	General population	Mean 17.4 years	Risk of developing events in people classed into baseline BP groups	Congestive HF	SBP values 87-125 mmHg 126-141 mmHg ≥161 mmHg DBP values 49-74 mmHg 75-82 mmHg ≥83 mmHg	Both SBP and DBP were associated with CHF, but SBP conferred greater risk than DBP. Increased risk of events with increased BP value.
Benetos et al., 2003(39) Case-control	34776	NT, HT and HT (Tx)	8-12 years	Risk of developing events in people iwth higher and lower BP values (and in Tx and un-Tx HT).	CVD, CHD and associated mortality	Treated (mean BP ~151/93 mmHg) Untreated (mean BP ~136/83 mmHg) High BP (≥140/90 mmHg) Lower BP(<140/90)	Treated HTs had higher SBP (+ 15 mmHg) and higher DBP (+ 9 mmHg), and a higher prevalence of associated risk factors and diseases. Treated HTs vs. untreated HTs presented a two-fold increase in the RR for CV mortality and CHD mortality. Adjustment for unmodifiable risk factors only slightly decreased the excess CV risk observed in treated people. After additional adjustment for modifiable associated risk factors, the increased mortality in treated people persisted. Only after additional adjustment for SBP were CV mortality and CHD mortality similar in the two groups of people. Therefore, the increased CV mortality in treated HT vs. untreated HT is mainly due to high SBP levels under treatment.
Weitzman et al., 2006(40) Cohort	9611	General population (HT and NT)	23 years	Risk of developing events in people classed into	Mortality (stroke, CHD and all-cause)	SBP values 80-119 mmHg SBP values 80-119 mmHg	

				baseline BP groups		120-129 mmHg 130-136 mmHg 137-149 mmHg 150-260 mmHg DBP values 40-77 mmHg 78-80 mmHg 81-85 mmHg 86-90 mmHg 91-150 mmHg	120-129 mmHg 130-136 mmHg 137-149 mmHg 150-260 mmHg DBP values 40-77 mmHg 78-80 mmHg 81-85 mmHg 86-90 mmHg 91-150 mmHg	
Borghi et al., 2003(41) Cohort (Brisighella Heart Study)	2939	General population (HT and NT)	23 years	Risk of developing events in people classed into baseline BP groups	Mortality, CHD, MI, CeVD	SBP values <120 mmHg 120-139 mmHg 140-159 mmHg >159 mmHg DBP values <70 mmHg 70-79 mmHg 80-89 mmHg >89 mmHg	There is a consistent, strong, graded association between SBP (but not DBP) and cardiovascular events Increase in combined SHD and cerebrovascular disease risk was already evident with high-normal SBP
Fang et al., 2006(42) Cohort	26587	General population (HT and NT)	Mean 9.5 years	Risk of developing events in people classed into baseline BP groups	Stroke	ISH: ≥140 / <90 mmHg SDH: ≥140 / ≥90mmHg IDH: <140 / ≥90 mmHg (with or without a-HT Tx) MHT: <140 / <90 (and	Highest risk of stroke in people with ISH and SDH vs IDH and MHT. People with SDH are at the highest risk of stroke and should be treated more aggressively.

						controlled BP by a-HT Tx) NT: <140 / <90 (without history of HT)	
Home BP measurements – no studies (one included in Fagard meta-analysis)							
Ambulatory BP measurements							
Fagard et al., 2004(43) Cohort sub-analysis of RCT (Syst-Eur)	295	HT (SBP)	Median 7.5 years	Risk of developing events in people classed as normal, abnormal or high BP	CV events	Normal ABP: <140mmHg Abnormal ABP: 140-159mmHg High ABP: ≥160mmHg	Baseline ABP predicts cardiovascular events. Increased events with increase in BP
Inoue et al., 2007(44) Cohort; sub-analysis of RCT (OHASAMA)	1271	HT	Mean 11.2 years	Risk of developing events in people classed as HT (SBP-DBP; ISH, IDH) vs. NT	Stroke	NT: <135 / <80 mmHg SDH: ≥135 / ≥80 mmHg ISH: ≥135 / <80 mmHg IDH: <135 / ≥80 mmHg	ISH determined by ABPM was associated with a high risk of stroke, similar to that found for patients with combined systolic-diastolic HT.
Gustavsen et al., 2003(45) Cohort	566	General population (NT, HT and WCH)	Mean 10.2 years	Risk of developing events in people classed as NT, WCH and HT	Death and CV events	NT: <140; mean = 129.1 mmHg HT: SBP >140; mean = 160.3 mmHg WCH: CBP>140, mean = 136.3; ABPM <135/90 mmHg	There is an increased cardiovascular risk in WCH compared to normotensive controls; the level of risk is the same as that seen with EHs (even though WCH had a lower average ABP than NT).
Self-reported / unknown BP measurement method							
Britton et al., 2009(46) Cohort	18876	HT	Mean 20.7 years	Risk of developing events in people with different baseline BP values	HF	SBP values NT (not on Tx) <120 mmHg 120-129 mmHg 130-139 mmHg HT (or on Tx)	Linear relationship between NT SBP (120-129mmHg and 130-139mmHg) and risk of heart failure risk, as well as for HT SBP

						<130 mmHg 130-139 mmHg 140-149 mmHg 150-159 mmHg ≥160 mmHg	
Conen et al., 2007(47) Cohort (sub-analysis of RCT)	39322	NT and HT women	Median 10.2 years	Risk of developing events in people with different baseline BP values	CV death, stroke or MI	Optimal: <120/ <75 Normal: 120-129/75-84 High normal: 130-139/85-89 HT: ≥140 /≥90	The CV risk of women with high normal BP is higher than those with normal BP; there was a strong and consistent increase in events down to the optimal BP category.
Deckers, 2006(48) Post-hoc analysis of RCT (EUROPA)	12218	HT with CAD	Median 4.1 years	Risk of developing events in people with different baseline BP values	CV death, non-fatal MI	SBP values ≤130 mmHg >130-160 mmHg >160 mmHg	Higher baseline BP associated with increased risk.

Table 68

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP/DBP)** **[HRs given unless indicated. Available RRs or ORs have been given if no HRs available]**
Arima et al., 2006(22)	Stroke	SBP values (%, events/ person years) No HR values given 120 (median 114): 6.8% 120-139 (median 130) : 12.2% 140-159 (median 149): 12.5% ≥160 (median 169): 19.0%
Arima et al., 2009(23)	Stroke	Men Optimal: <120 /<80: Reference Men Normal: 120-129 /80-84: 1.64 (0.76-3.56) p>0.05 Men High normal: 130-139 /85-89: 1.52 (0.70-3.31) p>0.05 Men Grade 1 HT: 140-159 /90-99: 3.31 (1.73-6.32)p<0.05 Men Grade 2 HT: 160-179 /100-109: 4.22 (2.16-8.25)p<0.05 Men Grade 3 HT: ≥180 /110: 5.75 (2.93-11.30)p<0.05 Women Optimal: <120 /<80: Reference Women Normal: 120-129 /80-84: 1.53 (0.60-3.89)p>0.05 Women High normal: 130-139 /85-89: 2.19 (0.93-5.16)p>0.05

		Women Grade 1 HT: 140-159 /90-99: 3.92 (1.84-8.35)p<0.05 Women Grade 2 HT: 160-179 /100-109: 4.89 (2.24-10.67)p<0.05 Women Grade 3 HT: ≥180 /110: 7.51 (3.39-16.64)p<0.05
Assmann et al., 2005(24)	Major coronary event	NT: ≤140 /90 New HT: SBP >159 and/or DBP>94 Adequately treated HT: <160 /95 Inadequately treated HT: ≥160/95 No HR values given
Barengo et al(25)	CV mortality (MEN)	NT:<160/95 and no Tx : Reference HT (≥160 SBP or 95 DBP or Tx in last 7 days): No HR given HT treated and controlled (<160/95mmHg) 2.25 (1.70-2.99) HT: Tx and not controlled 2.41 (2.01-2.89) HT and aware (HT diagnosis or current Tx) but untreated 1.92 (1.65-2.23) HT but unaware 1.49 (1.33-1.68)
Benetos et al., 2003(39)	CVD, CHD and associated mortality	Treated (mean BP ~151/93 mmHg) Untreated (mean BP ~136/83 mmHg) High BP (≥140/90 mmHg) Lower BP(<140/90) No HRs given
Borghi et al., 2003(41)	Mortality	SBP values <120 mmHg Reference 120-139 mmHg 1.48 (1.04-2.10), p=0.0313 140-159 mmHg 1.92 (1.32-2.80), p=0.0006 >159 mmHg 2.38 (1.61-3.50), p<0.0001
Carlsson et al., 2009(27)	CV mortality	Men NT/optimal: <130 / <85 Reference Men Pre-HT: 130-139 and/or 85- 89 DBP 1.07 (0.58-1.97) Men High: 140 - 159 and/or 90-94 DBP 1.17 (0.66-2.09) Men Very high: ≥160 and/or DBP ≥95 3.12 (1.84-5.26) Women NT/optimal: <130 / <85 Reference Women Pre-HT: 130-139 and/or 85- 89 DBP 1.89 (0.76-4.68) Women High: 140 - 159 and/or 90-94 DBP 2.34 (1.01-5.45) Women Very high: ≥160 and/or DBP ≥95 3.84 (1.62-9.12)

Fang et al., 2006(42)	Stroke	NT: <140 / <90 (without history of HT) Reference ISH: ≥140 / <90 mmHg 2.35 (1.91-2.90) SDH: ≥140 / ≥90mmHg 2.96 (2.49-3.52) IDH: <140 / ≥90 mmHg (with or without a-HT Tx) 2.16 (1.69-2.76) MHT: <140 / <90 (and controlled BP by a-HT Tx) 1.33 (0.96-1.84)
Gudmundsson et al., 2005(28)	CV mortality	Men NT/high-NT:<140 /<90 Reference Men Mild-moderate HT: 140-179 /90-109 RR: 1.30 (0.79-2.14) Men Severe HT: ≥180 /≥110 RR: 1.23 (0.72-2.11) Women NT/high-NT:<140 /<90 Reference Women Mild-moderate HT: 140-179 /90-109 RR: 1.56 (0.85-2.86) Women Severe HT: ≥180 /≥110 RR: 2.57 (1.36-4.87) Only RRs given for above categories. However, per 1SD rise in SBP (22.4mmHg for men and 22.5 mmHg for women), HRs for Cv mortality are: 1.00 (0.87-1.15) for men and 1.34 (1.16-1.55),p<0.001 for women
Haider et al., 2003(38)	Congestive HF	SBP values 87-125 mmHg Reference 126-141 mmHg 1.48 (0.99-2.21), p=0.06 ≥161 mmHg 3.07 (2.10-4.49), p<0.001
Ishikawa et al., 2008(29)	Stroke	Men NT: <140/90, no treatment Reference Men HT: treated (receiving Tx, irrespective of current BP) RR:3.00 (2.00-4.51) Men C: Controlled (<140/90) RR 2.96 (1.66-5.26) Men U: Uncontrolled (≥140 and/or DBP ≥90) RR 3.05 (1.92-4.85) Men HT: untreated (≥140 /90 without Tx) RR 2.56 (1.83-3.57) Men M: Mild (SBP 140-159 or DBP 90-99) RR 2.34 (1.62-3.37) Men MS: Moderate-severe (SBP ≥160 and/or DBP ≥100) RR 3.17 (2.02-4.97) Women NT: <140/90, no treatment Reference Women HT: treated (receiving Tx, irrespective of current BP) RR 3.34 (2.29-4.87) Women C: Controlled (<140/90) RR 3.69 (2.20-6.17) Women U: Uncontrolled (≥140 and/or DBP ≥90) RR 3.16 (2.06-4.85) Women HT: untreated (≥140 /90 without Tx) RR 1.93 (1.35-2.76) Women M: Mild (SBP 140-159 or DBP 90-99) RR 1.95 (1.32-2.87)Women MS: Moderate-severe (SBP ≥160 and/or DBP ≥100) RR 1.87 (1.08-3.24) Only RRs given for above categories (but unclear). No HRs given
Kagiyama et al., 2008(30)	CV mortality	SBP values NT: <140: Reference Mild HT: 140-159: RR:1.71 (0.56-5.24) moderate-severe HT: >160: RR: 2.15 (0.51-8.97)

		Only RRs given for above categories. No HRs given
Kokubo et al., 2008(31)	CV events (MI or Stroke)	Men Optimal: <120 /<80 Reference Men Normal: 120-129 /80-84 2.04 (1.19-3.48) Men High normal: 130-139 /85-89 2.46 (1.46-4.14) Men Stage 1 HT: 140-159 /90-99 2.62 (1.59-4.32) Men Stage 2/3 HT: ≥160 /≥100 3.95 (2.37-6.58) Women Optimal: <120 /<80 Reference Women Normal: 120-129 /80-84 1.12 (0.59-2.13) Women High normal: 130-139 /85-89 1.54 (0.85-2.78) Women Stage 1 HT: 140-159 /90-99 1.35 (0.75-2.43) Women Stage 2/3 HT: ≥160 /≥100 2.86 (1.60-5.12) Overall Optimal: <120 /<80 Reference Overall Normal: 120-129 /80-84 1.62 (1.08-2.43) Overall High normal: 130-139 /85-89 2.08 (1.42-3.05) Overall Stage 1 HT: 140-159 /90-99 2.06 (1.42-2.98) Overall Stage 2/3 HT: ≥160 /≥100 3.53 (2.43-5.13)
Kono et al., 2005(32)	CV events	SBP values NT: <140 reference Mild HT: 140-159 Adjusted OR: 1.69 (1.10-2.60) moderate-severe HT: >160 Adjusted OR: 2.20 (1.08-4.45) Only adjusted ORs given. No HRs given
Kshirsagar et al., 2006(33)	CVD	Optimal: <120 /<80 Reference Normal: 120-129 /80-84 1.69 (1.37-2.09) High normal: 130-139 /85-89 2.33 (1.85-2.92)
Obara et al., 2007(34)	Onset of or death due to circulatory disease (stroke, angina, MI, cardiac death)	Optimal: <120 /<80 Normal: 120-129 /80-84 Reference High normal:130-139 /85-89 RR:1.19 (0.89-1.20), p=0.3 Grade 1-3 HT: 140->180 RR: 1.46 (1.00-1.17), p=0.011 Only adjusted RRs given. No HRs given
Okayama et al., 2006(35)	CV mortality	SBP values Group 1: <120 Reference Group 2: 120-139 Age adjusted RR: 2.36 (1.17-4.77) Group 3: 140-159 Age adjusted RR: 3.00 (1.51-5.94) Group 4: 160-179 Age adjusted RR: 3.46 (1.75-6.84)

		Group 5: >179 Age adjusted RR: 5.13 (2.59-10.16) No HRs given for categories above, but multivariate adjusted HRs for 1SD increase in SBP: 1.31 (1.17-1.47)
Sairenchi et al., 2005(36)	Mortality	Men Optimal: <120 /<80 Reference Men Normal: 120-129 /80-84 RR: 1.48 (0.50-4.44) Men High normal: 130-139 /85-89 RR:2.89 (1.07-7.86) Men Stage 1 HT: 140-159 /90-99 RR:3.06 (1.15-8.16) Men Stage 2/3 HT: ≥160 /≥100 RR:5.99 (2.13-16.8) Women Optimal: <120 /<80 Reference Women Normal: 120-129 /80-84 RR:0.86 (0.34-2.20) Women High normal: 130-139 /85-89 RR:1.19 (0.50-2.84) Women Stage 1 HT: 140-159 /90-99 RR:2.02 (0.93-4.38) Women Stage 2/3 HT: ≥160 /≥100 RR:4.09 (1.70-9.85) Only RRs for men and women aged 40-59 given above. No HRs given
Sleight et al., 2009(37)	CV events (CV death, MI, HF, Stroke)	SBP values (quartiles) CV death ≤130 mmHg Reference 130-142 mmHg 0.98 (0.86-1.12) 142-154 mmHg 0.93 (0.81-1.06) >154 mmHg 0.98 (0.86-1.11) MI ≤130 mmHg Reference 130-142 mmHg 0.87 (0.74-1.01) 142-154 mmHg 0.88 (0.75-1.02) >154 mmHg1.03 (0.88-1.20) CHF ≤130 mmHg Reference 130-142 mmHg 0.85 (0.71-1.01) 142-154 mmHg 0.87 (0.74-1.04) >154 mmHg0.84 (0.71-0.99) Stroke ≤130 mmHg Reference 130-142 mmHg 1.11 (0.92-1.33) 142-154 mmHg 1.32 (1.11-1.58) >154 mmHg1.51 (1.28-1.79)

Weitzman et al., 2006(40)	Mortality (stroke, CHD and all-cause)	SBP values 80-119 mmHg 120-129 mmHg 130-136 mmHg 137-149 mmHg 150-260 mmHg No HRs given, nor any other RRs or ORs relevant to the categories above.
Fagard et al., 2004(43)	CV events	Normal ABP: <140mmHg Reference Abnormal ABP: 140-159mmHg RR: 1.27 (0.64-2.52) High ABP: ≥160mmHg RR: 2.13 (1.09-4.13) No HRs given, but unadjusted RRs above calculated from data in outcome table.
Gustavsen et al., 2003(45)	CV events	NT: <140; mean = 129.1 mmHg Reference HT: SBP >140; mean = 160.3 mmHg HR p<0.001 WCH: CBP>140, mean = 136.3; ABPM <135/90 mmHg HR 6.6 (p<0.001) HR p values given as shown, but no CIs and no HR value for HT were provided.
Inoue et al., 2007(44)	Stroke	NT: <135 / <80 mmHg Reference SDH: ≥135 / ≥80 mmHg 2.39 (1.48-3.87), p=0.0004 ISH: ≥135 / <80 mmHg 2.24 (1.33-3.76), p=0.0024 IDH: <135 / ≥80 mmHg excluded from model as number of subjects (n=37) and events (number not stated) were too low
Britton et al., 2009(46)	HF	SBP values NT (not on Tx) <120 mmHg Reference 120-129 mmHg 1.10 (0.89-1.37) 130-139 mmHg 1.35 (1.09-1.68) HT (or on Tx) <130 mmHg 1.91 (1.36-2.68) 130-139 mmHg 2.61 (2.04-3.34) 140-149 mmHg 2.04 (1.63-2.55) 150-159 mmHg 2.66 (1.99-3.55) ≥160 mmHg 3.42 (2.33-5.04)
Conen et al., 2007(47)	Major CV event	Optimal: <120/ <75 0.51 (0.40-0.64) Normal: 120-129/75-84 0.61 (0.48-0.76) High normal: 130-139/85-89 Reference HT: ≥140 /≥90 1.30 (1.08-1.57) Age adjusted HR used
Deckers, 2006(48)	CV death	SBP values ≤130 mmHg

		>130-160 mmHg >160 mmHg HRs not provided for above comparisons but multivariate HR for a 1mmHg increase in systolic BP: 1.01 (1.00-1.01)

Table 69

Author's conclusions: Evidence statements

- Most studies showed a continuous relationship between BP and risk of developing clinical outcomes (ie. an increased risk of outcome with increasing BP value)
- This was true regardless of BP measurement method (office, ABPM, self-reported/ not specified)
- The MA of Law et al. showed that BP treatment reduced CVD risk regardless of pre-treatment BP

Reference	N	Population	BP measurement method	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Asayama, 2014 (49) MA of 6 cohorts (from the EPOCH-JAPAN database)	39 705	General population (HT and NT)	Clinic	Median 10.0 y	To evaluate risk of cardiovascular mortality among 6 blood pressure levels, and the usage of antihypertensive medication at baseline	Total cardiovascular mortality, mortality by coronary heart disease, heart failure mortality, stroke mortality	Optimal: <120/ <80 Normal: 120-129/80-84 High normal: 130-139/85-89 Grade 1 (mild) HT: 140-159/ 90-99 Grade 2 (moderate) HT: 160-179/ 100-109 Grade 3 (severe) HT: ≥180/110	Among untreated participants, the risks increased linearly with an increment of blood pressure category ($P \leq 0.011$). The risk increments per blood pressure category were higher in young participants (<60 years; 22% to 79%) than those in old people (≥60 years; 7% to 15%) with significant interaction for total cardiovascular, heart failure, and stroke mortality ($P \leq 0.026$) Among treated participants, the significant linear association was also observed for cardiovascular mortality ($P=0.0003$), whereas no stepwise increase in stroke death was observed ($P=0.19$)

Table 70 additional RCT found

Numerical values of HR's and their CI's not reported

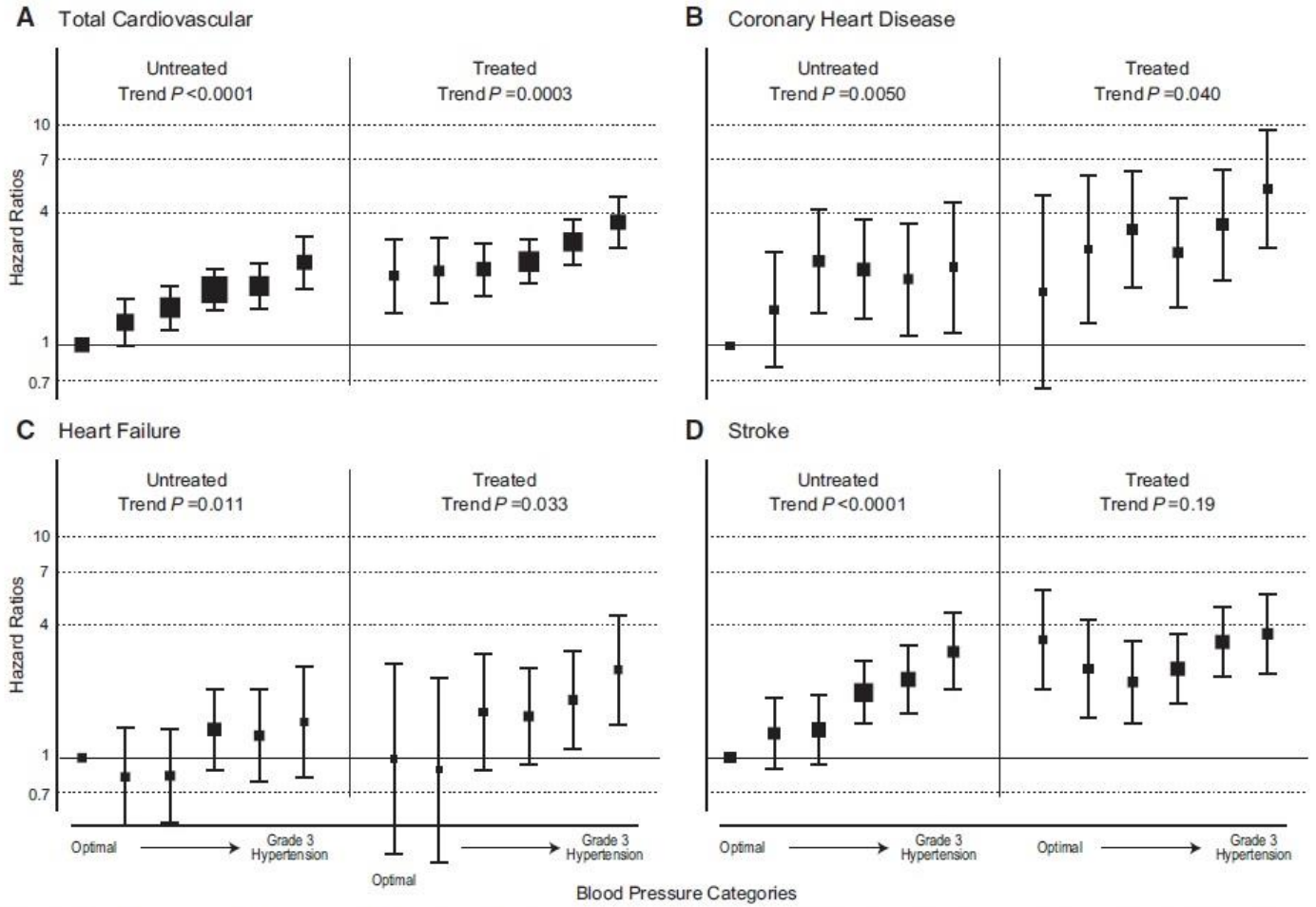


Figure 2. The risk among 12 categories defined by blood pressure levels and usage of antihypertensive medication at baseline for (**A**) total cardiovascular mortality, death from (**B**) coronary heart disease, (**C**) heart failure, and (**D**) stroke. Filled squares express hazard ratios and are sized in proportion to the number of events observed. Vertical bars indicate 95% confidence intervals in each category compared with untreated optimal blood pressure category. Blood pressure levels are defined from optimal (<120/<80 mm Hg), normal (120–129/80–84 mm Hg), high normal (130–139/85–89 mm Hg), grade 1 hypertension (140–159/90–99 mm Hg), grade 2 hypertension (160–179/100–109 mm Hg), and grade 3 hypertension (≥180/≥110 mm Hg) levels. Trend *P* values denote the linearity among 6 categories when treated and untreated participants are separated. Adjusted factors are sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort.

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Rapsomaniki 2014(50) Cohort study	1250000	Primary care population (HT and NT) initially free from cardiovascular disease	Median 5.2 years	Lifetime risk of developing events in people with different baseline BP values and ages (30-59y; 60-79y; ≥80y.	The initial presentation of cardiovascular disease as any of 12 cardiovascular diseases diagnosed in primary care secondary care, or at death, and total cardiovascular disease (all 12 cardiovascular diseases combined) (12 diseases= (Stable angina, unstable angina, myocardial infarction, unheralded coronary heart disease death, heart failure, cardiac arrest, transient ischaemic attack, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, peripheral arterial disease, abdominal aortic aneurysm)	SBP values 90-114 115-129 130-139 140-149 160-179 ≥180 DBP values 60-74 75-84 85-89 90-94 95-99 ≥100	In each age group, the lowest risk for cardiovascular disease was in people with systolic blood pressure of 90–114 mm Hg and diastolic blood pressure of 60–74 mm Hg, with no evidence of a J-shaped increased risk at lower blood pressures. The effect of high blood pressure varied by cardiovascular disease endpoint, from strongly positive to no effect. Associations with both systolic and diastolic blood pressure decreased with age for all outcomes at varying rates for different outcomes.

Table 71 additional study found

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
Rapsomaniki 2014 (50)		See figures below

Table 72 details of Rapsomaniki 2014

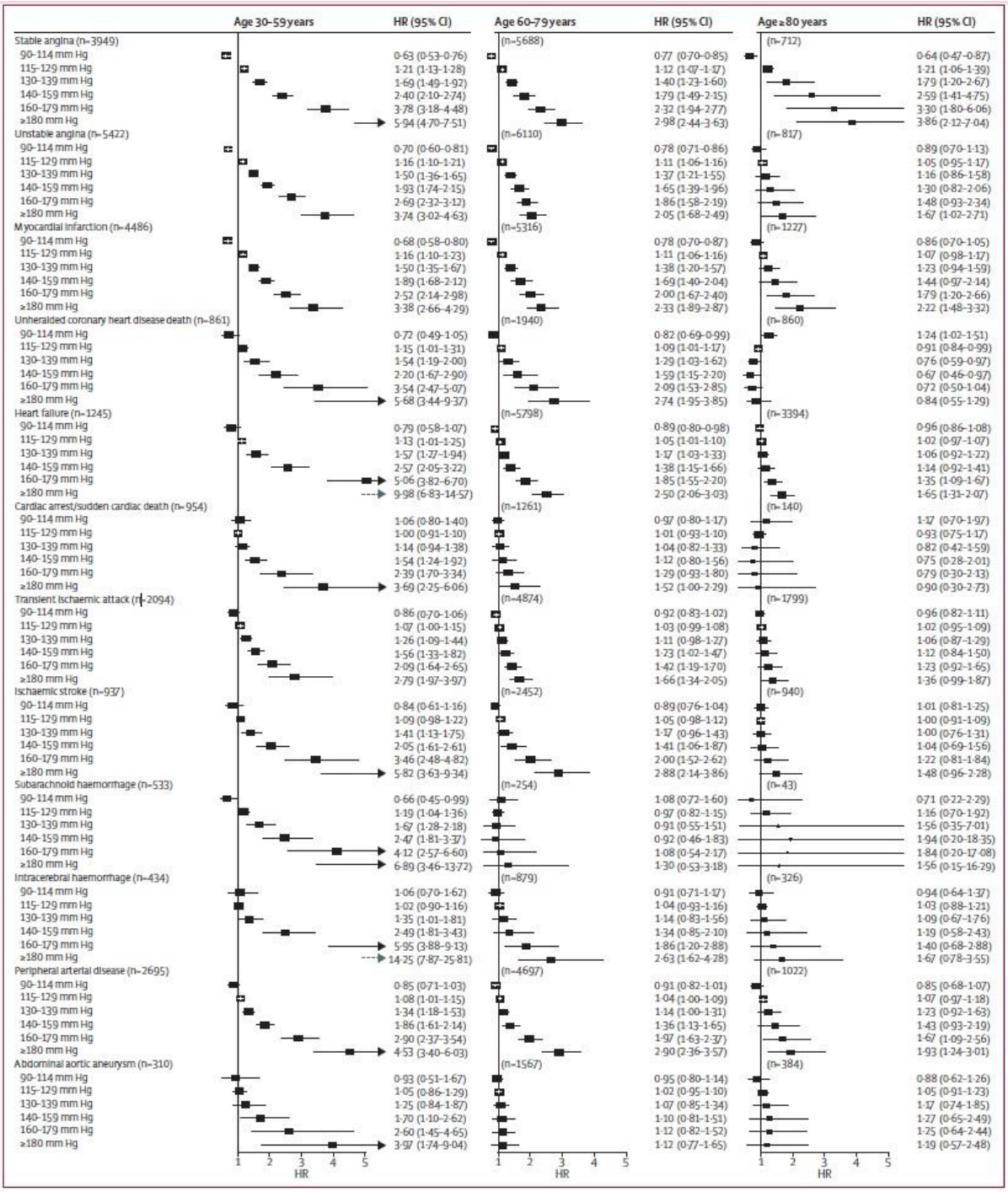


Figure 1 Forest plots of HRs (95% CIs) for different cutoffs of systolic blood pressure (vs reference 115 mmHg) adjusted for age and sex

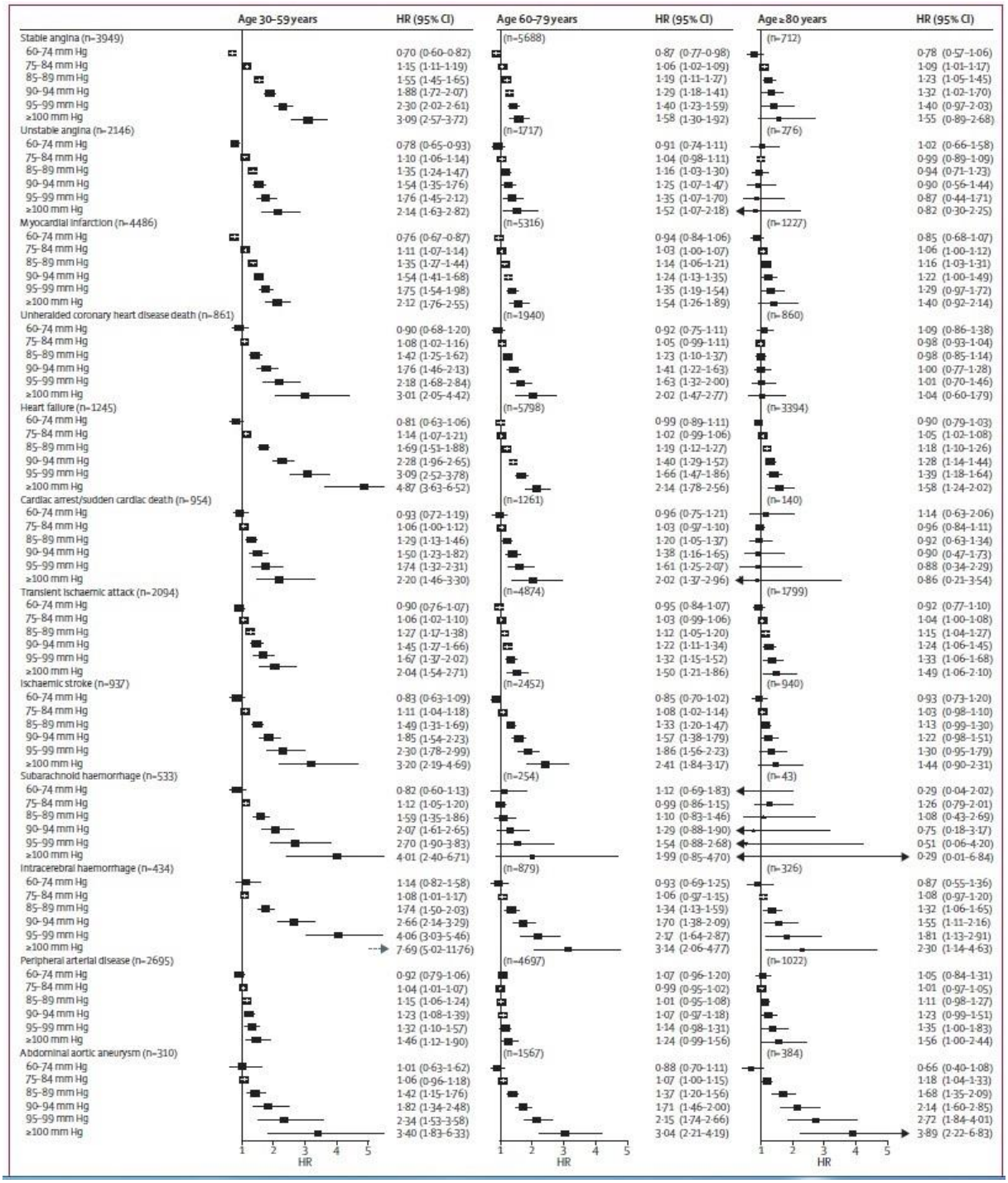


Figure 2 Forest plot of HRs (95% CIs) for different cutoffs of diastolic blood pressure (vs reference 75 mmHg) adjusted for age and sex

4.1.1.4 *Summary and conclusions of observational data : Treatment threshold in adults with or without additional risk factors*

Nice Hypertension 2011(3) did a systematic review to determine a threshold for initiating antihypertensive treatment. Studies were excluded if they did not stratify results into more than one different BP value / threshold. Data from the included studies was not pooled into a meta-analysis, because of differences in design, stratification and analysis.

1 meta-analysis of 108 RCTs was found (Law 2009(20)) by NICE, which concluded that BP treatment reduced risk of CVD and stroke, regardless of patients' pre-treatment BP (as low as 110 SBP and 70 DBP mmHg). However, the trials that were included in this RCT used different in/exclusion criteria and included patients with hypertension as well as post myocardial infarction patients or heart failure patients without hypertension. In the trials of patients without previous cardiovascular disease, the mean blood pressure at baseline however was usually high. Quality of included RCTs was low to high. The reliability of these statements for the lower BP values needs to be evaluated in RCTs that are specifically designed for this research question. See also previously: Cochrane Diao 2012.

2 meta-analyses of observational studies and 27 observational studies (cohort studies, case-control studies and post-hoc analyses of RCT data) were included by NICE. Our own search yielded one meta-analysis of 6 cohort studies and one cohort study.
Most studies included both hypertensive and normotensive people from the general population.
Length of follow-up ranged from 3.9 years to 32 years.

NICE concluded that most studies showed a continuous relationship between BP and risk of developing clinical outcomes (ie. an increased risk of outcome with increasing BP value).

The meta-analysis by Asayama 2014 (49) of 6 cohorts (with a median follow-up of 10 years) and the recent cohort study by Rapsomaniki 2014(50) (with a follow-up of 5.2 years) that we found in our additional search confirm the continuous relationship between BP and risk of developing clinical outcomes. The association of BP and risk of events seems comparable in both treated and untreated participants (Asayama 2014(49)).
Association of BP and risk of events seem to decrease with age(Asayama 2014, Rapsomaniki 2014(49, 50)).

4.1.2 Elderly patients

4.1.2.1 Clinical evidence profile: Hypertension treatment threshold in elderly patients ≥ 60 years

Trial, year **Population** **Sample size** **Trial duration**	**Overall Mortality**	**Coronary Heart Disease** (includes non-fatal MI, fatal MI, sudden death or combination)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal or combination)	**Heart Failure** (includes fatal, non-fatal, or combination)
EWPHE, 1985(51) Adults, ages ≥60 years, SBP 160-239 and DBP 90-119 mmHg Hydrochlorothiazide vs pla N = 840 Mean 4.6yrs Fair	**All-cause mortality:** 9% decrease in txt CI (-28,15) p = 0.41	**Cardiac mortality:** **38% reduction in txt group per 1000 py, p = 0.036** **Fatal cardiac events: at 1 year** **11% reduction in txt per 1000 py** **p < 0.05**	**Non-fatal cerebrovascular events, at 1 year: 11% decrease in txt per 1000 py,** **p < 0.05** **Cerebrovascular deaths:** 32% decrease in txt CI (-61, 19) p = 0.16	**Severe CHF: at 1 year:** **8% decrease in txt per 1000 py** **p < 0.05**

SHEP, 1991(17) Adults, ages ≥60 years, SBP 160-219 and DBP <90 mmHg Chlortalidone vs pla N = 4,736 Mean 4.5 years Good	**Total deaths:** RR: 0.87 CI (0.73, 1.05) p = NR	**Non-fatal MI:** **RR: 0.67 CI (0.47, 0.96)** **p = NR** **Symptomatic MI events:** **63 vs 98 (txt vs control)** **p = 0 .005** **CHD** **RR:0.75 CI (0.60, 0.94)** **p = NR** **Non-fatal MI or CHD deaths** **RR: 0.73 CI (0.57, 0.94)** **p = NR** **MI deaths:** RR: 0.57 CI (0.30-1.08) p = NR **Total CHD deaths:** RR: 0.80 CI (0.57, 1.13) p = NR **Sudden death** (<1 hour)**:** RR: 1.00 CI (0.56, 1.78) p = NR **Rapid deaths** (1-24 hours)**:** RR: 0.87 CI (0.48, 1.56) p = NR	**Non-fatal plus fatal stroke:** **RR: 0.64 (0.50, 0.82)** **p = 0.0003**	**Fatal and non-fatal HF:** **RR: 0.51 (0.37, 0.71)** **p < 0.001**

Syst-Eur, 1997 (52) Adults, ages ≥ 60 years, SBP 160-219 and DBP <95 mmHg Nitrendipine vs pla (+ nitrendipine and/or hydrochlorothiazide) N = 4,695 Median 24 months Good	**Total mortality:** Adj HR: 0.86 CI (0.67, 1.10) p = NR	**Fatal and non-fatal cardiac endpoints:** **Adj HR: 0.71 CI (0.54, 0.94) p < 0.05** **Fatal MI:** 56% decrease in txt group per1000 py, CI (-82, 9) p =0.08 **Non-fatal MI:** 20% decrease in txt group per 1000py CI (-53, 34) p = 0.40 **Coronary mortality:** 27% decrease in txt group per 1000 py, CI (-54, 15) p = 0.17 **Sudden death:** 12% decrease in txt group per 1000 py, CI (-49, 52) p =0.65 **Fatal and non-fatal MI:** 30% decrease in txt group per 1000 py, CI (-56, 9) p = 0.12	**Non-fatal stroke:** **44% decrease in active (rate/1000 py)** **CI (-63, -14),** **p = 0.007** **Death due to Stroke:** 27% decrease in txt group per 1000 py CI (-62, 39), p = 0.33 **Fatal and non-fatal stroke combined:** **Adj HR: 0.59 (0.38, 0.79)** **p < 0.01**	**Non-fatal HF:** 36% decrease in txt group per 1000 py CI (-60, 2) p = 0.06 **Fatal HF:** 24% decrease in active (rate/1000 py) CI (-70, 93) p = 0.57 **Fatal & non-fatal HF:** 29% decrease in txt group per 1000 py CI (-53, 10) p =0.12

Table 73

4.1.2.2 *Summary and conclusions: Hypertension treatment threshold in elderly patients ≥ 60 years*

Treatment versus no treatment in patients ≥ 60y at SBP thresholds ≥160 mmHg			
SHEP 1991(17) (a), Syst-Eur 1997(52) (b) (from JNC-8 2014(8))			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	9431 (2 studies)	a) RR: 0.87 (95%CI 0.73, 1.05) NS b) Adj HR: 0.86 (95%CI 0.67, 1.10) NR	⨁⨁⨁⨀ **MODERATE** Study quality: OK Consistency:ok Directness:ok Imprecision: -1 CI does not exclude possible benefit
Non-fatal MI	9431 (2 studies)	a) **RR: 0.67 (95%CI 0.47, 0.96)** **SS** b) 20% decrease in txt group per 1000py CI (-53, 34) NS	⨁⨁⨁⨀ **MODERATE** ⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: -1 Directness:(-1) doubt as to nature of treatment Imprecision:OK
Fatal and non-fatal cardiac endpoints	4695 (1study)	b) **Adj HR: 0.71 (95%CI 0.54, 0.94)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality:OK Consistency:na Directness:-1 Imprecision:ok
Non-fatal plus fatal stroke	9431 (2 studies)	**a) RR: 0.64 (95% CI 0.50, 0.82)** **SS** **b) Adj HR: 0.59 (95%CI 0.38, 0.79)** **SS**	⨁⨁⨁⨁ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
Heart failure	9431 (2 studies)	a) **RR: 0.51 (95%CI 0.37, 0.71)** **SS** b) 29% decrease in txt group per 1000 py CI (-53, 10) NS	⨁⨁⨁⨀ **MODERATE** ⨁⨁⨀⨀ **LOW** Study quality:ok Consistency:-1 Directness:(-1) Imprecision:ok

Table 74

Treatment versus no treatment at SBP thresholds ≥160 and DBP thresholds ≥90 mmHg in ≥60y			
EWPHE 1985(51) (from JNC-8 2014(8))			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	840 (1study) 4.6y	ARR: 9% decrease, 95%CI (-28,15) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 rated by JNC8 Consistency:na Directness:ok Imprecision:-1 CI does not exclude possible benefit
Cardiac mortality	840 (1study) 4.6y	**ARR:** **38% reduction per 1000 py** **SS**	⊕⊕⊖⊖ **LOW** Study quality:-1 rated by JNC8 Consistency:na Directness:-1 older study Imprecision:ok
Non-fatal cerebrovascular events	840 (1study) 4.6y	**ARR at 1 y:** **11% decrease per 1000 py** **SS**	⊕⊕⊖⊖ **LOW** Study quality:-1 rated by JNC8 Consistency:na Directness:-1 older study Imprecision:ok
Severe heart failure	840 (1study) 4.6y	**ARR at 1 y:** **8% decrease in txt per 1000 py** **SS**	⊕⊕⊖⊖ **LOW** Study quality:-1 rated by JNC8 Consistency:na Directness:-1 older study Imprecision:ok

Table 75

JNC-8 2014 conducted a systematic review that evaluated antihypertensive treatment versus no antihypertensive treatment in primary uncomplicated hypertension in patients of 60 years and older. Three of the included RCTs evaluated antihypertensive treatment versus no antihypertensive treatment in people aged ≥60y. 1 trial included people aged ≥80y, which will be discussed in the next chapter.

The 3 RCTs of people ≥60y included hypertensive patients with SBPs ranging from 160 to 239 mmHg. Two (SHEP 1991,Syst-Eur 1997) included only elderly people with isolated systolic hypertension (DBP <95 or 90 mmHg). The first line drug was chlortalidone in one trial and nitrendipine in the other trial. The third trial (EWPHE 1985) included only elderly people with both systolic and diastolic hypertension (DBP 90-119 mmHg), treated with hydrochlorothiazide or placebo.

Follow-up ranged from 2 to 4.6 years.

<u>Isolated systolic hypertension</u>

In the two trials with isolated systolic hypertension ≥160mmHg, **total mortality** was not significantly influenced by treatment compared to no treatment or placebo.

GRADE: MODERATE quality of evidence

In patients ≥60y and isolated systolic hypertension ≥160mmHg, treatment with chlortalidone decreased the risk of **non-fatal MI and coronary heart disease**.
In patients ≥60y and isolated systolic hypertension ≥160mmHg, treatment with nitrendipine (+/- additional drugs) decreased the risk **of total cardiac endpoints (fatal and nonfatal combined)**, but did not significantly alter the risk of non-fatal MI, fatal MI and coronary mortality when considered separately. It is possible that the difference in drug treatments is reflecting the difference between both studies.
GRADE: MODERATE to LOW quality of evidence

In patients ≥60y and isolated systolic hypertension ≥160mmHg, treatment of hypertension decreased the risk of the **stroke (fatal and non-fatal combined)**.
GRADE: HIGH quality of evidence

For people aged ≥60y with isolated systolic hypertension ≥160mmHg, treatment with chlortalidone decreased the risk of the **heart failure (fatal and non-fatal combined)** but treatment with nitrendipine (+/- additional drugs) did not significantly affected this risk. It is possible that the difference in drug treatments is reflecting the difference between both studies.
GRADE: MODERATE to LOW quality of evidence

<u>Systolic and diastolic hypertension</u>
In the trial with both systolic and diastolic hypertension, **total mortality** was also not significantly different between treatment and no treatment.
GRADE: LOW quality of evidence

In the trial with both systolic and diastolic hypertension, treatment with hydrochlorothiazide decreased the risk of **cardiac mortality**.
GRADE: LOW quality of evidence

In the trial with both systolic and diastolic hypertension, treatment with hydrochlorothiazide decreased the risk of **non-fatal cerebrovascular events**, but **not cerebrovascular deaths**.
GRADE: LOW quality of evidence

In the trial with both systolic and diastolic hypertension, treatment with hydrochlorothiazide decreased the risk of **severe congestive heart failure**.
GRADE: LOW quality of evidence

4.1.2.3 Observational data: Hypertension treatment threshold in elderly patients ≥ 60 years

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Rapsomaniki 2014(50) Cohort study	1250000	Primary care population (HT and NT) initially free from cardiovascular disease	Median 5.2 years	Lifetime risk of developing events in people with different baseline BP values and ages (30-59y; 60-79y; ≥80y.	The initial presentation of cardiovascular disease as any of 12 cardiovascular diseases diagnosed in primary care secondary care, or at death, and total cardiovascular disease (all 12 cardiovascular diseases combined) (12 diseases= (Stable angina, unstable angina, myocardial infarction, unheralded coronary heart disease death, heart failure, cardiac arrest, transient ischaemic attack, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, peripheral arterial disease, abdominal aortic aneurysm)	SBP values 90-114 115-129 130-139 140-149 160-179 ≥180 DBP values 60-74 75-84 85-89 90-94 95-99 ≥100	In each age group, the lowest risk for cardiovascular disease was in people with systolic blood pressure of 90–114 mm Hg and diastolic blood pressure of 60–74 mm Hg, with no evidence of a J-shaped increased risk at lower blood pressures. The effect of high blood pressure varied by cardiovascular disease endpoint, from strongly positive to no effect. Associations with both systolic and diastolic blood pressure decreased with age for all outcomes at varying rates for different outcomes.

Table 76

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]

Rapsomaniki 2014 (50)		See figures below

Table 77 details of Rapsomaniki 2014

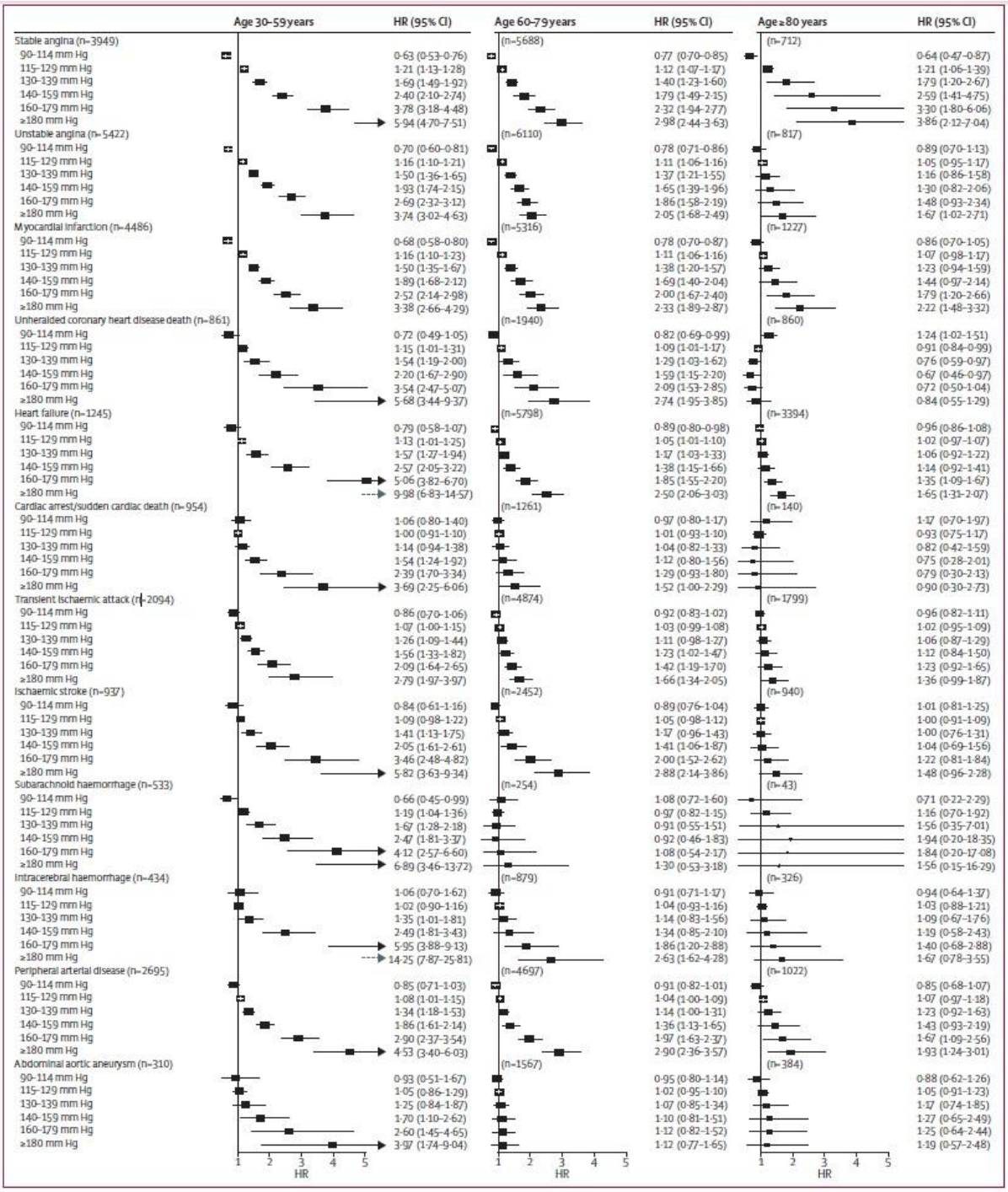


Figure 3 Forest plots of HRs (95% CIs) for different cutoffs of systolic blood pressure (vs reference 115 mmHg) adjusted for age and sex

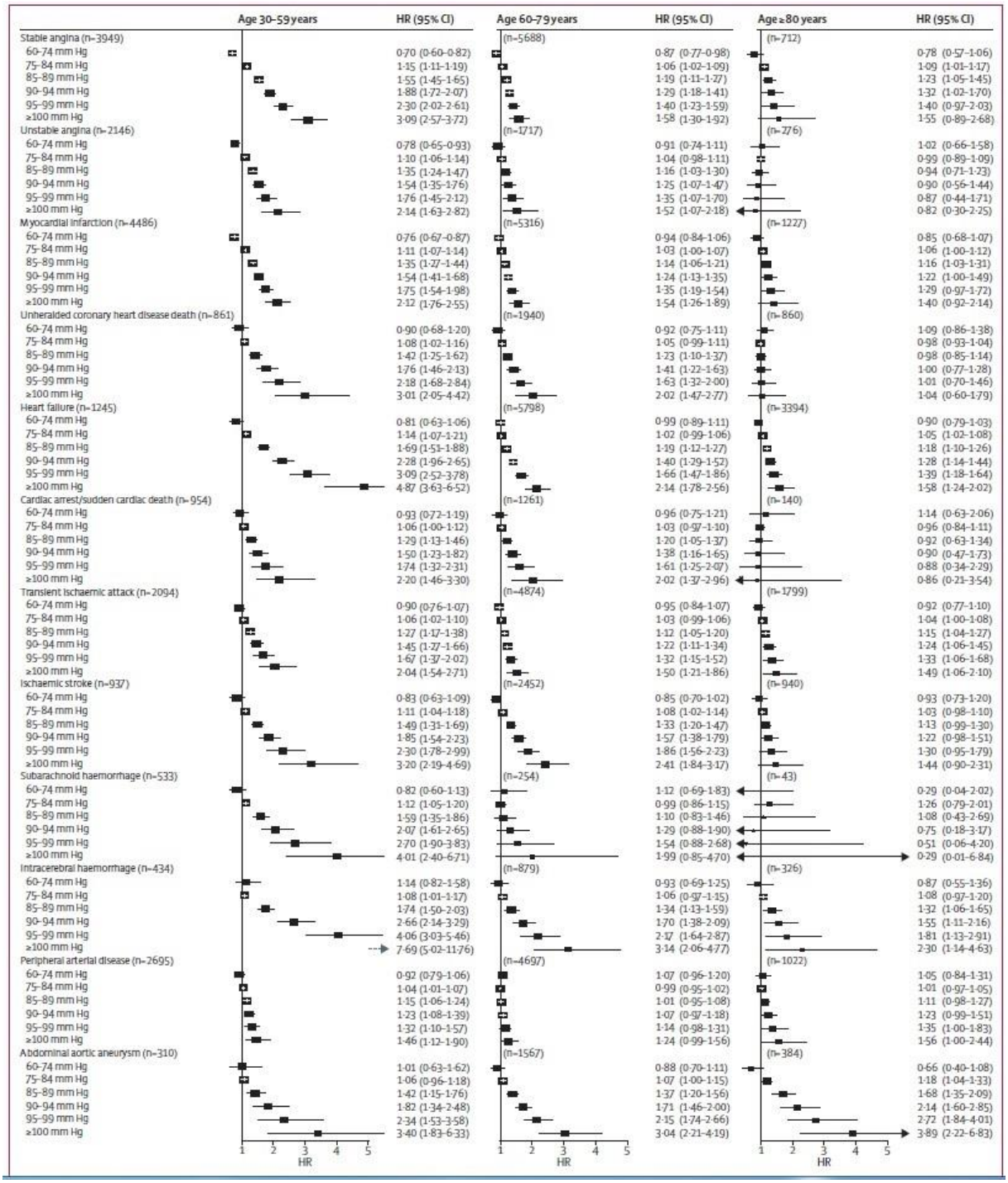


Figure 4 Forest plot of HRs (95% CIs) for different cutoffs of diastolic blood pressure (vs reference 75 mmHg) adjusted for age and sex

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Blom 2013(53) Analysis of data of a prospective cohort study (the Rotterdam study)	4612	≥55 y, without previous cardiovascular disease using or not using blood pressure lowering drugs	Median 14.9 years	Risk of mortality with different baseline SBP and in different age groups (55-64; 65-74; 75-84; ≥85y) (baseline SBP can be treated or non-treated BP)	Mortality (adjusted for age and sex)	SBP 140-159 ≥160	The predictive value of SBP for mortality differs with age in people aged 55 years and over without a history of CVD. Between age 55 and 75 years, high SBP predicts higher mortality risk, but from age 75 years onwards a significant trend shows that SBP levels no longer predict mortality risk (although hazard ratios per age group do not reach significance). From age 85 years onwards, high SBP even predicts lower mortality risk. When participants were stratified according to the use of antihypertensive medication at baseline, results in both strata were roughly similar.

Table 78

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement HRs versus reference SBP <140 mmHg**
Blom 2013(53)	All-cause mortality	<u>140-159</u> 55-64 y: HR= 1.2 (0.9 to 1.5) 65-74y: HR= 1.2 (1.0 to 1.4) 75-84y: HR= 1.1 (0.9 to 1.3) ≥85y: HR= 0.7 (0.5 to 1.1) *P for trend <0.001* <u>≥160</u> **55-64 y: HR= 1.7 (1.2 to 2.2)** 65-74y: HR= 1.3 (1.0 to 1.5) 75-84y: HR= 1.3 (1.0 to 1.6) ≥85y: HR= 0.7 (0.4 to 1.1) *P for trend <0.001*

	Cardiovascular mortality	<u>140-159</u> **55-64 y: HR= 2.1 (1.1 to 3.9)** 65-74y: HR= 1.3 (0.8 to 1.9) 75-84y: HR= 0.9 (0.6 to 1.4) ≥85y: HR= 1.3 (0.6 to 2.8) *P for trend <0.001* <u>≥160</u> **55-64 y: HR= 2.9 (1.4 to 5.9)** 65-74y: HR= 1.2 (0.7 to 2.0) 75-84y: HR= 1.3 (0.8 to 2.1) ≥85y: HR= 0.9 (0.3 to 2.1) *P for trend <0.001*

Table 79

When participants were categorized into 5-year age groups, the increased risk with higher SBPs was present up to age 75 years: in the age group 70–74 years, the HR140–159 is 1.4 (95% CI: 1.1, 1.7) and in the age group 75–79 years and over the HR reaches unity (HR140–159 1.1, 95% CI: 0.9, 1.4).
For the group with the highest SBPs, in the age group 70–74 years, the HR≥160 is 1.3 (95% CI: 1.0, 1.7). Relative risks in the age group 75–79 and 80–84 years are similar, whereas in the age group ≥85 years HR≥160 is 0.7 (95% CI: 0.4, 1.1). Using a reference group with SBP <150 mmHg shows similar results with HR150–159 0.8 (95% CI: 0.5, 1.3) and HR≥160 0.8 (95% CI: 0.5, 1.2) at age ≥85 years (data not shown).

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Butler 2011(54) Analysis using follow-up data from two cohort studies (Cardiovascular Health Study and Health ABC study)	4408	People aged 65-100y Mean age 72.8±4.9y HT and NT Not receiving antihypertensive drugs at baseline No prevalent heart failure	10 years	Risk of developing heart failure with different baseline SBP values	Incident heart failure (defined as first hospitalization for heart failure)	SBP values <120 120-139 140-159 ≥160	There is a continuous positive association between SBP and heart failure risk in the elderly for levels of SBP as low as <115 mmHg; over half of incident heart failure events occur in individuals with SBP <140 mmHg.

Table 80

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP) HRs versus optimal SBP (<120 mmHg)**
Butler 2011(54)	Heart failure	<120 mmHg: HR=1 **120-139 mmHg: HR= 1.63 (95%CI 1.23 to 2.16) p=0.001** **140-159 mmHg: HR= 2.21 (95%CI 1.65 to 2.96) p<0.001** **≥160 mmHg: HR= 2.60 (95%CI 1.85 to 3.64) p<0.001**

Table 81

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Lohr 2015(55) Retrospective cohort study	15221	≥70 y No CKD at baseline Veterans (1.9% female) HT and NT	Mean 16.38 quarters	Risk of developing events with different baseline SBP values	Incident CKD, mortality	SBP values <110 110-119 120-129 130-139 140-149 150-159 ≥160 DBP values <60 60-69 70-79 ≥80	The optimal achieved systolic blood pressure in predominantly male elderly patients to prevent the development of CKD was <140 mm Hg. However, lowering the systolic blood pressure below 130 mm Hg was associated with increased mortality.

Table 82

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **RRs versus reference SBP (130-139 mmHg) and reference DBP (70-79 mmHg)**
Lohr 2015(55)	Incidence of chronic kidney disease	SBP values <110: RR=0.95 (0.73 to 1.17) 110-119: RR=1.01 (0.86 to 1.15) 120-129 RR= 1.01 (0.90 to 1.13) **140-149 RR= 1.22 (1.08 to 1.35)** **150-159 RR= 1.30 (1.12 to 1.49)** **≥160 RR= 1.51 (1.26 to 1.76)** DBP values <60 RR= 1.04 (0.89 to 1.20) 60-69 RR= 1.11 (1.00 to 1.28)

		≥80 RR= 1.10 (0.97 to 1.23)
	Mortality	SBP values **<110: RR= 2.00 (1.69 to 2.36)** **110-119: RR= 1.84 (1.62 to 2.09)** **120-129 RR= 1.32 (1.17 to 1.49)** 140-149 RR= 0.92 (0.79 to 1.06) 150-159 RR= 0.82 (0.66 to 1.01) ≥160 RR= 1.00 (0.80 to 1.27) DBP values <60 RR= 0.92 (0.81 to 1.04) 60-69 RR= 1.08 (0.98 to 1.19) ≥80 RR= 0.92 (0.78 to 1.07)

Table 83

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Gutiérrez-Misis 2013(56) Data from cohort study	1182	≥65y Mediterranean HT and NT	17 years	Risk of mortality with different baseline BP values	Mortality	SBP values <110 110-119 120-129 130-139 140-159 160-179 ≥180 DBP values <60 60-69 70-79	Based on the dynamic association between blood pressure and mortality, a U-shaped relationship was found for systolic blood pressure and a negative relationship for diastolic blood pressure and all-cause mortality.

						80-84 85-89 90-99	

Table 84

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement HRs versus referent SBP (136 mmHg) and reference DBP (80-84 mmHg)**
Gutiérrez-Misis 2013(56)	Mortality	SBP 80: HR= 1.53 (0.97 to 2.41) 90: HR= 1.33 (0.95 to 1.86) 100: HR=1.19 (0.95 to 1.50) 110: HR= 1.10 (0.95 to 1.27) 120: HR= 1.04 (0.96 to 1.12) 130: HR= 1.01 (0.98 to 1.03) 140: HR= 1.00 (0.99 to 1.02) 150: HR= 1.02 (0.98 to 1.08) 160: HR= 1.08 (0.99 to 1.17) **170: HR= 1.16 (1.02 to 1.33)** **180: HR= 1.29 (1.06 to 1.56)** **190: HR= 1.46 (1.11 to 1.93)** **200: HR= 1.71 (1.17 to 2.49)** DBP **<60: HR=1.53 (1.05 to 2.23)** HR for higher DBP categories NS compared to reference DBP; numerical values not reported

Table 85

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Hadaegh 2013(57) Prospective cohort study	6273 (5064 middle age and 1209 elderly with mean ages 42.5 and 66.3,	≥30 y No CVD at baseline HT and NT	Median 9.3 y	Risk of incident CVD with different baseline SBP/DBP values, in middle aged (30-59y) vs	Incident CVD	Optimal: <120/<80 Normal: 120-129/80-84 High normal: 130-139/85-89	High normal BP (130-139/85-89) is a risk factor for incident CVD only among middle-aged Iranian

Iran	respectively) male/female ratio 2694/3579)			elderly (≥60y) patients		Hypertensive: ≥140/≥90 *(if SBP and DBP fell into different categories, patients were assigned to the highest category)*	populations.

Table 86

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference optimal SBP/DBP (<120/<80 mmHg)**
Hadaegh 2013(57)	Cardiovascular disease	<u>Middle-aged (30≥age<60y)</u> Normal BP: HR= 1.06 (0.71 to 1.57) **High normal BP: HR= 1.62 (1.11 to 2.37)** **Hypertensive: HR= 2.20 (1.57 to 3.09)** <u>Elderly (≥60y)</u> Normal BP: HR= 0.83 (0.47 to 1.46) High normal BP: HR= 0.89 (0.51 to 1.54) **Hypertensive: HR= 2.09 (1.36 to 3.21)**
	Coronary heart disease	<u>Middle-aged</u> Normal BP: HR= 0.99 (0.66 to 1.52) **High normal BP: HR= 1.71 (1.16 to 2.53)** **Hypertensive: HR= 2.28 (1.61 to 3.22)** <u>Elderly</u> Normal BP: HR= 0.71 (0.38 to 1.31) High normal BP: HR= 0.64 (0.34 to 1.21) **Hypertensive: HR= 1.63 (1.03 to 2.59)**

Table 87

4.1.2.4 Summary and conclusions of observational data: Hypertension treatment threshold in elderly patients ≥ 60 years

Blom 2013 (53)
This prospective cohort study followed 4621 Dutch people aged ≥55 y, without previous cardiovascular disease for a median of 14.9 years. Using 10 year age groups, only people 55y-54y with SBP ≥160mmHg show increased **all-cause mortality** rates compared to the reference SBP<140mmHg, and increased cardiovascular mortality rates from 140mmHg and higher.
When participants were categorized into 5-year age groups, the increased risk with higher SBPs was present up to age 75 years, but 95% confidence intervals of hazard ratios were close to 1(= no difference in risk).
The authors conclude: between age 55 and 75 years, high SBP predicts higher **mortality** risk, but from age 75 years onwards a significant trend shows that SBP levels no longer predict mortality risk.
Blom 2013 also refers to 17 other observational studies that found that **high SBP does not predict mortality from age 75y onwards**.

Gutiérrez-Misis 2013(56)
This Mediterranean cohort study followed 1182 people ≥65 years over a period of 17 years. The association between risk of **mortality** and different baseline SBP and DBP values was examined.
Compared to a referent SBP of 136mmHg, an SBP of 170mmHg and higher was associated with a higher mortality rate. SBP of 160mmHg and lower (up to SBP 80mmHg) did not show a statistically significant difference in mortality rates compared to a reference SBP of 136mmHg. However, confidence intervals were wide in the lower ranges of the SBP and thus a U-shaped relationship was found between SBP and mortality.
Compared to a referent DBP of 80-84mmHg, a DBP <60mmHg was associated with a higher mortality rate.

Lohr 2015 Lohr 2015(55)
This retrospective cohort study of 15,221 veterans ≥70 y without chronic kidney disease at baseline examined the association between different baseline SBP values and the risk of **CKD** or **mortality**. Follow-up was +/- 4 years.
A baseline systolic blood pressure of 140 mmHg and higher was associated with an increased incidence of **chronic kidney disease**, compared to a reference SBP of 130-139mmHg. No association was found for different diastolic BP levels.
A baseline systolic blood pressure of 140 mmHg or higher was not associated with a different **mortality rate** compared to a reference SBP of 130-139 mmHg. A baseline systolic blood pressure <129 mmHg was associated with a higher mortality rate, compared to a reference SBP of 130-139 mmHg. Again, No association was found for different diastolic BP levels.

Rapsomaniki 2014(50)
This cohort study of 1,250,000 patients with 5.2 years of follow-up, in a population with no cardiovascular disease at baseline, suggests that the lowest risk for **cardiovascular disease** in people aged 60-79y (as well as in other age groups), was observed with a baseline systolic blood pressure of 90–114 mmHg and diastolic blood pressure of 60–74 mmHg, with no evidence of a J-shaped

increased risk at lower blood pressures. Although increased blood pressure was associated with increased cardiovascular risk across all age groups, associations with both systolic and diastolic blood pressure decreased with age for all outcomes (at varying rates for different outcomes). No information on all-cause mortality was given.

Hadaegh 2013(57)
This prospective cohort study of 6237 people with no cardiovascular disease at baseline was conducted in Iran over a median of 9.3 years. The risk of **incident cardiovascular disease** with different baselines SBP/DBP values in the middle aged (30-59y) was compared to the elderly (≥60y). In the middle aged group, a blood pressure of 130-139/85-89 and of ≥140/≥90 were associated with an increased risk of cardiovascular disease, when compared to an SBP/DBP <120/80 mmHg. In people ≥60y, only a blood pressure of ≥140/≥90 was associated with an increased risk of cardiovascular disease.

Butler 2011(54)
This analysis using data from 2 cohort studies comprising of 4408 people aged 65-100y, not receiving antihypertensive drugs at baseline, found that risk of **heart failure** increased with increasing systolic blood pressure.

Conclusion: the strength of the association between high blood pressure and cardiovascular morbidity seems to decrease with age. From a certain age, high blood pressure is not associated with increased all-cause mortality.

GRADE: LOW quality of evidence

The association between very low blood pressure values and morbidity/mortality will be discussed in the chapter about target blood pressure.

4.1.2.5 Clinical evidence profile: Hypertension treatment threshold in elderly patients ≥80 years

Meta-analysis: Bejan-Angoulvant 2010(58)

Inclusion criteria: patients who were ≥80 years old who had been randomised to treatment with either anti-hypertensive drugs or placebo. Data in the MA came from either sub-group analyses of RCTs (data from only the ≥80 year-old people in the trial), or from RCTs in which only people ≥80 years were enrolled
Search strategy: Medline up to oct 2009

Assessment of quality of included trials: yes (by NICE 2011): GRADE
ITT analysis: unclear

Ref	Comparison	N/n	Outcomes	Result
Bejan-Angoulvant 2010(58) Design: SR/MA Search date: Nov 2010	Antihypertensive treatment Versus placebo	N= 8 / n= 6701 (SHEP-Pilot 1989; SHEP 1991; EWPHE 1985; Coope 1986*; STOP 1991; Syst-Eur 1997;HYVET-pilot 2003; HYVET 2008)	**All-cause mortality** **(follow-up 0-11.6 years)**	RR: 1.06 (95% CI: 0.89 to 1.25)
		N= 6 n= not given	**Coronary events** **(follow-up 0-11.6 years)**	RR: 0.83 (95% CI: 0.56 to 1.22)
		N= 7 n= not given	**Stroke** **(follow-up 0-11.6 years)**	**RR: 0.65 (95% CI 0.52 to 0.83)**
		N = 6 n= not given	**CV events (follow-up 0-11.6 years)**	**RR: 0.73 (95% CI: 0.62 to 0.86)**
		N = 6	**Heart failure (follow-up 0-11.6 years)**	**RR: 0.50 (95% CI: 0.33 to 0.76)**

		N= not given		
		N=7 n= not given	**coronary death (follow-up 0-11.6 years)**	RR: 0.99 (95% CI: 0.69, 1.41)
		N = 8 n = 6701	**Stroke death (follow-up 0-11.6 years)**	RR: 0.80 (95% CI: 0.80, 1.11)
		N = 8 n = 6701	**CV death (follow-up 0-11.6 years)**	RR: 0.98 (95% CI: 0.83, 1.15)

Table 88

Ref + design	n	Population	Duration	Intervention	Comparison	Results	Methodology (quality assessment by NICE 2011 and JNC8 2014)
SHEP 1991(17)	4736	Adults, ages ≥60 years, SBP 160-219 and DBP <90 mmHg Subgroup selected for MA: Adults >80 years of age (n=650)	Mean: 4.5 years	For step 1 of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was 25 mg/d. For step 2, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d	placebo	Statistically significant reduction with treatment of: Non-fatal plus fatal stroke: RR: 0.64 (0.50, 0.82) p = 0.0003 Fatal and non-fatal HF: RR: 0.51 (0.37, 0.71) p < 0.001	JNC8 gives a good rating to 4 studies out of 6 evaluated (SHEP 1991, Syst-Eur 1997, Coope and warrender 1986, HYVET 2003) and a fair rating to the other 2 (EWPHE 1985, STOP 1991). NICE does not mention any serious limitations or inconsistence, safe for the outcome “CV death”, where there is significant heterogeneity. NICE does not mention any problems with indirectness. NICE mentions serious imprecision for outcomes “mortality” and “stroke death” (95% confidence interval includes both 1) no effect and 2) the MID (appreciable benefit or appreciable harm); or only just crosses the MID) NICE mentions very serious imprecision for the outcomes “coronary death” and “CV death” (95%
SHEP pilot 1989(59)	551	Adults, ages ≥60 years SBP 160-219 and DBP <90 mmHg MA: Adults >80 years of age (n=85)	Mean: 34 months	Step 1: chlortalidone 25 to 50 mg/d or placebo Step 2: Another medication was added if BP was not under control (hydralazine, reserpine, meoprolol)	placebo	Significant differences between groups for SBP and DBP but not for stroke or death rates	

EWPHE 1985(51)	840	Adults, ages ≥60 years, SBP 160-239 and DBP 90-119 mmHg MA: Adults >80 years of age (n=155)	Mean: 4.6 years	Hydrochlorothiazide + triamterene Methyldopa added if BP was not under control with first medication	placebo	Significant reduction of cardiac mortality in treatment group Significant reduction of non-fatal cerebrovascular events in treatment group Significant reduction of deaths from myocardial infarction	confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm)
Coope and Warrender, 1986(60)	884	Adults, age 60 to 79, SBPs ≥ 170 or DBP ≥ 105 mmHg (only 7 participants from this trial included in meta-analysis apparently >80y)	Mean: 4.4 years	Atenolol & Bendrofluazide	placebo	Statistically significant reduction for: Fatal stroke Rate of txt/rate of control (95% CI): 0.30 (0.11, 0.84) p < 0.025 All stroke Rate of txt/rate of control (95% CI): 0.58 (0.35, 0.96) p < 0.03	
STOP 1991(61)	1627	Adults, ages 70 to 84 years, treated or untreated for hypertension, with SBPs of 180 to 230 and DBP ≥ 90 or DBPs of 105 to 120 irrespective	Mean 25 months	Atenolol 50 mg, hydrochlorothiazide 25 mg plus amiloride 2-5 mg, metoprolol 100 mg, or pindolol 5 mg.	placebo	Statistically significant reductions for: All stroke (first endpoint): RR (CI): 0.53 (0.33, 0.86) Fatal stroke (first endpoint): RR (CI): 0.24 (0.04, 0.91) Total primary endpoint	

		of SBP during run-in MA: Adults >80 years of age (n=235)				[stroke, MI, other CV death] (first to happen): RR (CI): 0.60 (0.43, 0.85)	
Syst-Eur 1997(52)	4695	Adults, ages ≥ 60 years, SBP 160-219 and DBP <95 mmHg MA: Adults >80 years of age (n=441)	Median 24 months	Nitrendipine 10-40 mg daily, with the possible addition of enalapril 5-20 mg daily and hydrochlorothiazide 12.5-25.0 mg daily	placebo	Statistically significant reduction for: Fatal and non-fatal cardiac endpoints: Adj HR: 0.71 CI (0.54, 0.94) p < 0.05 Non-fatal stroke: 44% decrease in active (rate/1000 py) CI (-63, -14), p = 0.007 Fatal and non-fatal stroke combined: Adj HR: 0.59 (0.38, 0.79) p < 0.01	
HYVET-pilot 2003(62)	1283	Adults ≥80 years, SBP of 160-219/90-109 mmHg	Mean 13 months	A diuretic-based regimen (usually bendroflumethiazide; n = 426), an angiotensin-converting enzyme inhibitor regimen (usually lisinopril; n = 431)	No treatment	Statistically significant reduction in stroke events relative hazard rate (RHR) was 0.47 [95% confidence interval (CI) 0.24 to 0.93] and the reduction in stroke mortality RHR was 0.57 (95% CI 0.25 to 1.32) Total mortality: (RHR 1.23, 95% CI 0.75 to 2.01)	
HYVET	3845	Adults, ages ≥	Mean	Indapamide sr	No	Statistically significant	

2008(63)		80 yrs, SBP ≥ 160 and DBP 90-109 at start of trial but relaxed later to <110 mmHg	2.1 years	1.5mg/day	treatment	reduction of: Death from stroke: Unadj HR: 0.61 CI (0.38, 0.99) p = 0.046 Fatal or non-fatal HF: Unadj HR: 0.36 CI (0.22, 0.58) p < 0.001	

Table 89

Study details	n/Population	Comparison	Outcomes		Methodological
Beckett, 2008 (63) HYVET Design: RCT (DB, PG) Duration of follow-up: median 1.8 y	n= 3845 AT= 1933 PL=1912 Mean age: 83.6 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1% Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 % Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80	Indapamide (sustained release, 1.5mg) Vs Placebo *At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.*	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: **33.7 %**
			Stroke (fatal and non-fatal) (PO)	AT: 51/1000 patient-years (12.4%) PL: 69/1000 patient-years (17.7%) HR: 0.70 (95%CI 0.49 to 1.01) NS p 0.06	
			Death from any cause (SO)	**AT: 196/1000 patient-years (47.2%)** **PL: 235/1000 patient-years (59.6%)** **HR:0.79 (95%CI 0.65 to 0.95)** **SS** **P: 0.02 in favour of AT**	
			Death from cardiovascular causes (SO)	AT: 99/1000 patient-years (23.9%) PL: 121/1000 patient-years (30.7%) HR: 0.77 (95%CI 0.60 to 1.01) NS P: 0.06	
			Death from cardiac causes (SO)	AT: 25/1000 patient-years (6.0%) PL: 33/1000 patient-years (8.4%) HR: 0.71 (95%CI 0.42 to 1.19) NS	

	years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg). (At the start of the trial in 2000, the mean diastolic blood pressure while seated had to be 90 to 109 mm Hg, but in 2003 a protocol amendment relaxed this criterion to be under 110 mm Hg, allowing for the inclusion of patients with isolated systolic hypertension <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with	Target: SBP <150 mmHg DBP <80 mmHg		P: 0.19	• Described: yes • Balanced across groups: yes ITT: Yes Data from patients were analyzed for the groups to which the patients were assigned, regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available. SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that these
			Death from stroke (SO)	**AT: 27/1000 patient-years (6.5%)** **PL: 42/1000 patient-years (10.7%)** **HR: 0.61 (95%CI 0.38 to 0.99)** **SS** **P: 0.046 in favour of AT**	
			Safety		
			Serious adverse events	**AT: 358/1933** **PL: 448/1912** **P: 0.001 in favour of AT**	
			Serious adverse events possibly due to trial medication	AT: 2 PL: 3	

	antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.				centers failed to provide complete and accurate data. Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.

Table 90

Study details	n/Population	Comparison	Outcomes subgroup analyses		Methodological
Beckett, 2014 (64) HYVET Design: Prespecified subgroup analysis (data from RCT (DB, PG))	n= 3845 AT= 1933 PL=1912 Mean age: 83.5±3.2 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1% Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 %	Indapamide (sustained release, 1.5mg) Vs Placebo *At each visit (or at the discretion of the investigator), if needed to reach the target blood*	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the
			Total mortality	Hazard ratio	
			Age • 80-84.9y • ≥85y	 **0.76 (95%CI 0.60 to 0.97)** 0.88 (95%CI 0.64 to 1.20)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.82 (95%CI 0.60 to 1.11) 0.83 (95%CI 0.62 to 1.12) 0.69 (95%CI 0.45 to 1.04)	
			Previous CVD • History of CVD • No history of CVD	 0.76 (95%CI 0.48 to 1.21) **0.81 (95%CI 0.66 to 0.99)**	
			Cardiovascular mortality		
			Age • 80-84.9y	 0.75 (95%CI 0.55 to 1.05)	

Duration of follow-up: median 1.8 y	Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg). <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of	*pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.* Target: SBP <150 mmHg DBP <80 mmHg	• ≥85y	0.82 (95%CI 0.53 to 1.32)	protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: 33.7 % • Described: yes • Balanced across groups: yes ITT: Yes Data from patients were analyzed for the groups to which the patients were assigned, regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available. SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for
			Initial SBP		
			• 160-169 mmHg	0.73 (95%CI 0.47 to 1.15)	
			• 170-179 mmHg	0.93 (95%CI 0.62 to 1.45)	
			• ≥180 mmHg	0.61 (95%CI 0.36 to 1.04)	
			Previous CVD		
			• History of CVD	0.64 (95%CI 0.33 to 1.24)	
			• No history of CVD	0.81 (95%CI 0.61 to 1.09)	
			Stroke (PO)		
			Age		
			• 80-84.9y	0.70 (95%CI 0.46 to 1.06)	
			• ≥85y	0.59 (95%CI 0.27 to 1.29)	
			Initial SBP		
			• 160-169 mmHg	0.82 (95%CI 0.46 to 1.48)	
			• 170-179 mmHg	0.63 (95%CI 0.36 to 1.12)	
			• ≥180 mmHg	0.54 (95%CI 0.24 to 1.22)	
			Previous CVD		
			• History of CVD	0.76 (95%CI 0.33 to 1.78)	
			• No history of CVD	0.67 (95%CI 0.45 to 1.01)	
			Heart failure		
			Age		
			• 80-84.9y	**0.28 (95%CI 0.15 to 0.51)**	
			• ≥85y	0.62 (95%CI 0.26 to 1.49)	
			Initial SBP		
			• 160-169 mmHg	**0.21 (95%CI 0.09 to 0.51)**	
			• 170-179 mmHg	**0.46 (95%CI 0.22 to 0.97)**	
			• ≥180 mmHg	0.59 (95%CI 0.19 to 1.79)	
			Previous CVD		
			• History of CVD	0.45 (95%CI 0.14 to 1.43)	
			• No history of CVD	**0.34 (95%CI 0.20 to 0.59)**	

	less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.		Cardiovascular events		at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that these centers failed to provide complete and accurate data. Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.
			Age • 80-84.9y • ≥85y	 **0.64 (95%CI 0.49 to 0.83)** 0.75 (95%CI 0.50 to 1.12)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 **0.65 (95%CI 0.46 to 0.93)** 0.75 (95%CI 0.53 to 1.06) **0.58 (95%CI 0.36 to 0.94)**	
			Previous CVD • History of CVD • No history of CVD	 0.75 (95%CI 0.44 to 1.25) **0.66 (95%CI 0.52 to 0.84)**	

Table 91

4.1.2.6 Summary and conclusions: treatment threshold in elderly patients ≥80 years

Antihypertensive treatment versus no treatment in hypertensives ≥80 years.			
Bibliography: Bejan-Angoulvant 2010(58), HYVET 2008(63)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	6701 (8 studies) 13m- 4.6y	RR: 1.06 (95% CI: 0.89 to 1.25) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:OK(heterogeneity NS when HYVET removed) Directness:OK Imprecision: -1 95% confidence interval includes both 1) no effect and 2) the MID (appreciable benefit or appreciable harm); or only just crosses the MID
*HYVET 2008		* **HR:0.79 (95%CI 0.65 to 0.95)** **SS**	
CV death	6701 (8 studies) 13m- 4.6y	RR: 0.98 (95% CI: 0.83 to 1.15) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: Consistency:-1 significant heterogeneity Directness: Imprecision: 2 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
*HYVET 2008		*HR: 0.77 (95%CI 0.60 to 1.01)	
CV events	NR (6 studies) 13m- 4.6y	**RR: 0.73 (95% CI: 0.62 to 0.86)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
Coronary events	NR (6 studies) 13m- 4.6y	RR: 0.83 (95% CI: 0.56 to 1.22) NS	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:OK Directness:OK Imprecision:-2 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
Stroke	NR (7 studies) 13m- 4.6y	**RR: 0.65 (95% CI 0.52 to 0.83)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
*HYVET 2008		*HR: 0.70 (95%CI 0.49 to 1.01)	
Heart failure	NR (6 studies) 13m- 4.6y	**RR: 0.50 (95% CI: 0.33 to 0.76)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
Serious adverse events *HYVET 2008	3845 (1 study) 1.8y	**Treatment: 358/1933** **Placebo: 448/1912** **p: 0.001 in favour of treatment** **SS**	⊕⊕⊖⊖ **LOW** Study quality:ok Consistency:na Directness:-2 Imprecision:ok

Table 92

In this meta-analysis of 8 RCT's, antihypertensive treatment versus placebo or no treatment was evaluated in hypertensive patients (3 trials with isolated systolic hypertension SBP ≥ 160mmHg, 2 trials with systolic and diastolic hypertension (SBP ≥ 160mmHg DBP ≥ 90mmHg), 3 trials with mixed systolic and/or diastolic hypertension). The data concerning patients ≥80 years of age was extracted from these RCT's. The mean follow-up ranged from 13 months to 4.6 years. Two of these RCT's (HYVET-pilot and HYVET) included only patients ≥80 years old.
Results from the HYVET trial are also shown in the table above.

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, did not result in a statistically significant difference in **mortality** rates compared to placebo or no treatment.
GRADE: MODERATE quality of evidence

Nor did not result in a statistically significant difference in **cardiovascular death** compared to placebo or no treatment.
GRADE: VERY LOW quality of evidence

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, decrease risk of **cardiovascular events**, of **stroke** and of **heart failure**.
GRADE: HIGH quality of evidence

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, did not result in a statistically significant difference in **coronary events** compared to placebo or no treatment.
GRADE: LOW quality of evidence

We do not have a lot of information on adverse events

The HYVET trial included 3845 patients aged aged ≥80 years, with a sustained SBP ≥ 160mmHg. (Inclusion criteria for diastolic blood pressure were modified during recruitment admitting also patients with isolated systolic hypertension). Patients were given indapamide or placebo and were followed for a median of 1.8years, to a target of SBP <150 mmHg and DBP <80 mmHg.
The primary endpoint was stroke (fatal and non-fatal), which did not yield a statistically significant difference between treatment and placebo-group.
In this trial, all-cause mortality (which was a secondary endpoint) is statistically significantly lower with treatment compared to placebo.
Information from a prespecified subgroup analysis from the HYVET trial (Beckett 2014(64)) suggests that for ages ≥85y, compared to ≥80 years, the benefit of treatment on total mortality, heart failure and cardiovascular events may be attenuated. In further subgroup analyses, no clear relationship has arisen between initial SBP (devided into strata of 160-179; 170-179 and ≥180 mmHg) and outcomes. Lack of statistical power diminishes the reliability of these results.

Conclusions for treatment threshold in people aged ≥80y:
Since the inclusion criteria for blood pressure differed between trials, it is difficult to formulate a conclusion about a specific threshold at which the benefit of antihypertensive treatment outweighs the harms.

4.1.2.7 Observational data: Hypertension treatment tresholds in elderly patients ≥ 80 years

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Rapsomaniki 2014(50) Cohort study	1250000	Primary care population (HT and NT) initially free from cardiovascular disease	Median 5.2 years	Lifetime risk of developing events in people with different baseline BP values and ages (30-59y; 60-79y; ≥80y.	The initial presentation of cardiovascular disease as any of 12 cardiovascular diseases diagnosed in primary care secondary care, or at death, and total cardiovascular disease (all 12 cardiovascular diseases combined) (12 diseases= (Stable angina, unstable angina, myocardial infarction, unheralded coronary heart disease death, heart failure, cardiac arrest, transient ischaemic attack, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, peripheral arterial disease, abdominal aortic aneurysm)	SBP values 90-114 115-129 130-139 140-149 160-179 ≥180 DBP values 60-74 75-84 85-89 90-94 95-99 ≥100	In each age group, the lowest risk for cardiovascular disease was in people with systolic blood pressure of 90–114 mm Hg and diastolic blood pressure of 60–74 mm Hg, with no evidence of a J-shaped increased risk at lower blood pressures. The effect of high blood pressure varied by cardiovascular disease endpoint, from strongly positive to no effect. Associations with both systolic and diastolic blood pressure decreased with age for all outcomes at varying rates for different outcomes.

Table 93

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
Rapsomaniki 2014 (50)		See figures below

Table 94 details of Rapsomaniki 2014

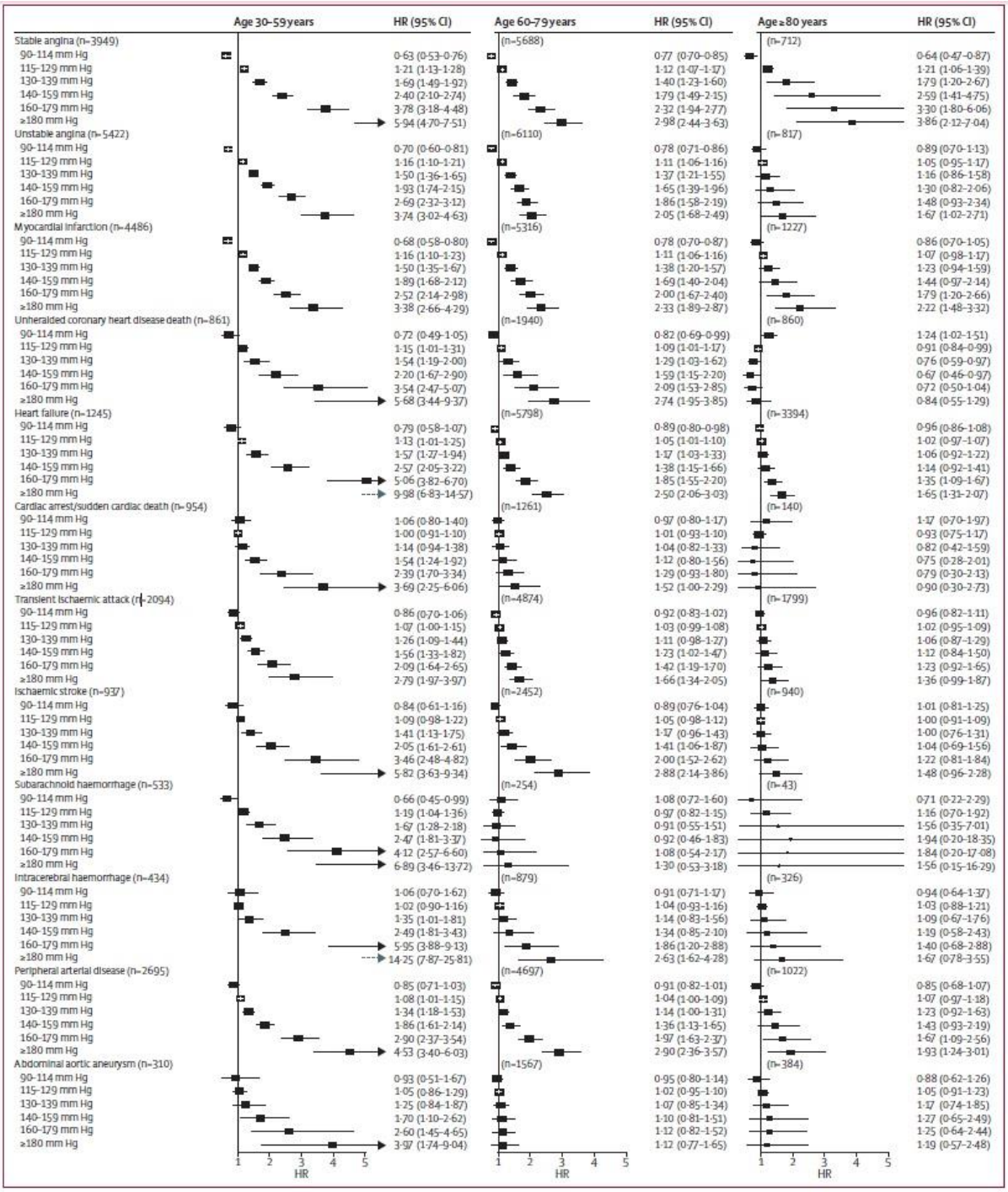


Figure 5 Forest plots of HRs (95% CIs) for different cutoffs of systolic blood pressure (vs reference 115 mmHg) adjusted for age and sex

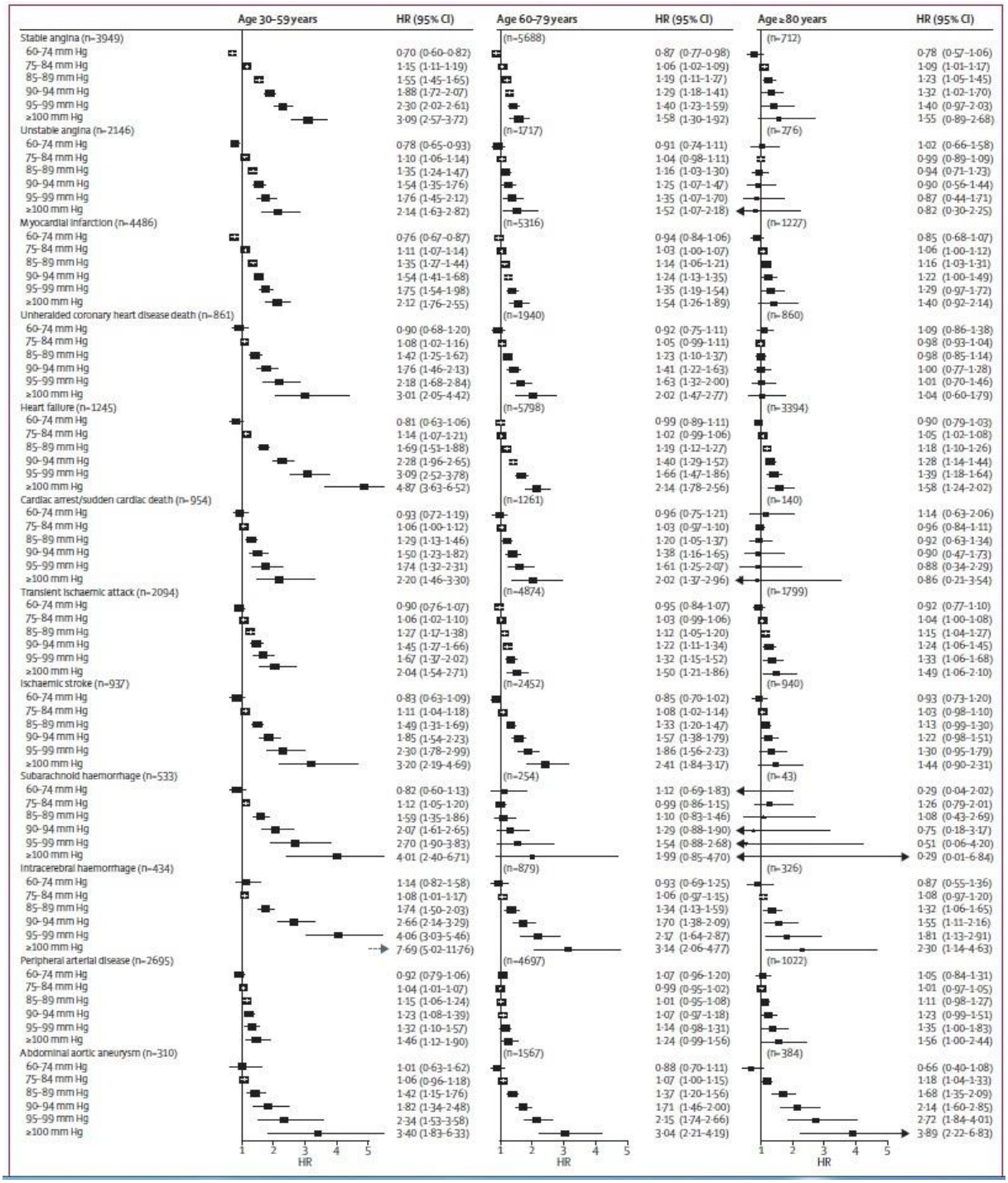


Figure 6 Forest plot of HRs (95% CIs) for different cutoffs of diastolic blood pressure (vs reference 75 mmHg) adjusted for age and sex

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Blom 2013(53) Analysis of data of a prospective cohort study (the Rotterdam study)	4612	≥55 y, without previous cardiovascular disease using or not using blood pressure lowering drugs	Median 14.9 years	Risk of mortality with different baseline SBP and in different age groups (55-64; 65-74; 75-84; ≥85y) (baseline SBP can be treated or non-treated BP)	Mortality (adjusted for age and sex)	SBP 140-159 ≥160	The predictive value of SBP for mortality differs with age in people aged 55 years and over without a history of CVD. Between age 55 and 75 years, high SBP predicts higher mortality risk, but from age 75 years onwards a significant trend shows that SBP levels no longer predict mortality risk (although hazard ratios per age group do not reach significance). From age 85 years onwards, high SBP even predicts lower mortality risk. When participants were stratified according to the use of antihypertensive medication at baseline, results in both strata were roughly similar.

Table 95

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement HRs versus reference SBP <140 mmHg**
Blom 2013(53)	All-cause mortality	140-159 55-64 y: HR= 1.2 (0.9 to 1.5)

		65-74y: HR= 1.2 (1.0 to 1.4) 75-84y: HR= 1.1 (0.9 to 1.3) ≥85y: HR= 0.7 (0.5 to 1.1) *P for trend <0.001* <u>≥160</u> **55-64 y: HR= 1.7 (1.2 to 2.2)** 65-74y: HR= 1.3 (1.0 to 1.5) 75-84y: HR= 1.3 (1.0 to 1.6) ≥85y: HR= 0.7 (0.4 to 1.1) *P for trend <0.001*
	Cardiovascular mortality	<u>140-159</u> **55-64 y: HR= 2.1 (1.1 to 3.9)** 65-74y: HR= 1.3 (0.8 to 1.9) 75-84y: HR= 0.9 (0.6 to 1.4) ≥85y: HR= 1.3 (0.6 to 2.8) *P for trend <0.001* <u>≥160</u> **55-64 y: HR= 2.9 (1.4 to 5.9)** 65-74y: HR= 1.2 (0.7 to 2.0) 75-84y: HR= 1.3 (0.8 to 2.1) ≥85y: HR= 0.9 (0.3 to 2.1) *P for trend <0.001*

Table 96

When participants were categorized into 5-year age groups, the increased risk with higher SBPs was present up to age 75 years: in the age group 70–74 years, the HR140–159 is 1.4 (95% CI: 1.1, 1.7) and in the age group 75–79 years and over the HR reaches unity (HR140–159 1.1, 95% CI: 0.9, 1.4).
For the group with the highest SBPs, in the age group 70–74 years, the HR≥160 is 1.3 (95% CI: 1.0, 1.7). Relative risks in the age group 75–79 and 80–84 years are similar, whereas in the age group ≥85 years HR≥160 is 0.7 (95% CI: 0.4, 1.1). Using a reference group with SBP <150 mmHg shows similar results with HR150–159 0.8 (95% CI: 0.5, 1.3) and HR≥160 0.8 (95% CI: 0.5, 1.2) at age ≥85 years (data not shown).

4.1.2.8 *Summary and conclusions of observational data: treatment threshold in elderly patients ≥80 years*

Blom 2013 (53)
This prospective cohort study followed 4621 Dutch people aged ≥55 y, without previous cardiovascular disease was discussed in the previous chapter.
The authors conclude: between age 55 and 75 years, high SBP predicts higher **mortality** risk, but from age 75 years onwards a significant trend shows that SBP levels no longer predict mortality risk. Blom 2013 also refers to 17 other observational studies that found that **high SBP does not predict mortality from age 75y onwards**.

Rapsomaniki 2014(50)
This cohort study of 1,250,000 patients with 5.2 years of follow-up, in a population with no cardiovascular disease at baseline was discussed in the previous chapter. In the age group ≥80y,when stratified for BP, risk of heart failure, myocardial infarction, peripheral arterial disease was significantly increased with SBP 160-179mmHg and SBP ≥180mmHg, compared to a reference SBP of 115mmHg. The risk of stable angina was increased with SBP 115mmHg-130mmHg and all higher SBPs, compared to the reference SBP.
Associations with both systolic and diastolic blood pressure decreased with age.

GRADE: LOW quality of evidence

4.1.3 Type 2 diabetes

4.1.3.1 Clinical evidence profile: Hypertension treatment threshold in adults with type 2 diabetes

We found no high quality studies that examine the optimal threshold for blood pressure lowering in hypertensives with type 2 diabetes.
We found 1 meta-analysis of RCTs (Emdin 2015(65)) that based its analyses on the mean baseline blood pressure of included participants in the individual RCTs. It will be reported due to lack of other data.

Reference	N	Population	BP measurement method	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Emdin, 2015(65) SR/MA of data from 40 RCT's	100345	Diabetics (HT and NT)	NA	NA; Minimum 1000 patient-years in each randomized group	Prognostic: Risk (HR) of developing clinical outcomes	Mortality, Cardiovascular disease, coronary heart disease, stroke, heart failure, renal failure	(Studies with) mean SBP ≥140 vs. (studies with) mean SBP <140	Significant interactions were observed for mortality, CHD, CVD, and heart failure (all P < .1), with lower relative risks observed among those trials with mean baseline systolic BP of 140 mm Hg or greater and no significant associations among the group with baseline systolic BP of less than 140 mm Hg. BP-lowering treatment was associated with lower risks of stroke and albuminuria, regardless of initial systolic BP.

Table 97

For more details on methodology of Emdin 2015, see also 4.3.4

Summary of numerical results for prognostic studies (for selected outcomes)			
Study	**Outcome**	**RR (95% CI) for BP measurement (SBP/DBP) (Standardized Associations per 10–mmHg Lower Systolic BP)**	**RR (95% CI) for BP measurement (SBP/DBP) (Unadjusted)**
Emdin, 2015(65)	**Mortality**	**Mean SBP ≥140 : 0.73 (0.64 to 0.84)** Mean SBP <140: 1.07 (0.92 to 1.26) **Overall: 0.87 (0.78 to 0.96)** **P for interaction: <0.001**	**Mean SBP ≥140 :0.88 0.82-0.94)** Mean SBP <140: 0.96 (0.90-1.04) **Overall: 0.92 (0.87-0.96)** **P for interaction NR**
	Cardiovascular events	**Mean SBP ≥140 : 0.74 (0.65 to 0.85)** Mean SBP <140: 0.96 (0.88 to 1.05) **Overall: 0.89 (0.83 to 0.95)** **P for interaction: =0.001**	**Mean SBP ≥140 : 0.87(0.82-0.92)** Mean SBP <140: 0.92(0.85-0.99) **Overall: 0.89 (0.85-0.99)** **P for interaction NR**
	Coronary heart disease	**Mean SBP ≥140 : 0.73 (0.61 to 0.87)** Mean SBP <140: 0.97 (0.86 to 1.10) **Overall: 0.88 (0.80 to 0.98)** **P for interaction =0.01**	**Mean SBP ≥140 : 0.81 (0.73-0.89)** Mean SBP <140: 1.00 (0.89-1.13) Overall: 0.88 (0.81-1.13) **P for interaction NR**
	Heart failure	**Mean SBP ≥140 :0.75 (0.59 to 0.94)** Mean SBP <140: 0.97 (0.79 to 1.19) Overall: 0.86 (0.74 to 1.00) P for interaction: 0.09	**Mean SBP ≥140 : 0.84(0.76-0.93)** Mean SBP <140: 0.78 (0.71-0.85) **Overall: 0.81 (0.76-0.86)** **P for interaction NR**
	Stroke	**Mean SBP ≥140 : 0.74 (0.64 to 0.86)** **Mean SBP <140: 0.69 (0.52 to 0.92)** **Overall: 0.73 (0.64 to 0.83)** P for interaction= 0.70	**Mean SBP ≥140 : 0.87(0.81-0.94)** Mean SBP <140: 0.98(0.82-1.19) **Overall: 0.89(0.83-0.96)** **P for interaction NR**
	Renal failure	Mean SBP ≥140 : 0.75 (0.52 to 1.08) Mean SBP <140: 1.00 (0.77 to 1.29) Overall: 1.91 (0.74 to 1.12) P for interaction= 0.21	**Mean SBP ≥140 : 0.83(0.72-0.96)** Mean SBP <140: 0.98(0.81-1.19) **Overall: 0.88(0.79-0.99)** **P for interaction NR**

Table 98

4.1.3.2 Summary and conclusions: Hypertension treatment threshold in adults with type 2 diabetes

⊕⊖⊖⊖ **LOW to VERY LOW**
Risk of bias: -1 trials >140mmHg and <140mmHg may differ in other patient characteristics, no primary endpoint defined
Consistency: some inconsistency for outcomes in population with mean SBP<140mmHg
Directness:-1 no clear threshold to evaluate
Imprecision:ok

This meta-analysis by Emdin 2015(65) with data from 40 RCT's evaluated the risk of developing clinical outcomes with antihypertensive treatment versus no antihypertensive treatment in a diabetic population. The trials were stratified by mean baseline SBP values (trials in which the mean baseline SBP was ≥140 mmHg and trials in which the mean baseline SBP was <140 mmHg). Since a population with a mean SBP ≥140 mmHg will also consist of participants with SBP<140 mmHg and SBP much higher than 140 mmHg, the conclusions will be inaccurate to make a solid estimate of the optimal threshold for blood pressure lowering.
This meta-analysis did not examine adverse events.

BP-lowering treatment **in a diabetic population with a baseline mean SBP ≥140 mmHg** significantly **decreased mortality, cardiovascular disease, coronary heart disease, and heart failure**, while BP-lowering treatment in a diabetic population with a baseline mean SBP <140 mmHg did not.

In patients with type 2 diabetes, BP-lowering treatment significantly **decreased stroke rate, regardless of mean baseline BP value**.

BP-lowering treatment **did not significantly decrease renal failure**, regardless of mean baseline BP value.

GRADE: LOW to VERY LOW quality of evidence to determine ideal treatment threshold.

4.1.3.3 Observational data: Hypertension treatment threshold in adults with type 2 diabetes

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Sundstrom 2013(66) Analysis of data from retrospective cohort study (ROSE)	34009	Primary care Type 2 diabetes >35y (mean age 64y) No cardiovascular disease HT and NT Treated and untreated	Median 4.5 y	Risk of developing events with different baseline SBP and DBP values; in people with and without antihypertensive drug use	Cardiovascular events and mortality	SBP <130 130-140 140-149 149-160 >160 DBP <73 73-78 78-81 81-87 >87	In a large primary care-based sample of patients with type-2 diabetes, associations of SBP and DBP with risk of major cardiovascular events and mortality were U-shaped. The lowest risk of cardiovascular events was observed at a SBP of 135–139 mmHg and a DBP of 74–76 mmHg, and the lowest mortality risk at a SBP of 142–150 mmHg and a DBP of 78–79 mmHg, in both antihypertensive drug-untreated and drug-treated persons.

Table 99

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP)** **Adj. HRs versus reference SBP (<130 mmHg) or DBP (<73 mmHg) in people without antihypertensive drug use**
Sundstrom 2013	Cardiovascular events (composite of nonfatal or fatal acute MI, heart failure,stroke or cardiovascular mortality)	SBP <130: HR=1 130-140: HR= 1.24 (0.91 to 1.70) 140-149: HR= 1.35 (0.95 to 1.93) 149-160: HR= 1.29 (0.91 to 1.82) **>160: HR= 1.79 (1.17 to 2.74)** Lowest risk observed at 135 (133-139)* DBP <73: HR=1 **73-78: HR= 1.65 (1.17 to 2.32)** 78-81: HR= 1.11 (0.75 to 1.64) 81-87: HR= 1.36 (0.93 to 1.99) **>87: HR= 2.01 (1.35 to 2.98)** Lowest risk observed at 76 (74-80)*
	All-cause mortality	SBP <130: HR=1 130-140: HR= 1.00 (0.71 to 1.41) 140-149: HR= 1.02 (0.68 to 1.53) 149-160: HR= 0.90 (0.60 to 1.35) >160: HR= 0.90 (0.50 to 1.64) Lowest risk observed at 142 (140-240) DBP <73: HR=1 73-78: HR= 0.97 (0.68 to 1.39) 78-81: HR= 0.77 (0.52 to 1.16) 81-87: HR= 0.94 (0.62 to 1.40) >87: HR= 0.82 (0.49 to 1.38) Lowest risk observed at 78 (76-86)*

Table 100

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP)** **Adj. HRs versus reference SBP (<130 mmHg) or DBP (<73 mmHg) in people with antihypertensive drug use**
Sundstrom 2013	Cardiovascular events (composite of nonfatal or fatal acute MI, heart failure,stroke or cardiovascular mortality)	SBP <130: HR=1 130-140: HR= 0.94 (0.76 to 1.16) 140-149: HR= 1.03 (0.83 to 1.28) 149-160: HR= 0.98 (0.79 to 1.20) **>160: HR= 1.37 (1.11 to 1.70)** Lowest risk observed at 139 (135-143)* DBP <73: HR=1 73-78: HR= 1.00 (0.83 to 1.21) 78-81: HR=0.89 (0.72 to 1.10) 81-87: HR= 0.93 (0.76 to 1.14) **>87: HR= 1.24 (1.01 to 1.52)** Lowest risk observed at 74 (69-77)*
	All-cause mortality	SBP <130: HR=1 **130-140: HR= 0.75 (0.60 to 0.93)** **140-149: HR= 0.63 (0.49 to 0.80)** **149-160: HR= 0.65 (0.51 to 0.81)** **>160: HR= 0.72 (0.56 to 0.92)** Lowest risk observed at 150 (144-154)* DBP <73: HR=1 **73-78: HR= 0.78 (0.63 to 0.96)** **78-81: HR= 0.77 (0.61 to 0.98)** **81-87: HR= 0.69 (0.54 to 0.88)** >87: HR= 0.93 (0.73 to 1.19) Lowest risk observed at 79 (76-83)*

Table 101

4.1.3.4 Summary and conclusions on observational data: Hypertension treatment threshold in adults with type 2 diabetes

Sundstrom 2013(66))
This analysis of data from a retrospective cohort study, in a primary care setting and with a median follow-up of 4.5 years, included 34009 type 2 diabetics with no cardiovascular disease at baseline. The risk of developing events with different SBP and DBP values in patients with and without antihypertensive drug use was evaluated. The association of risks of events and BP followed a U-shaped curve, in both treated and untreated patients.

In type 2 diabetics not treated with antihypertensive medication, the lowest risk of developing **cardiovascular events** was at a BP of 135/76 mmHg, while the lowest risk of **mortality** was observed at a BP of 142/78 mmHg.

In type 2 diabetics treated with antihypertensive medication, the lowest risk of developing **cardiovascular events** was at a BP of 139/74 mmHg, while the lowest risk of **mortality** was observed at a BP of 150/79 mmHg.

GRADE: LOW quality of evidence

4.1.4 Chronic kidney disease

4.1.4.1 Clinical evidence profile: Hypertension treatment threshold in adults with chronic kidney disease

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.1.4.2 Observational data: Hypertension treatment threshold in adults with chronic kidney disease

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Chiang 2014(67) Prospective observational study Taiwan	2144	CKD stage 3-4 Mean age 64.2±13.5y	Median 2.91 y	Risk of developing events with different baseline SBPs; in people with and without diabetes and by proteinuria status	Mortality, cardiovascular events and need for renal replacement therapy (dialysis or Tx)	SBP 96-110 111-120 121-140 >140	DM modifies the J-shaped relationship of SBP with cardiovascular and renal outcomes in stage 3 and 4 CKD patients. Diabetic CKD patients are at 2.5-fold and 3.1-fold increased risk for cardiovascular and renal outcomes, respectively, at SBP 96–110 mm Hg compared with SBP 111–120 mm Hg, but the J-shaped relationship is not observed in nondiabetic CKD patients. These findings suggest that the optimal SBP range may be narrower in diabetic CKD patients than in nondiabetic ones.

Table 102

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP)** **Adj. HRs versus reference SBP (111-120mmHg)**
Chiang 2014	All-cause mortality	<u>Total</u> 96-110: HR= 1.18 (0.68–2.07) 111-120: HR=1 121-140: HR= 1.15 (0.75–1.74) >140: HR= 1.25 (0.82–1.90) <u>Non-diabetics</u> 96-110: HR= 1.40 (0.63–3.10) 111-120: HR=1 121-140: HR= 1.58 (0.86–2.91) >140: HR= 1.60 (0.87–2.94) <u>Urine protein/creatinine ratio <1g/g</u> 96-110: HR= 1.22 (0.40–3.71) 111-120: HR=1 121-140: HR= 1.62 (0.68–3.84) >140: HR= 1.46 (0.58–3.73) <u>Urine protein/creatinine ratio ≥1g/g</u> 96-110: HR= 2.28 (0.61–8.58) 111-120: HR=1 121-140: HR= 2.33 (0.87–6.23) >140: HR= 2.36 (0.94–5.93) <u>Diabetics</u> 96-110: HR= 1.37 (0.60–3.08) 111-120: HR=1 121-140: HR= 0.85 (0.46–1.55) >140: HR= 1.03 (0.58–1.86) <u>Urine protein/creatinine ratio <1g/g</u> 96-110: HR= 1.75 (0.58–5.26) 111-120: HR=1 121-140: HR= 0.80 (0.32–1.99) >140: HR= 0.84 (0.33–2.14) <u>Urine protein/creatinine ratio ≥1g/g</u>

		96-110: HR= 1.82 (0.45–7.41) 111-120: HR=1 121-140: HR= 1.10 (0.45–2.70) >140: HR= 1.59 (0.68–3.72)
	Cardiovascular events	<u>Total</u> 96-110: HR= 1.22 (0.67–2.23) 111-120: HR=1 121-140: HR= 1.20 (0.78–1.84) >140: HR= 1.29 (0.84–1.98) <u>Non-diabetics</u> 96-110: HR= 0.53 (0.19–1.49) 111-120: HR=1 121-140: HR= 1.02 (0.55–1.91) >140: HR= 1.04 (0.56–1.95) <u>Urine protein/creatinine ratio <1g/g</u> 96-110: HR= 0.42 (0.08–2.09) 111-120: HR=1 121-140: HR= 1.33 (0.56–3.19) >140: HR= 1.49 (0.59–3.78) <u>Urine protein/creatinine ratio ≥1g/g</u> 96-110: HR= 0.59 (0.14–2.50) 111-120: HR=1 121-140: HR= 0.62 (0.24–1.64) >140: HR= 0.62 (0.25–1.51) <u>Diabetics</u> **96-110: HR= 3.14 (1.16–8.49)** 111-120: HR=1 121-140: HR= 1.64 (0.82–3.29) **>140: HR= 2.92 (1.51–5.66)** <u>Urine protein/creatinine ratio <1g/g</u> **96-110: HR= 4.40 (1.29–14.99)**

		111-120: HR=1 121-140: HR= 2.70 (0.92–7.95) >140: HR= 1.87 (0.62–5.63) <u>Urine protein/creatinine ratio ≥1g/g</u> 96-110: HR= 1.90 (0.55–6.58) 111-120: HR=1 121-140: HR= 0.99 (0.44–2.20) >140: HR=1.44 (0.68–3.07)
	Need for renal replacement therapy	<u>Total</u> 96-110: HR= 1.41 (0.73–2.74) 111-120: HR= 1 121-140: HR= 1.27 (0.80–2.01) **>140: HR= 1.75 (1.13–2.71)** <u>Non-diabetics</u> 96-110: HR= 0.65 (0.26–1.64) 111-120: HR=1 121-140: HR= 0.83 (0.43–1.58) >140: HR= 0.89 (0.48–1.69) <u>Urine protein/creatinine ratio <1g/g</u> 96-110: HR= 1.90 (0.41–8.79) 111-120: HR=1 121-140: HR= 1.23 (0.34–4.42) >140: HR= 2.04 (0.57–7.32) <u>Urine protein/creatinine ratio ≥1g/g</u> 96-110: HR= 0.27 (0.06–1.10) 111-120: HR=1 121-140: HR= 0.74 (0.33–1.67) >140: HR= 0.74 (0.33–1.65) <u>Diabetics</u> **96-110: HR= 3.14 (1.16–8.49)** 111-120: HR=1 121-140: HR= 1.64 (0.82–3.29) **>140: HR= 2.92 (1.51–5.66)** <u>Urine protein/creatinine ratio <1g/g</u>

		96-110: HR= 1.72 (0.13–22.5) 111-120: HR=1 121-140: HR= 0.68 (0.07–6.73) >140: HR= 3.69 (0.41–3.38) <u>Urine protein/creatinine ratio ≥1g/g</u> **96-110: HR= 4.07 (1.18–13.99)** 111-120: HR=1 121-140: HR= 1.90 (0.89–4.06) **>140: HR= 3.27 (1.58–6.74)**

Table 103

Reference	N	Population	Follow-up	Study design	Outcomes	BP values (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Kovesdy 2013(68) US Retrospective cohort study	651749	Veterans (only 2.7% women) Non-dialysis dependent CKD Mean age 73.8±9.7y	Median 5.8y	Risk of mortality at different SBP/DBP values	All-cause mortality	SBP and DBP were examined as all possible combinations of each other in 96 categories (from lowest of <80/<40 mmHg to highest of >210/>120 mmHg, in increments of 10 mmHg	We describe a J-shaped association between SBP and DBP and all-cause mortality in patients with non-dialysis dependent CKD. The combination of low SBP and low DBP is associated with the highest mortality in this population. In addition, DBP levels below approximately 70 mmHg appear to confer increased mortality even in patients with moderately high SBP. The optimal blood pressure in patients with CKD appears to be 130–149/70–89 mmHg. It may not be advantageous to achieve ideal SBP levels at the expense of lower-than-ideal DBP levels in adults with CKD.

Table 104

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference SBP/DBP of 120-139/80-89 mmHg**
Kovesdy 2013	All-cause mortality	**<120/<80: HR= 1.42 (1.41 to 1.43)** 120-139/80-89: HR= 1 **140-159/90-99: HR= 0.95 (0.94 to 0.96)** **≥160/≥100: HR= 1.05 (1.03 to 1.07)**

Table 105

4.1.4.3 Summary and conclusions of observational data: Hypertension treatment threshold in adults with chronic kidney disease

Kovesdy 2013(68)
This retrospective cohort study evaluated clinical data of 651749 veterans with non-dialysis dependent chronic kidney disease over a median of 5.8 years. Risk of **all-cause mortality** was evaluated for different combinations of SBP and DBP. A J-shaped association between SBP and DBP and all-cause mortality was observed, with increased risk above and below a BP range of 120-139/80-89 mmHg.

Chiang 2014(67)
In this prospective observational study, 2144 patients with stage 3-4 chronic kidney disease were followed over a median of 2.9 years. The risk of **cardiovascular events**, **need for renal replacement therapy** (dialysis or transplantation) and **all-cause mortality** with different baseline SBP values (range: 96 to>140 mmHg) was evaluated. A baseline SBP of >140 mmHg was associated with a larger risk of need for renal replacement therapy, but not of mortality or cardiovascular events, when observing the whole study population. In diabetic CKD patients, but not in non-diabetic CKD , there seemed to be a J-shaped association between renal and cardiovascular outcomes and SBP, with worse outcomes associated with both very low (96-110 mmHg) and high (>140 mmHg) SBP.

Conclusion: In patients with chronic kidney disease, there seems to be an association between an SBP >140 mmHg and an increased risk of events.

GRADE: LOW quality of evidence

The association between very low blood pressure values and morbidity/mortality will be discussed in the chapter about target blood pressure.

4.1.5 Coronary disease

4.1.5.1 Clinical evidence profile: Hypertension treatment threshold in adults with coronary disease

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.1.5.2 Observational data: Hypertension treatment threshold in adults with coronary disease

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Dorresteijn, 2012 (69) Data from cohort study (SMART)	5788	Patients with either a history or a recent diagnosis of clinically manifest vascular disease. (coronary artery disease, cerebrovascular disease or peripheral artery disease) HT and NT	Median 5.0 years	Risk of developing new event with different baseline BP values	New vascular event, all-cause mortality	BP value as a continuous variable	Overall, the covariate-adjusted relationship between mean baseline systolic, diastolic, or pulse pressure and the occurrence of vascular events followed a J-curve with increased event rates above and below the nadir blood pressure of 143/82 mm Hg.

Table 106

Summary of numerical results for prognostic studies (for selected outcomes)	
Outcome	**HR (95% CI) for BP measurement (SBP/DBP)**
Vascular events	Adjusted hazard ratios for vascular events by baseline mean systolic blood pressure (SBP). Nadir: 143 mmHg. (BP terms: χ_2=12.04, degrees of freedom (*df*)=2, *P*<0.01. Nonlinear BP terms: χ2=8.61, *df*=1, *P*<0.01) Adjusted hazard ratios for vascular events by baseline mean diastolic BP (DBP). Nadir: 82 mmHg. (BP terms: χ_2=14.29, degrees of freedom (*df*)=2, *P*<0.01. Nonlinear BP terms: χ2=12.95, *df*=1, *P*<0.01)
All-cause mortality	Adjusted hazard ratios for all-cause mortality by baseline mean SBP. Nadir: 140 mmHg. (BP terms: χ_2=4.60, degrees of freedom (*df*)=2, *P*=0.10. Nonlinear BP terms: χ2=2.63, *df*=1, *P*=0.10) Adjusted hazard ratios for all-cause mortality by baseline mean DBP. Nadir 84 mmHg. (BP terms: χ_2=8.99, degrees of freedom (*df*)=2, *P*=0.01. Nonlinear BP terms: χ2=8.97, *df*=1, *P*<0.01)

Table 107

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Bangalore, 2010 (70) Post-hoc analysis of RCT (TNT study)	10001	Patients with coronary artery disease and LDL cholesterol level <130 mg/dL, randomized to atorvastatin 80 vs. 10 mg HT and NT	Median 4.9 years	Risk of developing new cardiovascular event with different baseline and post-baseline BP values	Composite of death from coronary disease, non-fatal MI, resuscitated cardiac arrest, and fatal or non-fatal stroke (PO).	Post-baseline, time-dependent SBPs and DBPs, categorized into 10 mmHg increments from ≤110 to >160 mmHg for SBP and ≤60 to >100 for DPB	The relationship between SBP or DBP and primary outcome followed a J-curve with increased event rates above and below the reference BP range (SBP >130 to ≤140; DBP >70 to ≤80 mmHg). A time-dependent, non-linear, multivariate Cox proportional hazard model identified a nadir of 146.3/81.4 mmHg where the event rate was lowest.

Table 108

Summary of numerical results for prognostic studies (for selected outcomes)	
Outcome	**HR (95% CI) for BP measurement (SBP/DBP)**
PO (Composite of death from coronary disease, non-fatal MI, resuscitated cardiac arrest, and fatal or non-fatal stroke)	SBP Nadir: 146.3 mmHg linear and quadratic time-dependent, BP terms (x2 = 7.5,df = 2, P = 0.02) DBP Nadir: 81.4 mmHg linear and quadratic BP terms (x2 = 15.0, df = 2, P = 0.0006)

Table 109

Prognostic studies							
Reference	**N**	**Population**	**Follow-up**	**Study design**	**Outcomes**	**BP values at baseline (groups / thresholds); mmHg**	**Best BP threshold (authors' conclusions)**
Bangalore, 2010 (71) Post-hoc analysis of RCT (PROVE-IT TIMI)	4162	Acute coronary syndrome patients randomized to pravastatin 40 mg versus atorvastatin 80 mg). HT and NT	Average 24 months	Risk of developing new cardiovascular event with different post-baseline BP values	Composite of death due to any cause, myocardial infarction, unstable angina requiring rehospitalization, revascularization after 30 days, and stroke (PO)	The average follow-up BP (systolic and diastolic) was categorized into 10-mm Hg increments.	After acute coronary syndrome, a J- or U-shaped curve association existed between BP and the risk of future cardiovascular events, with lowest event rates in the BP range of approximately 130 to 140 mm Hg systolic and 80

							to 90 mm Hg diastolic and a relatively flat curve for systolic pressures of 110 to 130 mm Hg and diastolic pressures of 70 to 90 mm Hg.

Table 110

Summary of numerical results for prognostic studies (for selected outcomes)	
Outcome	**HR (95% CI) for BP measurement (SBP/DBP)**
PO	SBP: A nonlinear Cox proportional hazards model with systolic pressure on a continuous scale ($\chi 2=49$, $P<0.0001$) identified a nadir of 136 mm Hg at which the event rate was the lowest. DBP: A nonlinear Cox proportional hazards model with diastolic BP on a continuous scale ($\chi 2=52$, $P<0.0001$) identified a nadir of 85 mm Hg at which the event rate was the lowest.

Table 111

4.1.5.3 Summary and conclusions of observational data: Hypertension treatment threshold in adults with coronary disease

Dorresteijn, 2012(69)
This analysis using data from a cohort study that followed 5788 patients with a history of clinically manifest vascular disease for a median of 5.0 years, assessed the risk of developing a **new vascular event** and of **all-cause mortality** with different baseline BP values. The relationship between outcomes and blood pressure followed a J-shaped curve with increased event rates above and below the nadir blood pressure of 143-82 mmHg for vascular events and 140/84 mmHg for all-cause mortality.

Bangalore, 2010 (70)
This is a post-hoc analysis of an RCT that evaluated 10001 patients with coronary artery disease. Median follow-up was 4.9 years. The relationship between the development of **new cardiovascular events** and different SBP or DBP values followed a J-curve with increased event rates above and below the reference BP range (SBP>130 to ≤140; DBP >70 to ≤80). A nadir blood pressure of 146.3/81.4 mmHg was identified.

Bangalore, 2010 (71)
This post-hoc analysis of an RCT evaluated 4162 patients with acute coronary syndrome that were followed for an average of 24 months. A J- or U-shaped curve association was found between BP and the risk of developing **new cardiovascular events**, with lowest event rates in the BP range of approximately 130 to 140 mm Hg systolic and 80 to 90 mm Hg diastolic. A nadir blood pressure of 136/85 mmHg was identified.

Conclusion: In adults with coronary disease, the association between BP values and new cardiovascular events seems to follow a J-shaped curve, with lowest event rates associated with an SBP ranging from 136-146 mmHg and a DBP ranging from 81-85.

GRADE: LOW quality of evidence

4.1.6 Heart failure

4.1.6.1 Clinical evidence profile: Hypertension treatment threshold in adults with heart failure

Our search yielded no MA's, RCTs or observational data meeting our inclusion criteria.

4.1.7 Previous stroke

4.1.7.1 Clinical evidence profile: Hypertension treatment threshold in adults with previous stroke

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.1.7.2 Observational data : Hypertension treatment threshold in adults with previous stroke

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Arima et al., 2006 (22) Sub-analysis of RCT (PROGRESS)	6105	HT and NT (history of stroke or TIA but not subarachnoid haemorrhage)	Mean 3.9 years	Risk of developing events in people with different baseline BP values	Stroke, CV events, mortality	SBP values <120 120-139 140-159 ≥160	The benefits of treatment were comparable for patients who were or were not HT at baseline, for baseline BP levels extending down to 115/75mmHg.

Table 112

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**Relative risk reduction(RRR) (%) (95% CI) for BP measurement (SBP/DBP) treated vs. untreated**
Arima et al., 2006 (22)	Stroke	SBP values <120: RRR= 0 (-123 to 55) 120-139: RRR= 14 (-13 to 35) 140-159: RRR= 31 (-11 to 46) ≥160: RRR= 39 (-21 to 53) *P for trend=0.05* DBP values Not reported
	Major vascular events (non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause)	Not reported
		Relative risk (95% CI) for BP measurement (SBP/DBP) treated vs. untreated
	Mortality	SBP values <120: RR= 1.02 (0.47 to 2.21) 120-139: RR= 1.07 (0.78 to 1.48) 140-159: RR= 0.99 (0.77 to 1.28) ≥160: RR= 0.85 (0.65 to 1.11) *P for trend=0.3* DBP values Not reported

Table 113

4.1.7.3 Summary and conclusions of observational data: Hypertension treatment threshold in adults with previous stroke

Arima(22)
This post hoc analysis of an RCT evaluated the data of 6105 patients with a history of stroke, followed for a mean of 3.9 years. Risk of developing events in people with different baseline and within-study BP values in treated versus untreated was analysed. In treated versus untreated patients, risk of a new stroke and mortality was not significantly increased in any stratum of baseline BP value.

GRADE: LOW quality of evidence

4.2 Targets for treatment

4.2.1 Primary uncomplicated hypertension

4.2.1.1 Clinical evidence profile: treatment target in adults with primary uncomplicated hypertension

More versus less intense treatment studies										
Study details and results for optimal blood pressure targets (trials comparing more vs. less intense blood pressure lowering treatment regimens were used to assess this)										
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Target BP for Treatment (SBP / DBP, mmHg)**	**Outcomes**	**Final mean BP (SBP/DBP mmHg) and number people reaching target**	**Best Target BP (authors' conclusions)**	**QUALITY**
BPLTTC, 2008 (72) SR/MA	190,606 31 RCTs	HT not clear if underlying diabetes / CKD	Clinic	165/104 (<65 years) 173/104 (≥65 years)	Minimum of 1000 patient years in each trial	Not specified (just more vs. less intense)	CV events : stroke (non-fatal stroke or death from cerebrovascular disease), coronary heart disease (non-fatal myocardial infarction or death from coronary heart disease including sudden death) and heart failure (causing death or resulting in admission to hospital).	not reported	NS difference between more vs. less intense BP lowering regimens; extent of risk reduction was directly related to the degree of BP lowering	LOW and VERY LOW (age <65 and >65 respectively); based on moderate quality SR/MA which included low to high quality RCTs)
Hosohata et al., 2007 RCT (HOMED-BP)	971	HT	Home	152/90 (more and less)	12 months	More intense <125/80 Less intense	BP changes/achievement of target BP	More: 132/80; 25% Less: 133/79; 45%	NS difference between more vs. less intense BP lowering	MODERATE AND LOW

						125-134/80-84			regimens for change in BP; More people in less intense reached target BP.	
JATOS study group 2005 and 2008(73, 74) RCT (JATOS)	4320	HT	Clinic	172/89 (strict and mild)	12 months and 2 years	Strict control <140 SBP Mild control 140-160 SBP	BP changes/achievement of target BP; morbidity (CVD and renal failure) and mortality = cerebrovascular disease (cere bral hemorrhage, cerebral infarction, transient ischemic attack, and subarachnoid hemorrhage), cardiac and vascular disease (myocardial infarction, angina pectoris requiring hos-pitalization, heart failure, sudden death, dissecting aneurysms of the aorta, and occlusive arterial disease), and renal failure	12 months: Strict: 139/76; 60% Mild: 147/79; 67% 2 years: Strict: 136/75 Mild: 146/78	Strict treatment group was SS better for: lower final BP value (1 and 2 years) But was SS worse for number of people achieving target BP (1 year) There was NS difference for morbidity and mortality at 2 years	MODERATE [2]
Solomon et al., 2010 RCT (EXCEED)	228	HT	Clinic	161/90 (intensive) 162/94 (standard)	24 weeks	Intensive treatment <130 SBP Standard treatment <140 SBP	BP changes/achievement of target BP	Intensive: 131/75 Standard: 137/80 Intensive: 46% <130; 82% <140	More intense treatment was SS better for: lower final BP value More intense	MODERATE AND LOW

								Standard: 60% <140	treatment increased chance of achieving SBP <140 mmHg	
Verdecchia et al., 2009(75) RCT (Cardio-Sis)	1111	HT	Clinic	163/90 (tight and usual control)	2 years	Tight control <130 SBP Usual control <140 SBP	BP changes/achievement of target BP; CV endpoint = composite of all-cause mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, transient ischaemic attack, congestive heart failure of New York Heart Association stages III or IV requiring admission to hospital, angina pectoris with objective evidence of myocardial ischaemia, new-onset atrial fi brillation, coronary revascularisation, *aortic dissection, occlusive peripheral arterial disease, and renal failure requiring dialysis.(endpoints in italics: removed from composite when reporting)*	Tight: 132/77 Usual: 136/79 Achieved <140: Tight 79% Usual 67% Achieved <130: Tight 72% Usual 27%	Tight control group was SS better for: reduction in CV events percentage achieving SBP (<130 and <140) reduction in BP value	MODERATE

Ichihara et al., 2003[282] RCT	140	HT	Clinic (pulse pressure analyser)	177/101 (mean)	12 months	Intense control <130/85 Moderate control <140/90	BP changes	Intense: 129/78 Moderate: 152/87	Intense control group was SS better for: reduction in BP value	LOW
Ogihara et al., 2003463 RCT (VALISH)	3260	ISH	Clinic	169/81 (mean)	3.07 years (median)	Strict control <140 Moderate control ≥140 to <150 mmHg	BP changes/achievement of target BP; CV endpoint composite of cardio-vascular events: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death because of heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction (doubling of serum creatinine to a level ・ 2.0 mg per 100 mL or introduction of dialysis)	Strict: 137/75 Moderate: 142/77 78% and 48% achieved target (strict and moderate groups respectively)	Strict control group was SS better for: percentage achieving target BPs (<140 and ≥140 to <150) reduction in BP value There was NS difference between the groups for:: reduction in CV events	MODERATE AND LOW

Table 114

Within-treatment blood pressure studies									
Study details and results for within-treatment / achieved blood pressure studies assessing the optimal blood pressure target for treatment									
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**	**QUALITY**

Wang 2005(76) SR/MA	12903 young (30-49 years ≥160/95mmHg) 3 trials; 14323 old (60-79 years ≥160mmHg/ <95mmHg) 5 trials; 1209 very old patients (≥80 years ≥160mmHg / <95mmHg)	HT	Clinic	young: 154/100 old: 174/83 very old: 176/78	Median young: 5 years; old: 3.9 years; very old: 3.8 years	CV events; CV mortality	young: ≥160 / ≥95 old and very old: ≥160 / <95 (ISH)	Anti-hypertensive treatment improves outcomes mainly by lowering SBP; Patients with >median SBP reduction risk of outcome decreased regardless of decrease in DBP or achieved DBP. Active treatment tended to reduce the risk of any outcome to a similar extent (i.e. DBP did not lead to differences in cardiovascular outcome as long as SBP substantially decreased.	MODERATE quality SR/MA based on low quality observational studies
Zanchetti 2009(77) SR of different studies	a) low-risk patients (n=13 trials); b) elderly patients (n=11 trials); c) diabetic patients (n=11 trials; these would be outside our inclusion criteria); d) high-risk	HT (diabetic studies assessed by subgroup analysis)	Clinic	n/a	n/a	Total mortality; CV events; CV mortality	Risk groups (High, medium, low)	Achieved level of risk does not appear to correlate closely with the SBP values achieved. In high risk patients there is a 'ceiling effect' for treatment benefits. Delaying therapeutic correction of CV risk factors until a	MODERATE quality SR/MA based on low quality observational studies

	patients (n=18 trials)							high level of risk is achieved,blunts the full benefits of interventions.	
Arima et al., 2006(22) RCT (PROGRESS) Treated as observational study as not using randomised groups	6105	Cerebrovascular disease (not necessarily HT)	Clinic	Stratified into: <120; 120-139; 140-159; ≥160	Median 3.9 years	Risk of Stroke	Stratified into: <120; 120-139; 140-159; ≥160	Patients with cerebrovascular disease would have lowest risk of recurrence of stroke with BP lowered to approximately 115/75mmHg	LOW
Coca 2008(78) Treated as observational study as not using randomised groups RCT (INVEST)	22,576	HT	Clinic	Stratified into: SBP <140 vs. ≥140 DBP: <90 vs. ≥90	61,836 patient years	Fatal/non-fatal stroke; Achieving target BP <140/90	SBP Stratified into: <140 vs. ≥140 DBP Stratified into: <90 vs. ≥90	Patients who achieved follow up SBP <140mmHg had lower risk of stroke than those with SBP ≥140mmHg; DBP <90mmHg had lower risk than ≥90mmHg.	LOW
Fagard 2007(79) Post-hoc analysis of RCT (Syst-Eur) Treated as observational study as not using randomised groups	4583	HT (systolic)	Clinic	Mean 174/86	median 2 years; further 4 years+ follow-up	Cerebrovascular events; CHD events; mortality; CV events; CV mortality	DBP Stratified into: ≥95; <9585; <85-75; <75-65; <65-55; <55	Antihypertensive treatment can be intensified to prevent cardiovascular events when systolic BP is not under control in older patients with systolic hypertension, at least until diastolic	LOW

								BP reaches 55mmHg, except in patients with coronary heart disease (MI/angina), in whom diastolic should not be lowered to <70mmHg.	
Shimamoto 2008(80) Within-group comparison study (J-HEALTH)	26,512	HT	Clinic	Mean 166/95	Mean 3 years	Composite of CV events	SBP Stratified into: <130; 130-139; 140-149; 150-159; ≥160 DBP Stratified into: <75; 75-79; 80-84; 85-90; ≥90	Clear relationship between BP control and cardiovascular events; incidence of events increased in patients with SBP ≥140/85mmHg (≥140/90mmHg in very elderly) and in diabetic patients with BP ≥130/85mmHg during treatment. Results suggest that BP should be below 140/90 for reducing the risk of CV events. BP was controlled below 140.90 mmHg in the very elderly patients (≥85 years) and they also had a lower risk of CV events.	LOW

Denardo 2010(81) A-priori subanalysis of RCT (INVEST) Treated as observational study as not using randomised groups	22,576	HT	Clinic	Overall mean: 149.5/86.3	24 months	Mortality, MI stroke	Stratified into age-groups and SBP / DBP nadirs.*			J-shaped relationship (among each age-group) with on-treatment SBP and DBP and clinical end-points / events. SBP at HR nadir increased with increasing age – highest for teh very old (140 mmHg). DBP at HR nadir was only slightly lower for the very old (70 mmHg). Therefore optimal management may involve a higher target SBP and lower target DBP for very old people (≥80 years) vs other age-groups.	LOW
							Age	BP nadirs			
								SBP	DBP		
							<60	110	75		
							60-<70	115	75		
							70-<80	135	75		
							≥80	140	70		

Table 115

Study details	n/Population	Comparison	Outcomes		Methodological
Asayama 2012(82) HOMED-BP Design: RCT OL, PG	n= 3518 n UC: 1759 n TC: 1759 Mean age: 59.6 y Previous CV disease:	Usual control (BP 125-134/80-84 mmHg) Vs	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: no Personnel: no
			Cardiovascular death, non-fatal stroke and non-fatal myocardial infarction (PO)	UC: 25/1759 TC: 26/1759 HR: 1.02 (95%CI 0.59 to 1.77) NS P=0.94	
			All cardiovascular	UC:49 /1759	

Duration of follow-up: median 5.3 years	3.0% Diabetes: 15.3% Current Smoker: 21.9% <u>Inclusion</u> Patients with mild-to-moderate hypertension with a minimum age of 40 years. Treatment naive patients as well as previously treated patients, whose antihypertensive drug treatment could be discontinued for at least 2 weeks, qualified for enrollment. Off treatment, they had to maintain a self-measured HBP of 135–179mmHg systolic or 85–119mmHg diastolic. The clinic blood pressure off treatment had to be lower than 220mmHg systolic and	Tight control (BP<125/<80 mmHg) *First, the doctors started the first-line drug to which the patients had been randomized (ACEI, ARB or CCB) at a lower dose, which was increased in the second and third steps. The third step also included association of a diuretic. The fourth step involved the association of a a- or b-blocker and the fifth step the addition of any antihypertensive*	(Stroke, ischemic heart disease and total mortality) (SO)	TC: 57/1759 HR: 1.14 (95%CI 0.78 to 1.67) NS	Assessors: yes Remarks on blinding method: PROBE design FOLLOW-UP: Lost-to follow-up: % Drop-out and Exclusions: 40.4% • Described: yes/no • Balanced across groups: yes/no ITT: Yes SELECTIVE REPORTING: no Other important methodological remarks: Only the first event of each outcome was considered Sponsor: The study is funded by grants from the Japan Cardiovascular Research Foundation, the Japan Arteriosclerosis Prevention Fund and Tohoku University. Fujitsu Systems East Limited (Tokyo,
			Stroke (SO)	UC: 16/1759 TC: 20/1759 HR: 1.23 (95%CI 0.64 to 2.37) NS	
			Ischemic heart disease (SO)	UC: 28/1759 TC: 25/1759 HR: 0.87 (95%CI 0.51 to 1.49) NS	
			All-cause mortality (SO)	UC: 31/1759 TC: 27/1759 HR: 0.85 (95%CI 0.51 to 1.43) NS	
			Safety		
			Withdrawn for severe side effects	UC: 3 (0.17%) TC: 4 (0.23%)	

	125mmHg diastolic. Eligible patients should have no contra-indication for treatment with ACEIs, ARBs, CCBs, b-blockers, a-blockers or diuretics. <u>Exclusion</u> Patients meeting the systolic criteria for the HBP did not qualify if the diastolic was <65mmHg, while those meeting the diastolic range were excluded if systolic blood pressure was <110mmHg.	*agent. When the HBP was <110mmHg systolic or 65mmHg diastolic, treatment was tailored down to avoid orthostatic hypotension.*			Japan) and Omron Healthcare Co. (Kyoto, Japan) developed and maintained the internet-based infrastructure for the measurement of blood pressure at home and the management of patients.

Table 116: UC= usual control; TC= tight control

4.2.1.2 *Summary and conclusions: treatment target in adults with primary uncomplicated hypertension*

Blood pressure target in patients with uncomplicated hypertension

More intensive versus less intensive blood pressure target (unspecified) in people aged < 65 years			
Bibliography: BPLTTC 2008 (72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CV events : stroke (non-fatal stroke or fatal), coronary heart disease (fatal or nonfatal including sudden death) and heart failure (causing death or resulting in admission to hospital).	190,605 (31studies)	RR 0.88 (95%CI 0.75 to 1.04) NS	⨁⨁⊖⊖ **LOW** Study quality:-1 RCTs included were of low to high quality; the SR/MA itself was of moderate quality Consistency:ok Directness:ok Imprecision:-1 95%CI crosses both no effect and appreciable benefti

Table 117

More intensive versus less intensive blood pressure target (unspecified) in people aged ≥ 65 years			
Bibliography: BPLTTC 2008 (72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CV events : stroke (non-fatal stroke or fatal), coronary heart disease (fatal or nonfatal including sudden death) and heart failure (causing death or resulting in admission to hospital).	190,605 (31studies)	RR 1.03 (95%CI 0.85 to 1.24) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 RCTs included were of low to high quality; the SR/MA itself was of moderate quality Consistency:ok Directness:ok Imprecision:-2 95%CI crosses both appreciable benefit and appreciable harm

Table 118

Tight BP control (<130mmHg SBP) to usual control (<140mmHg SBP) in patients without diabetes			
Bibliography: Verdecchia 2009(75)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality, cardiovascular and cerebrovascular disease, heart failure, renal	1,111 (1study) 2y	**HR 0.50 (95%CI 0.31 to 0.79) SS**	⨁⨁⊖⊖ **LOW** Study quality:-2 Inadequate allocation concealment and blinding; SELECTIVE REPORTING: composite differs from original protocol Consistency:NA

failure, atrial fibrillation		Directness:ok Imprecision:OK

Table 119

Usual home BP control (125-134/80-84 mmHg) versus tight home BP control <125/<80 mmHg			
Bibliography: Asayama 2012(82)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular death, non-fatal stroke and non-fatal myocardial infarction	3,518 (1 study) median 5.3y	HR: 1.02 (95%CI 0.59 to 1.77) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment, large drop out and exclusions Consistency:NA Directness:Japanese? Imprecision:OK

Table 120

Blood pressure target <140mmHG versus > 140mmHg in elderly Japanese patients			
Bibliography: JATOS 2008(73)(a), VALISH trial 2010(83)(b)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4,320 (1study) 2y	a) RR 1.12 (95%CI 0.43 to 2.9) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency:ok Directness:Japanese? Imprecision: wide CI
Cerebrovascular disease, cardiac and vascular disease and renal failure	4,320 (1study) 2y	a) RR 1.0 (95%CI0.74 to 1.33) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 Inadequate allocation concealment Consistency:ok Directness:Japanese? Imprecision:wide CI
Cardiovascular mortality, stroke, MI, unplanned CV hospitalization and renal dysfunction	3,260 (1 study) 3y	b) HR 0.89 (0.6 to 1.31) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 Inadequate allocation concealment and blinding Consistency: ok Directness: Japanese? Imprecision:wide CI

Table 121

The systematic review performed by NICE 2011(3) found 7 publications (meta-analyses or RCTs) comparing more versus less intense blood pressure lowering. Four of these (BPLTTC 2008(72) , Verdecchia 2009(75), (73), VALISH 2010(83)). reported hard endpoints.

The BPLTTC 2008(72) systematic review and meta-analysis included 31 RCTs with a total of 190,606 participants with hypertension. It was not clear if there was underlying diabetes or chronic kidney disease. A more intense BP target was compared to a less intense BP target, but the exact blood

pressure value for the target was not specified. A distinction was made between participants <65years and participants ≥65 years. The quality of this SR/MA was reported by NICE 2011 to be moderate, mainly because of including low to high quality RCTs.
In hypertensive patients <65 years with uncomplicated hypertension, unspecified more intense BP lowering did not result in a statistically significant risk reduction of **cardiovascular events** (a composite of fatal and nonfatal stroke, coronary artery disease and heart failure), compared to unspecified less intense BP lowering
GRADE: LOW quality of evidence
In hypertensive patients ≥65 years with uncomplicated hypertension, unspecified more intense BP lowering did not result in a statistically significant risk reduction **of cardiovascular events**(a composite of fatal and nonfatal stroke, coronary artery disease and heart failure), compared to unspecified less intense BP lowering.
GRADE: VERY LOW quality of evidence

A subsequent RCT by Verdecchia 2009(75) compared tight BP control (<130mmHg SBP) to usual control (<140mmHg SBP) in 1111 hypertensive patients with a systolic blood pressure of 150mmHg or greater and no diabetes. The primary end point was left ventricular hypertrophy. A composite **cardiovascular endpoint** (including mortality, cardiovascular and cerebrovascular disease, heart failure, renal failure, atrial fibrillation) was a secondary outcome.
After 2 years, tight control was statistically significantly better for reducing a large composite endpoint of cardiovascular events.
GRADE: LOW quality of evidence

We found one additional RCT by Asayama 2012(82) that compared a usual home blood pressure target of 125-134/80-84mmHg) to a tighter home blood pressure control <125/<80mmHg) in Japanese patients with mild to moderate hypertension. Follow-up was for a median of 5.3 years.
No statistically significant difference in a composite outcome of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction was observed between usual home blood pressure control and tight home blood pressure control in Japanese patients.
GRADE: MODERATE quality of evidence

The JATOS 2005(74) and 2008(73) study compared a blood pressure target of <140mmHg to a target of 140-160mmHg in 4320 elderly Japanese hypertensive patients (age 65-85years) with a systolic blood pressure ≥ 160mmHg. Follow up was respectively 12 months and 2 years.
No significant difference for **mortality** and **morbidity** (cerebrovascular disease, cardiac and vascular disease and renal failure) was observed at 2 years, when aiming for a blood pressure target of <140mmHg SBP compared to a target of 140-160mmHg SBP in elderly Japanese patients.
GRADE: MODERATE quality of evidence

The VALISH trial 2010(83) compared strict control <140mmHg versus moderate control (≥140 to <150 mmHg) in 3260 elderly Japanese patients (70-84 years old) with isolated systolic hypertension.

After a median study duration of 3 years, there was no significant difference between groups for reduction in a composite endpoint of **cardiovascular events** (including cardiovascular mortality, stroke, MI, unplanned CV hospitalization and renal dysfunction).
GRADE: MODERATE quality of evidence

4.2.1.3 Observational data: treatment target in adults with primary uncomplicated hypertension

Treatment target blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**Target BPs**	**Best Target BP (authors' conclusions)**
Reboldi 2014(84) Post-hoc analysis of RCT	1111	Treated hypertension patients nondiabetic SBP≥ 150 mmHg and one additional CV risk factor Stratified to patients with (n=216) and without CV disease (n=895)	Clinic	In patients with CV disease: Standard control: 159.4/85.5 Tight control: 158.2/84.3	2 years	Composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, TIA, congestive heart failure, angina pectoris, new-onset atrial fibrillation, coronary revascularization, aortic dissection, occlusive peripheral arterial disease, and renal failure requiring dialysis (SO)	SBP Tight control: <130 Standard control <140	This study shows that an intensive antihypertensive treatment aimed to lower systolic BP<130 mm Hg reduces left ventricular hypertrophy and improves clinical outcomes to a similar extent in patients with hypertension with and without overt cardiovascular disease at baseline.

Table 122

Study	**Outcome**	**HR (95% CI) for BP measurement** **Unadjusted HR versus reference : SBP <140 mmHg**
Reboldi 2014(84)	Composite secondary outcome (mortality and CV and renal events)*	With and without CV disease at baseline: **<130: HR= 0.50 (0.31 to 0.79)** <140: HR=1 Without CV disease at baseline: **<130: HR= 0.40 (0.21 to 0.77)** <140: HR=1 With CV disease at baseline:

		<130: HR= 0.68 (0.35 to 1.35) <140: HR=1

Table 123: * New-onset atrial fibrillation and coronary revascularization were the components of the composite secondary outcome that differed significantly between the groups (no numerical data)

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**
Sim 2014(85) Retrospective cohort study	398419	Treated hypertension patients 30% diabetes	Clinic	131/73	Mean 4.0 y	Mortality, ESRD	SBP <110 110-119 120-129 140-149 150-159 160-169 ≥170 DBP <50 50-59 60-69 70-79 80-89 90-99 ≥100	Both higher and lower treated BP compared with 130 to 139 mm Hg systolic and 60 to 79 mm Hg diastolic ranges had worsened outcomes.

Table 124

Summary of numerical results (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference SBP/DBP of 130-139/80-89 mmHg**
Sim 2014(85)	Composite: mortality or ESRD	SBP **<110: HR= 4.10 (3.87-4.33)** **110-119: HR= 1.81 (1.74 to 1.88)**

		120-129: HR= 1.12 (1.08 to 1.15) 130-139: HR= 1 **140-149: HR= 1.44 (1.39 to 1.50)** **150-159: HR= 2.34 (2.22 to 2.47)** **160-169: HR= 3.33 (3.05 to 3.63)** **≥170: HR= 4.91 (4.41 to 5.47)** DBP **<50: HR= 3.14 (2.73–3.61)** 50-59: HR= 0.96 (0.91–1.02) **60-69: HR= 0.72 (0.69–0.76)** **70-79: HR= 0.70 (0.67–0.73)** 80-89: HR=1 **90-99: HR= 1.92 (1.73–2.13)** **≥100: HR= 3.83 (3.04–4.83)**
	Mortality	SBP: not reported DBP **<50: HR= 3.32 (2.88–3.83)** 50-59: HR= 0.98 (0.92–1.04) **60-69: HR= 0.73 (0.69–0.76)** **70-79: HR= 0.71 (0.68–0.74)** 80-89: HR=1 **90-99: HR= 1.99 (1.77–2.24)** **≥100: HR= 3.65 (2.77–4.80)**
	ESRD	SBP: not reported DBP **<50: HR= 2.54 (1.65–3.90)** 50-59: HR= 1.12 (0.98–1.27) **60-69: HR= 0.82 (0.74–0.90)** **70-79: HR= 0.72 (0.66–0.79)** 80-89: HR=1 **90-99: HR= 1.56 (1.26–1.92)** **≥100: HR= 3.30 (2.18–5.00)**

Table 125

ESRD: End-stage renal disease

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**
Kario 2014(86) Analysis using data from a prospective cohort study (HONEST)	21591	Essential hypertension Japan	Home blood pressure (HBP) and clinic	Not reported	Mean 2.0 years	Major cardiovascular events	Home BP <125 125 to <135 135 to <145 145 to <155 ≥155 Clinic BP <130 130 to <140 140 to <150 150 to <160 ≥160	First, we found that on-treatment morning HSBP ≥145 mm Hg is associated with a significant increase in cardiovascular risk for 2 years. Second, morning HSBP associated with minimum risk was 124 mm Hg. Finally, the risk of cardiovascular events is high in patients with masked hypertension and uncontrolled morning HSBP, although their CSBP is not increased. Based on this evidence, it is essential to control morning HSBP to <145 mm Hg as a first step, even in patients with controlled CSBP. These real-world findings emphasize the importance of HBP monitoring in clinical practice

Table 126

Summary of numerical results (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference SBP <125 mmHg (home BP) or <130 (Clinic BP)**
Kario 2014(86)	Major cardiovascular events	Clinic BP <130: HR= 1 130 to <140: HR= 0.78; NS 140 to <150: HR= 1.09; NS **150 to <160: HR= 1.69 (1.10 to 2.60)** **≥160: HR= 4.38; SS** Nadir SBP= 131 mmHg Morning home BP <125: HR= 1

		125 to <135: HR= 0.98; NS 135 to <145: HR= 1.18; NS **145 to <155: HR= 1.83 (1.12 to 2.99)** **≥155: HR= 5.03; SS** Nadir SBP= 124 mmHg Evening home BP <125: HR= 1 125 to <135: HR= 0.77; NS 135 to <145: HR= 1.15; NS **145 to <155: HR= 1.63 (1.01 to 2.61)** **≥155: HR= 6.32; SS** Nadir SBP= 144 mmHg Averaged morning and evening home BP <125: HR= 1 125 to <135: HR= 1.08 ; NS 135 to <145: HR= 1.31; NS **145 to <155: HR= 2.36 (1.44 to 3.85)** **≥155: HR= 6.60; SS** Nadir SBP= 148 mmHg

Table 127

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**
Howard 2015(87) Prospective cohort study	26875	>45 years No previous stroke at baseline	Clinic	Not reported	6.3 years	Incident stroke	SBP <120 120-139 140-159 ≥160	Maintaining the normotensive status solely through pharmacological treatment has a profound impact, as nearly half of this general population cohort were treated to guideline (SBP<140 mm Hg) but failed to return to risk levels similar to normotensive individuals. Even with successful treatment, there is a substantial potential gain by prevention or delay of hypertension.

Table 128

Summary of numerical results (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference normotensive untreated patients SBP <120 mmHg**
Howard 2015(87)	Incident stroke	Untreated <120: HR= 1.0 **120-139: HR= 1.44 (1.04–2.01)** **140-159: HR= 2.19 (1.45–3.31)** **≥160: HR= 3.35 (1.78–6.28)** 1 antihypertensive medication <120: HR= 1.42 (0.94–2.15) **120-139: HR= 2.00 (1.44–2.77)** **140-159: HR= 1.67 (1.09–2.54)** **≥160: HR= 3.00 (1.71–5.26)** 2 antihypertensive medications **<120: HR= 1.60 (1.06–2.42)** **120-139: HR= 1.88 (1.35–2.62)** **140-159: HR= 2.84 (1.95–4.13)** ≥160: HR= 1.42 (0.67–2.99) 3 antihypertensive medications **<120: HR= 2.48 (1.63–3.77)** **120-139: HR= 2.34 (1.66–3.32)** **140-159: HR= 3.35 (2.28–4.92)** **≥160: HR= 4.62 (2.84–7.51)**

Table 129

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**

Barengo 2013(88) Prospective cohort study	26113	HT and NT No coronary heart disease, heart failure or cancer at baseline	Clinic	Not reported	Median 16 years	Cardiovascular disease, all-cause mortality	<140 AND <90 <140 AND >90 >140 AND <90 >140 AND >90; <u>6 categories:</u> -Normotensive (untreated) -Hypertensive and untreated -Hypertensive and controlled -Hypertensive, SBP controlled, DBP uncontrolled -Hypertensive, SBP uncontrolled, DBP controlled -Hypertensive, SBP AND DBP uncontrolled	Treated patients with both SBP and DBP controlled did not have an increased risk of CVD mortality when compared with normotensive people. The risk of CVD mortality was statistically significantly higher in treated hypertensive people with SBP alone, DBP alone or both SBP and DBP uncontrolled. Our study indicates that uncontrolled SBP alone and DBP alone are risk factors of all-cause and CVD mortality.

Table 130

Summary of numerical results (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference normotensive untreated patients <140/<90 mmHg**
Barengo 2013 (88)	Total mortality	Normotensive <140 AND <90: HR= 1 Treated hypertensive, <140 AND <90: HR= 0.80 (0.53–1.19) **Treated hypertensive, <140 AND >90: HR= 1.45 (1.04–2.02)** **Treated hypertensive, >140 AND <90: HR= 1.48 (1.09–2.01)** **Treated hypertensive, >140 AND >90: HR= 1.61 (1.39–1.88)** **Untreated hypertensive, >140 AND >90: HR= 1.26 (1.13–1.42)**
	Cardiovascular mortality	Normotensive <140 AND <90: HR= 1

		Treated hypertensive, <140 AND <90: HR= 1.18 (0.65–2.15) **Treated hypertensive, <140 AND >90: HR= 2.32 (1.44–3.74)** **Treated hypertensive, >140 AND <90: HR= 2.87 (1.89–4.35)** **Treated hypertensive, >140 AND >90: HR= 2.74 (2.14–3.51)** **Untreated hypertensive, >140 AND >90: HR= 1.95 (1.57–2.41)**

Table 131

4.2.1.4 *Summary and conclusions of observational data: treatment target in adults with primary uncomplicated hypertension*

For assessing the optimal blood pressure target, NICE 2011 also reported studies that assess the relationship between the achieved blood pressure on treatment versus clinical outcomes.

NICE states clearly that these studies, "using post-hoc stratifaction of on-treatment achieved blood pressures versus outcomes are not randomised and are potentially confounded by the fact that the blood pressure response to treatment may reflect underlying vascular damage,…. Moreover, such studies did not usually adjust the results according to baseline blood pressure, age and other key variables."

NICE found 2 systematic reviews and 5 analyses of RCTs.

- In 2 studies and 1 SR/MA, a **higher achieved blood pressure was associated with increased risk of cardiovascular events** (Denardo 2010(81)=A-priori subanalysis of INVEST, Shimamoto 2008(80)=within-group comparison of J-HEALTH, Wang 2005(76)= SR/MA).
- In 1 SR/MA, the achieved systolic blood pressure **did not correlate with the risk of cardiovascular events**. However, diastolic blood pressure did not lead to risk differences as long as systolic blood pressure substantially decreased. (Zanchetti 2009(77))
- In 2 studies, blood pressure **<140/90 had a lower risk of cardiovascular events**. (Coca 2008(78); Shimamoto 2008(80)=within-group comparison of J-HEALTH)
- In 1 study, the **lowest risk of stroke** was at blood pressure 115/75mmHg49. In another study, the lowest risk of stroke was at a diastolic blood pressure <90mmHg. (Coca 2008(78))
- In elderly patients with isolated systolic hypertension, lowering diastolic BP to as low as about 55mmHg is not associated with increased cardiovascular mortality but low DBP is associated with higher noncardiovascular mortality, except for patients with MI/angina, where DBP <70mmHg was associated with increased risk of cardiovascular events. (Fagard 2007(79) =post-hoc analysis of Syst-Eur).

In our subsequent literature search, we found some additional analyses that assess the relationship between the blood pressure on treatment versus clinical outcomes.

Reboldi 2014(84)
This post hoc analysis of an RCT by Verdecchia 2009(75) in 1111 nondiabetic, treated hypertension patients, stratified to patients with and without cardiovascular disease, evaluated tight control (SBP <130 mmHg) versus standard control (SBP <140 mmHg) for a **composite outcome of all-cause mortality, cardiovascular and renal events**. In hypertensive patients without cardiovascular disease at baseline, a target SBP of <130 mmHg was associated with a significant reduction of the composite outcome after 2 years of follow-up, in contrast to patients with CV disease. New-onset atrial fibrillation and coronary revascularization were the components of the composite secondary outcome that differed significantly between the groups.

Sim 2014(85)

This retrospective cohort study in 398419 treated hypertensive patients, with a mean follow-up of 4 years, evaluated the risk of **mortality and end-stage renal disease** in different achieved blood pressure values. Systolic blood pressures both above and below a range of 130-139 mmHg were significantly associated with an increase of the composite endpoint (mortality or ESRD). High (>90 mmHg), as well as very low (<50 mmHg) diastolic blood pressure were significantly associated with increased risk, compared to a diastolic blood pressure of 80-89 mmHg, while diastolic blood pressure in the range of 60-79 mmHg seemed associated with the least risk.

Kario 2014(86)
This analysis using data from a prospective cohort study in 21591 Japanese hypertension patients, followed over 2 years, evaluated the risk of **major cardiovascular events** in different on-treatment blood pressure values, measured at home and at the clinic. Clinic-measured blood pressure values of >150 mmHg and morning home BP >145 mmHg was associated with a significantly increased risk, compared to a low achieved blood pressure (<130 mmHg for clinic and <125 mmHg for home measured BP). There was no significant difference of risk in the range of <130 to <150 mmHg (clinic-measured BP) or <125 to <145 mmHg (morning home measured BP).

Howard 2015(87)
This prospective cohort study in 26875 patients older than 45, with no previous stroke at baseline, and a follow-up of 6.3 years, evaluated the risk of **incident stroke** in different achieved systolic blood pressure values, stratified by number of antihypertensive drugs taken (0 to 3). Compared with a blood pressure of <120 mmHg in untreated patients, risks seemed to rise significantly with both rising blood pressure and rising number of antihypertensive drugs. The risk of incident stroke was significantly higher in patients taking 2 or 3 antihypertensives, even if their blood pressure was low (<120 mmHg).

Barengo 2013(88)
In this prospective cohort study, 26113 patients, both normo- and hypertensive and with no history of coronary heart disease, heart failure or cancer at baseline, were followed over a median of 16 years. Compared with normotensive (<140/<90 mmHg), untreated subjects, there was no significant difference in risk of **cardiovascular disease** and **all-cause mortality** in treated hypertensive patients with an achieved BP of <140/<90 mmHg. There was a significantly increased risk of cardiovascular disease and mortality in treated hypertensives in which either systolic or diastolic blood pressure, or both, were uncontrolled (SBP >140 AND/OR DBP >90 mmHg).

GRADE: LOW quality of evidence

NICE 2011 states as a conclusion " …that most clinical trials had adopted a treatment target of <140/90 mmHg and that there was no convincing evidence supporting a lower treatment target for the pharmacological treatment of hypertension. That said, the evidence specifically examining optimal treatment targets for hypertension is inadequate and consequently the optimal treatment target could not be clearly defined with certainty."

4.2.2 Cardiovascular risk factors

4.2.2.1 Clinical evidence profile: treatment target in adults with cardiovascular risk factors

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.2.2.2 Observational data: treatment target in adults with cardiovascular risk factors

Treatment target blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**Target BPs**	**Best Target BP (authors' conclusions)**
Reboldi 2014(84) Post-hoc analysis of RCT	1111	Treated hypertension patients nondiabetic SBP≥ 150 mmHg and one additional CV risk factor Stratified to patients with (n=216) and without CV disease (n=895)	Clinic	In patients with CV disease: Standard control: 159.4/85.5 Tight control: 158.2/84.3	2 years	Composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, TIA, congestive heart failure, angina pectoris, new-onset atrial fibrillation, coronary revascularization, aortic dissection, occlusive peripheral arterial disease, and renal failure requiring dialysis (SO)	SBP Tight control: <130 Standard control <140	This study shows that an intensive antihypertensive treatment aimed to lower systolic BP<130 mm Hg reduces left ventricular hypertrophy and improves clinical outcomes to a similar extent in patients with hypertension with and without overt cardiovascular disease at baseline.

Table 132

Study	**Outcome**	**HR (95% CI) for BP measurement** **Unadjusted HR versus reference : SBP <140 mmHg**

Reboldi 2014(84)	Composite secondary outcome (mortality and CV and renal events)*	With and without CV disease at baseline: **<130: HR= 0.50 (0.31 to 0.79)** <140: HR=1 Without CV disease at baseline: **<130: HR= 0.40 (0.21 to 0.77)** <140: HR=1 With CV disease at baseline: <130: HR= 0.68 (0.35 to 1.35) <140: HR=1

Table 133* New-onset atrial fibrillation and coronary revascularization were the components of the composite secondary outcome that differed significantly between the groups (no numerical data)

Reference	N	Population	Follow-up	Study design	Outcomes	BP targets / achieved BP); mmHg	Best BP threshold (authors' conclusions)
Weber, 2013(89) Data from RCT (ACCOMPLISH)	10705	Hypertensive patients at high risk of cardiovascular events established by previously documented cardiovascular conditions.	35.7 months	Risk of developing cardiovascular events in different achieved BP values	Cardiovascular death or nonfatal myocardial infarction or nonfatal stroke	SBP: >140 130 to <140 120 to <130 110 to <120	In high-risk hypertensive patients, major cardiovascular events are significantly lower in those with systolic blood pressures <140 mmHg and <130 mmHg than in those with levels >140 mm Hg. There are stroke benefits at levels <120 mm Hg, but they are offset by increased coronary events. Renal function is best protected in the 130 to 139 mm Hg range.

Table 134

Summary of numerical results for prognostic studies (for selected outcomes)	
Outcome	**HR (95% CI) for BP measurement (SBP/DBP)**
First occurrence of cardiovascular death or nonfatal myocardial infarction or nonfatal stroke (PO)	**130 to <140 vs ≥140: HR= 0.62(0.50 to 0.77)** 120 to <130 vs 130 to <140: HR= 0.91 (0.74 to 1.13) 110 to <120 vs 120 to <130: HR= 1.09 (0.82 to 1.45)
Cardiovascular death	**130 to <140 vs ≥140: HR= 0.64 (0.44 to 0.92)** 120 to <130 vs 130 to <140: HR= 0.83 (0.57 to 1.21) 110 to <120 vs 120 to <130: HR= 1.31 (0.80 to 2.12)
Total mortality	**130 to <140 vs ≥140: HR= 0.72 (0.56 to 0.93)** 120 to <130 vs 130 to <140: HR= 0.94 (0.73 to 1.21) **110 to <120 vs 120 to <130: HR= 1.37 (1.01 to 1.86)**
Total stroke (fatal or nonfatal)	**130 to <140 vs ≥140: HR= 0.53 (0.38 to 0.75)** 120 to <130 vs 130 to <140: HR= 1.22 (0.87 to 1.71) 110 to <120 vs 120 to <130: HR= 0.60 (0.35 to 1.01)
Total myocardial infarction (fatal or nonfatal)	**130 to <140 vs ≥140: HR= 0.63 (0.46 to 0.85)** 120 to <130 vs 130 to <140: HR= 0.73 (0.53 to 1.02) 110 to <120 vs 120 to <130: HR= 1.52 (1.00 to 2.29)
Clinical coronary events (total MI, hospitalized angina pectoris, or sudden cardiac death)	**130 to <140 vs ≥140: HR= 0.66 (0.51 to 0.85)** 120 to <130 vs 130 to <140: HR= 0.78 (0.60 to 1.02) **110 to <120 vs 120 to <130: HR= 1.63 (1.18 to 2.24)**
Increased serum creatinine (increase from baseline of >50%)	**130 to <140 vs ≥140: HR= 0.75 (0.64 to 0.88)** **120 to <130 vs 130 to <140: HR= 1.29 (1.12 to 1.49)** **110 to <120 vs 120 to <130: HR= 1.22 (1.03 to 1.45)**

Table 135

4.2.2.3 *Summary and conclusions of observational data: treatment target in adults with cardiovascular risk factors*

Reboldi 2014(84)
This post hoc analysis of an RCT in 1111 nondiabetic, treated hypertension patients, stratified to patients with and without cardiovascular disease, evaluated tight control (SBP <130 mmHg) versus standard control (SBP <140 mmHg) for a **composite outcome of all-cause mortality, cardiovascular and renal events**. In hypertensive patients with cardiovascular disease at baseline, a target SBP of <130 mmHg was not associated with a significant reduction of the composite outcome after 2 years of follow-up, in contrast to patients without CV disease.

Weber, 2013(89)
This analysis of data from an RCT in 10705 hypertensive patients at a high risk of cardiovascular events, with 35.7 months of follow-up, evaluated the risk of cardiovascular events and mortality at different achieved blood pressures values. An achieved SBP 130 to <140 mmHg, compared to >140 mmHg, was significantly associated with a decrease of the primary outcome (**cardiovascular death, nonfatal myocardial infarction or nonfatal stroke**) and all of the secondary outcomes (**cardiovascular death, total mortality, total stroke, total myocardial infarction, clinical coronary events, >50% increased serum creatinine**). An SBP of 120 to <130 mmHg, compared to 130- <140 mmHg, was not significantly associated with a further risk decrease, except for the renal outcome. A very low SBP (110 to <120 mmHg), compared to an SBP of 120 – <130 mmHg, was significantly associated with an increase in total mortality and clinical coronary events.

Conclusion: In hypertensive patients with high cardiovascular risk, both systolic blood pressure targets of >140 mmHg and <120 mmHg seem associated with an increased risk of morbidity and mortality. A systolic blood pressure target of <130 mmHg does not seem to be associated with a clear risk reduction of morbidity and mortality, compared to a target of <140 mmHg.

GRADE: LOW quality of evidence

4.2.3 Elderly people

4.2.3.1 Clinical evidence profile: treatment target in elderly people ≥60 years

Systolic target

	BP Goal Achieved BP Differences between groups	**Overall Mortality**	**Coronary Heart Disease** (includes fatal MI, non-fatal MI, sudden death, or combinations)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal,orcombination)	**Heart Failure** (includes fatal, non-fatal or combination)	**Primary Composite Outcomes**
Systolic Goals < 140 mmHg						

JATOS, 2008 Adults, ages 65 to 85 with essential HTN; SBP ≥ 160 and DBP < 120 N = 4,418 104 weeks Good *NOTE: all outcomes are strict treatment versus mild treatment*	SBP Goal: Strict txt: <140 Mild txt: ≥140 to <160 mmHg <u>At start of trial</u> Baseline SBP, mmHg (SD): Strict: 171.6 (9.7) Mild: 171.5 (9.8) <u>At 2 years</u> Achieved SBP, mmHg (SD) Strict: 135.9 (11.7) Mild: 145.6 (11.1) . p = NR SBP differences between groups, mmHg: 9.7 p < 0.001	**Death from any cause** Events: 54 vs 42 p = 0.22	**Cardiac and vascular disease:** Events: 26 vs 28 p = 0.78 **Fatal cardiac and vascular disease:** Events: 6 vs 4 p = 0.53 **MI:** Events: 6 vs 6 p = NS **Fatal MI:** Events: 1 vs 0 p = NS **Sudden deaths:** Events: 1 vs 1 p = NS	**Cerebrovascular disease:** Events: 52 vs 49 p = 0.77 **Fatal cerebrovascular disease:** Events: 3 vs 3 p = 1.00	**CHF:** Events: 8 vs 7 p = NS **Fatal CHF:** Events: 4 vs 1 p = NS	**Composite of cerebrovascular, cardiac and vascular disease and renal failure events and deaths:** Events: 86 vs 86 p = 0.99 **Composite of cerebrovascular, cardiac and vascular disease and renal failure deaths:** Events: 9 vs 8 p = 0.81

VALISH, 2010 Adults, ages 70-85 with HTN (SBP ≥ 160 and DBP < 90 mmHg) N = 3,260 Mean 2.85 years Good	SBP Goal: Strict control: <140 Moderate control: ≥140 to <150 mmHg <u>At start of</u> trial Baseline SBP, mmHg (SD): Strict: 169.5 (7.9) Moderate: 169.6 (7.9) <u>At mean 2.85 years</u> Achieved SBP, mmHg (SD) Strict: 136.6 (13.3) Moderate: 142 (12.5) p < 0.001 <u>At 36 months</u> SBP differences between groups, mmHg 5.6 p <0.001	**All cause death:** HR: 0.78 CI (0.46, 1.33) p = 0.362	**Fatal and non-fatal MI:** HR: 1.23 CI (0.33, 4.56) p = 0.761 **Sudden death:** HR: 0.73 CI (0.25, 2.11) p = 0.564	**Fatal or non-fatal stroke:** HR: 0.68 CI (0.36, 1.29) p = 0.237		**Composite of CV events:** HR: 0.89 CI (0.60, 1.31) p = 0.383 **CV death:** HR: 0.97 CI (0.42, 2.25) p = 0.950
Systolic Goals ≤ 150 mmHg						
Syst-Eur, 1997 Adults, ages ≥ 60 years, SBPs 160-219 and DBPs of < 95 mmHg N = 4,695 Median 24 months Good	SBP Goal: <150 and decrease SBP by ≥ 20 mmHg <u>At start of trial</u> Baseline SBP, mmHg (SD): Txt: 173.8 (6.7) Placebo: 173.9 (10.1) <u>At 2 years</u> Achieved SBP: not	**Total mortality:** adj HR: 0.86 CI (0.67, 1.10) p = NR	**Fatal and non-fatal cardiac endpoints:** adj HR: 0.71 CI (0.54, 0.95) p < 0.05 **Fatal MI** Rate per 1000 py: 56% ↓ in txt group CI (-82, 9) p =0.08	**Non-fatal stroke:** Rate per 1000 py: 44% ↓ in txt group CI (-63,-14) p = 0.007 **Death due to stroke:** Rate per 1000 py: 27% ↓ in txt group CI (-62, 39) p = 0.33	**Non-fatal HF:** Rate per 1000 py: 36% ↓ in txt group CI (-60, 2) p = 0.06 **Fatal HF:** Rate per 1000 py: 24% ↓ in txt group CI (-70, 93) p = 0.57	

	reported numerically, results illustrated in a figure and showed that drug group had consistently lower SBPs and DBPs versus placebo from year 1 through year 4 Mean fall in sitting SBP, mmHg (SD) Txt: 23 (16) Placebo: 13 (17) p = NR SBP differences between groups, mmHg (95% CI) 10.1 (8.8, 11.4) p = NR % at target Txt: 43.5% Placebo: 21.4% p < 0.001 <u>At 4 years</u> Differences between groups, SBP (95% CI) 10.7 (8.8, 12.5) p = NR		**Non-fatal MI:** Rate per 1000 py: 20% ↓ in txt group CI (-53, 34) p = 0.40 **Coronary mortality:** Rate per 1000 py: 27% ↓ in txt group CI (-54, 15) p = 0.17 **Sudden death:** Rate per 1000 py: 12% ↓ in txt group CI (-49, 52) p =0.65 **Fatal and non-fatal MI:** Rate per 1000 py: 30% ↓ in txt group CI (-56, 9) p = 0.12	**Fatal and non-fatal stroke combined** adj HR: 0.59 CI (0.38, 0.79) p < 0.01	**Fatal and non-fatal HF** Rate per 1000 py: 29% ↓ in txt group CI (-53, 10) p =0.12	
Systolic Goals < 160 mmHg (also includes lower goals)						
SHEP, 1991 Adults, ages ≥ 60 years, SBPs 160- 219 and DBPs of < 90	SBP Goal: For individuals with SBPs of >180 mmHg: <160	**Total deaths** RR: 0.87 CI (0.73, 1.05)	**Non-fatal MI** RR: 0.67 CI (0.47, 0.96)	**Non-fatal plus fatal stroke** RR: 0.64 CI (0.50, 0.82) p = 0.0003	**Fatal and non-fatal HF** RR: 0.51	

mmHg N = 4,736 Mean 4.5 years Good *NOTE: Outcome events reported as treatment versus placebo*	For those with SBPs of 160-179: a reduction of at least 20 mmHg <u>At start of trial</u> Baseline SBP, mmHg (SD): Txt: 170.5 (9.5) Placebo: 170.1 (9.2) <u>At 5 years</u> Achieved SBP, mmHg (SD) Txt: 144.0 (19.3) Placebo: 155.1 (20.9) p = NR SBP change from baseline, mmHg Txt: -26.5 Placebo: -15 p = NR		**Symptomatic MI Events:** 63 vs 98 p = 0.005 **CHD** RR:0.75 CI (0.60, 0.94) **Non-fatal MI or CHD deaths** RR: 0.73 CI (0.57, 0.94) **MI deaths:** RR: 0.57 CI (0.30-1.08) **Total CHD deaths:** RR: 0.80 (0.57, 1.13) **CHD death - sudden** (<1 hr) RR: 1.00 CI (0.56, 1.78) **CHD death - rapid** (1-24 hrs) RR: 0.87 CI (0.48, 1.56)		CI (0.37, 0.71) p < 0.001	

Table 136

<u>Mixed SBP and DBP targets</u>

Trial, year **Sample characteristics** **Sample size Duration** **Quality Rating**	**BP Goal Achieved BP** **Differences between groups**	**Overall Mortality**	**Coronary Heart Disease** (includes fatal MI, non- fatal MI, sudden death, or combinations)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal, or combination)	**Heart Failure** (includes fatal, non-fatal or combination)	**Primary Composite Outcomes**

SCOPE, 2003 Adults, ages 70 to 89, previously treated or untreated with SBPs of 160 to 179 mmHg and/or DBPs of 90 to 99 mmHg and MMSE scores of ≥ 24 N = 4964 Mean 3.7 years Fair *NOTE: all rates are treatment versus control with p = NR*	Goal: Not explicitly stated, drug titration began at SBP > 160 or DBP > 85 or 90 depending upon step <u>At start of t</u>rial Baseline SBP/DBP, mmHg: Txt: 166.0/90.3 Control: 166.5/90.4 <u>At mean 3.7 years</u> Difference in achieved SBP and DBP of treatment versus control, mmHg (95% CI) SBP: 3.2 (-4.4, -1.9) P <0.001 DBP: 1.6 (-2.1, -0.9) p <0.001	**Total mortality** Rate per 1000 py: 27.9 vs 29.0	**Non-fatal MI** Rate per 1000 py: 5.9 vs. 5.2 **All MI** Rate per 1000 py: 7.6 vs. 6.9 **Fatal MI** Rate per 1000 py: 1.9 vs. 2.0	**Non-fatal stroke** Risk reduction (CI): 27.8 (1.3, 47.2) **All stroke** Risk reduction (CI): 23.6 (-0.7, 42.1) **Fatal stroke** Rate per 1000 py: 2.6 vs. 2.8		**Major CV events composite of CV death, non-fatal stroke, and non-fatal MI** Risk reduction (CI): 10.9 (-6, 25.1)

STOP, 1991 Adults, ages 70 to 84 years, treated or untreated for hyper-tension, with SBPs of 180 to 230 and DBP ≥ 90 or DBPs of 105 to 120 irrespective of SBP during run-in N = 1,627 Mean 25 months Fair	SBP/DBP Goal: <160/95 mmHg <u>At start of trial</u> Baseline SBP/DBP, mmHg (SD): Txt: 195/102 (14/7) Control: 195/102 (14/7) <u>At 4 years followup</u> Achieved SBP/DBP (SD) Txt: 166/85 (21/10) Placebo: 193/95 (20/11) p = NR SBP/DBP change from baseline Txt: -29/-17 Placebo: -2/-7 p = NR	**Total deaths** (irrespective of preceding non-fatal endpoint): RR (CI): 0.57 (0.37, 0.87)	**All MI** (first endpoint)**:** RR (CI): 0.87 (0.49,1.56) **Fatal MI** (first endpoint)**:** RR (CI): 0.98 (0.26, 3.66)	**All stroke (first endpoint):** **RR (CI): 0.53 (0.33, 0.86)** **Fatal stroke (first endpoint):** **RR (CI): 0.24 (0.04, 0.91)**	**CHF endpoint**s: 19 vs. 39 (txt vs placebo) p = NR	**Total primary endpoint** [stroke, MI, other CV death] (first to happen)**:** RR (CI): 0.60 (0.43, 0.85)

Coope and Warrender, 1986 Adults, age 60 to 79, SBPs ≥ 170 or DBP ≥ 105 mmHg N = 884 Mean 4.4 years Good	Goal: Not explicitly stated, however additional therapy added if at the end of 3 months, SBP > 170 or DBP >105 mmHg <u>At start of trial</u> Baseline SBP/DBP, mmHg (SD): Txt: 196.2/99.7 (16.7/12.0) Control: 196.1/98.0 (15.6/11.8) <u>During follow-up</u> Achieved SBP: NR SBP/DBP achieved differences between groups, mmHg 18/11 p = NR Reduction in SBP/DBP mmHg Txt: NR Control: 16/10 p = NR <u>At 1 year</u> % of patients at or below SBP 170 mmHg Txt: 36% Control: 20% p = NR	**All deaths** Rate of txt/rate of control (95% CI): 0.97 (0.70, 1.42) p = NS	**Fatal coronary attacks** Rate of txt/rate of control (95% CI): 1.00 (0.58, 1.71) p = NS **Non-fatal coronary attacks** Rate of txt/rate of control (95% CI): 1.11 (0.46, 2.68) p = NS **All coronary attacks** Rate of txt/rate of control (95% CI): 1.03 (0.63, 1.63) p = NS	**Fatal stroke** **Rate of txt/rate of control (95% CI):** **0.30 (0.11, 0.84)** **p < 0.025** **All stroke** **Rate of txt/rate of control (95% CI): 0.58 (0.35, 0.96)** **p < 0.03**	**Fatal ventricular failure** Rate of txt/rate of control (95% CI): 1.11 (0.28, 4.45) p = NS **Non-fatal ventricular failure** Rate of txt/rate ofcontrol (95% CI): 0.63 (0.35, 1.11) p = NS	

	<u>At 8 years</u> % of patients at or below SBP 170 mmHg Txt: 62% Control: 31% p = NR					

Table 137

Study details	n/Population	Comparison	Outcomes		Methodological
Wei 2013(90) Design: RCT OL, PG China Duration of follow-up: Mean 4 years	n= 724 n IT= 363 n ST=361 Mean age: IT: 76.6±4.6 ST: 76.5±4.5 Previous stroke: 6.6% Diabetes:23.3 % Smoking: 24.9% <u>Inclusion</u> *older than 70 years *classified as hypertensive, SBP ≥150 mmHg and/or diastolic BP (DBP) ≥90 mmHg or diagnosed with hypertension and currently receiving antihypertensive treatment. <u>Exclusion</u> Secondary hypertension, valvular	Target BP BP≤140/90 mmHg (IT) Vs Target BP≤150/90 mmHg (ST) *Randomized patients were started with single-drug treatment of an angiotensin-converting enzyme (ACE) inhibitor (benzene enalapril 10 mg/d), a b-blocker (bisoprolol 2.5–5 mg or metoprolol 50–100 mg/d), a*	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: no Personnel: no Assessors: yes Remarks on blinding method: PROBE study (blinded-endpoint assessment) FOLLOW-UP: Lost-to follow-up: 0.4% Drop-out and Exclusions: 2.1% • Described: yes • Balanced across groups: not reported ITT: Yes "An intent-to-treat analysis was performed to ensure that all study participants were followed until the conclusion of the study, irrespective of whether the participant was still receiving or complying with the treatment.
			Incidence of fatal/nonfatal stroke, acute myocardial infarction, and other cardiovascular deaths (sudden death and heart failure death) (PO)	**IT: 40/363 (11.0%)** **ST: 67/361 (18.6%)** **SS** **p=0.004**	
			All-cause mortality (SO)	**IT: 51/363 (14.0%)** **ST: 87/361 (24.1%)** **SS** **p=0.001**	
			Total stroke	**IT: 21/363** **ST: 36/361** **SS** **p=0.036**	
			All cardiovascular events	**IT: 40/363** **ST: 67/361** **SS** **p= 0.004**	
			Acute myocardial infarction	IT: 9/363 ST: 9/361 NS p= 0.991	
			Cardiovascular death	**IT: 25/363** **ST: 50/361** **SS** **p=0.002**	

	heart disease, chronic kidney dysfunction (serum creatinine ≥3.0 mg/dL), previous myocardial infarction or stroke in the past 6 months, New York Heart Association (NYHA) class III or higher congestive heart failure, echocardiography determining left ventricular ejection fraction (LVEF) <40%, hepatic dysfunction, autoimmune disorders, malignant tumor, Alzheimer's disease, and other noncardiovascular diseases potentially causing death before the end of the study.	*calcium channel blocker (CCB) (amlodipine 5–10 mg/d), or a diuretic (indapamide 1.5–2.5 mg/d). To achieve the target BP, 1, 2, or 3 additional antihypertensive drugs could be added stepwise. If quadruple antihypertensive therapy (CCB + b-blocker + ACE inhibitor + diuretics) failed to achieve the BP goal, increasing the dose of antihypertensive drugs was recommended.*			Participants who were lost to follow-up or died of other causes were censored and were also included in the final analyses for the actual follow-up period." SELECTIVE REPORTING: no Sponsor: Not reported

Table 138: IT=intensive therapy; ST= standard therapy

4.2.3.2 Summary and conclusions: treatment target in elderly people ≥60 years

More intensive versus less intensive blood pressure target (unspecified) in people aged ≥ 65 years			
Bibliography: BPLTTC 2008 (72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
CV events : stroke (non-fatal stroke or fatal), coronary heart disease (fatal or nonfatal including sudden death) and heart failure (causing death or resulting in admission to hospital).	190,605 (31studies)	RR 1.03 (95%CI 0.85 to 1.24) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 RCTs included were of low to high quality; the SR/MA itself was of moderate quality Consistency:ok Directness:ok Imprecision:-2 95%CI crosses both appreciable benefit and appreciable harm

Table 139

Blood pressure target <140mmHG versus > 140mmHg in elderly Japanese patients			
Bibliography: JATOS 2008(73)(a), VALISH trial 2010(83)(b)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4,320 (1study) 2y	a) RR 1.12 (95%CI 0.43 to 2.9) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 unclear allocation concealment Consistency:ok Directness:Japanese? Imprecision: wide CI
Cerebrovascular disease, cardiac and vascular disease and renal failure	4,320 (1study) 2y	a) RR 1.0 (95%CI0.74 to 1.33) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 Inadequate allocation concealment Consistency:ok Directness:Japanese? Imprecision:wide CI
Cardiovascular mortality, stroke, MI, unplanned CV hospitalization and renal dysfunction	3,260 (1 study) 3y	b) HR 0.89 (0.6 to 1.31) NS	⨁⨁⨁⊖ **MODERATE** Study quality:-1 Inadequate allocation concealment and blinding Consistency: ok Directness: Japanese? Imprecision:wide CI

Table 140

BP target ≤140/90 mmHg versus BP target ≤150/90 in hypertensive patients older than 70 years.			
Bibliography: Wei 2013(90)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Mortality	724 (1 study)	**<140: 51/363 (14.0%)** **<150: 87/361 (24.1%)** **SS** **p=0.001**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: ok Directness: Chinese population Imprecision: -1 unclear: no numerical values for risk; no confidence interval
Cardiovascular death	724 (1 study)	**<140: 25/363 (6.9%)** **<150: 50/361 (13.9%)** **SS** **p=0.002**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: ok Directness: Chinese population Imprecision: -1 unclear: no numerical values for risk; no confidence interval
Stroke	724 (1 study)	**<140: 21/363 (5.8%)** **<150: 36/361 (10.0%)** **SS** **p=0.036**	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: ok Directness: Chinese population Imprecision: -1 unclear: no numerical values for risk; no confidence interval
Cardiovascular events	724 (1 study)	**<140: 40/363 (11.0%)** **<150: 67/361 (18.6%)** **SS** **p= 0.004**	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear allocation concealment Consistency: ok Directness: Chinese population Imprecision: -1 unclear: no numerical values for risk; no confidence interval
Acute myocardial infarction	724 (1 study)	<140: 9/363 (2.5%) <150: 9/361 (2.5%) NS p= 0.991	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear allocation concealment Consistency: ok Directness: Chinese population Imprecision:-1 unclear: no numerical values for risk; no confidence interval

Table 141

The BPLTTC 2008(72) systematic review and meta-analysis included 31 RCTs with a total of 190,606 participants with hypertension. It was not clear if there was underlying diabetes or chronic kidney disease. A more intense BP target was compared to a less intense BP target, but the exact blood pressure value for the target was not specified. A distinction was made between participants <65years and participants ≥65 years. The quality of this SR/MA was reported by NICE 2011 to be moderate, mainly because of including low to high quality RCTs.

In hypertensive patients ≥65 years with uncomplicated hypertension, unspecified more intense BP lowering did not result in a statistically significant risk reduction **of cardiovascular events**(a composite of fatal and nonfatal stroke, coronary artery disease and heart failure), compared to unspecified less intense BP lowering.
GRADE: VERY LOW quality of evidence

JNC-8 conducted a systematic review that evaluated different hypertension treatment targets in primary uncomplicated hypertension. 8 of the included RCTs were conducted in patients aged ≥60y. One of these (HYVET) was conducted in patients aged ≥80 years. This trial will be discussed in the next chapter.

Out of the 7 RCTs in people ≥60y, 2 trials randomized its participants to different treatment targets.

The JATOS 2005(74) and 2008(73) study compared a blood pressure target of <140mmHg to a target of 140-160mmHg in 4320 elderly Japanese hypertensive patients (age 65-85years) with a systolic blood pressure ≥ 160mmHg. Follow up was respectively 12 months and 2 years.
No significant difference for **mortality** and **morbidity** (cerebrovascular disease, cardiac and vascular disease and renal failure) was observed at 2 years, when aiming for a blood pressure target of <140mmHg SBP compared to a target of 140-160mmHg SBP in elderly Japanese patients.
GRADE: MODERATE quality of evidence

The VALISH trial 2010(83) compared strict control <140mmHg versus moderate control (≥140 to <150 mmHg) in 3260 elderly Japanese patients (70-84 years old) with isolated systolic hypertension.
After a median study duration of 3 years, there was no significant difference between groups for reduction in a composite endpoint of **cardiovascular events** (including cardiovascular mortality, stroke, MI, unplanned CV hospitalization and renal dysfunction).
GRADE: MODERATE quality of evidence

Of the 7 RCTs in people ≥60y, 5 evaluated treatment versus no treatment for a set treatment target. As this is a very indirect way to assess the most appropriate treatment target, we will only describe these RCTs briefly, without rating the outcomes separately:
Syst-Eur 1997(52) compared treatment versus placebo at an SBP target of <150 mmHg in 4695 elderly people, with a median follow-up of 2 years. There was a significant decrease of the primary ouctome stroke in the treatment group.
SHEP 1991(17) compared treatment versus placebo in 4736 elderly people, with a mean follow-up of 4.5 years. The target for individuals with a baseline SBP of >180 mmHg was <160 mmHg. For those with an SBP of 160 -179 mmHg, the target was a reduction of at least 20 mmHg. There was a significant decrease in stroke rate in treated versus untreated people in this trial.
SCOPE 2003(91) compared treatment versus placebo in 4664 elderly people, with a mean follow-up of 3.7 years. The treatment target was not explicitly stated, but drug titration began at an SBP >160 mmHg or DBP >85-90 mmHg. There was no significant difference between treatment and no treatment for the primary outcome: a composite of cardiovascular death, non-fatal stroke and non-fatal myocardial infarction.
STOP 1991(61) compared treatment versus placebo at a BP target of <160/95 mmHg in 1627 elderly people, with a mean follow-up of 25 months. There was a significant decrease of the primary composite outcome: stroke, myocardial infarction and other cardiovascular death.
Coope and Warrender 1986(60) compared treatment versus no treatment in 884 elderly people, with a mean follow-up of 4.4 years. The treatment target was no explicitly stated, however, additional therapy was added if at the end of 3 months, SBP was >170mmHg or DBP was >105 mmHg. There was a significant decrease in stroke rate among treated versus untreated patients, but no difference in mortality or coronary attacks.

We found one additional RCT by Wei 2013(92)
In this open-label RCT in a relatively healthy Chinese population of 724 hypertensive patients older than 70, an intensive treatment target (BP ≤140/90 mmHg) was compared to a standard treatment target (≤150/90 mmHg).

In an elderly Chinese population, there was a significant decrease in **mortality, cardiovascular death**, **cardiovascular events** and **stroke** at a blood pressure target ≤140/90 mmHg, compared to a less strict target of ≤150/90 mmHg.
GRADE: LOW quality of evidence

In an elderly Chinese population, there was no significant difference of **acute myocardial infarction** at a blood pressure target ≤140/90 mmHg, compared to a less strict target of ≤150/90 mmHg.
GRADE: LOW quality of evidence

4.2.3.3 Clinical evidence profile: treatment target in elderly people ≥80 years

Study details	n/Population	Comparison	Outcomes		Methodological
Beckett, 2008 (63) HYVET Design: RCT (DB, PG) Duration of follow-up: median 1.8 y	n= 3845 AT= 1933 PL=1912 Mean age: 83.6 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1% Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 % Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined	Indapamide (sustained release, 1.5mg) (AT) Vs Placebo *At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.* Target: SBP <150 mmHg	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: 33.7 % • Described: yes • Balanced across groups: yes ITT: Yes
			Stroke (fatal and non-fatal) (PO)	AT: 51/1000 patient-years (12.4%) PL: 69/1000 patient-years (17.7%) HR: 0.70 (95%CI 0.49 to 1.01) NS p 0.06	
			Death from any cause (SO)	**AT: 196/1000 patient-years (47.2%)** **PL: 235/1000 patient-years (59.6%)** **HR:0.79 (95%CI 0.65 to 0.95)** **SS** **P: 0.02 in favour of AT**	
			Death from cardiovascular causes (SO)	AT: 99/1000 patient-years (23.9%) PL: 121/1000 patient-years (30.7%) HR: 0.77 (95%CI 0.60 to 1.01) NS P: 0.06	
			Death from cardiac causes (SO)	AT: 25/1000 patient-years (6.0%) PL: 33/1000 patient-years (8.4%) HR: 0.71 (95%CI 0.42 to 1.19) NS P: 0.19	
			Death from stroke (SO)	**AT: 27/1000 patient-years (6.5%)** **PL: 42/1000 patient-years (10.7%)** **HR: 0.61 (95%CI 0.38 to 0.99)** **SS**	

	as a sustained systolic blood pressure of 160 mm Hg). (At the start of the trial in 2000, the mean diastolic blood pressure while seated had to be 90 to 109 mm Hg, but in 2003 a protocol amendment relaxed this criterion to be under 110 mm Hg, allowing for the inclusion of patients with isolated systolic hypertension <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months,	DBP <80 mmHg		**P: 0.046 in favour of AT**	Data from patients were analyzed for the groups to which the patients were assigned, regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available. SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that
			Safety		
			Serious adverse events	**AT: 358/1933** **PL: 448/1912** **P: 0.001 in favour of AT**	
			Serious adverse events possibly due to trial medication	AT: 2 PL: 3	

	heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.				these centers failed to provide complete and accurate data. Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.

Table 142: AT= active treatment; PL= placebo

Study details	n/Population	Comparison	Outcomes subgroup analyses		Methodological
Beckett, 2014 (64) HYVET Design: Prespecified subgroup analysis (data from RCT (DB, PG))	n= 3845 AT= 1933 PL=1912 Mean age: 83.5±3.2 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1%	Indapamide (sustained release, 1.5mg) Vs Placebo *At each visit (or at the discretion*	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end
			Total mortality	Hazard ratio	
			Age • 80-84.9y • ≥85y	 **0.76 (95%CI 0.60 to 0.97)** 0.88 (95%CI 0.64 to 1.20)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.82 (95%CI 0.60 to 1.11) 0.83 (95%CI 0.62 to 1.12) 0.69 (95%CI 0.45 to 1.04)	
			Previous CVD • History of CVD	 0.76 (95%CI 0.48 to 1.21)	

Duration of follow-up: median 1.8 y	Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 % Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg). <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension,	*of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.* Target: SBP <150 mmHg DBP <80 mmHg	• No history of CVD	**0.81 (95%CI 0.66 to 0.99)**	points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: 33.7 % • Described: yes • Balanced across groups: yes ITT: Yes Data from patients were analyzed for the groups to which the patients were assigned, regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available.
			Cardiovascular mortality		
			Age • 80-84.9y • ≥85y	 0.75 (95%CI 0.55 to 1.05) 0.82 (95%CI 0.53 to 1.32)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.73 (95%CI 0.47 to 1.15) 0.93 (95%CI 0.62 to 1.45) 0.61 (95%CI 0.36 to 1.04)	
			Previous CVD • History of CVD • No history of CVD	 0.64 (95%CI 0.33 to 1.24) 0.81 (95%CI 0.61 to 1.09)	
			Stroke (PO)		
			Age • 80-84.9y • ≥85y	 0.70 (95%CI 0.46 to 1.06) 0.59 (95%CI 0.27 to 1.29)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.82 (95%CI 0.46 to 1.48) 0.63 (95%CI 0.36 to 1.12) 0.54 (95%CI 0.24 to 1.22)	
			Previous CVD • History of CVD • No history of CVD	 0.76 (95%CI 0.33 to 1.78) 0.67 (95%CI 0.45 to 1.01)	
			Heart failure		
			Age • 80-84.9y • ≥85y	 **0.28 (95%CI 0.15 to 0.51)** 0.62 (95%CI 0.26 to 1.49)	

	hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.		Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 **0.21 (95%CI 0.09 to 0.51)** **0.46 (95%CI 0.22 to 0.97)** 0.59 (95%CI 0.19 to 1.79)	SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that these centers failed to provide complete and accurate data. Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.
			Previous CVD • History of CVD • No history of CVD	 0.45 (95%CI 0.14 to 1.43) **0.34 (95%CI 0.20 to 0.59)**	
			Cardiovascular events		
			Age • 80-84.9y • ≥85y	 **0.64 (95%CI 0.49 to 0.83)** 0.75 (95%CI 0.50 to 1.12)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 **0.65 (95%CI 0.46 to 0.93)** 0.75 (95%CI 0.53 to 1.06) **0.58 (95%CI 0.36 to 0.94)**	
			Previous CVD • History of CVD • No history of CVD	 0.75 (95%CI 0.44 to 1.25) **0.66 (95%CI 0.52 to 0.84)**	

Table 143: AT= active treatment; PL= placebo

4.2.3.4 Summary and conclusions: treatment target in elderly people ≥80 years

Antihypertensive treatment versus no treatment in hypertensives ≥80 years. Treatment target <150/80 mmHg.			
Bibliography: Beckett, 2008(63)(HYVET)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	3845 (1 study)	**HR:0.79 (95%CI 0.65 to 0.95) SS In favour of treatment**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency:-1 only one study Directness:-1 Relatively healthy population (no heart failure, dementia or nursing care) Imprecision: ok
Stroke	3845 (1 study)	HR: 0.70 (95%CI 0.49 to 1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency:-1 only one study Directness:-1 Relatively healthy population (no heart failure, dementia or nursing care) Imprecision: ok
Cardiovascular mortality	3845 (1 study)	HR: 0.77 (95%CI 0.60 to 1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency:-1 only one study Directness:-1 Relatively healthy population (no heart failure, dementia or nursing care) Imprecision: ok
Stroke mortality	3845 (1 study)	**HR: 0.61 (95%CI 0.38 to 0.99) SS In favour of treatment**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency:-1 only one study Directness:-1 Relatively healthy population (no heart failure, dementia or nursing care) Imprecision: ok
Serious adverse events	3845 (1 study)	**Treatment: 358/1933 Placebo: 448/1912 P: 0.001 In favour of treatment**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency:-1 only one study Directness:-1 Relatively healthy population (no heart failure, dementia or nursing care) Imprecision: ok

Table 144

The HYVET trial included 3845 patients aged aged ≥80 years, with a sustained SBP ≥ 160mmHg. (Inclusion criteria for diastolic blood pressure were modified during recruitment admitting also patients with isolated systolic hypertension). Patients were given indapamide or placebo and were followed for a median of 1.8 years, to a target of SBP <150 mmHg and DBP <80 mmHg.

The primary endpoint was **stroke** (fatal and non-fatal), which did not yield a statistically significant difference between treatment and placebo-group.

In this trial, **all-cause mortality** and **death from stroke** (which were secondary endpoints) are statistically significantly lower with treatment compared to placebo.

Information from a prespecified subgroup analysis from the HYVET trial (Beckett 2014(64)) suggests that for ages ≥85y, compared to ≥80 years, the benefit of treatment on total mortality, heart failure and cardiovascular events may be attenuated. In further subgroup analyses, no clear relationship has arisen between initial SBP (devided into strata of 160-179; 170-179 and ≥180 mmHg) and outcomes. Lack of statistical power diminishes the reliability of these results.

Antihypertensive treatment to a target of <150/80 mmHg in people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, resulted in a decrease of **mortality rate**, *stroke mortality* and **serious adverse events**, compared to placebo.
GRADE: LOW quality of evidence

Antihypertensive treatment to a target of <150/80 mmHg in people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, did not result in a decrease of **stroke** rate, or **cardiovascular mortality**, compared to placebo.
GRADE: LOW quality of evidence

4.2.3.5 Observational data: treatment target in elderly people ≥80 years

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved BPs			Best Target BP (authors' conclusions)
Denardo 2010(81) A-priori subanalysis of RCT (INVEST) Treated as observational study as not using randomised groups	22,576	HT	Clinic	Overall mean: 149.5/86.3	24 months	Mortality, MI stroke	Stratified into age-groups and SBP / DBP nadirs.*			J-shaped relationship (among each age-group) with on-treatment SBP and DBP and clinical end-points / events. SBP at HR nadir increased with increasing age – highest for the very old (140 mmHg). DBP at HR nadir was only slightly lower for the very old (70 mmHg). Therefore optimal management may involve a higher target SBP and lower target DBP for very old people (≥80 years) vs other age-groups.
							Age	BP nadirs		
								SBP	DBP	
							<60	110	75	
							60-<70	115	75	
							70-<80	135	75	
							≥80	140	70	

Table 145

4.2.3.6 Summary and conclusions of observational data: treatment target in elderly people ≥80 years

Denardo 2010(81)
This prespecified subgroup analysis of an RCT in 22576 hypertensive patients evaluated the association between achieved blood pressure and the risk of a **composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke**, stratified into age-groups. This association followed a J-curve. The nadir blood pressure, above and below which the risk of the composite endpoint was increased, was 140/70 mmHg in elderly people aged ≥80. This SBP was higher, and the DBP slightly lower compared to the nadir blood pressures in younger age groups.

GRADE: LOW quality of evidence

4.2.4 Type 2 diabetes

4.2.4.1 Clinical evidence profile: treatment target in adults with type 2 diabetes

Meta-analysis:

Inclusion criteria: RCT's, trials where individuals were randomized to a 'lower' compared with a 'standard' target blood pressure. adults with diabetes mellitus and elevated blood pressure, documented in a standard way on at least two occasions, or already receiving treatment for elevated blood pressure. Trials were not limited by any concomitant disease, other factor or baseline cardiovascular risk. There was no language restriction.

Search strategy: The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for related reviews. The following electronic databases were searched for primary studies: the Hypertension Group Specialised Register (January 1946- October 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 9), MEDLINE (January 1946 - October 2013), EMBASE (January 1974 - October 2013) and ClinicalTrials.gov. The electronic databases was searched using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision maximizing version (2008 revision) with selected MeSH terms and free-text terms relating to diabetes and hypertension. The MEDLINE search strategy (Appendix 1) was translated into EMBASE (Appendix 2), CENTRAL (Appendix 3), The Hypertension Group Specialised Register (Appendix 4), and ClinicalTrials.gov (Appendix 5) using the appropriate controlled vocabulary as applicable. The latest search date for all databases was October 2013.

Assessment of quality of included trials: yes, Two review authors independently performed the assessment of risk of bias for each study, using the six domains of the 'Risk of bias' Tool according to the method described in the Cochrane Handbook for Systematic Reviews of Interventions.
ITT analysis: yes
Other methodological remarks:
The main potential bias is due to the fact that studies were not blinded. Trials cannot be blinded to blood pressure targets because the treating physicians must know the target to which each participant has been assigned in order to make the proper adjustment in the therapy to achieve the blood pressure goal.

Table 146

Ref	Comparison	N/n	Outcomes	Result

Arguedas 2013(93) Design: Search date: October 2013 N=5 n=7314	Lower targets (LT)(<130/85 mmHg) versus standard targets (ST) (<140-160/90-100 mmHg)	N= 1 n= 4733 ACCORD BP 2010	Total mortality (PO)	<u>Systolic BP target:</u> LT: 150/2363 ST: 144/2371 RR: 1.05 (95% (CI) 0.84 to 1.30) NS, p = 0.69
		N= 4 n= 2580 ABCD-2V 2006, ABCD-H 1998, ABCD-N 2002, HOT 1998		<u>Diastolic BP target:</u> LT: 75/1540 ST: 72/1040 RR: 0.73 (95% CI 0.53 to 1.01) NS, p= 0.05
		N= 1 n= 4733 ACCORD BP 2010	Cardiovascular mortality (PO)	<u>Systolic BP target:</u> LT: 60/2363 ST: 58/2371 RR: 1.04 (95% CI 0.73 to 1.48) NS, p= 0.84
		N= 3 n= 2451 ABCD-H 1998, ABCD-N 2002, HOT 1998		<u>Diastolic BP target:</u> LT: 47/1474 ST: 41/977 RR: 0.73 (95% CI 0.53 to 1.01) NS, p = 0.05
		N= 1 n= 4733 ACCORD BP 2010	Myocardial infarction	<u>Systolic BP target:</u> LT: 133/2363 ST: 151/2371 RR: 0.88 (95% CI 0.71 to 1.11) NS, p = 0.28
		N= 3 n= 2451 ABCD-H 1998, ABCD-N 2002, HOT 1998		<u>Diastolic BP target:</u> LT: 50/1474 ST: 43/977 RR: 0.95 (95% CI 0.64 to 1.40) NS, p = 0.79

		N= 1 n= 4733 ACCORD BP 2010	Stroke	**<u>Systolic BP target:</u>** LT: 36/2363 ST: 62/2371 **RR 0.58 (95% CI 0.39 to 0.88)** **SS, p = 0.009**
		N= 3 n= 2451 ABCD-H 1998, ABCD-N 2002, HOT 1998		<u>Diastolic BP target:</u> LT: 38/1474 ST: 39/977 RR: 0.67 (95%CI 0.42 to 1.05) NS, p = 0.08
		N= 1 n= 4733 ACCORD BP 2010	Congestive heart failure	<u>Systolic BP target:</u> LT: 83/2363 ST: 90/2371 RR: 0.93 (95% CI 0.69 to 1.24) NS, p= 0.60
		N= 2 n= 950 ABCD-H 1998, ABCD-N 2002		<u>Diastolic BP target:</u> LT: 21/474 ST: 20/476 RR: 1.06 (95% CI 0.58 to 1.92) NS, p= 0.86
		N= 1 n= 4733 ACCORD BP 2010	End-stage renal disease	<u>Systolic BP target:</u> LT: 59/2363 ST: 58/2371 RR: 1.02 (95% CI 0.71 to 1.46) NS, p= 0.84
		N= 0 n= 0		<u>Diastolic BP target:</u> Not reported
		N= 1 n= 4733 ACCORD BP 2010	Total serious adverse events (PO) (total serious morbidity and mortality)	<u>Systolic BP target:</u> LT: 518/2363 ST: 513/2371 RR 1.01: (95% CI 0.91 to 1.13) NS, p= 0.81

		N= 0 n= 0		Diastolic BP target: Not reported
		N= 1 n= 4733 ACCORD BP 2010	All other serious adverse events (excluding myocardial infarction, stroke, congestive heart failure and end-stage renal failure)	Systolic BP target: LT: 77/2363 ST: 30/2371 RR 2.58 (95% CI 1.70 to 3.91) SS, p < 0.00001
		N= 0 n= 0		Diastolic BP target: Not reported

Table 147: LT= Lower targets; ST= standard target

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
ABCD-2V 2006(94) RCT, OL	129	Type-2 diabetic participants, 40 to 81 years of age, with a systolic BP < 140 mmHg, a diastolic BP between 80 and 90 mmHg, and without evidence of overt albuminuria (< 200µg/min). Exclusion criteria included pregnant or lactating women, **need for any antihypertensive medications,** documented myocardial infarction or cerebrovascular accident within the past 6 months, severe peripheral vascular disease, history of bilateral renal artery stenosis or stenosis in a solitary kidney, evidence of severe liver disease, hyperkalemia, or history of active cancer.	Mean 1.9y	Intensive BP control aiming for a diastolic BP goal of 75 mmHg versus moderate BP control aiming to maintain DBP between 80 and 90 mmHg.	ALLOCATION CONC: Unclear: not reported RANDO: Unclear: not reported BLINDING : Participants: no/ personnel:no/ assessors: yes Unclear: blinding of participant and investigator not possible FUNDING: Industry funded NOTE: trial was terminated early because of funding restraints (unclear risk of attrition bias)
ABCD-H 1998(95)	472	Ages 40 to 74 years, with type 2	5 years	"Intensive" treatment with	ALLOCATION CONC:

RCT, OL		diabetes mellitus and a diastolic blood pressure equal to or higher than 90 mm Hg were included. Exclusion criteria included myocardial infarction or a cerebrovascular accident within the previous 6 months, coronary artery bypass surgery within the previous 3 months, unstable angina pectoris within the previous 6 months, congestive heart failure NYHA class III or IV, a demonstrated absolute need for ACE inhibitors or CCB, and a serum creatinine level > 3 mg/dL		a diastolic blood pressure goal of 75 mmHg Versus "Moderate" treatment with a diastolic blood pressure goal of 80-89 mmHg.	Unclear: not reported RANDO: Inadequate: Participants assigned to "moderate" treatment had a greater prevalence of established vascular disease, which became significant when combined with ABCD-N. BLINDING : Participants: no/ personnel:no/ assessors: yes Unclear: blinding of participant and investigator not possible FOLLOW-UP: data on losses to follow-up was not reported (high risk of attrition bias) FUNDING: Not reported Not all outcomes reported
ABCD-N 2002(96) RCT, OL	480	aged 40 - 74 years, with type 2 diabetes mellitus were included. All of them had a baseline diastolic blood pressure between 80 and 89 mmHg and were not receiving antihypertensive medications at the randomization visit The main exclusion criteria were: myocardial infarction or cerebrovascular accident within the previous 6 months, coronary artery bypass surgery within the previous 3	5 years	'intensive' treatment: goal: to achieve a decrease of 10 mmHg below baseline in diastolic blood pressure (i.e. 70 - 79 mmHg) Versus 'moderate' treatment : goal: to maintain a diastolic blood pressure between 80 and 89 mmHg	ALLOCATION CONC: Unclear: not reported RANDO: Inadequate: Participants assigned to "moderate" treatment had a greater prevalence of established vascular disease, which became significant when combined with ABCD-N. BLINDING : Participants: no/ personnel:no/ assessors: yes Unclear: blinding of participant and

		months, unstable angina pectoris within the previous 6 months, congestive heart failure NYHA class III or IV, a demonstrated absolute need for ACE inhibitors or CCB, and a serum creatinine level > 3 mg/dl			investigator not possible FOLLOW-UP: data on losses to follow-up was not reported (high risk of attrition bias) FUNDING: Not reported Not all outcomes reported
ACCORD BP 2010(97) RCT, OL	4733	Type 2 diabetes mellitus; 40 years of age or older with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Participants with a systolic blood pressure between 130 and 180 mmHg who were taking 3 or fewer antihypertensive medications and who had the equivalent of a 24-hour protein excretion rate of less than 1.0 g were also eligible for the blood pressure trial Exclusion criteria included a body mass index of more than 45, a serum creatinine level of more than 1.5 mg per deciliter, and other serious illness	Mean 4.7 years	Intensive therapy: target systolic blood pressure < 120 mmHg Versus standard therapy: target systolic blood pressure< 140 mmHg	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants: no/ personnel: no/ assessors: yes Unclear: blinding of participant and investigator not possible FUNDING: National Heart, Lung, and Blood Institute from the United States
HOT 1998(98)	18790 (1501	Patients with elevated blood pressure, aged 50 - 80 years. Of these, 1501	Average 3.8 years	Participants were randomly assigned to one of 3	ALLOCATION CONC: Unclear; subgroup analysis

RCT, OL	included in Cochrane analysis)	participants had diabetes at baseline and constitute the population included in this analysis. Baseline diastolic blood pressure between 100 mmHg and 115 mmHg on 2 occasions, at least 1 week apart, was an inclusion criterion. The main exclusion criteria were malignant hypertension, secondary hypertension, diastolic blood pressure > 115 mmHg, stroke or myocardial infarction within 12 months prior to randomization, decompensated congestive heart failure, other serious concomitant diseases which could affect survival during the next 2 - 3 years, participants who required a beta-blocker, ACE inhibitor or diuretic for reasons other than hypertension, participants who required antiplatelet or anticoagulant therapy, and insulin-treated diabetics.		diastolic blood pressure target groups: ≤ to 90 mmHg, ≤ 85 mmHg or ≤ 80 mmHg	RANDO: Unclear; subgroup analysis BLINDING : Participants: no/ personnel: no/ assessors: yes Unclear: blinding of participant and investigator not possible FOLLOW-UP: Data on losses to follow-up was not reported ITT:yes/no ('author's definition') FUNDING: Industry funded Note: Data on participants with diabetes represent a subgroup analysis of the entire HOT trial. The baseline characteristics in the subgroup of participants with diabetes are unknown, and therefore an unbalance at baseline cannot be ruled out.

Table 148

Author's conclusions:

At the present time the best available evidence from randomized controlled trials (RCTs) does not support blood pressure (BP) targets lower than 140/90 mmHg in people with elevated blood pressure and diabetes. This review analyzed lower systolic and diastolic blood pressure (SBP,DBP) targets separately,with similar findings for both targets. The isolated small reduction in stroke associated with a lower SBP targetmust be weighed against a larger increase in serious adverse events.

Therefore, the lower target for blood pressure recommended for people with diabetes in many clinical guidelines is not supported by evidence from randomized controlled trials.

Trial, year Sample characteristics Sample size Duration Quality Rating	**BP Goal Baseline BP Achieved BP Differences between groups**	**Overall Mortality**	**Coronary Heart Disease** (includes fatal MI, non- fatal MI, sudden death, or	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal, or combination)	**Heart Failure** (includes fatal, non-fatal or combination)	**Primary Composite Outcomes**	**Kidney Outcomes**
Trials with Systolic Goals							

SHEP, 1996(99) Adults, ages ≥ 60 years, SBPs 160- 219 and DBPs of < 90 mmHg N = 4,736 in overall trial population; **583 with diabetes at baseline. This exhibit represents only the diabetes subgroup.** Mean 4.5 years Good (primary paper); Fair (diabetes subgroup analysis). Subgroup analysis downgraded to fair based on reduced power due to	SBP Goal: • For individuals with SBPs of >180 mmHg: Goal was SBP <160 • For those with SBPs of 160-179: goal was reduction of at least 20 mmHg in SBP <u>At start of trial</u> For diabetes subpopulation: Baseline SBP, mmHg (SD): Active: 170.2 (9.2) Placebo: 170.2 (9.2) <u>During follow-up</u> For diabetes subpopulation, SBP difference between txt and placebo, mmHg: 9.8 p=NR Achieved BP: NR for diabetes subpopulation	**All cause mortality** RR (95% CI): 0.74 (0.46, 1.18) p=NR	**Non-fatal MI and fatal CHD** RR (95% CI): 0.46 (0.24, 0.88) p=NR	**Non-fatal and fatal strokes** RR (95% CI): 0.78 (0.45, 1.34) p=NR			

Syst-Eur, 1999(100) Adults, ages ≥ 60 years, SBPs 160-219 and DBPs < 95 mmHg N = 4,695 in overall trial population; **492 with diabetes at baseline. This exhibit represents only the diabetes subgroup.** Median 24 months Good (primary paper); Fair (diabetes subgroup analysis). Diabetes subgroup analysis downgraded to fair because the analysis was not prespecified and there was reduced power due	SBP Goal: <150 and decrease SBP by ≥ 20 mmHg At start of trial NR for those with diabetes, Full sample presented below: Baseline SBP, mmHg (SD) Txt: 173.8 (6.7) Placebo: 173.9 (10.1) At 2 years Achieved SBP: NR for diabetes subpopulation (NR as numerical values for full sample though achieved results are graphically illustrated in a figure demonstrating that txt groups had consistently lower SBPs and DBPs versus placebo from year 1 through year 4) Mean fall in SBP/DBP for diabetes subpopulation, mmHg (SD) Txt: 22.1/6.8 (14.5/8.2) Placebo: 13.5/2.9 (16.5/7.8) p = NR SBP/DBP difference between active and placebo groups in patients with	**Overall mortality:** Benefit of treatment* (95% CI): 41% (-9 to 69) p = 0.09 *(p for interaction between diabetes status and treatment group = 0.04)* *Benefit of treatment = % reduction in event rate for active txt group	**Fatal and nonfatal cardiac events:** Benefit of treatment (95% CI): 57% (-6 to 82) p=0.06 *(p for interaction between diabetes status and treatment group = 0.12)*	**Fatal and nonfatal stroke** Benefit of treatment (95% CI): 69% (14 to 89) p=0.02 *(p for interaction between diabetes status and treatment group = 0.13)*			

to a small sample of patients with diabetes at baseline.	diabetes, mmHg 8.6/3.9 p for difference in SBP 0.40 p for difference in DBP 0.44						
Trials with Mixed Goals							

UKPDS, 1998(101) Adults, ages 25 to 65, with newly diagnosed diabetes and SBP/DBPs ≥ 150/85 for those receiving anti-HTN, or ≥ 160/90 for those not previously receiving anti-HTN, and fasting plasma glucose > 6 mmol/l N: 1,148 Mean 8.4 years Fair	SBP/DBP Goal: Tight control: < 150/85 Less tight control: < 180/105 mmHg At start of trial Baseline SBP/DBP, mmHg (SD): Tight control: 159/94 (20/10) Less tight: 160/94 (18/9) At 9 years Achieved SBP, mmHg (SD) Tight control: 144/ 82 (14/7) Less tight control: 154/87 (16/7) p < 0.0001/ p < 0.0001 SBP change, mmHg Tight: -15 Less tight: -6 p=NR DBP change, mmHg Tight: -12 Less tight: -7 p=NR	**All cause mortality** RR (95% CI): 0.82 (0.62, 1.08) p = 0.17	**MI** RR (95% CI): 0.79 (0.59, 1.07) p = 0.13 **Sudden death** RR (99% CI): 1.39 (0.31, 6.26) p = 0.57	**Stroke** RR (95% CI): 0.56 (0.35, 0.89) p = 0.013	**HF** RR (99% CI): 0.44 (0.20, 0.94) p = 0.0043	**Any DM related endpoint** RR (95% CI): 0.76 (0.62, 0.92) p = 0.0046 *[Note: includes sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction]* **Death related to DM** RR (95% CI): 0.68 (0.49, 0.94) p = 0.019 *[Note: includes sudden death or death due to stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia]*	**Death from renal failure** RR (99% CI): 0.35 (0.03 to 3.66) p=0.23 **Renal failure** RR (99% CI): 0.58 (0.15-2.21) p= 0.29

Table 149

4.2.4.2 Summary and conclusions: treatment target in adults with type 2 diabetes

Lower targets (LT)(<130/85 mmHg) versus standard targets (ST) (<140-160/90-100 mmHg) in people with diabetes			
Bibliography: Cochrane Arguedas 2013(93) Including 5 RCTs: ABCD-2V 2006(94), ABCD-H 1998(95), ABCD-N 2002(96), ACCORD BP 2010(97), HOT 1998(98).			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4733 (1 study) 4.7y	SBP RR: 1.05 (95% (CI) 0.84 to 1.30) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: only one study Directness: ok Imprecision: confidence interval includes a 25% increase
	2580 (4 studies) 1.9-5y	DBP RR: 0.73 (95% CI 0.53 to 1.01) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: Inadequate randomization, no blinding, subgroup analysis, early termination Consistency: ok Directness: ok Imprecision: ok
Cardiovascular mortality	4733 (1 study) 4.7y	SBP RR: 1.04 (95% CI 0.73 to 1.48) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: only one study Directness: ok Imprecision: CI includes both appreciable benefit and harm
	2451 (3 studies) 3.8-5y	DBP RR: 0.73 (95% CI 0.53 to 1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: Inadequate randomization, no blinding, subgroup analysis Consistency: ok Directness: ok Imprecision: ok
Myocardial infarction	4733 (1 study) 4.7y	SBP RR: 0.88 (95% CI 0.71 to 1.11) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: only one study Directness: ok Imprecision: ok
	2451 (3 studies) 3.8-5y	DBP RR: 0.95 (95% CI 0.64 to 1.40) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: Inadequate randomization, no blinding, subgroup analysis Consistency: ok Directness: ok Imprecision: CI includes both appreciable benefit and harm
Stroke	4733 (1 study) 4.7y	SBP **RR 0.58 (95% CI 0.39 to 0.88) SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: only one study Directness: ok Imprecision: ok
	2451 (3 studies) 3.8-5y	DBP RR: 0.67 (95%CI 0.42 to 1.05) NS	⊕⊕⊖⊖ **LOW** Study quality: Inadequate randomization, no blinding, subgroup analysis

			Consistency: ok Directness: ok Imprecision:
Congestive heart failure	4733 (1 study) 4.7y	SBP RR: 0.93 (95% CI 0.69 to 1.24) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: only one study Directness: ok Imprecision: CI includes both appreciable benefit and harm
	950 (2 studies) 5y	DBP RR: 1.06 (95% CI 0.58 to 1.92) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: Inadequate randomization, no blinding Consistency: ok Directness: ok Imprecision: CI includes both appreciable benefit and harm
End-stage renal disease	4733 (1 study) 4.7y	SBP RR: 1.02 (95% CI 0.71 to 1.46) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: only one study Directness: ok Imprecision: CI includes both appreciable benefit and harm
Total serious adverse events (total serious morbidity and mortality)	4733 (1 study) 4.7y	SBP RR 1.01: (95% CI 0.91 to 1.13) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: Only one RCT Directness: ok Imprecision: ok
All other serious adverse events (excluding myocardial infarction, stroke, congestive heart failure and end-stage renal failure)	4733 (1 study) 4.7y	**SBP** **RR 2.58 (95% CI 1.70 to 3.91)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: only one study Directness: ok Imprecision: ok

Table 150

In this Cochrane meta-analysis of 5 RCT's, a lower BP target (defined as <130/85 mmHg) was compared to standard targets (defined as <140-160/90-100 mmHg) in people with diabetes. Outcomes for systolic and diastolic targets were calculated separately. Included patients were 40 to 81 years old. Follow-up in studies varied from 1.9 to 5 years. Only one study evaluated systolic blood pressure targets. The four studies that evaluated diastolic blood pressure targets had some serious methodological flaws, such as inadequate methods of randomization and incomplete reporting of outcome data, which limits our confidence in their results.

Three other MA's (Bangalore 2011(102), Reboldi 2011(103), Mcbrien 2012(104)) have evaluated similar questions, but have not been chosen for this review because they have either evaluated achieved rather than targeted BP(102), because they have grouped SBP and DBP targets together(104), or because targets that are now considered quite high (<150/85) were grouped into the "intensive target" group(103). Even so, these MA's show similar results to those of the Cochrane MA.

The systematic review by JNC-8 included three more (older) studies (SHEP 1996(99), Syst-Eur 1999(100), UKPDS 1998(101)) that evaluated BP targets in diabetic patients. However, they evaluated BP targets that would be considered too high by today's standards (SBP <150- <160) and as such were not reported in detail in this document.

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease mortality, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower DBP target (<85 mmHg) does not significantly decrease mortality, compared to a standard DBP target (<90-100 mmHg).
GRADE: VERY LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease cardiovascular mortality, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower DBP target (<85 mmHg) does not significantly decrease cardiovascular mortality, compared to a standard DBP target (<90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease myocardial infarction rate, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: MODERATE quality of evidence

In hypertensive people with diabetes, a lower DBP target (<85 mmHg) does not significantly decrease myocardial infarction rate, compared to a standard DBP target (<90-100 mmHg).
GRADE: VERY LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) significantly decreases stroke rate, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: MODERATE quality of evidence

In hypertensive people with diabetes, a lower DBP target (<85 mmHg) does not significantly decrease stroke rate, compared to a standard DBP target (<90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease congestive heart failure rate, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower DBP target (<85 mmHg) does not significantly decrease congestive heart failure rate, compared to a standard DBP target (<90-100 mmHg).
GRADE: VERY LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease the rate of end stage renal disease, compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) does not significantly decrease total serious adverse events (total serious morbidity and mortality), compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: LOW quality of evidence

In hypertensive people with diabetes, a lower SBP target (<130 mmHg) significantly increases all other serious adverse events (excluding myocardial infarction, stroke, congestive heart failure and end-stage renal failure), compared to a standard SBP target (<140-160/90-100 mmHg).
GRADE: MODERATE quality of evidence

4.2.4.3 Observational data: treatment target in adults with type 2 diabetes

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**
Cooper-DeHoff 2010 Post-hoc analysis of RCT (INVEST) Treated as observational study as not using randomised groups	6400 (of 22576 in RCT)	HT, ≥50 years, Diabetes and coronary artery disease Treatment target in study: <130/<85	Clinic	Not reported for total subgroup	16893 patient-years	All-cause death, nonfatal MI, or nonfatal stroke	Categorized into 3 groups by average SBP: Tight control:<130 mmHg; Usual control= 130-<140 mmHg; Uncontrolled: >140 mmHg	Decreasing systolic BP to lower than 130 mmHg in patients with diabetes and CAD was not associated with further reduction in morbidity beyond that associated with systolic BP lower than 140 mmHg, and, in fact, was associated with an increase in risk of all-cause mortality.

Table 151

Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HR versus reference : 130-<140 mmHg**
Cooper-DeHoff 2010	First occurrence of all-cause death, nonfatal MI or nonfatal stroke (PO)	<130 : 1.11 (0.93 to 1.32) 130-<140 : 1 **>140 : 1.46 (1.25 to 1.71)**
	Mortality	<130 : 1.20 (0.99-1.45) 130-<140 : 1 >140 : Not reported
	Mortality (extended follow-up analysis (5 years after close of INVEST))	**<130 : 1.15 (1.01-1.32)** 130-<140 : 1 >140 : Not reported

Table 152

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**
Vamos 2012 Prospective cohort study	126092	Adults, newly diagnosed with type 2 diabetes, HT (43.6%) and NT	Clinic	Mean +/- 146/83 mmHg	Median 3.5 years	All-cause mortality	Categorized by average SBP and DBP: Tight control: SBP<130; DBP <80 Usual control: SBP 130 to <140; DBP 80 to <85 Uncontrolled: SBP ≥140; DBP ≥85 Tight and uncontrolled were further categorized in 10 and 5 mmHg segments, resulting in 7 groups.	Blood pressure below 130/80 mm Hg was not associated with reduced risk of all cause mortality in patients with newly diagnosed diabetes, with or without known cardiovascular disease. Low blood pressure, particularly below 110/75 mm Hg, was associated with an increased risk for poor outcomes.

Table 153

Study	Outcome	HR (95% CI) for BP measurement Adj. HR versus reference : SBP 130-139 and DBP 80-84
Vamos 2012	All-cause mortality	SBP **<110 : HR= 2.56 (1.89 to 3.47)** **110-119: HR= 1.47 (1.22 to 1.76)** 120-129: HR= 1.08 (0.93 to 1.25) 130-139: HR=1 140-149: HR= 0.89 (0.79 to 1.00) 150-159: HR= 1.01 (0.88 to 1.15)

		≥160: HR= 1.09 (0.95 to 1.25) DBP **<70: HR= 1.59 (1.41 to 1.80)** **70-74: HR= 1.21 (1.07 to 1.37)** 75-79: HR= 0.89 (0.79 to 1.00) 80-84: HR=1 85-89: HR= 1.01 (0.88 to 1.14) 90-94: HR= 0.96 (0.82 to 1.13) ≥95: HR= 1.18 (0.98 to 1.43)

Table 154

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Sundstrom 2013(66) Analysis of data from retrospective cohort study (ROSE)	34009	Primary care Type 2 diabetes >35y (mean age 64y) No cardiovascular disease HT and NT Treated and untreated	Median 4.5 y	Risk of developing events with different baseline SBP and DBP values; in people with and without antihypertensive drug use	Cardiovascular events and mortality	SBP <130 130-140 140-149 149-160 >160 DBP <73 73-78 78-81 81-87 >87	In a large primary care-based sample of patients with type-2 diabetes, associations of SBP and DBP with risk of major cardiovascular events and mortality were U-shaped. The lowest risk of cardiovascular events was observed at a SBP of 135–139mmHg and a DBP of 74–76mmHg, and the

							lowest mortality risk at a SBP of 142–150mmHg and a DBP of 78–79 mmHg, in both antihypertensive drug-untreated and drug-treated persons.

Table 155

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP)** **Adj. HRs versus reference SBP (<130 mmHg) or DBP (<73 mmHg) in people with antihypertensive drug use**
Sundstrom 2013	Cardiovascular events (composite of nonfatal or fatal acute MI, heart failure,stroke or cardiovascular mortality)	SBP <130: HR=1 130-140: HR= 0.94 (0.76 to 1.16) 140-149: HR= 1.03 (0.83 to 1.28) 149-160: HR= 0.98 (0.79 to 1.20) **>160: HR= 1.37 (1.11 to 1.70)** Lowest risk observed at 139 (135-143)* DBP <73: HR=1 73-78: HR= 1.00 (0.83 to 1.21) 78-81: HR=0.89 (0.72 to 1.10) 81-87: HR= 0.93 (0.76 to 1.14) **>87: HR= 1.24 (1.01 to 1.52)** Lowest risk observed at 74 (69-77)*

	All-cause mortality	SBP <130: HR=1 **130-140: HR= 0.75 (0.60 to 0.93)** **140-149: HR= 0.63 (0.49 to 0.80)** **149-160: HR= 0.65 (0.51 to 0.81)** **>160: HR= 0.72 (0.56 to 0.92)** Lowest risk observed at 150 (144-154)* DBP <73: HR=1 **73-78: HR= 0.78 (0.63 to 0.96)** **78-81: HR= 0.77 (0.61 to 0.98)** **81-87: HR= 0.69 (0.54 to 0.88)** >87: HR= 0.93 (0.73 to 1.19) Lowest risk observed at 79 (76-83)*

Table 156

*Data are SBP and DBP corresponding to specified levels of predicted risk (lower and higher 95% confidence limits) of cardiovascular events and mortality from multivariable regression spline models (adjusting for age and sex, stratified by antihypertensive treatment use).

4.2.4.4 *Summary and conclusions of observational data: treatment target in adults with type 2 diabetes*

Cooper-DeHoff 2010
This post-hoc analysis of an RCT in a subgroup of 6400 patients with 16893 patient-years of follow-up, evaluated mortality and cardiovascular events in hypertensive patients with diabetes and coronary artery disease. They analysed achieved systolic blood pressure and compared event rate in patients with tight control (<130 mmHg), usual control (130-<140 mmHg) and uncontrolled hypertension (>140 mmHg). In patients with an achieved SBP lower than 130 mmHg, there was no significant decrease in **a composite endpoint of all-cause mortality, nonfatal MI or nonfatal stroke**, and a borderline non-significant increase in **all-cause mortality**, which became significant in the extended follow-up analysis.

Vamos 2012
This prospective cohort study in 126092 newly diagnosed type 2 diabetics and with a median follow-up of 3.5 years, did not find a reduced risk of **all-cause mortality** in patients with an achieved BP below 130/80 mmHg, compared to patients with "usual control" (SBP of 130 to <140 mmHg and DBP 80 to <85 mmHg). Low blood pressure, below 120/75 mmHg, was significantly associated with an increased risk for all-cause mortality.

Sundstrom 2013(66))
This analysis of data from a retrospective cohort study, in a primary care setting and with a median follow-up of 4.5 years, included 34009 type 2 diabetics with no cardiovascular disease at baseline. The risk of developing events with different SBP and DBP values in patients with and without antihypertensive drug use was evaluated. The association of risks of events and BP followed a U-shaped curve, in both treated and untreated patients.

In type 2 diabetics not treated with antihypertensive medication, the lowest risk of developing **cardiovascular events** was at a BP of 135/76 mmHg, while the lowest risk of **mortality** was observed at a BP of 142/78 mmHg. Compared to an SBP of <130 mmHg, an SBP >160 mmHg was associated with a significantly higher risk of cardiovascular events, but not of mortality.

In type 2 diabetics treated with antihypertensive medication, the lowest risk of developing **cardiovascular events** was at a BP of 139/74 mmHg, while the lowest risk of **mortality** was observed at a BP of 150/79 mmHg.

Conclusion:
In hypertensive patients with type 2 diabetes, a very strict target BP (SBP <130 mmHg), does not seem associated with further decrease of cardiovascular events or mortality, compared to a usual target (SBP <140 mmHg). Low blood pressure (SBP <120-<130 mmHg) does seem associated with an increased risk of mortality.

GRADE: LOW quality of evidence

4.2.5 Chronic kidney disease

4.2.5.1 Clinical evidence profile: treatment target in adults with chronic kidney disease

Ref	Comparison	Results		
AHRQ-CER37(105)	**Strict Versus Standard Blood Pressure Target Treatment**	**Strict BP** Mean (SD) or event rate	**Usual BP** Mean (SD) or event rate	**RR (95% CI)**
Mortality				
Ruggenenti (REIN-2) 2005(106), Shulman (HDFP) 1989(107), Toto 1995(108) Wright (AASK) 2002(109)		Total (N=4, n=1806)		
		Strict BP=96/908 (10.6%)	Standard BP=103/895 (11.5%)	RR=0.86 (0.68-1.09) NS I^2:0%
Cardiovascular mortality				
Ruggenenti (REIN-2) 2005(106), Shulman (HDFP) 1989(107)		Total (N=2, n=332)		
		Strict BP=33/326 (10.1%)	Standard BP=35/306 (11.4%)	RR=0.83 (0.54-1.26) NS I^2:0%
CV events: MI (fatal)				
Ruggenenti (REIN-2) 2005(106)		Total (N=1, n=335)		
		Strict BP=1/167 (0.6%)	Standard BP=1/168 (0.6%)	RR=1.01 (0.06-15.95) NS
CV events: stroke (fatal)				
Ruggenenti (REIN-2) 2005(106), Shulman (HDFP) 1989(107)		Total (N=2, n=632)		
		Strict BP=6/326 (1.8%)	Standard BP=5/306 (1.6%)	RR=1.09 (0.34-3.47) NS I^2:0%
End-stage renal disease				
Ruggenenti (REIN-2) 2005(106), Toto 1995(108), Wright (AASK) 2002(109)		Total (N=3, n=1506)		

	Strict BP=126/749 (16.8%)	Standard BP=126/757 (16.6%)	RR=1.03 (0.77-1.38) NS I^2:22%
Any or serious adverse events leading to study withdrawal			
Ruggenenti (REIN-2), 2005(106)	Total (N=1, n=338)		
	Strict BP=6/169 (3.6%)	Standard BP=3/169 (1.8%)	NT

Table 157

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Ruggenenti 2005(106) REIN-2 Multi-center Italy Followup period (median): 19 months	<u>Inclusion Criteria</u> - Age 18–70 years - nondiabetic nephropathy - persistent proteinuria (urinary proteinexcretion >1 g/24 - no ACEI therapy for at least 6 weeks. - Patients with proteinuria of 1–3 g /24 hr were included if their creatinine clearance was less than 45 mL/min per 1·73m2; those with a proteinuria >3 g /24 h were included if their creatinine clearance was less than 70 mL/min per 1·73 m2. <u>Exclusion Criteria</u> - Urinary tract Infection - NYHA class III or IV heart failure - CV event in past 6m - severe uncontrolled hypertension - evidence or suspicion of	N= 338 Age (yr): 53.8 Gender (Male %): 74.9 Race/Ethnicity (%): NR BP (mm Hg): 137/84 MAP (mm Hg): 101.6 Proteinuria (g/day): 2.85 Serum creatinine (mg/dL): 2.7 Creatinine Clearance (ml/min/1.73m2): 38.8 Measured GFR (ml/min/1.73m2): 35.0 Diabetes (%): NR	Conventional BP control (n=169), with target DBP <90 mmHg, irrespective of SBP Vs Intensified BP control (n=169), with target <130/80 mm Hg, using felodipine, initially at 5 mg/day then titrated up as needed to 10mg/day.	- Allocation Concealment: Adequate. - Randomization: adequate - Blinding: No. - Intention to Treat Analysis (ITT): 'modified' ITT - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 15.4 Other methodological remarks: - After randomization, adjustment of concomitant BP meds (excluding ACEI, ARB, or dihydropiridine CCB other than felodipine) allowed to meet BP target/avoid hypotension. Funding: Industry and other

	renovascular disease - obstructive uropathy - type 1 DM - cancer - "higher" serum aminotransferase concentrations - chronic cough			(nonprofit research institute)
Wright, 2002(109) AASK Multi-center USA Followup period: median 3.8 yrs (median 4.1 yr in ramipril and metoprolol groups, and 3.0 yr in amlodipine group)	<u>Inclusion Criteria</u> - African Americans - hypertension - aged 18 to 70 yr - GFR 20 to 65 mL/min per 1.73 m2, - no other identified causes of renal insufficiency. <u>Exclusion Criteria</u> - DBP 95 mm Hg, - known history of diabetes mellitus - urinary protein to creatinine ratio >2.5 - malignant hypertension - secondary hypertension - evidence of non–BP-related causes of chronic kidney disease - serious systemic disease - heart failure	N=1094 Age (yr): 54.6 Gender (Male %): 61.2 Race/Ethnicity (%): African American 100 BP (mm Hg): 151/96 MAP (mm Hg): 114 Proteinuria (g/24h): 0.53 Urine protein/creatinine ratio: 0.33 Serum creatinine (mg/dL): 2.0 Creatinine Clearance (ml/min/1.73m2): NR Measured GFR (ml/min/1.73m2): 45.6 Diabetes (%): 0	Target MAP 102-107 mm Hg (n=554) Vs Target MAP <92 mm Hg (n=540)	- Allocation Concealment Unclear - Blinding: No - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawal: 8% Other methodological remarks: Study was 3x2 factorial design, including 2 target BP groups and 3 BP drug groups (amlodipine, metoprolol or ramipril Funding Source: Industry and Government
Toto 1995(108) Multi-center USA	<u>Inclusion Criteria</u> - Age 25 to 73 yr - hypertensive nephrosclerosis - DBP >95 mm Hg serum creatinine >1.6 mg/dl - GFRf <70 ml/min/1.73 m2	N= 77 Age (yr): 55.7 Gender (Male %): 62.3 Race/Ethnicity (%): Black 75.3, Nonblack 24.7	Conventional target DBP 85- 95 mm Hg (n=35) vs Strict target DBP 65-80 mm	- Allocation Concealment Unclear - Blinding: Double - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts

Followup period (Mean): 3.4 years	- longstanding hypertension - urinary protein excretion rate <2 g/day patients <u>Exclusion Criteria</u> - Diabetes mellitus - recent history (<4 months) of malignant hypertension, stroke or AMI - acute renal failure of any cause, polycystic kidney disease, rapidly progressive glomerulonephritis - significant hepatic dysfunction - renovascular hypertension - serum creatinine >7.0 mg/dl	Systolic BP (mm Hg): 123 Diastolic BP (mm Hg): 76 MAP (mm Hg) 92 Proteinuria (mg/day): 359 Serum creatinine (mg/dL): 2.3 Creatinine Clearance (ml/min/1.73m2): NR Measured GFR (ml/min/1.73m2): 37.8 Diabetes (%): 0	Hg (n=42)	adequately described: Unclear - Study withdrawals (%): R Other methodological remarks: - 3-6 m run-in before randomization Funding Source Government and Industry
Shulman 1989(107) HDFP Location United States Followup period: 5 yrs	<u>Inclusion Criteria</u> - 30 to 69 years - average home screening DBP of 95 mm Hg or above - confirmed follow-up average diastolic pressure of 90 mm Hg or above. <u>Exclusion Criteria</u>: - Terminally ill and institutionalized persons - Treated hypertensives with DBP below 95.	N=297 (subgroup analysis of subjects with baseline serum creatinine ≥1.7 mg/dl from overall study of N=10, 940) Age (yr): NR Gender (Male %): 68.4 Race/Ethnicity (%): White 40.4, Black 59.6 Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR MAP (mm Hg): NR CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR	Stepped care (n= 5,485; of which n=159 had creatinine ≥1.7 mg/dl). Target goal DBP ≤90 mm Hg for those entering trial on BP drug treatment or with baseline DBP >100 mm Hg, or goal 10mm Hg DBP decrease if baseline DBP 90-99 mm Hg. vs Referred care (n=5,455; of which n=138 had creatinine ≥1.7 mg/dl)	- Allocation Concealment Adequate - Blinding: No - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: No - Study withdrawals (%): NR **Post hoc analysis** Funding Source: Government

		Albuminuria: NR Proteinuria (1+) : 35.0 % Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 15.8		

Table 158

4.2.5.2 Summary and conclusions: treatment target in adults with chronic kidney disease

Strict blood pressure target versus standard blood pressure target			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1806 (4 studies) 2-5 y	RR=0.86 (0.68-1.09) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 (>50% of participants are African Americans) Imprecision: OK
Cardiovascular mortality	332 (2 studies)	RR=0.83 (0.54-1.26) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (fatal)	335 (1 study)	RR=1.01 (0.06-15.95) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
Stroke (fatal)	632 (2 studies)	RR=1.09 (0.34-3.47) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1 Directness: OK Imprecision: -1 for sparse data
ESRD	1506 (3 studies)	RR=1.03 (0.77-1.38) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1 Directness: -1 (>70% of participants are African Americans) Imprecision: OK

Table 159

In this meta-analysis, a strict blood pressure target was compared to a standard blood pressure target. In general, studies established blood pressure targets for their strict control group about 10-15 mm Hg lower than for their standard control group, though there was variability between trials in the absolute blood pressure targets selected. The specific antihypertensive agents utilized to achieve these blood pressure targets varied between trials. Few study participants had diabetes.

Compared with standard blood pressure control, there was no significant reduction in risk of all-cause or cardiovascular mortality with strict blood pressure control.
GRADE: MODERATE quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of fatal myocardial infarction with strict blood pressure control.
GRADE: MODERATE quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of fatal stroke with strict blood pressure control.
GRADE: LOW quality of evidence

Compared with standard blood pressure control, there was no significant reduction in risk of end-stage renal disease with strict blood pressure control.
GRADE: LOW quality of evidence

4.2.5.3 Observational data: treatment target in adults with chronic kidney disease

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Chiang 2014(67) Prospective observational study Taiwan	2144	CKD stage 3-4 Mean age 64.2±13.5y	Median 2.91 y	Risk of developing events with different baseline SBPs; in people with and without diabetes and by proteinuria status	Mortality, cardiovascular events and need for renal replacement therapy (dialysis or Tx)	SBP 96-110 111-120 121-140 >140	DM modifies the J-shaped relationship of SBP with cardiovascular and renal outcomes in stage 3 and 4 CKD patients. Diabetic CKD patients are at 2.5-fold and 3.1-fold increased risk for cardiovascular and renal outcomes, respectively, at SBP 96–110 mm Hg compared with SBP 111–120 mm Hg, but the J-shaped relationship is not observed in nondiabetic CKD patients. These findings suggest that the optimal SBP range may be narrower in diabetic CKD patients than in nondiabetic ones.

Table 160

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP)** **Adj. HRs versus reference SBP (111-120mmHg) in patients treated with antihypertensives**
Chiang 2014	All-cause mortality	<u>Total</u> 96-110: HR= 1.84 (0.73–4.59) 111-120: HR= 1 121-140: HR= 1.65 (0.83–3.27) >140: HR= 1.89 (0.96–3.71) <u>Non-diabetics</u> 96-110: HR= 2.87 (0.78–10.62) 111-120: HR=1 121-140: HR= 1.87 (0.71–4.94) >140: HR= 2.12 (0.81–5.54)

		Diabetics 96-110: HR= 1.40 (0.37–5.35) 111-120: HR=1 121-140: HR= 1.41 (0.52–3.80) >140: HR= 1.75 (0.66–4.61)
	Cardiovascular events	Total **96-110: HR= 2.76 (1.26–6.02)** 111-120: HR=1 121-140: HR= 1.82 (0.98–3.38) **>140: HR= 1.93 (1.05–3.55)** Non-diabetics 96-110: HR= 0.78 (0.15–4.12) 111-120: HR=1 121-140: HR= 1.27 (0.51–3.19) >140: HR= 1.31 (0.53–3.24) Diabetics **96-110: HR= 5.01 (1.85–13.56)** 111-120: HR=1 121-140: HR= 2.28 (0.96–5.38) **>140: HR= 2.34 (1.005–5.46)**
	Need for renal replacement therapy	Total 96-110: HR= 1.69 (0.78–3.67) 111-120: HR=1 121-140: HR= 1.30 (0.76–2.22) **>140: HR= 1.84 (1.11–3.04)** Non-diabetics 96-110: HR= 0.70 (0.21–2.32) 111-120: HR=1 121-140: HR= 0.85 (0.39–1.87) >140: HR= 0.86 (0.40–1.89)

		Diabetics 96-110: HR= 2.85 (0.98–8.30) 111-120: HR=1 121-140: HR= 1.49 (0.71–3.12) **>140: HR= 2.60 (1.29–5.26)**

Table 161

Reference	N	Population	Follow-up	Study design	Outcomes	BP values (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Kovesdy 2013(68) US Retrospective cohort study	651749	Veterans Non-dialysis dependent CKD Mean age 73.8±9.7y	Median 5.8y	Risk of mortality at different SBP/DBP values	All-cause mortality	SBP and DBP were examined as all possible combinations of each other in 96 categories (from lowest of <80/<40 mmHg to highest of >210/>120 mmHg, in increments of 10 mmHg	We describe a J-shaped association between SBP and DBP and all-cause mortality in patients with non-dialysis dependent CKD. The combination of low SBP and low DBP is associated with the highest mortality in this population. In addition, DBP levels below approximately 70 mmHg appear to confer increased mortality even in patients with moderately high SBP. The optimal blood pressure in patients with CKD appears to be 130–149/70–89 mmHg. It may not be advantageous to achieve ideal SBP levels at the expense of lower-than-ideal DBP levels in adults with CKD.

Table 162

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference SBP/DBP of 120-139/80-89 mmHg**
Kovesdy 2013	All-cause mortality	**<120/<80: HR= 1.42 (1.41 to 1.43)** 120-139/80-89: HR= 1 **140-159/90-99: HR= 0.95 (0.94 to 0.96)** **≥160/≥100: HR= 1.05 (1.03 to 1.07)**

Table 163

Mortality HRs Associated With Mutually Exclusive Categories of SBP and DBP Combinations*

Variable	HR														
	SBP <80 mm Hg	SBP of 80–89 mm Hg	SBP of 90–99 mm Hg	SBP of 100–109 mm Hg	SBP of 110–119 mm Hg	SBP of 120–129 mm Hg	SBP of 130–139 mm Hg	SBP of 140–149 mm Hg	SBP of 150–159 mm Hg	SBP of 160–169 mm Hg	SBP of 170–179 mm Hg	SBP of 180–189 mm Hg	SBP of 190–199 mm Hg	SBP of 200–209 mm Hg	SBP ≥210 mm Hg
DBP															
Adjusted model†															
<40 mm Hg	2.56	2.42	2.55	2.15	1.73	1.69	1.91								
40–49 mm Hg	2.99	2.69	2.31	1.77	1.58	1.39	1.37	1.30	1.50	1.83					
50–59 mm Hg	3.25	2.88	2.24	1.77	1.51	1.27	1.14	1.17	1.27	1.32	1.63	1.20			
60–69 mm Hg		3.11	2.32	1.82	1.48	1.23	1.09	1.09	1.12	1.13	1.28	1.36	1.00		
70–79 mm Hg			2.05	1.70	1.34	1.14	1.01	1.01	1.04	1.07	1.12	1.19	1.11	1.17	1.26
80–89 mm Hg				1.82	1.27	1.08	0.98	Reference	1.01	1.07	1.13	1.22	1.43	1.25	1.35
90–99 mm Hg					1.57	1.26	1.08	1.10	1.15	1.18	1.25	1.23	1.16	1.38	1.04
100–109 mm Hg							1.53	1.16	1.31	1.33	1.37	1.30	1.62	1.40	1.42
110–119 mm Hg									1.11	1.28	1.81	1.35	1.89	1.85	1.71
≥120 mm Hg											1.62			2.44	2.06

DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.

Figure 7

Reference	N	Population	Follow-up	Study design	Outcomes	BP values (groups / targets); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Kovesdy 2014(110) US	77765	Veterans Non-dialysis dependent CKD	Median 6.0y	Risk of mortality at different SBP values	All-cause mortality	SBP <120 120-139	in a cohort of patients with CKD and uncontrolled hypertension lowering of the SBP to <120 mmHg was associated with higher all-cause mortality compared to an SBP of 120–139 mmHg.

Retrospective cohort study		Uncontrolled systolic hypertension*					

Table 164

*Defined as: baseline SBP 130–180 mmHg on 0 or 1 antihypertensives, or SBP 130–170 mmHg on up to 2 antihypertensives, or SBP 130–160 mmHg on up to 3 antihypertensives, or SBP 130–150 mmHg on up to 4 antihypertensives.

Summary of numerical results for prognostic studies (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HRs versus reference SBP of 120-139mmHg**
Kovesdy 2013	All-cause mortality	**<120: HR= 1.61 (1.51 to 1.71)** 120-139: HR= 1

Table 165

4.2.5.4 *Summary and conclusions of observational data: treatment target in adults with chronic kidney disease*

Kovesdy 2013(68)
This retrospective cohort study evaluated clinical data of 651749 veterans with non-dialysis dependent chronic kidney disease over a median of 5.8 years. Risk of **all-cause mortality** was evaluated for different combinations of SBP and DBP. A J-shaped association between SBP and DBP and all-cause mortality was observed, with increased risk above and below a BP range of 130–149/70–89 mmHg.

Kovesdy 2014(110)
This retrospective cohort study evaluated clinical data of 77765 veterans with non-dialysis dependent chronic kidney disease and uncontrolled systolic hypertension over a median of 6 years. Risk of all-cause mortality was evaluated for an SBP <120 mmHg versus 120-139 mmHg. In these patients, an achieved SBP <120 mmHg was associated with a significant increase **in all-cause mortality**, compared to an achieved SBP of 120-139 mmHg.

Chiang 2014(67)
In this prospective observational study, 2144 patients with stage 3-4 chronic kidney disease were followed over a median of 2.9 years. The risk of **cardiovascular events**, **need for renal replacement therapy** (dialysis or transplantation) and **all-cause mortality** with different baseline SBP values (range: 96 to>140 mmHg) was evaluated. A baseline SBP of >140 mmHg was associated with an increased risk of need for renal replacement therapy, but not of mortality or cardiovascular events, when observing the whole study population. In patients treated with antihypertensive medication, a very low SBP (96-110 mmHg) was associated with a significantly increased risk of cardiovascular events, and a high SBP (>140 mmHg) was associated with an increased risk of cardiovascular events and need for renal replacement therapy, compared to an SBP of 111-120 mmHg.

Conclusion: In patients with chronic kidney disease, a low blood pressure seems associated with increased risk of morbidity and mortality, but the definition of low blood pressure differs between studies (<110, <120, or <130).

GRADE: LOW quality of evidence

4.2.6 Coronary disease

4.2.6.1 Clinical evidence profile: treatment target in adults with coronary disease

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.2.6.2 Observational data: treatment target in adults with coronary disease

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**
Messerli 2006(111) Post-hoc analysis of RCT (INVEST)	22576	Hypertensive patients with coronary artery disease and ≥50y	Clinic	Not reported	Median 2.7 years	All-cause mortality, nonfatal MI, nonfatal stroke (PO)	SBP ≤110 >110-120 >120-130 >130-140 >140-150 >150-160 >160 DBP ≤60 >60-70 >70-80 >80-90 >90-100 >100-110 >110	The relationship between blood pressure and the primary outcome, all-cause death, and total MI was J- shaped, particularly for diastolic pressure, with a nadir at 119/84* mm Hg. The risk for the primary outcome, all-cause death, and MI, but not stroke, progressively increased with low diastolic blood pressure. Excessive reduction in diastolic pressure should be avoided in patients with CAD who are being treated for hypertension.

Table 166

*Unadjusted HR

Study	**Outcome**	**HR (95% CI) for BP measurement**

		Adj. HR
Messerli 2006(111)	All-cause mortality, nonfatal MI, nonfatal stroke (PO)	No numerical results for HR reported SBP : Nadir 129.5 mmHg DBP : Nadir 73.8 mmHg

Table 167

Within-treatment blood pressure studies								
Reference / study type (112)	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**
Bangalore 2014 Post-hoc analysis of RCT (INVEST)	8354	Hypertensive patients with coronary artery disease Subgroup with baseline SBP >150 mmHg and age ≥60y	Clinic	SBP>150	22308 patient-years	All-cause death, nonfatal MI, nonfatal stroke	SBP: <140 140-<150 ≥150	In hypertensive patients with CAD who are ≥60 years of age, achieving a BP target of 140 to <150 mm Hg as recommended by the JNC-8 panel was associated with less benefit than the previously recommended target of <140 mm Hg.

Table 168

Study	Outcome	HR (95% CI) for BP measurement Adj. HR versus reference : SBP <140 mmHg
Bangalore 2014(112)	All-cause mortality, nonfatal MI or nonfatal stroke (PO)	<140: HR= 1 140-<150: HR= 1.12 (0.95 to 1.32) **≥150: HR= 1.85 (1.59 to 2.14)**
	All-cause mortality	<140: HR= 1 140-<150: HR= 1.03 (0.86 to 1.24) **≥150: HR= 1.64 (1.40 to 1.93)**
	Cardiovascular mortality	140: HR= 1 **140-<150: HR= 1.34 (1.01 to 1.77)** **≥150: HR= 2.29 (1.79 to 2.93)**

	Total myocardial infarction	<140: HR= 1 140-<150: HR= 1.20 (0.90 to 1.60) **≥150: HR= 2.39 (1.87 to 3.05)**
	Total stroke	140: HR= 1 **140-<150: HR= 1.89 (1.26 to 2.82)** **≥150: HR= 2.93 (2.01 to 4.27)**
	Heart failure	Hazard risks not reported; risks were similar and low across BP groups
	Adverse experiences	Hazard risks not reported; No significant increases across BP groups

Table 169

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**
Winchester 2013(113) Analysis using data of RCT and its extended follow-up mortality data (INVEST)	16951	Hypertensive patients with coronary artery disease and ≥50y	Clinic	Not reported	Median 8.37 years	All-cause mortality	SBP: Tightly controlled: <130 Controlled: 130-139 Uncontrolled: ≥140	In hypertensive coronary artery disease patients, uncontrolled BP (≥140 mmHg), was associated with increased mortality.

Table 170

Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HR versus reference : SBP 130-139 mmHg**

Winchester 2013(113)	All-cause mortality	<130 = not reported, NS 130-139: HR=1 **≥140: HR= 1.29 (1.20-1.40)**

Table 171

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs**	**Best Target BP (authors' conclusions)**
Maddox 2010(114) Prospective cohort study	22430; 9569 with no diabetes or CKD 12861 with diabetes and/or CKD	Adults with coronary artery disease and hypertension	Clinic	Not reported	Mean 1.8 years	All-cause mortality, MI or revascularization procedure	SBP trajectories defined by: Good: values around 120 Borderline: values around 130 Improved: elevated SBP that declined to normal levels during observation period Poor control: persistently at or above 140 mmHg (no DM or CKD group) or 130 (DM and/or CKD group)	Better BP control trajectories were associated with fewer MIs and revascularization procedures.

Table 172

Study	**Outcome**	**HR (95% CI) for BP measurement** **Adj. HR ; versus poor control**
Maddox 2010(114)	All-cause mortality, MI or revascularization procedure	No diabetes or CKD cohort : Good control: HR= 1.08 (0.83 to 1.42) Borderline control: HR= 0.88 (0.67 to 1.15) Improved control: HR= 1.05 (0.72 to 1.54) Poor control: HR= 1

		Diabetes and/or CKD cohort : Good control: HR= 0.98 (0.82 to 1.17) Borderline control: HR= 0.84 (0.71 to 1) Improved control: HR= 1.11 (0.88 to 1.4) Poor control: HR= 1
	All-cause mortality	No diabetes or CKD cohort : Good control: HR= 1.03 (0.73 to 1.46) Borderline control: HR= 0.88 (0.63 to 1.24) Improved control: HR= 0.88 (0.53 to 1.47) Poor control: HR= 1 Diabetes and/or CKD cohort : Good control: HR= 1.23 (0.98 to 1.54) Borderline control: HR= 0.93 (0.75 to 1.17) Improved control: HR= 1.16 (0.86 to 1.55) Poor control: HR= 1
	Myocardial infarction	No diabetes or CKD cohort : Good control: HR= 0.78 (0.4 to 1.55) Borderline control: HR= 0.67 (0.35 to 1.31) Improved control: HR= 1.19 (0.49 to 2.89) Poor control: HR= 1 Diabetes and/or CKD cohort : **Good control: HR= 0.53 (0.34 to 0.84)** **Borderline control: HR= 0.61 (0.4 to 0.93)** Improved control: HR= 0.92 (0.52 to 1.63) Poor control: HR= 1

Table 173

4.2.6.3 Summary and conclusions of observational data: treatment target in adults with coronary disease

Maddox(114)
This prospective cohort study in 22430 hypertensives with coronary artery disease, and a mean follow-up of 1.8 years, evaluated the association between systolic blood pressure trajectories (serial blood pressure measurements over time) and **a composite of all-cause mortality, myocardial infarction or revascularization procedures.** Patients were stratified into a group with no diabetes or CKD at baseline, and a group with diabetes or CKD. BP trajectory categories were defined as good (values around 120 mmHg), borderline (values around 130 mmHg), improved (elevated SBP that declined to normal levels during the observation period) and poor control (persistently at or above 140 mmHg (for the no diabetes or CKD group) or 130 mmHg (for the diabetes or CKD group). In both groups, there was no significant association between blood pressure trajectory and the primary outcome. Only in the diabetes or CKD cohort, good and borderline controlled blood pressure was associated with a significant reduction of **myocardial infarction**, compared to poor control.

The three following studies are post hoc analyses of the same open-label RCT (INVEST(115)) that evaluated a verapamil-based strategy versus an atenolol-based strategy in hypertensive patients ≥ 50 years old with coronary disease. In this study, there was a blood pressure target of <140/90 mmHg for most patients, and a target of <130/85 mmHg in patients with diabetes or renal impairment.

Messerli 2006(111)
This post hoc analysis of an RCT in 22576 hypertensive patients with coronary artery disease that were followed over 2.7 years, evaluated the association of achieved blood pressure and a **composite outcome of mortality, non-fatal myocardial infarction and non-fatal stroke**. A J-shaped association was observed between blood pressure and the primary outcome, with a nadir blood pressure of 130/74 mmHg, above and below which events increased.

Bangalore 2014(112)
This post hoc analysis of an RCT with 22308 patient-years of follow-up, in 8354 hypertensive patients with coronary artery disease, aged ≥60 years, and with a baseline systolic blood pressure of >150 mmHg, evaluated the association between achieved blood pressure and all-cause mortality, myocardial infarction and stroke. Compared to an achieved blood pressure of <140 mmHg, an achieved blood pressure of 140 to <150 mmHg was not significantly associated with an increase of the primary outcome: **a composite of all-cause mortality, non-fatal MI or non-fatal stroke**, nor with **all-cause mortality** or **total myocardial infarction**. However, the higher BP was associated with a significant increase in **cardiovascular mortality** and **total stroke.**

Winchester 2013(113)
This analysis using data of an RCT and its extended follow-up mortality data, in 16951 hypertensive patients with coronary artery disease and with a median follow-up of 8.37 years, evaluated the association between achieved systolic blood pressure and **all-cause mortality.** Compared to usual blood pressure control (SBP 130-139 mmHg), tight control (SBP <130 mmHg) was not associated with a significant difference of all-cause mortality. An achieved blood pressure of ≥140 mmHg, however, was significantly associated with an increase of all-cause mortality, compared to usual control.

Conclusion
In hypertensive patients with coronary disease, an achieved blood pressure of <140 mmHg is associated with better outcomes than an achieved blood pressure of ≥140 mmHg. There does not seem to be a clear added benefit of a stricter systolic blood pressure of <130 mmHg.

GRADE: LOW quality of evidence

4.2.7 Heart failure

4.2.7.1 Clinical evidence profile: treatment target in adults with heart failure

Our search yielded no MA's, RCTs or observational data meeting our inclusion criteria.

4.2.8 Previous stroke

4.2.8.1 Clinical evidence profile: treatment target in adults with previous stroke

Study details	n/Population	Comparison	Outcomes		Methodological
Benavente / SPS3 2013(116) Design: RCT OL,PG Duration of follow-up: mean 3.7 years	n= 3020 n lower= 1501 n higher= 1519 Mean age: 63±11 y **Hypertension: 75%** Ischaemic heart disease: 10% Previous stroke or TIA: 15% Diabetes: 37% Smoking: 20% Age >80y: unknown <u>Inclusion</u> 30 years or older, were normotensive or hypertensive, had had a recent (within 180 days), symptomatic, MRI-confi rmed	Higher (130-149 mmHg) SBP target Vs Lower (<130 mmHg) SBP target	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: no Personnel: no Assessors: yes Remarks on blinding method: PROBE design FOLLOW-UP: Lost-to follow-up: 3% Drop-out and Exclusions: 15% • Described: yes • Balanced across groups: not reported ITT: Yes SELECTIVE REPORTING: no (
			All stroke(PO)	Lower: 125/1501 Higher: 152/1519 HR= 0.81 (0.64 to 1.03); p= 0.08 NS	
			Acute myocardial infarction (SO)	Lower: 36/1501 Higher: 40/1519 HR= 0.88 (0.56 to 1.39); p= 0.59 NS	
			Death (SO)	Lower: 106/1501 Higher: 101/1519 HR= 1.03 (0.79 to 1.35); p= 0.82 NS	
			Vascular death (SO)	Lower: 36/1501 Higher: 41/1519 HR= 0.86 (0.55 to 1.35); p=0.52 NS	
			Pre-specified subgroup analysis with only hypertensive population (n=2706)		
			All stroke	Lower: 113 (2.25%) Higher: 152 (2.85%) HR= 0.80 (95% CI 0.62 to 1.02) NS	
			Safety (n=3020)		

	lacunar stroke, and were without surgically amenable ipsilateral carotid artery stenosis or high-risk cardioembolic sources. <u>Exclusion</u> Disabling stroke (modifi ed Rankin score of 4 or higher), previous intracranial haemorrhage from non-traumatic causes, or cortical ischaemic stroke		All serious adverse events related to hypotension and blood-pressure management	Lower: 23/1501 Higher: 15/1519 HR= 1.53 (0.80 to 2.93); p=0.20 NS	Sponsor: National Institutes of Health-National Institute of Neurological Disorders and Stroke (NIH-NINDS)
			Orthostatic syncope	Lower: 11/1501 Higher: 5/1519 HR= 2.18 (0.76 to 6.27); p=0.14 NS	
			Stroke associated with hypotension	Lower: 2/1501 Higher: 1/1519 HR= 2.00 (0.18 to 22.09) p=0.57 NS	
			Myocardial infarction	Lower: 0/1501 Higher: 0/1519 HR= NA	
			Fall with injury	Lower: 3/1501 Higher: 0/1519 HR= NA	

Table 174

4.2.8.2 Summary and conclusions: treatment target in adults with previous stroke

Lower (<130 mmHg) versus higher (130-149 mmHg) blood pressure target in patients with recent lacunar stroke			
Bibliography: Benavente 2013 (SPS3)(116)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke	2706 (1 studies)	HR= 0.80 (95% CI 0.62 to 1.02) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: subgroup analysis, no blinding Consistency: only one study Directness: only lacunar strokes Imprecision: ok

Table 175

This is an open-label RCT in 3020 patients with recent lacunar stroke, and a mean age of 63, followed over a mean duration of 3.7 years and evaluating the effect of a higher (130-149 mmHg) versus a lower (<130 mmHg) blood pressure target on **stroke rate**. However, this RCT included both normotensive and hypertensive patients. We chose to report the results of the prespecified subgroup analysis with only the hypertensive patients (2706 patients). This result was similar to that of the whole study population.

In hypertensive patients with previous stroke, a low blood pressure target (<130 mmHg) did not significantly decrease stroke rate, compared to a higher blood pressure target of 130-149 mmHg.
GRADE: VERY LOW quality of evidence

4.2.8.3 Observational data: treatment target in adults with previous stroke

Within-treatment blood pressure studies								
Reference / study type	**N**	**Population**	**BP measurement method**	**Baseline mean BP (SBP/DBP mmHg)**	**Follow-up**	**Outcomes**	**In-treatment / achieved BPs (mmHg)**	**Best Target BP (authors' conclusions)**
Arima et al., 2006 (22) Sub-analysis of RCT (PROGRESS)	6105	HT and NT (history of stroke or TIA but not subarachnoid haemorrhage)	Clinic	Grouped in: <120 (median 114) 120-139 (median 130) 140-159 (median 149) ≥160 (median 169)	Mean 3.9 years	Stroke, CV events, mortality	Grouped in: <120 (median 112) 120-139 (median 130) 140-159 (median 148) ≥160 (median 168)	Although the optimum targets for BP lowering are unlikely to be established without additional data from randomized controlled trials evaluating the effects of treating patients with cerebrovascular disease to lower BP targets, clinicians should feel confident in using multiple therapies to achieve the current goals of less than 130–140/ 80–90 mmHg recommended in existing guidelines. We also believe that for patients with cerebrovascular disease the progressive reduction of BP levels towards targets of approximately 115/75 mmHg over a period of time should be both safe and maximally protective, provided it is well tolerated.

Table 176

Summary of numerical results (for selected outcomes)		
Study	**Outcome**	**HR (95% CI) for BP measurement (SBP/DBP)**
Arima et al., 2006 (22)	Stroke	No numerical results reported
	Major vascular events (non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause)	Not reported

Table 177

4.2.8.4 *Summary and conclusions of observational data: treatment target in adults with previous stroke*

Arima 2006(22)
This post hoc analysis of an RCT evaluated the data of 6105 patients with a history of stroke, followed for a mean of 3.9 years. Risk of developing events in people with different achieved BP values was analysed. Numerical results for the selected outcomes were not reported in this paper.

The authors concluded: "The association of **stroke** incidence with achieved follow-up SBP level was continuous with no evidence of a J-curve in the range of achieved follow-up SBP from 112 to 168 mmHg. Results of analyses based on achieved follow-up DBP showed similar patterns for a range of achieved follow-up DBP levels from 72 to 102 mmHg. There was also a strong and continuous relationship of achieved follow-up BP levels with the outcome **'major vascular events'**."

GRADE: LOW quality of evidence

4.3 Antihypertensive treatment

4.3.1 Adults with hypertension, with or without additional risk factors

4.3.1.1 Information on placebo-controlled and head to head trial from the JNC-8 systematic search

4.3.1.1.1 Diuretics versus other drugs

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovasular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
MRC, 1985 Adults, ages 35-64 years, with mild to moderate HTN BEN: Bendrofluazide: 10 mg QD PRO: Propranolol: 240 mg QD N: 17,354 5.5 years Fair	**All deaths** 6.0 per 1000 py BEN vs 5.5 per 1000 py PRO p=0.71	**Coronary events** 5.6 per 1000 py BEN vs 4.8 per 1000 py PRO p=0.24	**Stroke** 0.8 per 1000 py BEN vs 1.9 per 1000 py PRO p=0.002		**All CV events** 6.6 per 1000 py BEN vs 6.7 per 1000 py PRO p=0.76		
ALLHAT, 2002 Adults, ≥ 55 years of age with at least one additional risk factor for CHD CHL: Chlorthalidone: 12.5, 25 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD N: 33,357 Mean 4.9 years	**All-cause mortality** LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) p = 0.90 **All-cause mortality** AML vs CHL: RR (95% CI): 0.96 (0.89, 1.02) p = 0.20	**CHD (combined fatal CHD and nonfatal MI)** LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) p = 0.81 **CHD (combined fatal CHD and nonfatal MI)** AML vs CHL:	**Stroke** LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) p = 0.02 **Stroke** AML vs. CHL: RR (95% CI): 0.93 (0.82, 1.06) p = 0.28	**HF** LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) p < 0.001 **HF** AML vs. CHL: RR (95% CI): 1.38 (1.25, 1.52) p < 0.001	**Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient**	**Kidney disease death** LIS vs. CHL: 0.5 per 100 persons LIS vs 0.4 per 100 persons CHL RR (95% CI): NR p = 0.37 **Kidney disease**	**Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL:** LIS vs. CHL: 8.1% LIS vs 11.6% CHL p < 0.001

Good		RR (95% CI): 0.98 (0.90, 1.07) p = 0.65 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11) p = 0.18 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** AML vs. CHL: RR (95% CI): 1.00 (0.94, 1.07) p = 0.97 **Coronary revascularization** LIS vs. CHL: RR (95% CI): 1.10 (1.00, 1.21) p = 0.05 **Coronary revascularization** AML vs. CHL: RR (95% CI): 1.09 (1.00, 1.20) p = 0.06 **MI death** LIS vs. CHL 2.2 per 100 persons LIS vs 2.4 per 100 persons CHL RR (95% CI): NR p = 0.25	**Death from stroke** LIS vs. CHL: 1.7 per 100 persons LIS vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.06 **Death from stroke** AML vs. CHL: 1.4 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.71	**Hospitalized/ Fatal HF** LIS vs. CHL: RR (95% CI): 1.10 (0.98, 1.23) p = 0.11 **Hospitalized/ Fatal HF** AML vs. CHL: RR (95% CI): 1.35 (1.21, 1.50) p < 0.001 **HF death** LIS vs. CHL: 1.1 per 100 persons LIS vs 1.0 per 100 persons CHL RR (95% CI): NR P = 0.98 **HF death** AML vs CHL: 1.4 per 100 persons AML vs 1.0 per 100 persons CHL RR (95% CI): NR p = 0.17	**revascularization)** LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) p < 0.001 **Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)** AML vs. CHL: RR (95% CI): 1.04 (0.99, 1.09) p = 0.12 **Cardiovascular death** LIS vs. CHL: 8.5 per 100 persons LIS vs 8.0 per 100 persons CHL RR (95% CI): NR p = 0.39 **Cardiovascular death** AML vs. CHL: 8.5 per 100 persons AML vs 8.0 per 100 persons CHL RR (95% CI): NR p = 0.76 **Other CVD death:** LIS vs. CHL: 1.5 per 100 persons LIS vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.66 **Other CVD death** AML vs. CHL:	**death** AML vs CHL: 0.5 per 100 persons AML vs 0.4 per 100 persons CHL RR (95% CI): NR p = 0.68 **ESRD** LIS vs CHL: RR (95% CI): 1.11 (0.88, 1.38) p = 0.38 **ESRD** AML vs. CHL: RR (95% CI): 1.12 (0.89, 1.40) p = 0.33	**Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL:** AML vs. CHL: 9.8% AML vs 11.6% CHL p = 0.04 **Angioedema** AML vs. CHL <0.1% AML vs 0.1% CHL p = NR **Angioedema** LIS vs. CHL 0.4% LIS vs 0.1% CHL p < 0.001

		MI death AML vs. CHL 2.3 per 100 persons AML vs 2.4 per 100 persons CHL RR (95% CI): NR p = 0.66 **Definite CHD death** LIS vs. CHL 1.0 per 100 persons LIS vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.52 **Definite CHD death** AML vs. CHL 1.2 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.88 **Possible CHD death** LIS vs. CHL 1.4 per 100 persons LIS vs 1.1 vs 100 per persons CHL RR (95% CI): NR p = 0.10 **Possible CHD death** AML vs. CHL 1.1 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.62			1.7 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.46		

ALLHAT, 2003 Adults, ages ≥ 55 years, with at least one additional risk factor for CHD CHL: Chlorthalidone: 12.5, 25 mg QD DOX: Doxazosin: 2, 4, or 8 mg QD N: 24,316 Mean 3.2 years Good *Doxazosin arm terminated early because of a 25% greater incidence of combined CVD events compared with chlorthalidone*	**All-cause mortality** RR (95% CI): 1.03 (0.94, 1.13) p = 0.50	**Non-fatal MI and fatal CHD** RR (95% CI): 1.03 (0.92, 1.15) p = 0.62 **Death from MI** RR (95% CI): 0.96 (0.76, 1.22) p = 0.75 **Death from definite CHD** RR (95% CI): 1.16 (0.77, 1.74) p = 0.49 **Coronary revascularization** 7.08 per 100 CHL vs 8.02 per 100 DOX RR (95% CI): 1.12 (1.00, 1.25) p = 0.05 **Lower extremity PAD** RR (95% CI): 0.97 (0.82, 1.15) p = 0.76	**Stroke** 4.08 per 100 CHL vs 5.49 per 100 DOX RR (95% CI): 1.26 (1.10, 1.46) p = 0.001 **Death from stroke** 0.79 per 100 CHL vs 1.25 per 100 DOX RR (95% CI): 1.39 (1.03, 1.89) p = 0.03	**Fatal, hospitalized, treated CHF** 5.35 per 100 CHL vs 8.89 per 100 DOX RR (95% CI): 1.80 (1.61, 2.02) p < 0.001 **Fatal, hospitalized CHF** 4.41 per 100 CHL vs 6.63 per 100 DOX RR (95% CI): 1.66 (1.46, 1.89) p < 0.001 **Death from CHF** RR (95% CI): 1.20 (0.81,1.78) p = 0.36	**Combined CHD** 14.87 per 100 CHL vs 16.00 per 100 DOX RR (95% CI): 1.07 (0.99, 1.66) p = 0.07 **Combined CVD** 25.09 per 100 CHL vs 28.56 per 100 DOX RR (95% CI): 1.20 (1.13 1.27) p < 0.001 **CV mortality** 4.74 per 100 CHL vs 5.60 per 100 DOX RR (95% CI): 1.15 (1.01, 1.32) p = 0.03 **Other CV death** RR (95% CI): 1.25 (0.92, 1.70) p = 0.15	**Kidney disease death** RR (95% CI): 1.69 (0.76, 3.77) p = 0.20 **ESRD** RR (95% CI): 1.04 (0.76,1.42) p = 0.80 **Doubling of serum Cr from baseline:** 0.8% CHL vs 0.5% DOX p = 0.02	

SHELL, 2003 Adults ≥ 60 years with isolated systolic HTN CHL: Chlorthalidone: 12.5, 25 mg QD LAC: Lacidipine: 4, 6 mg QD N: 1,882 Fair	**All-cause mortality** 122 events CHL vs 145 events LAC HR (95% CI): 1.23 (0.97,1.57) p = 0.09	**Fatal and non-fatal MI** HR (95% CI): 0.85 (0.39-1.83) p = 0.67 **Sudden death** HR (95% CI): 1.22 (0.58, 2.53) p = 0.60 **Revascularization** HR (95% CI): 0.50 (0.09, 2.70) p = 0.41	**Fatal and non-fatal stroke** HR (95% CI): 0.96 (0.61, 1.51) p = 0.87 **TIA** HR (95% CI): 1.14 (0.54-2.40) p = 0.72	**Fatal and non-fatal HF** HR (95% CI): 1.20 (0.65, 2.20) p= 0.56	**Composite primary endpoint** (fatal and non-fatal stroke, sudden death, fatal and non-fatal MI, fatal and non-fatal CHF, myocardial revascularization and carotid endarterectomy) HR (95% CI): 1.01 (0.75, 1.36) p = 0.94		**Orthostatic hypotension** 2.5% CHL vs 1.9% LAC p = NR **Edema** 4.9% CHL vs 14.3% LAC p = NR **Cough** 4.0% CHL vs 3.5% LAC p = NR **Dizziness** 12.4% CHL 12.7% LAC p = NR **Fatigue** 20.5% CHL 13.7% LAC p = NR

VHAS, 1997 Adults, ages 40-65 years, with HTN CHL: Chlorthalidone: 25 mg QD VER: Verapamil: slow release 240 mg QD N: 1,414 2 years Fair	**Death by any cause** 4 events CHL vs 5 events VER p = NR	**MI** 5 events CHL vs 5 events VER p = NR **Revascularization procedures** 3 events CHL vs 4 events VER p = NR **Cardiac deaths** 4 events CHL vs 3 events VER p = NR	**Strokes** 4 events CHL vs 3 events VER p = NR **TIA** 7 events CHL vs 7 events VER p = NR **Cerebrovascular deaths** 0 events CHL vs 2 events VER p = NR	**CHF** 0 events CHL vs 2 events VER p = NR	**Non-fatal CV events** 39 events CHL vs 37 events VER p = NR **Major CV events** 9 events CHL vs 8 events VER p = NR **Minor CV events** 30 events CHL vs 29 events VER p = NR **CV deaths** 4 events CHL vs 5 events VER p = NR		**Hypokalemia** 24.6% CHL vs 4.4% VER p < 0.01 **Hyperuricemia** 10.8% CHL vs 3.9% VER p < 0.01 **Glucose, mg/dl (SD)** +1.8 change CHL vs -1.2 change VER p = 0.01 **Severe hypokalemia** 8 events CHL vs 4 events VER p = NR **Constipation** 3.1% CHL vs 13.7% VER p = NR

INSIGHT, 2000 Men and women age 55-80 years, high risk patients with HTN; one additional CV risk factor Co-am: Co-amilozide: HCTZ 25 mg and amiloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amiloride 5 mg QD NIFE: Nifedipine: 30, 60 mg QD N: 6,321 Maximum 51 months F/U Good	**All deaths (first event)** OR (95% CI): 1.01 (0.80-1.27) p = 0.95	**Non-fatal MI** OR (95% CI): 1.09 (0.76-1.58) p = 0.52 **Fatal MI** OR (95% CI): 3.22 (1.18-8.80) p = 0.017	**Non-fatal stroke** OR (95% CI): 0.87 (0.61-1.26) P= 0.52 **Fatal stroke** OR (95% CI): 1.09 (0.48-2.48) p = 0.84 **TIA** OR (95% CI): 1.00 (0.57-1.75) p = 1.0	**Non-fatal HF** OR (95% CI): 2.20 (1.07-4.49) p = 0.028 **Fatal HF** OR (95% CI): 2.01 (0.18-22.13) p = 0.63	**Primary composite** (death from any CV or cerebrovascular cause, together with non-fatal stroke, MI and HF) OR (95% CI): 1.11 (0.90-1.36) p = 0.34 **Secondary composite** (primary outcome plus non-CV deaths, renal failure, angina and TIA) OR (95% CI): 0.96 (0.83-1.12) p = 0.62 **Other CV death** OR (95% CI): 1.09 (0.50-2.38) p = 0.85 **CV Deaths** OR (95% CI): 1.16 (0.80-1.69) p = 0.45 **Non-fatal primary CV events** OR (95% CI): 1.08 (0.85-1.38) p = 0.53 **Non-fatal CV events** OR (95% CI): 0.94 (0.78-1.13) p = 0.50	**Renal Failure (defined as creatinine >2.94 mg/dl)** OR (95% CI): 0.62 (0.26-1.49) p = 0.38	**Serious AEs** 28% Co-am vs 25% NIFE p < 0.02 **DM reported as AE** 4.3% Co-am vs 3.0% NIFE p = 0.01 **New onset DM reported as an outcome** 5.6% Co-am vs 4.3% NIFE p = 0.02 **Impaired renal function as an adverse event** 4.6% Co-am vs 1.8% NIFE p < 0.0001 **Hyperglycemia,** 7.7% Co-am vs 5.6% NIFE p = 0.001 **Hypokalemia** 6.2% Co-am vs 1.9% NIFE p < 0.0001 **Hyponatremia** 61 events Co-am vs 8 events NIFE p < 0.0001 **Dizziness** 10% Co-am vs 8% NIFE p < 0.006 **GFR, mL/min** Co-am vs.

							NIFE (95% CI): -2.3 (-3.8, 1.9) Co-am lower than NIFE p = NR **All AEs** 42% Co-am vs 49% NIFE p < 0.0001 **Peripheral edema** 4.3% Co-am vs 28% NIFE p < 0.0001 **Headache** 9.2% Co-am vs 12% NIFE p < 0.0002

MIDAS, 1996 Adults, ages ≥ 40 years, without hyperlipidemia, and presence of IMT 1.3-3.5 mm in the carotid artery; fasting TC and LDL-C ≤ 6.21 and 4.14 mmol/L (240 and 160 mg/dL) respectively HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID ISR: Isradipine: 2.5 to 5.0 mg BID N: 883 3 years Fair	**All-cause mortality** RR (95% CI): 0.89 (0.35-2.28) p = 0.81	**MI** RR (95% CI): 1.20 (0.37, 3.89) p = 0.77 **CABG** RR (95% CI): 1.00 (0.32, 3.07) p = 0.97 **Coronary angioplasty** 0.22 n per 100 HCTZ vs 1.13 n per 100 ISR RR (95% CI): 4.99 (0.59, 42.53) p = 0.10 **Sudden death** RR (95% CI): 1.00 (0.14, 7.05) p> 0.99	**Stroke** RR (95% CI): 2.00 (0.50, 7.93) p = 0.32	**CHF** 0.0 n per 100 HCTZ vs 0.45 n per 100 ISR RR (95% CI): NR p = 0.16	**Any major vascular event** 3.17 n per 100 HCTZ vs 5.65 n per 100 ISR RR (95% CI): 1.78 (0.94, 3.38) P = 0.07 **Major vascular events and procedures** 4.31 n per 100 HCTZ vs 6.78 n per 100 ISR RR (95% CI): 1.58 (0.90, 2.76) p = 0.10 **Other CVD death** RR (95% CI): 1.00 (0.06, 15.90) p > 0.99		**CV-related adverse reactions** 0.9% HCTZ vs 3.0% ISR p = NR

HAPPHY, 1987 Adult men, ages 40-64 years, with mild to moderate HTN DIUR: Diuretic: 50-100 mg HCTZ or 5-10 mg bendroflumethazide BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol N: 6,569 Mean 45.1 months Fair	**All deaths** OR (95% CI): 1.06 (0.80, 1.41) p > 0.20	**Non-fatal MI** OR (95% CI): 0.90 (0.66, 1.23) p > 0.20 **Fatal and/or non-fatal CHD** OR (95% CI): 0.88 (0.68, 1.14) p > 0.20 **Fatal CHD** OR (95% CI): 0.93 (0.64, 1.37) p > 0.20	**Non-fatal stroke** OR (95% CI): 1.11 (0.68, 1.83) p > 0.20 **Fatal and/or non-fatal stroke** OR (95% CI): 1.29 (0.82, 2.04) p > 0.20 **Fatal stroke** OR (95% CI): 3.37 (0.96, 9.53) p = 0.09	**Heart failure** 1.8 per 1000 py DIUR vs 2.6 per 1000 py BB p = NS (value NR)	**Patients with an endpoint of death, non-fatal MI, or non-fatal stroke** OR (95% CI): 0.98 (0.80, 1.20) p > 0.20 **Total endpoints of death, non-fatal MI, or non-fatal stroke** OR (95% CI): 1.00 (0.83, 1.21) p > 0.20 **Other deaths** OR (95% CI): 1.06 (0.69, 1.64) p > 0.20	**Change in serum Cr from baseline, (µmol/l)** +4.2 DIUR vs +4.0 BB p = NS (value NR)	**Dry mouth** 15.4% DIUR vs 12.5% BB p < 0.002 **Developed DM** 6.1 per 1000 py vs 6.9 per 1000 py BB p = NS (value NR) **Reporting any symptoms related to drug at 12 month visit** 16.8% DIUR vs 19.1% BB p < 0.001 **Cold hands and feet** 12.7% DIUR vs 21.4% BB p < 0.001 **Unusual tiredness** 15.4% DIUR vs 18.2% BB p < 0.005

MAPHY, 1988 Adult males, ages 40 to 64, either previously treated patients or newly detected and untreated HTN DIUR: Diuretic: HCTZ 50-100 mg/d or benfroflumethiazide 5-10 mg/d MET: Metoprolol: 200 mg/d N: 3,234 Median 4.16 years Fair *There was a protocol change in MAPHY that occurred more than 2 years after the first patient was randomized that allowed for additional centers that could randomize patients to atenolol or diuretics. The original study protocol did not include atenolol as an optional BB. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center are published separately as HAPPHY (see row above)*	**Total mortality at median 4.16 years** 9.3 per 1000 py DIUR vs 4.8 per 1000 py MET % difference (95% CI): -48 (-68, -17) **Total mortality at 10.8 years (end of study)** 10.3 per 1000 py DIUR vs 8.0 per 1000 py MET % difference: -22 p = 0.028 **Total sudden mortality at end of study** 45 events DIUR vs 32 events MET p = 0.017	**Fatal CHD (composite of MI or sudden coronary death) at 10.8 years** 43 events DIUR vs 36 events MET p = 0.048	**Fatal stroke at 10.8 years** 9 events DIUR vs 2 events MET p = 0.043	**Fatal HF at 10.8 years** 0 events DIUR vs 3 events MET p = NR	**CV mortality at median 4.16 years** 6.2 per 1000 py DIUR vs 2.6 per 1000 py MET % difference: -58 p = NR **CV mortality at 10.8 years (end of study)** 7.1 per 1000 py DIUR vs 5.2 per 1000 py MET % difference: -27 p = 0.012 **Sudden CV mortality at 10.8 years (end of study)** 5.6 per 1000 py DIUR vs 3.9 per 1000 py MET % difference: -30 p = 0.017 **Non-sudden CV mortality at 10.8 years (end of study)** 3.2 per 1000 py DIUR vs 2.8 per 1000 py MET % difference: -13 p = NS (value NR)		

ANBP2, 2003 Adults, ages 65 to 84, with absence of recent CV events DIU: Diuretic: HCTZ recommended; dose not specified ACE: ACE Inhibitor: Enalapril recommended; dose not specified N: 6,083 Median 4.1 years Fair	**Death from any cause** HR (95% CI): 0.90 (0.75, 1.09) p = 0.27	**Non-fatal MI** 5.8 per 1000 py DIUR vs 4.1 per 1000 py ACE HR (95% CI): 0.68 (0.47, 0.99) p = 0.05 **MI** 6.7 per 1000 py DIUR vs 4.7 per 1000 py ACE HR (95% CI): 0.68 (0.47, 0.98) p = 0.04 **Coronary event** HR (95% CI): 0.86 (0.70, 1.06) p = 0.16 **Fatal MI events** HR (95% CI): 0.79 (0.31, 1.99) p = 0.61 **Fatal coronary events** HR (95% CI): 0.74 (0.49, 1.11) p = 0.14	**Non-fatal Stroke** HR (95% CI): 0.93 (0.70, 1.26) p = 0.65 **Stroke** HR (95% CI): 1.02 (0.78, 1.33) p = 0.91 **Cerebrovascular event** HR (95% CI): 0.90 (0.73, 1.12) p = 0.35 **Fatal stroke events** 1.2 per 1000 py DIUR vs 2.3 per 1000 py ACE HR (95% CI): 1.91 (1.04, 3.50) p = 0.04	**Non-fatal HF** HR (95% CI): 0.85 (0.62, 1.17) p = 0.32 **HF** HR (95% CI): 0.85 (0.62, 1.18) p = 0.33 **Fatal HF events** HR (95% CI): 0.24 (0.03, 1.94) p = 0.18	**Non-fatal CV event** 32.8 per 1000 py DIUR vs 28.9 per 1000 py ACE HR (95% CI): 0.86 (0.74, 0.99) p = 0.03 **Non-fatal other CV** HR (95% CI): 0.84 (0.66, 1.07) p = 0.17 **All CV events or death from any cause** 59.8 per 1000 py DIUR vs 56.1 per 1000 py ACE HR (95% CI): 0.89 (0.79, 1.00) p = 0.05 **First CV event or death from any cause** 45.7 per 1000 py DIUR vs 41.9 per 1000 py ACE HR (95% CI): 0.89 (0.79, 1.01) p = 0.06 **First CV event** 37.1 per 1000 py DIUR vs 33.7 per 1000 py ACE HR (95% CI): 0.88 (0.77, 1.01) p = 0.07 **Other CV event** HR (95% CI): 0.90 (0.71, 1.14) p = 0.36 **Fatal CV events** HR (95% CI):		

					0.99 (0.72, 1.35) p = 0.94 **Other fatal CV events** HR (95% CI): 0.95 (0.46, 1.96) p = 0.89		

Table 178

4.3.1.1.2 Beta blockers versus other drugs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ASCOT-BPLA, 2005 Adults, age 40-79 years, with HTN and at least 3 CV risk factors ATN: Atenolol-based regimen: atenolol 50, 100 mg adding bendroflumethiazide 1.25, 2.5 mg + potassium and doxazosin GITS 4, 8 mg in steps AML: Amlodipine based regimen: amlodipine 5, 10 mg adding perindopril 4, 8 mg and doxazosin GITS 4, 8 mg in steps N: 19,342 Median 5.5 years Good	**All-cause mortality** 15.5 per 1000 pts ATN vs 13.9 per 1000 pts AML HR for AML (95% CI): 0.89 (0.81, 0.99) p = 0.0247	**Total coronary endpoint** 16.8 per 1000 pts ATN vs 14.6 per 1000 pts AML HR (95% CI) for AML: 0.87 (0.79, 0.96) p = 0.0070 **Silent MI** 0.6 per 1000 pts ATN vs 0.8 per 1000 pts AML HR (95% CI) for AML: 1.27 (0.80, 2.00) p = 0.3089 **PAD** 3.9 per 1000 pts ATN vs 2.5 per 1000 pts AML HR (95% CI) for AML: 0.65 (0.52, 0.81) p = 0.0001	**Fatal and non-fatal stroke** 8.1 per 1000 pts ATN vs 6.2 per 1000 pts AML HR (95% CI) for AML: 0.77 (0.66, 0.89) p = 0.0003	**Fatal and non-fatal HF** 3.0 per 1000 pts ATN vs 2.5 per 1000 pts AML HR (95% CI) for AML: 0.84 (0.66, 1.05) p = 0.1257	**Non-fatal MI (including silent MI) and fatal CHD** 9.1 per 1000 pts ATN vs 8.2 per 1000 pts AML HR (95% CI) for AML: 0.90 (0.79, 1.02) p = 0.1052 **Non-fatal MI (excluding silent MI) and fatal CHD** 8.5 per 1000 pts ATN vs 7.4 per 1000 pts AML HR (95% CI) for AML: 0.87 (0.76, 1.00) p = 0.0458 **Total CV events and procedures** 32.8 per 1000 pts ATN vs 27.4 per 1000 pts AML HR (95% CI) for AML: 0.84 (0.78, 0.90) p < 0.0001 **Composite of primary endpoints of non-fatal MI including silent MI and fatal CHD plus coronary revascularization procedures** 13.4 per 1000 pts ATN vs 11.5 per 1000 pts AML HR (95% CI) for AML: 0.86 (0.77, 0.96)		**Development of DM** 15.9 per 1000 pts ATN vs 11.0 per 1000 pts AML HR (95% CI) for AML: 0.70 (0.63, 0.78) p < 0.0001 **Dizziness** 16% ATN vs 12% AML p < 0.0001 **Dyspnea** 10% ATN vs 6% AML p < 0.0001 **Fatigue** 16% ATN vs 8% AML p < 0.0001 **Cough** 8% ATN vs 19% AML p < 0.0001 **Peripheral edema** 6% ATN vs 23% AML p < 0.0001 **Joint swelling** 3% ATN vs 14% AML p < 0.0001

					p = 0.0058 **CV death, MI and stroke** 18.4 per 1000 pts ATN vs 15.4 per 1000 pts AML (796) HR (95% CI) for AML: 0.84 (0.76, 0.92) p = 0.0003 **CV mortality** 6.5 per 1000 pts ATN vs 4.9 per 1000 pts AML HR (95% CI) for AML: 0.76 (0.65, 0.90) p = 0.0010		

LIFE, 2002 Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) N: 9,222 Mean 4.8 years Good Note: HR adjusted for degree of LVH and Framingham risk score at randomization	**Total mortality** 19.6 per 1000 py ATN vs 17.3 per 1000 py LOS AdjHR (95% CI) for LOS: 0.90 (0.78, 1.03) p = 0.128 UnadjHR (95% CI) for LOS: 0.88 (0.77, 1.01) p = 0.077	**MI** 8.7 per 1000 py ATN vs 9.2 per 1000 py LOS AdjHR (95% CI) for LOS: 1.07 (0.88, 1.31) p = 0.491 UnadjHR (95%CI) for LOS: 1.05 (0.86, 1.28) p = 0.628 **Revascularization** 13.3 per 1000 py ATN vs 12.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.94 (0.79, 1.11) p = 0.441 UnadjHR (95%CI) for LOS: 0.91 (0.77, 1.08) p = 0.292	**Stroke** 14.5 per 1000 py ATN vs 10.8 per 1000 py LOS AdjHR (95% CI) for LOS: 0.75 (0.63, 0.89) p = 0.001 UnadjHR (95% CI) for LOS: 0.74 (0.63, 0.88) p = 0.0006	**Heart Failure** 7.5 per 1000 py ATN vs 7.1 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97 (0.78, 1.21) p = 0.765 UnadjHR (95% CI) for LOS: 0.95 (0.76, 1.18) p = 0.622	**Primary composite endpoint of CV death, MI or stroke** 27.9 per 1000 py ATN vs 23.8 per 1000 py LOS AdjHR (95% CI) for LOS: 0.87 (0.77, 0.98) p = 0.021 UnadjHR (95% CI) for LOS: 0.85 (0.76, 0.96) p = 0.009 **CV mortality** 10.6 per 1000 py ATN vs 9.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.89 (0.73, 1.07) p = 0.206 UnadjHR (95% CI) for LOS: 0.87 (0.72, 1.05) p = 0.136		**New diabetes** 17.4 per 1000 py ATN vs 13.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001 UnadjHR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001 **Lower extremity** 14% ATN vs 12% LOS p = 0.002 **Albuminuria** 6% ATN vs 5% LOS p = 0.0002 **Hyperglycemia** 7% ATN vs 5% LOS p = 0.007 **Asthenia/Fatigue** 17% ATN vs 15% LOS p = 0.001 **Dyspnea** 14% ATN vs 10% LOS p < 0.0001 **Angioedema** 0.2% ATN vs 0.1% LOS p = 0.237 **Cough** 2% ATN vs 3% LOS p = 0.220

							Dizziness 16% ATN vs 17% LOS p = 0.247 **Chest pain** 10% ATN vs 11% LOS p = 0.068 **Hypotension** 2% ATN vs 3% LOS p = 0.001 **Back pain** 10% ATN vs 12% LOS p = 0.004

LIFE, 2002 *Subanalysis of Isolated Systolic Hypertension* Kjeldsen et al, 2002 Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if trough sitting SBP 160-200 mmHg with DBP <90 mmHg after 1 and 2 weeks placebo ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) N: 9,222 in full trial (1,326 with isolated systolic hypertension) Mean 4.7 years Fair NOTE: Adjusted RRs are adjusted for degree of LVH and Framingham risk score at randomization Interaction between treatment and ISH status was not statistically significant	*Subanalysis of patients with Isolated Systolic Hypertension* **Total mortality** 30.2 per 1000 py ATN vs 21.2 per 1000 py LOS AdjRR (95% CI) for LOS: 0.72 (0.53, 1.00) p = 0.046 UnadjRR (95% CI) for LOS: 0.70 (0.51, 0.96) p = 0.03 *Subanalysis of patients without Isolated Systolic Hypertension* **Total mortality** 17.9 per 1000 py ATN vs 16.7 per 1000 py LOS AdjRR (95% CI) for LOS: 0.95 (0.82, 1.11) p = 0.51 UnadjRR (95%CI) for LOS: 0.93 (0.80, 1.09) p = 0.38	*Subanalysis of patients with Isolated Systolic Hypertension* **MI** 11.9 per 1000 py ATN vs 10.2 per 1000 py LOS AdjRR (95% CI) for LOS: 0.89 (0.55, 1.44) p = 0.64 UnadjRR (95% CI) for LOS: 0.86 (0.53, 1.39) p = 0.54 **Revascularization** 14.4 per 1000 py ATN vs 16.4 per 1000 py LOS AdjRR (95% CI) for LOS: 1.17 (0.78, 1.77) p = 0.45 UnadjRR (95% CI) for LOS: 1.14 (0.76, 1.72) p = 0.53 *Subanalysis of patients without Isolated Systolic Hypertension* **MI** 8.2 per 1000 py ATN vs 9.0 per 1000 py LOS AdjRR (95% CI) for LOS: 1.12 (0.90, 1.40) p = 0.30 UnadjRR (95% CI) for LOS: 1.10 (0.88, 1.36) p = 0.41 **Revascularization**	*Subanalysis of patients with Isolated Systolic Hypertension* **Stroke** 18.9 per 1000 py ATN vs 10.6 per 1000 py LOS AdjRR (95% CI) for LOS: 0.60 (0.38, 0.92) p = 0.02 UnadjRR (95% CI) for LOS: 0.56 (0.36, 0.86) p = 0.008 *Subanalysis of patients without Isolated Systolic Hypertension* **Stroke** 13.8 per 1000 py ATN vs 10.8 per 1000 py LOS AdjRR (95% CI) for LOS: 0.79 (0.66, 0.95) p = 0.01 UnadjRR (95%CI) for LOS: 0.78 (0.65, 0.94) p = 0.01	*Subanalysis of patients with Isolated Systolic Hypertension* **Hospitalization for Heart Failure** 13.3 per 1000 py ATN vs 8.5 per 1000 py LOS AdjRR (95% CI) for LOS: 0.66 (0.40, 1.09) p = 0.11 UnadjRR (95% CI) for LOS: 0.64 (0.39, 1.05) p = 0.08 *Subanalysis of patients without Isolated Systolic Hypertension* **Hospitalization for Heart Failure** 6.5 per 1000 py ATN vs 6.8 per 1000 py LOS AdjRR (95% CI) for LOS: 1.06 (0.83, 1.36) p = 0.65 UnadjRR (95% CI) for LOS: 1.05 (0.82, 1.34) p = 0.72	*Subanalysis of patients with Isolated Systolic Hypertension* **Primary composite endpoint of CV death, MI or stroke** 35.4 per 1000 py ATN vs 25.1 per 1000 py LOS AdjRR (95% CI) for LOS: 0.75 (0.56, 1.01) p = 0.06 UnadjRR (95% CI) for LOS: 0.71 (0.53, 0.95) p = 0.02 **CV mortality** 16.9 per 1000 py ATN vs 8.7 per 1000 py LOS AdjRR (95% CI) for LOS: 0.54 (0.34, 0.87) p = 0.01 UnadjRR (95%CI) for LOS: 0.51 (0.32, 0.81) p = 0.004 *Subanalysis of patients without Isolated Systolic Hypertension* **Primary composite endpoint of CV death, MI or stroke** 26.7 per 1000 py ATN vs 23.6 per 1000 py LOS AdjRR (95% CI) for LOS: 0.90 (0.79, 1.02) p = 0.11 UnadjRR (95%CI) for LOS: 0.88 (0.78, 1.01) p = 0.06		**Bradycardia** 14.6% ATN vs 3.0% LOS p < 0.001 **Cold extremities** 6.6% ATN vs 4.1% LOS p = 0.05 **Angioedema** 0.3% ATN vs 0.3% LOS p = 0.99 **Cough** 2.9% ATN vs 4.1% LOS p = 0.23 *Subanalysis of patients with Isolated Systolic Hypertension* **New diabetes** 20.1 per 1000 py ATN vs 12.6 per 1000 py LOS AdjHR (95% CI) for LOS: 0.62 (0.40, 0.97) p = 0.04 UnadjHR (95%CI) for LOS: 0.63 (0.40, 0.99) p = 0.04 *Subanalysis of patients without Isolated Systolic Hypertension* **New diabetes** 17.0 per 1000 py ATN vs 13.1 per 1000 py LOS

		13.2 per 1000 py ATN vs 11.5 per 1000 py LOS AdjRR (95% CI) for LOS: 0.89 (0.74, 1.08) p = 0.23 UnadjRR (95% CI) for LOS: 0.87 (0.73, 1.05) p = 0.15			**CV mortality** 9.6 per 1000 py ATN vs 9.3 per 1000 py LOS AdjRR (95% CI) for LOS: 0.99 (0.80, 1.22) p = 0.90 UnadjRR (95%CI) for LOS: 0.97 (0.79, 1.19) p = 0.77		AdjRR (95% CI) for LOS: 0.77 (0.64, 0.92) p = 0.005 UnadjRR (95%CI) for LOS: 0.77 (0.64, 0.92) p = 0.004

LIFE, 2003 *Subanalysis of subjects with and without clinically evident vascular disease* Devereux et al, 2003 Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) N: 9,222 in full trial (6,886 without clinically evident vascular disease at baseline) Mean 4.8 years Fair NOTE: Adjusted HRs are adjusted for degree of LVH and Framingham risk score at randomization Interaction between treatment and presence or absence of arterial disease was not statistically significant for primary endpoint	*Subanalysis of subjects without clinically evident vascular disease* **Total mortality** 15.9 per 1000 py ATN vs 13.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.85 (0.71, 1.02) p = 0.080 *Subanalysis of subjects with clinically evident vascular disease* **Total mortality** 31.7 per 1000 py ATN vs 28.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.94 (0.75, 1.16) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **MI** 6.0 per 1000 py ATN vs 6.8 per 1000 py LOS AdjHR (95% CI) for LOS: 1.14 (0.87, 1.49) p > 0.2 **Revascularization** 9.0 per 1000 py ATN vs 7.6 per 1000 py LOS AdjHR (95% CI) for LOS: 0.85 (0.67, 1.08) p = 0.18 *Subanalysis of subjects with clinically evident vascular disease* **MI** 17.7 per 1000 py ATN vs 16.3 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97 (0.72, 1.31) p > 0.2 **Revascularization** 28.4 per 1000 py ATN vs 26.3 per 1000 py LOS AdjHR (95% CI) for LOS: 0.98 (0.78, 1.25) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **Stroke** 11.8 per 1000 py ATN vs 7.7 per 1000 py LOS AdjHR (95% CI) for LOS: 0.66 (0.53, 0.82) p < 0.001 *Subanalysis of subjects with clinically evident vascular disease* **Stroke** 23.7 per 1000 py ATN vs 20.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.87 (0.67, 1.13) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **Hospitalization for Heart Failure** 4.4 per 1000 py ATN vs 4.7 per 1000 py LOS AdjHR (95% CI) for LOS: 1.06 (0.77, 1.46) p > 0.2 *Subanalysis of subjects with clinically evident vascular disease* **Hospitalization for Heart Failure** 17.7 per 1000 py ATN vs 14.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.84 (0.62, 1.14) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **Primary composite endpoint of CV death, MI or stroke** 21.8 per 1000 py ATN vs 17.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.81 (0.69, 0.95) p = 0.008 **CV mortality** 7.8 per 1000 py ATN vs 6.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.80 (0.62, 1.04) p = 0.092 *Subanalysis of subjects with clinically evident vascular disease* **Primary composite endpoint of CV death, MI or stroke** 48.6 per 1000 py ATN vs 43.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.93 (0.77, 1.11) p > 0.2 **CV mortality** 19.8 per 1000 py ATN vs 18.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.95 (0.72, 1.25) p > 0.2		**Patients with at least one adverse event of any type** 17.3% ATN vs 12.7% LOS p < 0.001 **Patients with at least one drug related adverse event** 10.2% ATN vs 6.0% LOS p < 0.001 **Patients with at least one serious drug related adverse event** 1.0% ATN vs 0.5% LOS p = 0.018 **Asthenia or fatigue** 16.9% ATN vs 14.2% LOS p < 0.002 **Lower extremity edema** 13.6% ATN vs 11.5% LOS p < 0.008 **Dyspnea** 13.6% ATN vs 8.8% LOS p < 0.001 **Hyperglycemia** 6.7% ATN vs 5.4% LOS p = 0.023 **Patients with at least one serious**

							adverse event 4.4% ATN vs 3.8% LOS p > 0.2 **Back pain** 10.0% ATN vs 12.0% LOS p = 0.009 *Subanalysis of subjects without clinically evident vascular disease* **New diabetes** 17.7 per 1000 py ATN vs 12.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.69 (0.57, 0.84) p < 0.001 *Subanalysis of subjects with clinically evident vascular disease* **New diabetes** 16.4 per 1000 py ATN vs 15.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97(0.69, 1.36) p > 0.2

MAPHY Wilkstrand et al, 1988 Olsson et al, 1991 Wilkstrand et al, 1991 Adult males, ages 40 to 64, either previously treated patients or newly detected and untreated HTN MET: Metoprolol: 200 mg/d DIUR: Diuretic: HCTZ 50 mg/d or bendroflumethiazide 5 mg/d N: 3,234 Median 4.16 years Fair *There was a protocol change in MAPHY that occurred more than 2 years after the first patient was randomized that allowed for additional centers that could randomize patients to atenolol or diuretics.* *The original study protocol did not include atenolol as an optional BB. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center are published separately as HAPPHY*	At median 4.16 years **Total mortality** 4.8 per 1000 py MET vs 9.3 per 1000 py DIUR % difference (95% CI): -48 (-68, -17) p=NR At end of study (10.8 years) **Total mortality** 8.0 per 1000 py MET vs 10.3 per 1000 py DIUR % difference: -22 p=0.028 **Total sudden mortality** 32 events MET vs 45 events DIUR p= 0.017	At 10.8 years **Fatal CHD (composite of MI or sudden coronary death)** 36 events MET vs 43 events DIUR p = 0.048	At 10.8 years **Fatal stroke** 2 events MET vs 9 events DIUR p = 0.043	At 10.8 years **Fatal Heart Failure** 3 events MET vs 0 events DIUR p = NR	At median 4.16 years **First CV event: definite non-fatal acute MI** 5.7 per 1000 py MET vs 7.0 per 1000 py DIUR p = NR **First CV event: definite non-fatal silent MI** 4.8 per 1000 py MET vs 7.1 per 1000 py DIUR p = NR **First CV event: definite non-fatal stroke** 2.7 per 1000 py MET vs 2.4 per 1000 py DIUR p = NR **First CV event, all definite events** 17.3 per 1000 py MET vs 22.3 per 1000 py DIUR RR (95% CI): 0.60 (0.44, 0.81) p = 0.0009 **First CV event, all definite and possible events** 23.3 per 1000 py MET vs 30.5 per 1000 py DIUR p = 0.0011 **First CV event: fatal coronary event** 3.7 per 1000 py MET vs 4.5 per 1000 py DIUR p = NR		

					First CV event: fatal other CV event 0.1 per 1000 py MET vs 0.5 per 1000 py DIUR p = NR **First CV event: fatal stroke** 0.3 per 1000 py MET vs 0.9 per 1000 py DIUR p = NR		

IPPPSH, 1985 Adults, age 40 to 64 years with seated DBPs of 100 to 125 mmHg, either untreated or receiving anti- HTN at study entry BB: Slow-release oxprenolol 160 mg QD Non-BB: placebo as sole anti-HTN treatment given or initial step in otherwise open anti-HTN regimen N: 6,708 3 to 5 years (mean NR) Fair	**Total mortality** 8.3 per 1000 py BB vs 8.8 per 1000 py Non-BB RR (95% CI): 0.95 (0.73, 1.24) p = NR	**Non-fatal MI** 4.4 per 1000 py BB vs 5.2 per 1000 py Non-BB RR (95% CI): 0.84 (0.59, 1.20) p = NR **All MI** 4.7 per 1000 py BB vs 5.7 per 1000 py Non-BB RR (95% CI): 0.83 (0.59, 1.16) p = NR **All cardiac events** 7.6 per 1000 py BB vs 8.4 per 1000 py Non-BB RR (95% CI): 0.91 (0.69, 1.20) p = NR **Fatal MI** (first event analysis) 0.3 per 1000 py BB vs 0.5 per 1000 py Non-BB RR (95% CI): 0.66 (0.19, 2.34) p = NR **Fatal MI** (includes deaths following non-fatal events) 0.3 per 1000 py BB vs 0.8 per 1000 py Non-BB RR (95% CI): 0.40 (0.13, 1.29) p = NR **Sudden death** (first event analysis) 2.9 per 1000 py BB vs 2.7 per 1000 py Non-BB	**Non-fatal CVA** 3.1 per 1000 py BB vs 3.0 per 1000 py Non-BB RR (95% CI): 1.04 (0.67, 1.63) p = NR **All stroke (CVA)** 3.5 per 1000 py BB vs 3.6 per 1000 py Non-BB RR (95% CI): 0.97 (0.64, 1.47) p = NR **Fatal CVA** (first event analysis) 0.4 per 1000 py BB vs 0.6 per 1000 py Non-BB RR (95% CI): 0.62 (0.20, 1.90) p = NR **Fatal CVA** (includes deaths following non-fatal events) 0.4 per 1000 py BB vs 0.8 per 1000 py Non-BB RR (95% CI): 0.50 (0.17, 1.47) p = NR		**Critical events of sudden cardiac death, fatal or non-fatal definite MI and cerebrovascular accidents** 11.1 per 1000 py BB vs 12.0 per 1000 py Non-BB RR (95% CI): 0.99 (0.79, 1.24) p = NR **CV mortality** 2.6 per 1000 py MET vs 6.2 per 1000 py DIUR % difference: -58 p = NR **Sudden CV mortality** 2.1 per 1000 py MET vs 4.8 per 1000 py DIUR % difference: -56 p = NR At end of study (10.8 years) **First CV event, all definite events** MET vs. DIUR: RR (95% CI): 0.77 (0.61, 0.98) p=NR **CV mortality** 5.2 per 1000 py MET vs 7.1 per 1000 py DIUR % difference: -27 p = 0.012 **Sudden CV mortality** 3.9 per 1000 py MET vs 5.6 per 1000 py	**Impaired renal function (creatinine >177 µmol/l and urea >10 mmol/l)** 15 events BB vs 23 events Non-BB p = NR	**Cold extremities** 35.8 per 1000 patients BB vs 19.2 per 1000 patients Non-BB p < 0.01 **Dyspepsia** 114.9 per 1000 patients BB vs 101.5 per 1000 patients Non-BB p < 0.05 **Constipation** 349.4 per 1000 patients BB vs 324.3 per 1000 patients Non-BB p < 0.05 **Increased sweating** 494.6 per 1000 patients BB vs 464.2 per 1000 py Non-BB p < 0.05 **Serum potassium <3.0 mmol/l on at least 1 occasion during study** 2.6% BB vs 4.7% Non-BB p = NR **Serum potassium <3.5 mmol/l on at least 1 occasion during study** 18% BB vs 29% Non-BB p < 0.001 **Impotence and libido decrease** 79.8 per 1000 patients BB vs 100.1 per 1000 patients Non-BB p < 0.05

		RR (95% CI): 1.08 (0.68, 1.72) p = NR **Sudden death** (includes deaths following non-fatal events) 2.8 per 1000 py BB vs 2.8 per 1000 py Non-BB RR (95% CI): 1.01 (0.63, 1.60) p = NR			DIUR % difference: -30 p = 0.017		**Anxiety, depression, other emotional disorders** 148.5 per 1000 patients BB vs 176.5 per 1000 patients Non-BB p < 0.01 **Headache** 260.3 per 1000 patients BB vs 312.1 per 1000 patients Non-BB p < 0.01 **Dizziness** 142.5 per 1000 patients BB vs 154.8 per 1000 patients Non-BB p < 0.05 **Dry mouth** 423.2 per 1000 patients BB vs 478.3 per 1000 patients Non-BB p < 0.01 **Frequency and nocturia** 544.9 per 1000 patients BB vs 593.3 per 1000 patients Non-BB p < 0.01

MRC, 1985 Adults, ages 35-64 years, with mild to moderate HTN PRO: Propranolol: 240 mg QD BEN: Bendrofluazide: 10 mg QD N: 17,354 5.5	**All deaths** 5.5 per 1000 py PRO vs 6.0 per 1000 py BEN p = 0.71	**Coronary events** 4.8 per 1000 py PRO vs 5.6 per 1000 py BEN p = 0.24	**Strokes** 1.9 per 1000 py PRO vs 0.8 per 1000 py BEN p = 0.002		**All CV events** 6.7 per 1000 py PRO vs 6.6 per 1000 py BEN p = 0.76		

HAPPHY, 1987 Adult men, ages 40-64 years, with mild to moderate HTN BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol DIUR: Diuretic: 50 mg HCTZ or 5 mg bendroflumethazide N: 6,569 Mean 45.1 months Fair	**All deaths** OR (95% CI) for DIUR: 1.06 (0.80, 1.41) p > 0.20	**Non-fatal MI** OR (95% CI) for DIUR: 0.90 (0.66, 1.23) p > 0.20 **Fatal and/or non-fatal CHD** OR (95% CI) for DIUR: 0.88 (0.68, 1.14) p > 0.20 **Fatal CHD** OR (95% CI) for DIUR: 0.93 (0.64, 1.37) p > 0.20	**Non-fatal stroke** OR (95% CI) for DIUR: 1.11 (0.68, 1.83) p > 0.20 **Fatal and/or non-fatal stroke** OR (95% CI) for DIUR: 1.29 (0.82, 2.04) p > 0.20 **Fatal stroke** 0.24 per 1000 py BB vs 0.82 per 1000 py DIUR OR (95% CI) for DIUR: 3.37 (0.96, 9.53) p = 0.09	**Heart failure** 2.6 per 1000 py BB vs 1.8 per 1000 py DIUR p = NS (value NR)	**Patients with an endpoint of death, non-fatal MI, or non-fatal stroke** OR (95% CI) for DIUR: 0.98 (0.80, 1.20) p > 0.20 **Total endpoints of death, non-fatal MI, or non-fatal stroke** OR (95% CI) for DIUR: 1.00 (0.83, 1.21) p > 0.20 **Other deaths** OR (95% CI) for DIUR: 1.06 (0.69, 1.64) p > 0.20	**Change in serum Cr from baseline, (µmol/l)** +4.0 BB vs +4.2 DIUR p = NS (value NR)	**Reporting any symptoms related to drug at 12 month visit** 19.1% BB vs 16.8% DIUR p < 0.001 **Cold hands and feet** 21.4% BB vs 12.7% DIUR p < 0.001 **Unusual tiredness** 18.2% BB vs 15.4% DIUR p < 0.005 **Developed DM** 6.9 per 1000 py BB vs 6.1 per 1000 py DIUR p = NS **Dry mouth** 12.5% BB vs 15.4% DIUR p < 0.002

Table 179

4.3.1.1.3 Calcium channel blocker versus other drugs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebro-vascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ALLHAT, 2002 Adults, ≥ 55 years of age with at least one additional risk factor for CHD AML: Amlodipine: 2.5, 5, and 10 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD CHL: Chlorthalidone: 12.5, 25 mg QD N: 33,357 Mean 4.9 years Good	**All-cause mortality** AML vs CHL: RR (95% CI) for AML: 0.96 (0.89, 1.02) p = 0.20	**CHD (fatal CHD and nonfatal MI)** AML vs CHL: RR (95% CI) for AML: 0.98 (0.90, 1.07) p = 0.65 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** AML vs. CHL: RR (95% CI) for AML: 1.00 (0.94, 1.07) p = 0.97 **Coronary revascularization** AML vs. CHL: RR (95% CI) for AML: 1.09 (1.00, 1.20) p = 0.06 **Hospitalized or treated PAD** AML vs. CHL: RR (95% CI) for AML: 0.87 (0.75, 1.01) p = 0.06 **MI death** AML vs. CHL: 2.3 per 100 persons AML vs 2.4 per 100 persons CHL RR	**Stroke** AML vs. CHL: RR (95% CI) for AML: 0.93 (0.82, 1.06) p = 0.28 **Death from stroke** AML vs. CHL: 1.4 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.71	**HF** AML vs. CHL: RR (95% CI) for AML: 1.38 (1.25, 1.52) p < 0.001 **Hospitalized/fatal HF** AML vs. CHL: RR (95% CI) for AML: 1.35 (1.21, 1.50) p < 0.001 **HF death** AML vs CHL: 1.4 per 100 persons AML vs 1.0 per 100 persons CHL RR (95% CI): NR p = 0.17	**Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)** AML vs. CHL: RR (95% CI) for AML: 1.04 (0.99, 1.09) p = 0.12 **Cardiovascular death** AML vs. CHL: 8.5 per 100 persons AML vs 8.0 per 100 persons CHL RR (95% CI): NR p = 0.76 **Other CVD death** AML vs. CHL: 1.7 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.46	**ESRD** AML vs. CHL: RR (95% CI) for AML: 1.12 (0.89, 1.40) p = 0.33 **Kidney disease death** AML vs. CHL: 0.5 per 100 persons AML vs 0.4 per 100 persons CHL RR (95% CI): NR p = 0.68	**Angioedema** <0.1% AML vs 0.4% LIS vs 0.1% CHL p = NR At 4 years **Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL:** 9.8% AML vs 11.6% CHL p = 0.04

		(95% CI): NR p = 0.66 **Definite CHD death** AML vs. CHL: 1.2 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.88 **Possible CHD death** AML vs. CHL: 1.1 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.62					

ALLHAT, 2006 Adults, ≥ 55 years of age with at least one additional risk factor for CHD AML: Amlodipine: 2.5, 5, and 10 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD N: 18, 102 Mean 4.9 years Fair	**All-cause mortality** LIS vs AML: RR (95% CI): 1.05 (0.97, 1.13) p = 0.214	**CHD (fatal CHD and nonfatal MI)** LIS vs AML: RR (95% CI): 1.01 (0.91, 1.11) p = 0.854 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** LIS vs AML: RR (95% CI): 1.04 (0.97, 1.12) p = 0.243 **Coronary revascularization** LIS vs AML: RR (95% CI): 1.00 (0.91, 1.11) p = 0.943 **Hospitalized or fatal PAD** **LIS vs AML:** RR (95% CI): 1.19 (1.01, 1.40) p = 0.036	**Stroke** LIS vs AML: RR (95% CI): 1.23 (1.08, 1.41) p = 0.003	**HF** LIS vs AML: RR (95% CI): 0.87 (0.78, 0.96) P = 0.007 **Hospitalized/fatal HF** LIS vs AML: RR (95% CI): 0.81 (0.72, 0.92) p <0.001	**Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)** LIS vs AML: RR (95% CI): 1.06 (1.00, 1.12) p = 0.047	**ESRD** LIS vs AML: RR (95% CI): 0.99 (0.77, 1.26) p = 0.929	**Angioedema** 0.03% AML vs 0.42% LIS p <0.001 **Hospitalization for GI bleeding** 8.0 per 100 AML vs 9.6 per 100 LIS p = 0.04 At 4 years **DM (>=7.0 mmol/L) if no DM at baseline** 10.4% AML vs 9.4% LIS p = 0.30

CASE-J, 2008 Adults with high CVD risk AML: Amlodipine 2.5-10 mg/day CAN: Candesartan 4-12 mg/day N: 4,728 Mean 3.2 years Good	**All-cause death** 11.1 per 1000 p-y AML vs 9.4 per 1000 p-y CAN HR (95% CI): NR p = NS	**Acute MI** HR (95% CI) for CAN: 0.95 (0.49, 1.84) p = 0.870 **Sudden death** HR (95% CI) for CAN: 0.73 (0.34, 1.60) p = 0.434	**Cerebrovascular events** HR (95% CI) for CAN: 1.23 (0.85, 1.78) p = 0.282 **Stroke** HR (95% CI) for CAN: 1.28 (0.88, 1.88) p = 0.198 **TIA** HR (95% CI) for CAN: 0.50 (0.09, 2.73) p = 0.414	**Heart Failure** HR (95% CI) for CAN: 1.25 (0.65, 2.42) p = 0.498	**Primary composite endpoint** HR (95% CI) for CAN: 1.01 (0.79, 1.28) p = 0.969 **Cardiac events** HR (95% CI) for CAN: 0.92 (0.61, 1.39) p = 0.680 **Peripheral vascular events** HR (95% CI) for CAN: 1.57 (0.61, 4.05) p = 0.348	**Renal events** HR (95% CI) for CAN: 0.70 (0.39, 1.26) p = 0.230 **Creatinine abnormality** HR (95% CI) for CAN: 0.73 (0.40, 1.31) p = 0.287 **ESRD** HR (95% CI) for CAN: 0.40 (0.13, 1.29) p = 0.112	**New onset diabetes** HR (95% CI) for CAN: 0.64 (0.43, 0.97) p=0.033 **Hyperkalemia** 0.3% AML vs 1.0% CAN p = NR

ASCOT-BPLA, 2005 Adults, age 40-79 years, with HTN and at least 3 CV risk factors AML: Amlodipine based regimen: Step 1: Amlodipine 5 mg Step 2: Amlodipine 10 mg Step 3: Amlodipine 10 mg + perindopril 4 mg Step 4: Amlodipine 10 mg + perindopril 8 mg (2 x 4 mg) Step 5: Amlodipine 10 mg + perindopril 8 mg + doxazosin GITS 4 mg Step 6: Amlodipine 10 mg + perindopril 8 mg + doxazosin GITS 8 mg ATN: Atenolol-based regimen: Step 1: Atenolol 50 mg Step 2: Atenolol 100 mg Step 3: Atenolol 100 mg + bendroflumethiazide 1.25 mg + potassium Step 4: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium Step 5: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin GITS 4 mg Step 6: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin GITS 8 mg N: 19,342 Median 5.5 years Good	**All-cause mortality** HR (95% CI) for AML: 0.89 (0.81, 0.99) p = 0.0247	**Total coronary endpoint** HR (95% CI) for AML: 0.87 (0.79, 0.96) p = 0.0070 **Silent MI** HR (95% CI) for AML: 1.27 (0.80, 2.00) p = 0.3089 **PAD** HR (95% CI) for AML: 0.65 (0.52, 0.81) p = 0.0001	**Fatal and non-fatal stroke** HR (95% CI) for AML: 0.77 (0.66, 0.89) p = 0.0003	**Fatal and non-fatal HF** HR (95% CI) for AML: 0.84 (0.66, 1.05) p = 0.1257	**Non-fatal MI (including silent MI) and fatal CHD** HR (95% CI) for AML: 0.90 (0.79, 1.02) p = 0.1052 **Non-fatal MI (excluding silent MI) and fatal CHD** HR (95% CI) for AML: 0.87 (0.76, 1.00) p = 0.0458 **Total CV events and procedures** HR (95% CI) for AML: 0.84 (0.78, 0.90) p < 0.0001 **Composite of primary endpoints of non-fatal MI including silent MI and fatal CHD plus coronary revascularization procedures** HR (95% CI) for AML: 0.86 (0.77, 0.96) p = 0.0058 **CV death, MI and stroke** HR (95% CI) for AML: 0.84 (0.76, 0.92) p = 0.0003 **CV mortality** HR (95% CI) for AML: 0.76 (0.65, 0.90) p = 0.0010		**Cough** 19% AML vs 8% ATN p < 0.0001 **Peripheral edema** 23% AML vs 6% ATN p < 0.0001 **Joint swelling** 14% AML vs 3% ATN p < 0.0001 **Development of DM** HR (95% CI) for AML: 0.70 (0.63, 0.78) p < 0.0001 **Dizziness** 12% AML vs 16% ATN p < 0.0001 **Dyspnea** 6% AML vs 10% ATN p < 0.0001 **Fatigue** 8% AML vs 16% ATN p < 0.0001

VALUE, 2004 Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD AML: Amlodipine step-up therapy Step 1: amlodipine 5 mg Step 2: amlodipine 10 mg Step 3: amlodipine 10 mg + HCTZ 12.5 mg Step 4: amlodipine 10 mg + HCTZ 25 mg Step 5: other HTN drugs VAL: Valsartan step-up therapy Step 1: valsartan 80 mg Step 2: valsartan 160 mg Step 3: valsartan 160 mg + HCTZ 12.5 mg Step 4: valsartan 160 mg + HCTZ 25 mg Step 5: other HTN drugs N: 15,313 Mean exposure to study medication of 3.6 years; mean 4.2 years F/U Good	**All-cause death** HR (95% CI) for VAL: 1.04 (0.94, 1.14) p= 0.45	**Fatal and non-fatal MI** HR (95% CI) for VAL: 1.19 (1.02, 1.38) p= 0.02	**Fatal and non-fatal stroke** HR (95% CI) for VAL: 1.15 (0.98, 1.35) p= 0.08	**Fatal and non-fatal HF** HR (95% CI) for VAL: 0.89 (0.77, 1.03) p = 0.12	**Primary composite of time to first cardiac event** HR (95% CI) for VAL: 1.04 (0.94, 1.15) p= 0.49 **Cardiac morbidity** HR (95% CI) for VAL: 1.02 (0.91, 1.15) p= 0.71 **Cardiac mortality** HR (95% CI) for VAL: 1.01 (0.86, 1.18) p = 0.90		**New onset DM** OR (95% CI) for VAL: 0.77 (0.69, 0.86) p < 0.0001

NORDIL, 2000 Adults 50-74 years old with previously treated or untreated primary HTN DIL: Diltiazem 180-360 mg daily DIUR or BB: Thiazide diuretic or BB (dose NR) in first step; diuretic and BB combined in second step N: 10,916 Mean 4.5 years Good	**Total mortality** RR (95% CI) for DIL: 1.00 (0.83, 1.20) p = 0.99	**All MI** RR (95% CI) for DIL: 1.16 (0.94, 1.44) p = 0.17 **Fatal MI** RR (95% CI) for DIL: 1.10 (0.64, 1.88) p = 0.74 **All Cardiac Events** RR (95% CI) for DIL: 1.04 (0.91, 1.18) p = 0.57	**All Stroke** RR (95% CI) for DIL: 0.80 (0.65, 0.99) p = 0.04 **Fatal Stroke** RR (95% CI) for DIL: 0.96 (0.52, 1.74) p = 0.89 **All Stroke plus TIA** RR (95% CI) for DIL: 0.84 (0.70, 1.01) p = 0.07	**CHF** RR (95% CI) for DIL: 1.16 (0.81, 1.67) p = 0.42	**Primary endpoint (composite of fatal and nonfatal stroke, fatal and nonfatal MI, and other CV death)** RR (95% CI) for DIL: 1.00 (0.87, 1.15) p = 0.97 **CV Death** RR (95% CI) for DIL: 1.11 (0.87, 1.43) p = 0.41		**Headaches** 8.5% DIL vs 5.7% DIUR or BB p < 0.001 **Diabetes** RR (95% CI) for DIL: 0.87 (0.73, 1.04) p = 0.14 **Fatigue** 4.4% DIL vs 6.5% DIUR or BB p < 0.001 **Dyspnea** 2.9% DIL vs 3.9% DIUR or BB p = 0.006 **Impotence** 2.3% DIL vs 3.7% DIUR or BB p < 0.001

STOP Hypertension-2, 1999 Adults 70-84 years old with HTN CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5 mg QD ACE: ACE inhibitors: enalapril 10 mg, or lisinopril 10 mg BB or DIUR: atenolol 50 mg, or metoprolol 100 mg, or pindolol 5 mg, or fixed ratio HCTZ 25 mg plus amiloride 2.5 mg N: 6,614 Mean F/U unclear; authors report study duration of 60 months; max BP measurement reported is 54 months, and Kaplan-Meier curves extend to 6 years Good	**Total mortality** ACE vs. CCB: RR (95% CI) for ACE: 1.03 (0.69, 1.19) p = 0.71 **Total mortality** CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.66, 1.15) p = 0.90	**All MI** ACE vs CCB: RR (95% CI) for ACE: 0.77 (0.61, 0.96) p = 0.016 **All MI** CCB vs. BB or DIUR: RR (95% CI) for CCB: 1.18 (0.95, 1.47) p = 0.13 **Sudden death** 4.7 per 1000 p-y CCB vs 5.3 per 1000 p-y ACE vs 4.8 per 1000 p-y BB or DIUR p = NR **Fatal MI** 5.3 per 1000 p-y CCB vs 4.3 per 1000 p-y ACE vs 4.9 per 1000 p-y BB or DIUR p = NR	**All stroke** ACE vs CCB: RR (95% CI) for ACE: 1.02 (0.64, 1.24) p = 0.64 **All stroke** CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.66 (0.73, 1.06) p = 0.16 **Fatal stroke** 4.2 per 1000 p-y CCB vs 4.5 per 1000 p-y ACE vs 4.6 per 1000 p-y BB or DIUR p = NR	**Frequency CHF** ACE vs CCB: RR (95% CI) for ACE: 0.76 (0.63, 0.97) p = 0.025 **Frequency CHF** CCB vs BB or DIUR: RR (95% CI) for CCB: 1.06 (0.67, 1.31) p = 0.56	**All major CV events** ACE vs. CCB: RR (95% CI) for ACE: 0.95 (0.63, 1.06) p = 0.42 **All major CV events** CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.67, 1.12) p = 0.65 **CV mortality** ACE vs CCB RR (95% CI) for ACE: 1.04 (0.66, 1.26) p = 0.67 **CV mortality** CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.60, 1.17) p = 0.72 **Other CV mortality** 5.0 per 1000 p-y vs 6.2 per 1000 p-y vs BB or DIUR: 5.6 per 1000 p-y p = NR		**Frequency of DM** ACE vs. CCB: RR (95% CI) for ACE: 0.96 (0.74, 1.31) p = 0.91 **Frequency of DM** CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.73, 1.29) p = 0.63 **Ankle edema** 25.5% CCB vs 8.7% ACE vs 8.5% BB or DIUR p = NR **Dry cough** 30.1% ACE vs 5.7% CCB vs 3.7% BB or DIUR p = NR **Dizziness** 24.5% CCB vs 27.7% ACE vs 27.8% BB or DIUR p = NR

MIDAS, 1996 Adults, ages ≥ 40 years, without hyperlipidemia, and presence of IMT 1.3- 3.5 mm in the carotid artery; fasting TC and LDL-C ≤6.21 and 4.14 mmol/L (240 and 160 mg/dL) respectively ISR: Isradipine: 2.5 to 5.0 mg BID HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID N: 883 3 years Fair	**All-cause mortality** RR (95% CI) for ISR: 0.89 (0.35, 2.28) p = 0.81	**MI** RR (95% CI) for ISR: 1.20 (0.37, 3.89) p = 0.77 **CABG** RR (95% CI) for ISR: 1.00 (0.32, 3.07) p = 0.97 **Coronary angioplasty** RR (95% CI) for ISR: 4.99 (0.59, 42.53) p = 0.10 **Sudden death** RR (95% CI) for ISR: 1.00 (0.14, 7.05) p> 0.99	**Stroke** RR (95% CI) for ISR: 2.00 (0.50, 7.93) p = 0.32	**CHF** RR (95% CI) for ISR: NR p = 0.16	**Any major vascular event** RR (95% CI) for ISR: 1.78 (0.94, 3.38) P = 0.07 **Major vascular events and procedures** RR (95% CI) for ISR: 1.58 (0.90, 2.76) p = 0.10 **Other CVD death** HCTZ: 1 (0.22) RR (95% CI) for ISR: 1.00 (0.06, 15.90) p > 0.99		**CV-related adverse reactions** 3.0% ISR vs 0.9% HCTZ p = NR

ELSA, 2002 Adults, age 45 to 75 years, with fasting serum total cholesterol ≤320 mg/dl, fasting serum triglycerides ≤300 mg/dl, serum Cr ≤1.7 mg/dl, and a readable ultrasound carotid artery scan with maximum IMT no greater than 4.0 mm LAC: Lacidipine 4-6 g/day ATN: Atenolol 50-100 mg/day N: 2,334 Mean 3.75 years Fair	**All death** 3.59 per 1000 p-y LAC vs 4.68 per 1000 p-y ATN p = NS	**Fatal and non-fatal MI** 4.97 per 1000 p-y LAC vs 4.68 per 1000 p-y ATN p = NS	**Fatal and non-fatal Stroke** 2.49 per 1000 p-y LAC vs 3.86 per 1000 p-y ATN p = NS		**Major CV events** 7.46 per 1000 p-y LAC vs 9.09 per 1000 p-y ATN p = NS **Minor CV events** 12.42 per 1000 p-y LAC vs 11.59 per 1000 p-y ATN p = NS **All major and minor CV events** 19.04 per 1000 p-y LAC vs 19.85 per 1000 p-y ATN p = NS **CV death** 1.10 per 1000 p-y LAC vs 2.20 per 1000 p-y ATN p = NS		

SHELL, 2003 Adults ≥ 60 years with isolated systolic HTN LAC: Lacidipine: 4, 6 mg QD CHL: Chlorthalidone: 12.5, 25 mg QD N: 1,882 Median 32 months (95% CI, 30-33 months) Fair Panel Comments: Trial underpowered, 4800 needed over 5 years to achieve 80% power for primary outcome, but only 1882 patients randomized	**All-cause mortality** HR (95% CI) for LAC: 1.23 (0.97,1.57) p = 0.09	**Fatal and non-fatal MI** HR (95% CI) for LAC: 0.85 (0.39, 1.83) p = 0.67 **Sudden death** HR (95% CI) for LAC: 1.22 (0.58, 2.53) p = 0.60 **Revascularization** HR (95% CI) for LAC: 0.50 (0.09, 2.70) p = 0.41	**Fatal and non-fatal stroke** HR (95% CI) for LAC: 0.96 (0.61, 1.51) p = 0.87 **TIA** HR (95% CI) for LAC: 1.14 (0.54, 2.40) p = 0.72	**Fatal and non-fatal HF** HR (95% CI) for LAC: 1.20 (0.65, 2.20) p= 0.56	**Composite primary endpoint** HR (95% CI) for LAC: 1.01 (0.75, 1.36) p = 0.94		**Orthostatic hypotension** 1.9% LAC vs 2.5% CHL p = NR **Edema** 14.3% LAC vs 4.9% CHL p = NR **Cough** 3.5% LAC vs 4.0% CHL p = NR **Dizziness** 12.7% LAC vs 12.4% CHL p = NR **Fatigue** 13.7% LAC vs 20.5% CHL p = NR

JMIC-B, 2004 Adults, ages <75 years with HTN and CAD NIF: Nifedipine long-acting 10-20 mg BID ACE: ACE inhibitor: enalapril, 5-10 mg, or imidapril 5-10 mg, or lisinopril 10-20 mg N: 1,650 Median 35.7 months Fair	**Totally mortality** RR (95% CI) for NIF: 0.76 (0.35, 1.63) p = 0.48	**MI** RR (95% CI) for NIF: 1.31 (0.63, 2.74) p = 0.47 **Coronary intervention** RR (95% CI) for NIF: 1.04 (0.76, 1.43) p = 0.81 **Sudden death/cardiac death** RR (95% CI) for NIF: 0.96 (0.31, 3.04) p = 0.95 **Non-cardiac death** RR (95% CI) for NIF: 0.64 (0.23, 1.81) p = 0.40	**Cerebrovascular accidents** RR (95% CI) for NIF: 1.00 (0.50, 2.02) p = 0.99	**HF requiring hospitalization** RR (95% CI) for NIF: 1.25 (0.52, 2.98) p = 0.62	**Cardiac events** RR (95% CI) for NIF: 1.05 (0.81, 1.37) p = 0.75	**Worsening of renal dysfunction (serum Cr >353.6 µmol/l)** RR (95% CI) for NIF: 2.70 (0.54, 13.49) p = 0.23	*With drawals by AE* **Hypotension** 1.0% NIF vs 0.2% ACE p < 0.01 **Edema** 0.8% NIF vs 0% ACE p < 0.01 **Facial erythema, hot flushes** 0.7% NIF vs 0% ACE p < 0.05 **Dry cough** 0% NIF vs 7.3% ACE p < 0.01

INSIGHT, 2000 Men and women age 55-80 years, high risk patients with HTN; one additional CV risk factor NIF: Nifedipine: 30, 60 mg QD Co-am: Co-amilozide: HCTZ 25 mg and amiloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amiloride 5 mg QD N: 6,321 Maximum of 51 months F/U; BP outcomes reported at 48 months Good	**All deaths (first event)** OR (95% CI): 1.01 (0.80, 1.27) p = 0.95	**Non-fatal MI** OR (95% CI): 1.09 (0.76, 1.58) p = 0.52 **Fatal MI** OR (95% CI): 3.22 (1.18, 8.80) p = 0.017 **Sudden death** OR (95% CI): 0.74 (0.39, 1.39) p = 0.43	**Non-fatal stroke** OR (95% CI): 0.87 (0.61, 1.26) p = 0.52 **Fatal stroke** OR (95% CI): 1.09 (0.48, 2.48) p = 0.84 **TIA** OR (95% CI): 1.00 (0.57, 1.75) p = 1.0	**Non-fatal HF** OR (95% CI): 2.20 (1.07, 4.49) p = 0.028 **Fatal HF** OR (95% CI): 2.01 (0.18, 22.13) p = 0.63	**Primary outcome composite: death from any CV or cerebrovascular cause, together with non-fatal stroke, MI and HF** OR (95% CI): 1.11 (0.90, 1.36) p = 0.34 **Composite secondary outcomes: Primary outcomes plus non-CV deaths, renal failure, angina and TIA** OR (95% CI): 0.96 (0.83, 1.12) p = 0.62 **Other CV death** OR (95% CI): 1.09 (0.50, 2.38) p = 0.85 **CV Deaths** OR (95% CI): 1.16 (0.80, 1.69) p = 0.45 **Non-fatal primary CV events** OR (95% CI): 1.08 (0.85, 1.38) p = 0.53 **Non-fatal CV events** OR (95% CI): 0.94 (0.78, 1.13) p = 0.50	**Renal Failure** OR (95% CI): 0.62 (0.26, 1.49) p = 0.38	**All AEs** 49% NIF vs 42% Co-am p < 0.0001 **Peripheral edema** 28% NIF vs 4.3% Co-am p < 0.0001 **Headache** 12% NIF vs 9.2% Co-am p < 0.0002 **GFR, mL/min** Co-am vs. NIF (95% CI): -2.3 (-3.8, 1.9) Co-amilozide lower than nifedipine p = NR **Serious adverse events** 25% NIF vs 28% Co-am p < 0.02 **Impaired renal function as an adverse event** 1.8% NIF vs 4.6% Co-am p < 0.0001 **DM reported as an adverse event** 3.0% NIF vs 4.3% Co-am p = 0.01 **New onset DM reported as an outcome, n (%)** 4.3% NIF vs

							5.6% Co-am p = 0.02 **Hyperglycemia** 5.6% NIF vs 7.7% Co-am p = 0.001 **Hypokalemia** 1.9% NIF vs 6.2% Co-am p < 0.0001 **Hyponatremia** 8 events NIF vs 61 events Co-am p < 0.0001 **Dizziness** 8% NIF vs 10% Co-am p < 0.006

MOSES, 2005 Adults with HTN and history of a cerebrovascular event NIT: Nitrendipine 10 mg/day EPR: Eprosartan 600 mg/day N: 1,405 Mean 2.5 years Fair Notes: IDR: incidence density ratio	**All cause death** HR (95% CI) for EPR: 1.07 (0.73, 1.56) p = 0.725		**Fatal and non-fatal cerebrovascular events (including recurrent events)** IDR (95% CI): 0.75 (0.58, 0.97) p = 0.026 **First time occurrence of cerebrovascular event** HR (95% CI) for EPR: 0.88 (0.65, 1.20) p = 0.425		**Primary combined endpoint: cerebrovascular and CV events and non-CV death (including recurrent events)** IDR (95% CI): 0.79 (0.66, 0.96) p = 0.014 **Fatal and non-fatal CV events (including recurrent events)** IDR (95% CI): 0.75 (0.55, 1.02) p = 0.061 **First time occurrence of CV event** HR (95% CI) for EPR: 0.69 (0.50, 0.97) p = 0.031		**Dizziness /hypotension** 10.6% NIT vs 12.9% EPR p = NR **Pneumonia** 11.4% NIT vs 10.8% EPR p = NR **Metabolic disorder** 5.9% NIT vs 5.5% EPR p = NR

CONVINCE, 2003 Adults age >55 with HTN and 1 or more additional risk factor for CVD VER: Controlled-onset extended-release verapamil 180-360 mg ATN or HCTZ: atenolol 50-100 mg QD or HCTZ 12.5-25 mg QD N:16,602 Median F/U 3 years Fair Panel Comments: Sponsor closed study 2 years earlier than planned for "commercial reasons"	**Death** HR (95% CI) for VER: 1.08 (0.93, 1.26) p = 0.32	**Fatal or nonfatal MI** HR (95% CI) for VER: 0.82 (0.65, 1.03) p = 0.09 **Cardiac revascularization/ cardiac transplant** HR (95% CI) for VER: 1.01 (0.82, 1.26) p = 0.91	**Fatal or nonfatal stroke** HR (95% CI) for VER: 1.15 (0.90, 1.48) p = 0.26 **TIA or carotid endarterectomy** HR (95% CI) for VER: 0.87 (0.66, 1.15) p = 0.33	**Heart failure** HR (95% CI) for VER: 1.30 (1.00, 1.69) p = 0.05	**Primary composite outcome** HR (95% CI) for VER: 1.02 (0.88, 1.18) p = 0.77 **Primary event or CV hospitalization** HR (95% CI) for VER: 1.05 (0.95, 1.16) p = 0.31 **CVD-related death** HR (95% CI) for VER: 1.09 (0.87, 1.37) p = 0.47	**Renal failure (acute/chronic)** HR (95% CI) for VER: 0.81 (0.49, 1.35) p = 0.43	**Withdrawals due to constipation** 216 events VER vs 28 events ATN or HCTZ p = NR **Death or hospitalization due to serious adverse event** HR (95% CI) for VER: 1.04 (0.97, 1.12) p = 0.29 **Hospitalization for serious adverse event** HR (95% CI) for VER: 1.03 (0.95, 1.12) p = 0.44 **Withdrawals due to poor BP control** 115 events VER vs 207 events ATN or HCTZ p < 0.001

VHAS, 1997 Adults, ages 40-65 years with HTN VER: Verapamil: slow release 240 mg QD CHL: Chlorthalidone: 25 mg QD N: 1,414 2 years Fair	**Death by any cause** 5 events VER vs 4 events CHL p = NR	**MI** 5 events VER vs 5 events CHL p = NR **Revascularization procedures** 4 events VER vs 3 events CHL p = NR **Cardiac deaths** 3 events VER vs 4 events CHL p = NR	**Strokes** 3 events VER vs 4 events CHL p = NR **TIA** 7 events VER vs 7 events CHL p = NR **Cerebrovascular deaths** 2 events VER vs 0 events CHL p = NR	**CHF** 2 events VER vs 0 events CHL p = NR	**Non-fatal CV events** 37 events VER vs 39 events CHL p = NR **Major CV events** 8 events VER vs 9 events CHL p = NR **Minor CV events** 29 events VER vs 30 events CHL p = NR **CV deaths** 5 events VER vs 4 events CHL p = NR		**Constipation** 13.7% VER vs 3.1% CHL p = NR **Severe hypokalemia** 4 events VER vs 8 events CHL p = NR **Hyperuricemia** 3.9% VER vs 10.8% CHL p < 0.01 **Hypokalemia** 4.4% VER vs 24.6% CHL p < 0.01 **Glucose, mg/dl (SD)** -1.2 change VER vs +1.8 change CHL p = 0.01

Table 180

4.3.1.1.4 ACE-inhibitors versus other drugs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
CAPPP, 1999 Adults, ages 25 to 66 years, with treated or untreated primary HTN CAP: Captopril 50 mg QD – 100 BID BB or DIUR: atenolol 50-100 mg QD; metoprolol 50-100 mg QD; HCTZ 25 mg QD; bendrofluazide 2.5 mg QD N: 10,985 Mean 6.1 years Fair	**All fatal events** RR (95% CI) for CAP: 0.93 (0.76, 1.14) p = 0.49	**Non-fatal MI** 137 events CAP vs 128 events BB or DIUR p = NR **Ischemic heart disease** 258 events CAP vs 251 events BB or DIUR p = NR **MI, fatal and non-fatal** RR (95% CI) for CAP: 0.96 (0.77, 1.19) p = 0.68 **Fatal MI** 27 events CAP vs 35 events BB or DIUR p = NR **Sudden death** 6 events CAP vs 14 events BB or DIUR p = NR	**Non-fatal stroke** 173 events CAP vs 127 events BB or DIUR p = NR **Stroke, fatal and non-fatal** RR (95% CI) for CAP: 1.25 (1.01, 1.55) p = 0.044 **TIA** 31 events CAP vs 25 events BB or DIUR p = NR **Fatal stroke** 20 events CAP vs 22 events BB or DIUR p = NR	**CHF** 75 events CAP vs 66 events BB or DIUR p = NR	**Combination of fatal and non-fatal MI and stroke, and other CV deaths** RR (95% CI) for CAP: 1.05 (0.90, 1.22) p = 0.52 **All cardiac events** RR (95% CI) for CAP: 0.94 (0.83, 1.06) p = 0.30 **Fatal CV events** RR (95% CI) for CAP: 0.77 (0.57, 1.04) p = 0.092 **Other CV deaths** 23 events CAP vs 24 events BB or DIUR p = NR		**New onset DM** RR (95% CI) for CAP: 0.86 (0.74, 0.99) p = 0.039 Hansson et al 1999 *Reported as:* *RR (95% CI) for CAP:* *0.79 (NR)* *p=0.001 in Niskanen 2001*

ANBP2, 2003 Adults, ages 65 to 84, with absence of recent CV events ACE: ACE Inhibitor: Enalapril recommended; dose not specified DIU: Diuretic: HCTZ recommended; dose not specified N: 6,083 Median 4.1 years Fair	**Death from any cause** HR (95% CI) for ACE: 0.90 (0.75, 1.09) p = 0.27	**Non-fatal MI** HR (95% CI) for ACE: 0.68 (0.47, 0.99) p = 0.05 **Non-fatal coronary event** HR (95% CI) for ACE: 0.92 (0.73, 1.16) p = 0.49 **MI** HR (95% CI) for ACE: 0.68 (0.47, 0.98) p = 0.04 **Coronary event** HR (95% CI) for ACE: 0.86 (0.70, 1.06) p = 0.16 **Fatal MI events** HR (95% CI) for ACE: 0.79 (0.31, 1.99) p = 0.61 **Fatal coronary events** HR (95% CI) for ACE: 0.74 (0.49, 1.11) p = 0.14	**Non-fatal stroke** HR (95% CI) for ACE: 0.93 (0.70, 1.26) p = 0.65 **Stroke** HR (95% CI) for ACE: 1.02 (0.78, 1.33) p = 0.91 **Cerebrovascular event** HR (95% CI) for ACE: 0.90 (0.73, 1.12) p = 0.35 **Fatal stroke events** HR (95% CI) for ACE: 1.91 (1.04, 3.50) p = 0.04	**Non-fatal HF** HR (95% CI) for ACE: 0.85 (0.62, 1.17) p = 0.32 **HF** HR (95% CI) for ACE: 0.85 (0.62, 1.18) p = 0.33 **Fatal HF events** HR (95% CI) for ACE: 0.24 (0.03, 1.94) p = 0.18	**Non-fatal CV event** HR (95% CI) for ACE: 0.86 (0.74, 0.99) p = 0.03 **Non-fatal other CV event** HR (95% CI) for ACE: 0.84 (0.66, 1.07) p = 0.17 **All CV events or death from any cause** HR (95% CI) for ACE: 0.89 (0.79, 1.00) p = 0.05 **First CV event or death from any cause** HR (95% CI) for ACE: 0.89 (0.79, 1.01) p = 0.06 **First CV event** HR (95% CI) for ACE: 0.88 (0.77, 1.01) p = 0.07 **Other CV event** HR (95% CI) for ACE: 0.90 (0.71, 1.14) p = 0.36 **Fatal CV events** HR (95% CI) for ACE: 0.99 (0.72, 1.35) p = 0.94 **Fatal other CV events** HR (95% CI) for ACE: 0.95 (0.46, 1.96) p = 0.89		

ALLHAT, 2002 Adults, ≥ 55 years of age with at least one additional risk factor for CHD LIS: Lisinopril: 10, 20, and 40 mg QD CHL: Chlorthalidone: 12.5 or 25 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD N: 33,357 Mean 4.9 years Good	**All-cause mortality** LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) p = 0.90	**CHD (combined fatal CHD and nonfatal MI)** LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) p = 0.81 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11) p = 0.18 **Coronary revascularization** LIS vs. CHL: RR (95% CI) for LIS: 1.10 (1.00, 1.21) p = 0.05 **Hospitalized or treated PAD** LIS vs. CHL: RR (95% CI): 1.04 (0.90, 1.19) p = 0.63 **MI death** 2.2 per 100 persons LIS vs 2.4 per 100 persons CHL vs 2.3 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.25 **Definite CHD death** 1.0 per 100 persons LIS vs 1.1 per 100	**Stroke** LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) p = 0.02 **Death from stroke** 1.7 per 100 persons LIS vs 1.4 per 100 persons CHL vs 1.4 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.06	**HF** LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) p < 0.001 **Hospitalized/fatal HF** LIS vs. CHL: RR (95% CI) for LIS: 1.10 (0.98, 1.23) p = 0.11 **HF death** 1.1 per 100 persons LIS vs 1.0 per 100 persons CHL vs 1.4 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.98	**Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)** LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) p < 0.001 **Cardiovascular death** 8.5 per 100 persons LIS vs 8.0 per 100 persons CHL vs 8.5 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.39 **Other CVD death** 1.5 per 100 persons LIS vs 1.4 per 100 persons CHL vs 1.7 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.66	**ESRD** LIS vs CHL: RR (95% CI): 1.11 (0.88, 1.38) p = 0.38 **Kidney disease death** 0.5 per 100 persons LIS vs 0.4 per 100 persons CHL vs 0.5 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.37	At 6 years **Angioedema** 0.4% LIS vs 0.1% CHL vs <0.1% AML LIS vs. CHL: RR (95% CI): NR p < 0.001 At 4 years **Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL** 8.1% LIS vs 11.6% CHL vs 9.8% AML LIS vs. CHL: p < 0.001

		persons CHL vs 1.2 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.52 **Possible CHD death** 1.4 per 100 persons LIS vs 1.1 per 100 persons CHL vs 1.1 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.10					

ALLHAT, 2006 Adults, ≥ 55 years of age with at least one additional risk factor for CHD LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD N: 18, 102 Mean 4.9 years Fair	**All-cause mortality** LIS vs AML: RR (95% CI): 1.05 (0.97, 1.13) p = 0.214	**CHD (fatal CHD and nonfatal MI)** LIS vs AML: RR (95% CI): 1.01 (0.91, 1.11) p = 0.854 **Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)** LIS vs AML: RR (95% CI): 1.04 (0.97, 1.12) p = 0.243 **Coronary revascularization** LIS vs AML: RR (95% CI): 1.00 (0.91, 1.11) p = 0.943 **Hospitalized or fatal PAD** **LIS vs AML:** RR (95% CI): 1.19 (1.01, 1.40) p = 0.036	**Stroke** LIS vs AML: RR (95% CI): 1.23 (1.08, 1.41) p = 0.003	**HF** LIS vs AML: RR (95% CI): 0.87 (0.78, 0.96) P = 0.007 **Hospitalized/fatal HF** LIS vs AML: RR (95% CI): 0.81 (0.72, 0.92) p <0.001	**Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)** LIS vs AML: RR (95% CI): 1.06 (1.00, 1.12) p = 0.047	**ESRD** LIS vs AML: RR (95% CI): 0.99 (0.77, 1.26) p = 0.929	**Angioedema** 0.42% LIS vs 0.03% AML p <0.001 **Hospitalization for GI bleeding** 9.6 per 100 LIS vs 8.0 per 100 AML p = 0.04 At 4 years **DM (>=7.0 mmol/L) if no DM at baseline** 9.4% LIS vs 10.4% AML p = 0.30

JMIC-B, 2004 Adults, ages <75 years with HTN and CAD ACE:ACE inhibitor: enalapril 5-10 mg, or imidapril 5-10 mg, or lisinopril 10-20 mg NIF: Nifedipine long acting10-20 mg BID N: 1,650 Median 35.7 months Fair	**Total mortality** RR (95% CI) for NIF: 0.76 (0.35, 1.63) p = 0.48	**MI** RR (95% CI) for NIF: 1.31 (0.63, 2.74) p = 0.47 **Coronary intervention of PTCA, CABG, stenting** RR (95% CI) for NIF: 1.04 (0.76,1.43) p = 0.81 **Sudden death/ cardiac death** RR (95% CI) for NIF: 0.96 (0.31, 3.04) p = 0.95	**Cerebrovascular accidents** RR (95% CI) for NIF: 1.00 (0.50, 2.02) p = 0.99	**HF requiring hospitalization** RR (95% CI) for NIF: 1.25 (0.52, 2.98) p = 0.62	**Cardiac events (composite of cardiac or sudden death, MI, angina pectoris requiring hospitalization, HF requiring hospitalization, serious arrhythmia, coronary interventions)** RR (95% CI) for NIF: 1.05 (0.81, 1.37) p = 0.75 **Non-cardiac death** RR (95% CI) for NIF: 0.64 (0.23, 1.81) p = 0.40	**Worsening of renal dysfunction with serum Cr >353.6 µmol/l** RR (95% CI) for NIF: 2.70 (0.54, 13.49) p = 0.23	*Withdrawals by AE* **Dry cough** 7.3% ACE vs 0% NIF NIF: 0 p < 0.01 **Hypotension** 0.2% ACE vs 1.0% NIF p < 0.01 **Edema** 0% ACE vs 0.8% NIF p < 0.01 **Facial erythema, hot flushes** 0% ACE vs 0.7% NIF p < 0.05

STOP Hypertension-2 , 1999 Adults 70-84 years old with HTN ACE: ACE inhibitors: enalapril 10 mg, or lisinopril 10 mg CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5 mg QD BB or DIUR: atenolol 50 mg, or metoprolol 100 mg, or pindolol 5 mg, or fixed ratio HCTZ 25 mg plus amiloride 2.5 mg N: 6,614 Duration: Mean F/U unclear; authors report study duration of 60 months; max BP measurement reported is 54 months, and Kaplan-Meier curves extend to 6 years Good	**Total mortality** ACE vs CCB: RR (95%CI) for ACE: 1.03 (0.69, 1.19) p = 0.71 **Total mortality** ACE vs. BB or DIUR: RR (95% CI) for ACE: 1.02 (0.69, 1.16) p = 0.76	**All MI** ACE vs CCB: RR (95% CI) for ACE: 0.77 (0.61, 0.96) p = 0.016 **All MI** ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.90 (0.72, 1.13) p = 0.36 **Sudden death** 5.3 per 1000 p-y ACE vs 4.7 per 1000 p-y CCB vs 4.8 per 1000 p-y BB orDIUR p = NR **Fatal MI** 4.3 per 1000 p-y ACE vs 5.3 per 1000 p-y CCB vs 4.9 per 1000 p-y BB or DIUR p = NR	**All stroke** ACE vs. CCB: RR (95% CI) for ACE: 1.02 (0.64, 1.24) p = 0.64 **All stroke** ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.90 (0.74, 1.06) p = 0.24 **Fatal stroke** 4.5 per 1000 p-y ACE vs 4.2 per 1000 p-y CCB vs 4.6 per 1000 p-y p = NR	**Frequency of CHF** ACE vs. CCB: RR (95% CI) for ACE: 0.76 (0.63, 0.97) p = 0.025 **Frequency of CHF** ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.63 (0.67, 1.03) p = 0.095	**All major CV events** ACE vs. CCB: RR (95% CI) for ACE: 0.95 (0.63, 1.06) p = 0.42 **All major CV events** ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.94 (0.62, 1.07) p = 0.32 **CV mortality** ACE vs. CCB: RR (95% CI) for ACE: 1.04 (0.66, 1.26) p = 0.67 **CV mortality** ACE vs. BB or DIUR: RR (95% CI) for ACE: 1.01 (0.64, 1.22) p = 0.69 **Other CV mortality** 6.2 per 1000 p-y ACE vs 5.0 per 1000 p-y CCB vs 5.6 per 1000 p-y BB or DIUR p = NR		**Frequency of DM** ACE vs. CCB: RR (95% CI) for ACE: 0.96 (0.74, 1.31) p = 0.91 **Frequency of DM** ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.96 (0.72, 1.27) p = 0.77 **Ankle edema** 8.7% ACE vs 25.5% CCB vs 8.5% BB or DIUR p = NR **Dry cough** 30.1% ACE vs 5.7% CCB vs 3.7% BB or DIUR p = NR **Dizziness** 27.7% ACE vs 24.5% CCB vs 27.8% BB or DIUR p = NR

Table 181

4.3.1.1.5 ARBs versus other drugs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
CASE-J, 2008 Adults with high CVD risk CAN: Candesartan 4-12 mg/day AML: Amlodipine 2.5-10 mg/day N: 4,728 Mean 3.2 years Primary outcome: composite of sudden death, cerebrovascular events, cardiac events, renal events vascular events Good	**All-cause death** 9.4 per 1000 p-y CAN vs 11.1 per 1000 p-y AML HR (95% CI): NR p = NS	**Acute MI** HR (95% CI) for CAN: 0.95 (0.49, 1.84) p = 0.870 **Sudden death** HR (95% CI) for CAN: 0.73 (0.34, 1.60) p = 0.434	**Cerebrovascular events** HR (95% CI) for CAN: 1.23 (0.85, 1.78) p= 0.282 **Stroke** HR (95% CI) for CAN: 1.28 (0.88, 1.88) p = 0.198 **TIA** HR (95% CI) for CAN: 0.50 (0.09, 2.73) p = 0.414	**Heart failure** HR (95% CI) for CAN: 1.25 (0.65, 2.42) p = 0.498	**Primary composite endpoint of sudden death, cerebrovascular events, cardiac events, renal events and vascular events** HR (95% CI) for CAN: 1.01 (0.79, 1.28) p = 0.969 **Cardiac events** HR (95% CI) for CAN: 0.92 (0.61, 1.39) p = 0.680 **Peripheral vascular events** HR (95% CI) for CAN: 1.57 (0.61, 4.05) p = 0.348	**Renal events** HR (95% CI) for CAN: 0.70 (0.39, 1.26) p = 0.230 **Creatinine abnormality** HR (95% CI) for CAN: 0.73 (0.40, 1.31) p = 0.287 **ESRD** HR (95% CI) for CAN: 0.40 (0.13, 1.29) p = 0.112	**Hyperkalemia** 1.0% CAN vs 0.3% AML p = NR **New onset DM** HR (95% CI) for CAN: 0.64 (0.43, 0.97) p = 0.033
SCOPE, 2003 Adults, 70-89 years old with treated or untreated HTN and MMSE ≥ 24 CAN: Candesartan: Step 1: Candesartan 8 mg QD Step 2: If SBP >160 mmHg or reduction in SBP <10 mmHg or DBP >85, dose doubled	**Total mortality** 27.9 per 1000 p-y CAN vs 29.0 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS	**Non-fatal MI** 5.9 per 1000 p-y CAN vs 5.2 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS **All MI** 7.6 per 1000 p-y	**Non-fatal stroke** Risk Reduction (95% CI) for CAN: 27.8 (1.3, 47.2) p = 0.04 **All stroke** Risk Reduction (95% CI) for CAN: 23.6 (-0.7, 42.1)		**Major CV events** Risk Reduction (95% CI) for CAN: 10.9 (-6.0, 25.1) p = 0.19 **CV deaths** 15.6 per 1000 p-y CAN vs 16.6 per 1000 p-y CTL Risk	**Change in mean serum Cr, µmol/l** CAN: +9.6 CTL: +5.3 p = NR	**Dizziness/vertigo** 20.9% CAN vs 20.0% CTL p = NR **Accident/injury** 18.4% CAN vs 18.4% CTL p = NR

Step 3: If SBP remained ≥160 mmHg or DBP ≥90 mmHg, other anti-HTN drug added (ARB or ACE not allowed); recommendation was to start with HCTZ 12.5 mg QD CTL: Control: Step 1: Placebo QD Step 2: If SBP >160 mmHg or reduction in SBP <10 mmHg or DBP >85, dose doubled Step 3: If SBP remained ≥160 mmHg or DBP ≥90 mmHg, other anti-HTN drug added (ARB or ACE not allowed); recommendation was to start with HCTZ 12.5 mg QD N: 4,964 Mean 3.7 years Fair Panel Comments: Authors note that during the recruitment period it became necessary to recommend open-label active anti-HTN therapy in both treatment groups for patients whose BP remained high. Thus, the trial actually compared a candesartan-based regimen to usual treatment without candesartan. However, the initial intent was to compare candesartan to placebo.		CAN vs 6.9 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS	p = 0.056 **Fatal stroke** 2.6 per 1000 p-y CAN vs 2.8 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS		Reduction (95% CI): NR p = NS		**Back pain** 19.2% CAN vs 17.1% CTL p = NR **Bronchitis** 15.9% CAN vs 16.0% CTL p = NR **AEs indicating possible hypotension** 24.6% CAN vs 23.4% CTL p = NR **New Onset DM** 4.3% CAN vs 5.3% CTL p = 0.09

MOSES, 2005 Patients with HTN and history of a cerebrovascular event EPR: Eprosartan 600 mg/day NIT: Nitrendipine 10 mg/day N: 1,405 Mean 2.5 years Fair Panel Comments: IDR: incidence density ratio	**All cause death** HR (95% CI) for EPR: 1.07 (0.73, 1.56) p = 0.725		**Fatal and non-fatal cerebrovascular events** IDR (95% CI): 0.75 (0.58, 0.97) p = 0.026 **First time occurrence of cerebrovascular event** HR (95% CI) for EPR: 0.88 (0.65, 1.20) p = 0.425		**Primary combined endpoint: cerebrovascular and CV events and non- CV death** IDR (95% CI): 0.79 (0.66, 0.96) p = 0.014 **Fatal and non-fatal CV events** IDR (95% CI): 0.75 (0.55, 1.02) p = 0.061 **First time occurrence of CV event** HR (95% CI) for EPR: 0.69 (0.50, 0.97) p = 0.031		**Metabolic disorder** 5.5% EPR vs 5.9% NIT p = NR **Dizziness/ hypotension** 12.9% EPR vs 10.6% NIT p = NR **Pneumonia** 10.8% EPR vs 11.4% NIT p = NR

LIFE, 2002 Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG LOS: Losartan, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Losartan 50 mg Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) ATN: Atenolol, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Atenolol 50 mg Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) N: 9,222 Mean 4.8 years Good Panel Comments: Hazard ratios adjusted for degree of LVH and Framingham risk score	**Total mortality** 17.3 per 1000 py LOS vs 19.6 per 1000 py ATN Adj HR (95% CI) for LOS: 0.90 (0.78, 1.03) p = 0.128 Unadj HR (95% CI) for LOS: 0.88 (0.77, 1.01) p = 0.077	**MI** 9.2 per 1000 py LOS vs 8.7 per 1000 py ATN Adj HR (95% CI) for LOS: 1.07 (0.88, 1.31) p = 0.491 Unadj HR (95% CI) LOS: 1.05 (0.86, 1.28) p = 0.628 **Resuscitated cardiac arrest** 0.4 per 1000 py LOS vs 0.2 per 1000 py ATN Adj HR (95% CI) for LOS: 1.91 (0.64, 5.72) p = 0.250 Unadj HR (95% CI) for LOS: 1.80 (0.60, 5.36) p = 0.294 **Revascularization** 12.2 per 1000 py LOS vs 13.3 per 1000 py ATN ATN vs. LOS Adj HR (95% CI) for LOS: 0.94 (0.79, 1.11) p = 0.441 Unadj HR (95% CI) for LOS: 0.91 (0.77, 1.08) p = 0.292	**Stroke** 10.8 per 1000 py LOS vs 14.5 per 1000 py ATN Adj HR (95% CI) for LOS: 0.75 (0.63, 0.89) p = 0.001 Unadj HR (95% CI) for LOS: 0.74 (0.63, 0.88) p = 0.0006	**Heart failure** 7.1 per 1000 py LOS vs 7.5 per 1000 py ATN Adj HR (95% CI) for LOS: 0.97 (0.78, 1.21) p = 0.765 Unadj HR (95% CI) for LOS: 0.95 (0.76, 1.18) p = 0.622	**Primary composite endpoint of CV death, MI, and stroke** 23.8 per 1000 py LOS vs 27.9 per 1000 py ATN Adj HR (95% CI) for LOS: 0.87 (0.77, 0.98) p = 0.021 Unadj HR (95% CI) for LOS: 0.85 (0.76, 0.96) p = 0.009 **CV mortality** 9.2 per 1000 py LOS vs 10.6 per 1000 py ATN Adj HR (95% CI) for LOS: 0.89 (0.73, 1.07) p = 0.206 Unadj HR (95% CI) for LOS: 0.87 (0.72, 1.05) p = 0.136	**Change in creatinine, mmol/L (SD)** LOS: +11.2 (20.4) ATN: +11.0 (19.7) p = NR	**Hypotension** 3% LOS vs 2%% ATN p = 0.001 **Back pain** 12% LOS vs 10% ATN p = 0.004 **Chest pain** 11% LOS vs 10% ATN p = 0.068 **Angioedema** 1% LOS vs 2% ATN p = 0.237 **Cough** 3% LOS vs 2% ATN p = 0.220 **Dizziness** 17% LOS vs 16% ATN p = 0.247 **New DM** 13.0 per 1000 py LOS vs 17.4 per 1000 py ATN Adj HR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001 Unadj HR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001 **Lower extremity edema** 12% LOS vs 14% ATN

							p = 0.002 **Albuminuria** 5% LOS vs 6% ATN p = 0.0002 **Hyperglycemia** 5% LOS vs 7% ATN p = 0.007 **Dyspnea** 10% LOS vs 14% ATN p < 0.0001 **Asthenia/ Fatigue** 15% LOS vs 17% ATN p = 0.001

LIFE, 2002 *Subanalyses on those with Isolated Systolic Hypertension* Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if trough sitting SBP 160-200 mmHg with DBP <90 mmHg after 1 and 2 weeks placebo LOS: Losartan, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Losartan 50 mg Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) ATN: Atenolol, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Atenolol 50 mg Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) N: 9,222 randomized (1,326 with isolated hypertension) Mean 4.7 years Fair NOTE: Adjusted RRs are adjusted for degree of LVH and Framingham	*Subanalysis of patients with Isolated Systolic Hypertension* **Total mortality** 21.2 per 1000 py LOS vs 30.2 per 1000 py ATN AdjRR (95% CI) for LOS: 0.72 (0.53, 1.00) p = 0.046 UnadjRR (95% CI) for LOS: 0.70 (0.51, 0.96) p = 0.03 *Subanalysis of patients without Isolated Systolic Hypertension* **Total mortality** 16.7 per 1000 py LOS vs 17.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.95 (0.82, 1.11) p = 0.51 UnadjRR (95% CI) for LOS: 0.93 (0.80, 1.09) p = 0.38	*Subanalysis of patients with Isolated Systolic Hypertension* **MI** 10.2 per 1000 py LOS vs 11.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.89 (0.55, 1.44) p = 0.64 UnadjRR (95% CI) for LOS: 0.86 (0.53, 1.39) p = 0.54 **Revascularization** 16.4 per 1000 py LOS vs 14.4 per 1000 py ATN AdjRR (95% CI) for LOS: 1.17 (0.78, 1.77) p = 0.45 UnadjRR (95%CI) for LOS: 1.14 (0.76, 1.72) p = 0.53 *Subanalysis of patients without Isolated Systolic Hypertension* **MI** 9.0 per 1000 py LOS vs 8.2 per 1000 py ATN AdjRR (95% CI) for LOS: 1.12 (0.90, 1.40)	*Subanalysis of patients with Isolated Systolic Hypertension* **Stroke** 10.6 per 1000 py LOS vs 18.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.60 (0.38, 0.92) p = 0.02 UnadjRR (95%CI) for LOS: 0.56 (0.36, 0.86) p = 0.008 *Subanalysis of patients without Isolated Systolic Hypertension* **Stroke** 10.8 per 1000 py LOS vs 13.8 per 1000 py ATN AdjRR (95% CI) for LOS: 0.79 (0.66, 0.95) p = 0.01 Unadj RR (95% CI) for LOS: 0.78 (0.65, 0.94) p = 0.01	*Subanalysis of patients with Isolated Systolic Hypertension* **Hospitalization for Heart Failure** 8.5 per 1000 py LOS vs 13.3 per 1000 py ATN AdjRR (95% CI) for LOS: 0.66 (0.40, 1.09) p = 0.11 UnadjRR (95% CI) for LOS: 0.64 (0.39, 1.05) p = 0.08 *Subanalysis of patients without Isolated Systolic Hypertension* **Hospitalization for Heart Failure** 6.8 per 1000 py LOS vs 6.5 per 1000 py ATN AdjRR (95% CI) for LOS: 1.06 (0.83, 1.36) p = 0.65 UnadjRR (95%CI) for LOS: 1.05 (0.82, 1.34) p = 0.72	*Subanalysis of patients with Isolated Systolic Hypertension* **Primary composite endpoint of CV death, MI or stroke** 25.1 per 1000 py LOS vs 35.4 per 1000 py ATN AdjRR (95% CI) for LOS: 0.75 (0.56, 1.01) p = 0.06 UnadjRR (95% CI) for LOS: 0.71 (0.53, 0.95) p = 0.02 **CV mortality** 8.7 per 1000 py LOS vs 16.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.54 (0.34, 0.87) p = 0.01 UnadjRR (95% CI) for LOS: 0.51 (0.32, 0.81) p = 0.004 *Subanalysis of patients without Isolated Systolic Hypertension* **Primary composite endpoint of CV death, MI or stroke** 23.6 per 1000 py LOS vs 26.7 per 1000 py		**Angioedema** 0.3% LOS vs 0.3% ATN p = 0.99 **Cough** 4.1% LOS vs 2.9% ATN p = 0.23 **Cold extremities** 4.1% LOS vs 6.6% ATN p = 0.05 **Bradycardia** 3.0% LOS vs 14.6% ATN p < 0.001 *Subanalysis of patients with Isolated Systolic Hypertension* **New diabetes** 12.6 per 1000 py LOS vs 20.1 per 1000 py ATN AdjHR (95% CI) for LOS: 0.62 (0.40, 0.97) p = 0.04 UnadjHR (95% CI) for LOS: 0.63 (0.40, 0.99) p = 0.04 *Subanalysis of patients without Isolated Systolic Hypertension* **New diabetes** 13.1 per 1000 py LOS vs 17.0 per 1000 py ATN AdjRR (95% CI) for LOS:

risk score at randomization Interaction between treatment and ISH status was not statistically significant		p = 0.30 UnadjRR (95% CI) for LOS: 1.10 (0.88, 1.36) p = 0.41 **Revascularization** 11.5 per 1000 py LOS vs 13.2 per 1000 py ATN AdjRR (95% CI) for LOS: 0.89 (0.74, 1.08) p = 0.23 UnadjRR (95% CI) for LOS: 0.87 (0.73, 1.05) p = 0.15			ATN AdjRR (95% CI) for LOS: 0.90 (0.79, 1.02) p = 0.11 UnadjRR (95% CI) for LOS: 0.88 (0.78, 1.01) p = 0.06 **CV mortality** 9.3 per 1000 py LOS vs 9.6 per 1000 py ATN AdjRR (95% CI) for LOS: 0.99 (0.80, 1.22) p = 0.90 UnadjRR (95% CI) for LOS: 0.97 (0.79, 1.19) p = 0.77		0.77 (0.64, 0.92) p = 0.005 UnadjRR (95% CI) for LOS: 0.77 (0.64, 0.92) p = 0.004

LIFE, 2003 *Subanalysis of subjects with and without clinically evident vascular disease* Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG LOS: Losartan: titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Losartan 50 mg Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) ATN: Atenolol: titration upward if sitting DBP ≥90 mmHg or sitting SBP >=140 mmHg Step 1: Atenolol 50 mg Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Atenolol100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) N: 9,222 (6,886 without clinically evident vascular disease at baseline) Mean 4.8 years Fair NOTE: Adjusted HRs are adjusted for degree of LVH and Framingham risk score at randomization Interaction between treatment and presence or absence of arterial disease was not statistically significant for primary endpoint	*Subanalysis of subjects without clinically evident vascular disease* **Total mortality** 13.5 per 1000 py LOS vs 15.9 per 1000 py ATN AdjHR (95% CI) for LOS: 0.85 (0.71, 1.02) p = 0.080 *Subanalysis of subjects with clinically evident vascular disease* **Total mortality** 28.5 per 1000 py LOS vs 31.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.94 (0.75, 1.16) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **MI** 6.8 per 1000 py LOS vs 6.0 per 1000 py ATN AdjHR (95% CI) for LOS: 1.14 (0.87, 1.49) p > 0.2 **Revascularization** 7.6 per 1000 py LOS vs 9.0 per 1000 py ATN AdjHR (95% CI) for LOS: 0.85 (0.67, 1.08) p = 0.18 *Subanalysis of subjects with clinically evident vascular disease* **MI** 16.3 per 1000 py LOS vs 17.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.97 (0.72, 1.31) p > 0.2 **Revascularization** 26.3 per 1000 py LOS vs 28.4 per 1000 py ATN AdjHR (95% CI) for LOS:	*Subanalysis of subjects without clinically evident vascular disease* **Stroke** 7.7 per 1000 py LOS vs 11.8 per 1000 py ATN AdjHR (95% CI) for LOS: 0.66 (0.53, 0.82) p < 0.001 *Subanalysis of subjects with clinically evident vascular disease* **Stroke** 20.0 per 1000 py LOS vs 23.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.87 (0.67, 1.13) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **Hospitalization for Heart Failure** 4.7 per 1000 py LOS vs 4.4 per 1000 py ATN AdjHR (95% CI) for LOS: 1.06 (0.77, 1.46) p > 0.2 *Subanalysis of subjects with clinically evident vascular disease* **Hospitalization for Heart Failure** 14.2 per 1000 py LOS vs 17.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.84 (0.62, 1.14) p > 0.2	*Subanalysis of subjects without clinically evident vascular disease* **Primary composite endpoint of CV death, MI or stroke** 17.5 per 1000 py LOS vs 21.8 per 1000 py ATN AdjHR (95% CI) for LOS: 0.81 (0.69, 0.95) p = 0.008 **CV mortality** 6.2 per 1000 py LOS vs 7.8 per 1000 py ATN AdjHR (95% CI) for LOS: 0.80 (0.62, 1.04) p = 0.092 *Subanalysis of subjects with clinically evident vascular disease* **Primary composite endpoint of CV death, MI or stroke** 43.0 per 1000 py LOS vs 48.6 per 1000 py ATN AdjHR (95% CI) for LOS: 0.93 (0.77, 1.11) p > 0.2 **CV mortality** 18.0 per 1000 py LOS		**Back pain** 12.0% LOS vs 10.0% ATN p = 0.009 **Patients with at least one serious adverse event** 3.8% LOS vs 4.4% ATN p > 0.2 **Patients with at least one adverse event of any type** 12.7% LOS vs 17.3% ATN p < 0.001 **Patients with at least one drug related adverse event** 6.0% LOS vs 10.2% ATN p < 0.001 **Patients with at least one serious drug related adverse event** 0.5% LOS vs 1.0% ATN p = 0.018 **Asthenia or fatigue** 14.2% LOS vs 16.9% ATN p < 0.002 **Lower extremity edema** 11.5% LOS vs 13.6% ATN p < 0.008

		0.98 (0.78, 1.25) p > 0.2			vs 19.8 per 1000 py ATN AdjHR (95% CI) for LOS: 0.95 (0.72, 1.25) p > 0.2		**Dyspnea** 8.8% LOS vs 13.6% ATN p < 0.001 **Hyperglycemia** 5.4% LOS vs 6.7% ATN p = 0.023 *Subanalysis of subjects without clinically evident vascular disease* **New diabetes** 12.2 per 1000 py LOS vs 17.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.69 (0.57, 0.84) p < 0.001 *Subanalysis of subjects with clinically evident vascular disease* **New diabetes** 15.5 per 1000 py LOS vs 16.4 per 1000 py ATN AdjHR (95% CI) for LOS: 0.97 (0.69, 1.36) p > 0.2

Jikei Heart Study, 2007 Adults, 20-79 years of age with HTN, CHD, HF, or a combination of these CV disorders VAL: Valsartan 80 mg daily; flexibly adjusted to 40-160 mg per day as needed to control BP; patients with HF or CHD started on 40 mg QD and uptitrated as tolerated; non-ARB treatment could be added to achieve BP goal CT: Conventional therapy; given either an increased dose of their existing treatment or an additional conventional treatment to achieve BP goal N: 3,081 Median 3.1 years Good Panel Comments: Study terminated early after DSMB recommended that the study should be stopped for ethical reasons because additional valsartan treatment was associated with a reduction in the primary endpoint (p<0.001, adjusted for three interim analyses).	**All-cause mortality** HR (95% CI) for VAL: 1.09 (0.64. 1.85) p = 0.7537	**New or recurrent MI** HR (95% CI) for VAL: 0.90 (0.47, 1.74) p = 0.7545 **Dissecting aneurysm of the aorta** HR (95% CI) for VAL: 0.19 (0.04, 0.88) p = 0.0340	**Stroke or TIA** HR (95% CI) for VAL: 0.60 (0.38, 0.95) p = 0.0280	**New occurrence or exacerbation of HF needing hospitalization** HR (95% CI) for VAL: 0.53 (0.31, 0.94) p = 0.0293	**Composite of CV mortality and morbidity (hospital admissions for stroke or TIA; MI; admission for CHF; admission for angina pectoris; dissecting aneurysm of the aorta; doubling of serum Cr; or transition to dialysis)** HR (95% CI) for VAL: 0.61 (0.47,0.79) p = 0.0002 **CV mortality** HR (95% CI) for VAL: 1.03 (0.41, 2.60) p = 0.9545	**Transition to dialysis, doubling of serum Cr levels** HR (95% CI) for VAL: 0.93 (0.34, 2.61) p = 0.8966	**Any adverse event** 2.7% VAL vs 2.3% CT p = NS **Elevated serum potassium** 2 events VAL vs 0 events CT p = NR **Dry Cough** 1 event VAL vs 1 event CT p = NR

VALUE, 2004 Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD VAL: Valsartan step-up therapy Step 1: valsartan 80 mg Step 2: valsartan 160 mg Step 3: valsartan 160 mg + HCTZ 12.5 mg Step 4: valsartan 160 mg + HCTZ 25 mg Step 5: other HTN drugs AML: Amlodipine step-up therapy Step 1: amlodipine 5 mg Step 2: amlodipine 10 mg Step 3: amlodipine 10 mg + HCTZ 12.5 mg Step 4: amlodipine 10 mg + HCTZ 25 mg Step 5: other HTN drugs N: 15,313 Mean exposure to study medication 3.6 years; mean 4.2 years F/U Good	**All-cause death** HR (95% CI) for VAL: 1.04 (0.94, 1.14) p = 0.45	**Fatal and non-fatal MI** HR (95% CI) for VAL: 1.19 (1.02, 1.38) p = 0.02	**Fatal and non-fatal stroke** HR (95% CI) for VAL: 1.15 (0.98, 1.35) p = 0.08	**Fatal and non-fatal HF** HR (95% CI) for VAL: 0.89 (0.77, 1.03) p = 0.12	**Primary composite of time to first cardiac event** HR (95% CI) for VAL: 1.04 (0.94, 1.15) p = 0.49 **Cardiac morbidity** HR (95% CI) for VAL: 1.02 (0.91, 1.15) p = 0.71 **Cardiac mortality** HR (95% CI) for VAL: 1.01 (0.86, 1.18) p = 0.90		**Dizziness** 16.5% VAL vs 14.3% AML p <0.0001 **Headaches** 14.7% VAL vs 12.5% AML p <0.0001 **New onset DM** OR (95% CI) for VAL: 0.77 (0.69, 0.86) p < 0.0001 **Hypokalemia** 3.5% VAL vs 6.2% AML p <0.0001 **Peripheral edema** 14.9% VAL vs 32.9% AML p <0.0001

Kyoto Heart Study, 2009 Adults, ages ≥20 years, with uncontrolled HTN for at least 4 weeks and one or more CV risk factors VAL: Valsartan 80 mg daily; flexibly adjusted to a dose of 40-80 mg as needed to control BP; dose doubled after 4 weeks if initial dose could not achieve BP goal; after 8 weeks, anti-HTN drugs other than ARBs or ACE allowed if necessary CT: conventional therapy; anti-HTN drugs other than ARB and ACE provided to patients to reach target BP; "usual" dosage administered for first 4 weeks and titrated upward to "high" dosage if BP not controlled; other anti-HTN drugs (excluding ACE and ARBs) added at 8 weeks if necessary. N: 3,031 3.27 years Fair	**All-cause mortality** HR (95% CI) for VAL: 0.76 (0.4, 1.3) p = 0.32851	**Acute MI** HR (95% CI) for VAL: 0.65 (0.2, 1.8) p = 0.39466 **Dissecting aneurysm of aorta** HR (95% CI) for VAL: 0.60 (0.1, 2.5) p = 0.69987	**Stroke** HR (95% CI) for VAL: 0.55 (0.3, 0.9) p = 0.01488	**Heart failure** HR (95% CI) for VAL: 0.65 (0.3, 1.3) p = 0.20857	**Composite of fatal and non-fatal CV events (stroke, TIA, MI, new occurrence or exacerbation of angina pectoris, new occurrence or exacerbation of HF, dissecting aneurysm of the aorta, lower limb arterial bstruction, emergency thrombosis, transition to dialysis, and doubling of plasma Cr levels)** HR (95% CI) for VAL: 0.55 (0.4, 0.7) P = 0.00001 **CV death** HR (95% CI) for VAL: 0.66 (0.3, 1.6) p = 0.37121	**Transition to dialysis or doubling serum Cr** HR (95% CI) for VAL: 0.43 (0.2, 1.1) p = 0.34666	**New onset DM** HR (95% CI) for VAL: 0.67 (0.5, 0.9) p = 0.02817 **Dry cough** 0.1% VAL vs 0.3% CT p = NS **Elevated serum potassium** 0.3% VAL vs 0.1% CT p = NS

Table 182

4.3.1.1.6 Combination drugs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ACCOMPLISH, 2008 Adults, ages ≥ 60 with one risk factor or 55 to 59 with 2 or more risk factors BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25) BEN-AML: Benazepril-Amlodipine singe pill formulation: 20/5 mg QD (max: 40/10) N: 11,506 Mean 36 months Good Panel Comments: After mean 30 months treatment exposure, the DSMB observed a difference between the two treatment groups that exceeded the boundary of the prespecified stopping rule and recommended early termination of the study	**Death from any cause** HR (95% CI) for BEN-AML: 0.90 (0.76,1.07) p = 0.24	**Fatal and non-fatal MI** HR (95% CI) for BEN-AML: 0.78 (0.62, 0.99) p = 0.04 **Coronary revascularization procedure** HR (95% CI) for BEN-AML: 0.86 (0.74, 1.00) p = 0.04	**Fatal and non-fatal stroke** HR (95% CI) for BEN-AML: 0.84 (0.65, 1.08) p = 0.17	**Hospitalization for CHF** HR (95% CI) for BEN-AML: 1.04 (0.79, 1.38) p = 0.77	**Composite of CV events** HR (95% CI) for BEN-AML: 0.83 (0.73, 0.93) p = 0.002 **Primary end point plus hospitalization for CHF** HR (95% CI) for BEN-AML: 0.83 (0.74, 0.92) p = 0.0005 **Composite of CV events and death from CV causes** HR (95% CI) for BEN-AML: 0.80 (0.72, 0.90) p < 0.001 **Composite of death from CV events, non-fatal MI, and non-fatal stroke** HR (95% CI) BEN-AML: 0.79 (0.67, 0.92) p = 0.002 **Death from CV causes** HR (95% CI) for BEN-AML: 0.80 (0.62, 1.03) p = 0.08		**Any adverse event of dizziness** 25.4% BEN-HCTZ vs 20.7% BEN-AML p = NR **Any adverse event of peripheral edema** 13.4% BEN-HCTZ vs 31.2% BEN-AML p = NR **Serious adverse event of peripheral edema** 0.1% BEN-HCTZ vs 0.2% BEN-AML p = NR **Drug-related serious adverse event of peripheral edema** <0.1% BEN-HCTZ vs 0.1% BEN-AML p = NR **Any adverse event of dry cough** 21.2% BEN-HCTZ vs 20.5% BEN-AML p = NR p = NR **Serious adverse event of hypokalemia** 0.2% BEN-HCTZ vs <0.1% BEN-AML p = NR **Drug-related serious adverse event of hypokalemia** 0.0% BEN-HCTZ vs <0.1% BEN-AML p = NR

							Any adverse event of hypotension 3.6% BEN-HCTZ vs 2.5% BEN-AML p = NR **Serious adverse event of hypotension** 0.5% BEN-HCTZ vs 0.4% BEN-AML p = NR **Drug-related serious adverse event of hypotension** 0.2% BEN-HCTZ vs 0.1% BEN-AML p = NR **Drug-related serious adverse event of angioedema** 0.1% BEN-HCTZ vs <0.1% BEN-AML p = NR

ACCOMPLISH, 2010 *Prespecified secondary analysis of kidney outcomes* Bakris et al., 2010 Adults, ages ≥ 60 with one risk factor or 55 to 59 with 2 or more risk factors BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25) BEN-AML: BenazeprilAmlodipinesingle pill formulation: 20/5 mg QD (max: 40/10) N: 11,506 Mean F/U 2.9 years Fair Panel Comments: Trial stopped early because of 20% reduction in CV risk recorded in BEN-AML group					**Progression of CKD and CV death** HR (95% CI) for BEN-AML: 0.63 (0.53, 0.74) p <0.0001 **Progression of CKD and all-cause mortality** HR (95% CI) for BEN-AML: 0.73 (0.64, 0.84) p < 0.0001 *In patients aged >=65 years* **Progression of CKD and CV death** HR (95% CI) for BEN-AML: 0.68 (0.55, 0.83) p = 0.0002 **Progression of CKD and all-cause mortality** HR (95% CI) for BEN-AML: 0.81 (0.68, 0.95) p = 0.010	**Progression of CKD** HR (95% CI) for BEN-AML: 0.52 (0.41, 0.65) p <0.0001 **Doubling of serum Cr** HR (95% CI) for BEN-AML: 0.51 (0.39, 0.63) p <0.0001 **Dialysis** HR (95% CI) for BEN-AML: 0.53 (0.21, 1.35) p = 0.180 **eGFR <15 mL/min/1.73m²** BEN-AML: 1.06 (0.54, 2.05) p = 0.868 **GFR decline, mL/min/1.73m² (SD)** -4.22 (16.3) BEN-HCTZ vs -0.88 (15.6) BEN-AML p = 0.01 *In patients aged >=65 years* **Progression of CKD** HR (95% CI) for BEN-AML: 0.50 (0.37, 0.67) p <0.0001	*Patients without CKD at baseline* **Hypotension** 3.4% BEN-HCTZ vs 2.3% BEN-AML p = 0.0005 **Hypokalemia** 0.3% BEN-HCTZ vs 0.1% BEN-AML p = 0.003 **Dizziness** 25.5% BEN-HCTZ vs 20.3% BEN-AML p <0.0001 **Dry cough** 21.6% BEN-HCTZ vs 20.4% BEN-AML p = 0.14 **Hyperkalemia** 0.4% BEN-HCTZ vs 0.4% BEN-AML p = 0.85 **Angioedema** 0.6% BEN-HCTZ vs 0.9% BEN-AML p = 0.15 **Peripheral edema** 13.1% BEN-HCTZ vs 31.0% BEN-AML p <0.0001 *Patients with CKD at baseline* **Hypotension** 5.5% BEN-HCTZ vs 4.3% BEN-AML p = 0.36

						Doubling of serum Cr HR (95% CI) for BEN-AML: 0.49 (0.37, 0.67) p <0.0001 **Dialysis** HR (95% CI) for BEN-AML: 0.30 (0.08, 1.09) p = 0.053 **eGFR <15 mL/min/1.73m²** HR (95% CI) for BEN-AML: 1.00 (0.43, 2.31) p = 0.99 *In patients with CKD at baseline* **GFR decline, mL/min/1.73m² (SD)** -2.3 (10.6) BEN-HCTZ vs 1.6 (12.7) BEN-AML p = 0.001	**Hyperkalemia** 2.3% BEN-HCTZ vs 2.1% BEN-AML p = 0.89 **Hypokalemia** 0.2% BEK-HCTZ vs 0% BEN-AML p = 0.30 **Dizziness** 24.2% BEN-HCTZ vs 25.1% BEN-AML p = 0.73 **Dry cough** 17.5% BEN-HCTZ vs 21.4% BEN-AML p = 0.10 **Angioedema** 0.4% BEN-HCTZ vs 1.6% BEN-AML p = 0.04 **Peripheral edema** 16.0% BEN-HCTZ vs 33.7% BEN-AML p <0.0001

Table 183

4.3.1.2 Thiazide diuretics versus placebo

4.3.1.2.1 Clinical evidence profile

Meta-analysis: NICE 2011

Inclusion criteria:SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classess of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 184

Ref	Comparison	N/n	Outcomes	Result	Quality of evidence (GRADE) by NICE
ref*NICE 2011 Design: SR+MA Search date: nov 2010	Indapamide versus placebo	N= 2 n= 4774 PATS(117) HYVET(63)	**Overall mortality (follow-up mean 2.05 years)**	**HR 0.85 (0.74 to 0.99) SS**	MODERATE 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
			CHD event (follow-up mean 2.05 years)	**HR 0.53 (0.36 to 0.77) SS**	LOW Heterogeneity was 77%. This could be due to different populations. One trial recruited adults aged 80 years+ and the other trial recruited patients with a recent TIA or stroke
			Stroke (follow-up mean 2.05 years)	**HR 0.72 (0.61 to 0.87) SS**	MODERATE 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

			Cardiovascular event (follow-up mean 2.05 years)	**HR 0.77 (0.64 to 0.93) SS**	MODERATE 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 185

* Characteristics of included studies: see below

Study	**N**	**Intervention**	**Comparison**	**Follow-up**	**Results**	**Methodology (Quality assessment by NICE 2011)**
PATS(117)	5665	IND (2.5 mg/day)	Placebo	Mean 2 years	IND better for reduced stroke (fatal and non-fatal), total mortality, CV deaths and coronary deaths	Quality: Both had allocation concealment; attrition was >20% in one trial and no data provided in the other trial Imprecision: 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm Inconsistency: for outcome CHD event: Heterogeneity was 77%. This could be due to different populations. One trial recruited adults aged 80 years+ and the other trial recruited patients with a recent TIA or stroke.
HYVET(63)	3845	IND SR (1.5 mg/day)	Placebo	Mean 2.1 years	IND better for reduced MI (fatal and non-fatal), HF (fatal and non-fatal) and mortality. NS difference between groups for stroke	

Table 186

Meta-analysis: NICE 2011

Inclusion criteria:SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classess of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 187

Ref	Comparison	N/n	Outcomes	Result	Quality assessment NICE (GRADE)
ref*NICE 2011 Design: SR+MA Search date: nov 2010	Chlortalidone vs placebo	N = 3 n = 1012 (SHEP, SHEP-P, VA-NHLBI)	**Overall mortality (follow-up 4.1 to 4.9 years)**	HR 0.87 (0.73 to 1.04)	LOW No ITT analysis conducted on data in one study, attrition >20% in two studies 95%CI crosses both no effect and appreciable harm or benefit
			CHD events (follow-up 4.1 to 4.9 years)	HR 2.0 (0.86 to 4.67)	VERY LOW No ITT analysis conducted on data in one study, attrition >20% in two studies 95%CI crosses both no effect and appreciable harm or benefit
		N = 2 n = 5287	**Stroke (follow-up 4.1 to 4.9 years)**	HR 0.63 (0.49 to 0.80)	MODERATE Attrition >20%

		(SHEP, SHEP-P)			
		N = 2 n = 1012 (SHEP, VA-NHLBI)	**Cardiovascular events (follow-up 4.1 to 4.9 years)**	HR 4.31 (0.27 to 68.84)	MODERATE ITT analysis not conducted in one study and attrition > 20% in the other study

Table 188

* Characteristics of included studies: see below

Study	**N**	**Intervention**	**Comparison**	**Follow-up**	**Results**	**Methodology (Quality assessment by NICE 2011)**
SHEP Data from trial cited by: (118); (119); (120); (17)	4736	chlorthalidone 12.5-25mg/d	placebo	4.5 years	CTD better than placebo for reduced CHD events, reduced stroke and reduced cardiovascular events. NS difference for HF (fatal and non-fatal).	Serious limitations. Attrition >20% for SHEP and SHEP-P VA-NHLBI no ITT conducted
SHEP-P data from trial cited by (121);(59)	551	chlorthalidone 12.5-25mg/d	placebo	2.8 years	NS differences between groups	
VA-NHLBI data fom trial cited by (122)	1012	CTD 50 mg/d initially	placebo	2 years	NS differences between groups	

Table 189

4.3.1.2.2 Summary and conclusions

Indapamide versus placebo in hypertension with or without additional risk factors			
Bibliography: NICE 2011(3); including HYVET 2008(63) and PATS 1995(117)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4774 (2 studies) 2 years	**HR 0.85 (0.74 to 0.99)** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: attrition was >20% in one trial and no data provided in the other trial Consistency: ok Directness:ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Coronary heart disease event	4774 (2 studies) 2 years	**HR 0.53 (0.36 to 0.77)** **SS**	⨁⨁⊖⊖ **LOW** Study quality: attrition was >20% in one trial and no data provided in the other trial Consistency:-1 Heterogeneity was 77%. This could be due to different populations. One trial recruited adults aged 80 years+ and the other trial recruited patients with a recent TIA or stroke Directness:ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	4774 (2 studies) 2 years	**HR 0.72 (0.61 to 0.87)** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: attrition was >20% in one trial and no data provided in the other trial Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cardiovascular event	4774 (2 studies) 2 years	**HR 0.77 (0.64 to 0.93)** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: attrition was >20% in one trial and no data provided in the other trial Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 190

NICE 2011(3) conducted a systematic review and meta-analysis to evaluate indapamide versus placebo in hypertension patients with or without additional risk factors. It found 2 RCTs: HYVET 2008(63), which followed 3845 patients older than 80 years for a mean of 2 years and compared indapamide (sustained-release) 1.5 mg/day with placebo; and PATS 1995(117), which followed 3548 patients with a recent TIA or stroke for a mean of 2.1 years and compared indapamide 2.5 mg/day with placebo.

In hypertension patients with or without additional risk factors, indapamide significantly decreases mortality, stroke rate, and cardiovascular events, compared to placebo.
GRADE: MODERATE quality of evidence

In hypertension patients with or without additional risk factors, indapamide significantly decreases coronary heart disease events, compared to placebo.
GRADE: LOW quality of evidence

Chlortalidone versus placebo in hypertension with or without additional risk factors			
Bibliography: NICE 2011; including SHEP 1991(118),(119),(120),(17), SHEP-P(121);(59), VA-NHLBI(122)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1012 (3 studies) 4.1 to 4.9 years	HR 0.87 (0.73 to 1.04) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; No ITT analysis conducted on data in one study, attrition >20% in two studies Consistency: ok Directness: ok Imprecision:-1; 95%CI crosses both no effect and appreciable harm or benefit
Coronary heart disease events	1012 (3 studies) 4.1 to 4.9 years	HR 2.0 (0.86 to 4.67) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; No ITT analysis conducted on data in one study, attrition >20% in two studies Consistency:-1; Heterogeneity 59% Directness:ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Stroke	5287 (2 studies) 4.1 to 4.9 years	**HR 0.63 (0.49 to 0.80)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality:-1; attrition >20% in two studies Consistency:ok Directness:ok Imprecision:ok
Cardiovascular events	1012 (2 studies) 4.1 to 4.9 years	HR 4.31 (0.27 to 68.84) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; No ITT analysis conducted on data in one study, attrition >20% in two studies Consistency:ok Directness:ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Table 191

NICE 2011(3) conducted a systematic review and meta-analysis to evaluate chlortalidone versus placebo in hypertension patients with or without additional risk factors. 3 RCTs were identified, with 2 RCTs including patients >60 years with isolated systolic hypertension and one including only patients <50y with mild hypertension.
The follow-up ranged from 4.1 to 4.9 years.

In hypertension patients with or without additional risk factors, treatment with chlortalidone significantly decreases stroke rate, compared to placebo.
GRADE: MODERATE quality of evidence

In hypertension patients with or without additional risk factors, treatment with chlortalidone did not result in a statistically significant difference in mortality or cardiovascular events, compared to placebo.

GRADE: LOW quality of evidence

In hypertension patients with or without additional risk factors, treatment with chlortalidone did not result in a statistically significant difference in coronary heart disease events, compared to placebo.
GRADE: VERY LOW quality of evidence

4.3.1.3 Beta blockers versus placebo

4.3.1.3.1 Clinical evidence profile

Meta-analysis: WIYSONGE 2012 (Cochrane SR)

Inclusion criteria:
Studies: RCT with a duration of one year or more.
Participants: Men and non-pregnant women, aged 18 years and over, with hypertension as defined by cut-off points operating at the time of the study under consideration.
Intervention: The treatment group must have received a beta-blocker drug either as monotherapy or as a first-line drug in a stepped care approach. The control group could be a placebo, no treatment, or another anti-hypertensive drug (including a different beta-blocker or the same beta-blocker at a different dose).

Search strategy: On 08 May 2011, a comprehensive search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted and repeated on 02 December 2011. Reference list of relevant reviews were screened as were those of studies selected for inclusion in this review.

Assessment of quality of included trials: Yes, grade
ITT analysis: Yes

Table 192

Ref	Comparison	N/n	Outcomes	Result (RR, 95% CI)	Quality assessment (GRADE)
WIYSONGE 2012 Design: SR+MA Search date: dec	β-blockers versus placebo	N = 4 n = 23613 (IPPPSH 1985, MRC 1985,	**Total Mortality**	0.99 [0.88, 1.11]	MODERATE (The two studies that contribute to the most weight of the pooled RR have high risk of bias (especially incomplete outcome reporting due to attrition bias): rated down by 1.)
			CHD event	0.93 [0.81, 1.07]	
			Stroke	**0.80 [0.66, 0.96] SS**	

2011		Coope 1986, MRCOA 1992)			
			Cardiovascular mortality	0.93 [0.80, 1.09]	
			Cardiovascular disease	**0.88 [0.79, 0.97] SS**	
			Withdrawal due to adverse effects	3.38 (0.82 to 13.95)	LOW (Inconsistent results across studies (I-square = 100%): Rated down by 2 points.)
		N = 1 n = 6357 IPPPSH 1985	Withdrawal due to adv. effets: **Oxprenolol**	0.95 [0.87, 1.04]	
		N = 2 n = 16372 MRC 1985, MRCOA 1992	Withdrawal due to adv. effects: **Atenolol or propranolol**	6.35 [3.94, 10.22]	

Table 193

* Characteristics of included studies: see below

Study	**N**	**Population**	**Intervention**	**Comparison**	**Follow-up**	**Methodology** **(Quality assessment by Wiysonge 2012)**
IPPPSH 1985 (123)	6357	- age 40 to 64 years, mean 52.2 - seated DBPs of 100 to 125 mmHg, mean SBP at entry: 173 mmHg	Oxprenolol 160mg/d	Placebo	Mean: 4 years	ALLOC Conc.: Adequate RANDO: Adequate, computer generated BLINDING: Adequate Rated “Fair” by JNC-8

		- either untreated or receiving anti- HTN at study entry				
MRC 1985 (124)	17354	- age 35 to 64 years, mean 52 years - BP entry criteria: <200 mmHg, DBP 90-109 mmHg - mean BP at entry: 162/98mmHg - 29% smoking	Propranolol (up to 240 mg/d) or bendrofluazide (10 mg /d)	Placebo	Mean: 4.9 years	ALLOC Conc.: Unclear RANDO: Unclear BLINDING: Patients blinded, outcome assessors unblinded Loss to follow-up 19%. High risk of attrition bias Rated “Fair” by JNC-8
Coope 1986 (60)	884	- age 60 to 79 years, mean:65 years - SBPs ≥ 170 or DBP ≥ 105 mmHg - mean BP at entry: 196.4/ 98.8 mmHg - smoking 24%	Atenolol (100 mg / d)	No treatment	Mean: 4.4 years	ALLOC CONC: adequate RANDO: adequate BLINDING: unclear Rated “good” by JNC-8
MRCOA 1992 (125)	4396	- age 65 – 74 years, mean 70.3 - BP entry criteria: SBP 160-209 mmHg and DBP < 115 mmHg - mean BP at entry: 184/97 mmHg - smoking: 17.5%	Atenolol (50 to 100 mg/ d) Also: Diuretic arm with amiloride 2.5mg or 5 mg and hydrochlorothiazide 25 mg or 50 mg	Placebo	Mean: 5.8 years	ALLOC Conc.: Unclear RANDO: Unclear BLINDING: Patients blinded, providers not blinded, outcome assessors blinded Loss to follow-up 25%, high risk of attrition bias Not rated by JNC-8

Table 194

4.3.1.3.2 Summary and conclusions

Beta-blockers versus placebo for hypertension			
Bibliography: Wiysonge 2012(126); includes IPPPSH 1985(123), MRC 1985(124), Coope 1986(60), MRCOA 1992(125)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR, 95%CI)**	**Quality of the evidence (GRADE)**
Mortality	23613 (4 studies) 4 to 5.8 y	0.99 [0.88, 1.11] NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ;unclear randomization, allocation concealment and blinding; attrition >20% in one study Consistency: ok Directness: ok Imprecision: ok
Coronary heart disease event	23613 (4 studies) 4 to 5.8 y	0.93 [0.81, 1.07] NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ;unclear randomization, allocation concealment and blinding; attrition >20% in one study Consistency: ok Directness: ok Imprecision: ok
Stroke	23613 (4 studies) 4 to 5.8 y	**0.80 [0.66, 0.96]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1 ;unclear randomization, allocation concealment and blinding; attrition >20% in one study Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cardiovascular mortality	23613 (4 studies) 4 to 5.8 y	0.93 [0.80, 1.09] NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ;unclear randomization, allocation concealment and blinding; attrition >20% in one study Consistency: ok Directness: ok Imprecision: ok
Cardiovascular disease	23613 (4 studies) 4 to 5.8 y	**0.88 [0.79, 0.97]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1 ;unclear randomization, allocation concealment and blinding; attrition >20% in one study Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Withdrawal due to adverse effects	23613 (4 studies)	3.38 (0.82 to 13.95) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 ;unclear

	4 to 5.8 y		randomization, allocation concealment and blinding Consistency:-1 inconsistent results across studies Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Withdrawal due to adverse effects: atenolol or propranolol	16372 (2 studies) 4.9 to 5.8 y	**6.35 [3.94, 10.22]** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 ;unclear randomization and allocation; attrition >20% in one study concealment Consistency: ok Directness: ok Imprecision: ok

Table 195

This Cochrane systematic review and meta-analysis evaluated beta-blockers versus placebo in hypertension patients with or without additional risk factors. 4 RCTs were included, with patients aged 35 to 79 years and a mean follow-up ranging from 4 to 5.8 years. One RCT used oxprenolol in its comparison, which is not available in Belgium; two used atenolol, and one used propranolol.

In hypertension patients with or without additional risk factors, treatment with beta-blockers significantly decreases stroke and cardiovascular disease, compared to placebo.
GRADE: LOW quality of evidence

In hypertension patients with or without additional risk factors, treatment with beta-blockers (atenolol or propranolol) significantly increases withdrawal due to adverse effects, compared to placebo.
GRADE: MODERATE quality of evidence

In hypertension patients with or without additional risk factors, treatment with beta-blockers do not result in statistically significant differences in mortality, coronary heart disease, and cardiovascular mortality, compared to placebo.
GRADE: MODERATE quality of evidence

In hypertension patients with or without additional risk factors, treatment with beta-blockers do not result in statistically significant differences in withdrawal due to adverse events, compared to placebo.
GRADE: VERY LOW quality of evidence

4.3.1.4 Calcium channel blockers versus placebo

4.3.1.4.1 Clinical evidence profile

Meta-analysis: Wright 2009(127), "First-line drugs for hypertension"

Inclusion criteria: Randomized trials of at least one year duration comparing one of 6 major drug classes with a placebo or no treatment. Required was: baseline patient characteristics, clearly defined morbidity and mortality endpoints, and outcome data presented using the intention-to-treat principle. Trials that compared two specific antihypertensive first-line therapies without a placebo or untreated control were excluded.

More than 70% of people must have BP >140/90 mmHg at baseline.

Search strategy: The following literature sources were searched: (fromJanuary 1966-June 2008)MEDLINE, EMBASE, CINAHL, the Cochrane clinical trial register, Biomedical literature search, the WHO-ISH Collaboration register and bibliographic citations. The standard search strategy of the antihypertensive review group with additional terms was used to identify the relevant articles. In case of incomplete reports, further searches were done for connected papers or authors were contacted to retrieve missing information. Experts in the field were contacted about ongoing studies or trials about to be published. Previously published meta-analyses on the treatment of hypertension were used to help identify references to trials.
Assessment of quality of included trials: no
ITT analysis: yes
Other methodological remarks:
The analysis was also stratified by the thiazide dose.

Table 196

Ref	Comparison	N/n	Outcomes	Result (RR [95% CI])
Wright 2009(127), Design: MA+SR Search date:	CCB vs placebo	N= 1 n= 4695 (SYST-EUR 1997)	Total mortality	0.86 [0.68, 1.09]
		N= 1 n= 4695 (SYST-EUR	Total Stroke	**0.58 [0.41, 0.84] SS**

jun 2008		1997)		
		N= 1 n= 4695 (SYST-EUR)	Total CHD	0.77 [0.55, 1.09]
		N= 1 n= 4695 (SYST-EUR)	Heart failure	0.71 [0.45, 1.12]
		N= 1 n= 4695 (SYST-EUR)	Total cardiovascular event	**0.71 [0.57, 0.87] SS**

Table 197

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
SYST-EUR 1997(52)	4695	- aged ≥ 60 years, mean 70.2 -inclusion BP: SBP 160-219 and DBP <95 mmHg	Median 24 months	Nitrendipine 10 mg to 20 mg BID With possible addition of: Enalapril 5 mg to 20mg/d HCTZ: 12.5 mg to 25mg/d Matched placebos	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Participants yes, assessors yes Rated “Good” by JNC-8

Table 198

4.3.1.4.2 Summary and conclusions

Calcium channel blockers versus placebo for hypertension with or without additional risk factors			
Bibliography: Wright 2009(127), including Syst-Eur 1997(52)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR [95% CI])**	**Quality of the evidence (GRADE)**
Mortality	4695 (1 studies) 2 years	0.86 [0.68, 1.09] NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: only one study Directness:-1; isolated systolic hypertension Imprecision:-1; 95%CI crosses both no effect and appreciable harm or benefit
Stroke	4695 (1 studies) 2 years	**0.58 [0.41, 0.84]** **SS**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: only one study Directness: -1; isolated systolic hypertension Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Coronary heart disease	4695 (1 studies) 2 years	0.77 [0.55, 1.09] NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: only one study Directness: -1; isolated systolic hypertension Imprecision:-1; 95%CI crosses both no effect and appreciable harm or benefit
Heart failure	4695 (1 studies) 2 years	0.71 [0.45, 1.12] NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: only one study Directness: -1; isolated systolic hypertension Imprecision:-1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular events	4695 (1 studies) 2 years	**0.71 [0.57, 0.87]** **SS**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: only one study Directness: -1; isolated systolic hypertension Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 199

This Cochrane systematic review and meta-analysis compared calcium channel blockers to placebo in hypertension patients with or without additional risk factors. It included only one RCT with this comparison. This RCT included relatively healthy patients over 60 years old with isolated systolic hypertension, with a follow-up of 2 years. Nitrendipine was the calcium channel blocker used in this trial.

The paucity of the evidence limits our confidence in these results.

In hypertension patients with or without additional risk factors, treatment with calcium channel blockers significantly decreases stroke and cardiovascular events, compared to placebo.
GRADE: LOW quality of evidence

In hypertension patients with or without additional risk factors, treatment with calcium channel blockers did not result in a statistically significant difference in mortality, coronary heart disease, or heart failure, compared to placebo.
GRADE: LOW quality of evidence

4.3.1.5 ACE-inhibitors versus placebo

4.3.1.5.1 Clinical evidence profile

Meta-analysis: Wright 2009 “First-line drugs for hypertension”

Inclusion criteria: Randomized trials of at least one year duration comparing one of 6 major drug classes with a placebo or no treatment. Required was: baseline patient characteristics, clearly defined morbidity and mortality endpoints, and outcome data presented using the intention-to-treat principle. Trials that compared two specific antihypertensive first-line therapies without a placebo or untreated control were excluded.
Initial combined therapies with drug classes not in the defined categories were allowed. Supplemental drugs from other drug classes of interest were only allowed as stepped therapy and only as long as they were not taken by over 50% of the patients.

More than 70% of people must have BP >140/90 mmHg at baseline.

Search strategy: The following literature sources were searched: (fromJanuary 1966-June 2008)MEDLINE, EMBASE, CINAHL, the Cochrane clinical trial register, Biomedical literature search, the WHO-ISH Collaboration register and bibliographic citations. The standard search strategy of the antihypertensive review group with additional terms was used to identify the relevant articles. In case of incomplete reports, further searches were done for connected papers or authors were contacted to retrieve missing information. Experts in the field were contacted about ongoing studies or trials about to be published. Previously published meta-analyses on the treatment of hypertension were used to help identify references to trials.
Assessment of quality of included trials: no
ITT analysis: yes
Other methodological remarks: The analysis was also stratified by the thiazide dose. (low dose and high dose thiazides)

Table 200

Ref	Comparison	N/n	Outcomes	Result (RR [95% CI])
Wright 2009(127) Design: MA+SR	ACE-inhibitor vs placebo	N = 3 n = 6002 (HOPE HYP, HYVET, UKPDS-39-1998)	Total mortality	**0.83 [0.72, 0.95]** **SS**
			Total Stroke	**0.65 [0.52, 0.82]** **SS**
		N = 2	Total CHD	**0.81 [0.70, 0.94]**

Search date: june 2008		n = 5145 (HOPE HYP, UKPDS-39-1998)		**SS**
			Total cardiovascular event	**0.76 [0.67, 0.85]** **SS**

Table 201

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
HOPE HYP (128) RCT DB	4355	- Patients 55 or older with previous coronary artery disease, peripheral vascular disease or diabetes + 1 additional risk factor - 38% diabetes - predominantly secondary prevention -subgroup with hypertension at baseline	Mean: 4.5 years	Ramipril 2.5 mg titrating up to 10 mg or placebo.	ALLOC. CONC: Adequate - Run-in phase of 7-10 days with measurement of creatining and potassium. 1035 not randomized after this run in period - Not rated by JNC 8
HYVET(63) RCT DB	3845	80 years old or greater systolic blood pressure of 160 mmHg or greater	Mean 2.1 years	Step 1 indapamide 1.5 mg daily. Step 2 perinodopril 2 mg daily. Step 3 perindopril 4 mg daily. Control: identical appearing placebos for each step	ALLOC. CONC: Adequate Rated “good” by JNC-8
UKPDS-39-1998(129) RCT open label	1148	Newly diagnosed patients with type 2 diabetes mellitus and hypertension (BP > or = 160 and/or > or = 90 mmHg in patients not on antihypertensive therapy and > or = 150 and/or > or = 85 mmHg in patients on antihypertensive therapy	8.4 years	Tight BP control group (Captopril 25mg -50mg b.i.d. or atenolol 50mg o.d. to 100mg/day. Supplemental drugs added frusemide 20 - 40 mg b.i.d., slow release nifedipine 10 - 40 mg b.i.d.,	ALLOC. CONC: Unclear Rated “fair” by JNC-8

		mean age 56 years,		methyldopa 250-500 mg b.i.d., prazosin 1-5mg t.i.d. given sequentially to achieve target BP) . The control group were given treatment if BP > or = 200 and /or 105 mm Hg (frusemide, long acting nifedipine, methyldopa , prazosin given sequentially to control BP. If possible ACEI and beta-blockers were avoided)	

Table 202

4.3.1.5.2 Summary and conclusions

ACE-inhibitors versus placebo for hypertension with or without additional risk factors			
Bibliography: Wright 2009(127), including HOPE HYP2000(128), HYVET(63), UKPDS-39-1998(129)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR [95% CI])**	**Quality of the evidence (GRADE)**
Mortality	6002 (3 studies) 2.1 to 8.4 years	**0.83 [0.72, 0.95]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: unclear allocation in one RCT Consistency: ok Directness:-1; relatively high risk Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	6002 (3 studies) 2.1 to 8.4 years	**0.65 [0.52, 0.82]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: unclear allocation in one RCT Consistency: ok Directness: -1; relatively high risk Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Coronary heart disease	5145 (2 studies) 4.5 to 8.4 years	**0.81 [0.70, 0.94]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: unclear allocation in one RCT Consistency: ok Directness: -1; relatively high risk Imprecision:-1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cardiovascular events	5145 (2 studies) 4.5 to 8.4 years	**0.76 [0.67, 0.85]** **SS**	⊕⊕⊖⊖ **LOW** Study quality: unclear allocation in one RCT Consistency: ok Directness: -1; relatively high risk Imprecision:-1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 203

This Cochrane systematic review and meta-analysis compared treatment with ACE-inhibitors versus placebo in hypertensive patients with or without additional risk factors. It included 3 RCTs in relatively high-risk populations (one RCT in patients with previous cardiovascular events, one in diabetics and one in people older than 80) with a follow-up ranging from 2.1 to 8.4 years.

In hypertension patients with or without additional risk factors, treatment with ACE-inhibitors significantly decreases mortality, stroke rate, coronary heart disease, and cardiovascular events, compared to placebo.
GRADE: LOW quality of evidence

4.3.1.6 Angiotensin receptor blockers versus placebo

4.3.1.6.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Lithell 2003(91) SCOPE Design: RCT (DB) (PG) Duration of follow-up: Mean: 3.7 years	n= 4964 Mean age: 76.4 Previous CV event: 4.5% Previous stroke:3.9 % Heart failure: not given Diabetes: 12.8 % CKD: not given Smoking: 8.7% Age >80y: 21.3% Inclusion - age between 70 and 89 years - SBP 160-179 mmHg, DBP 90-99 mmHg after standardization of previous	Candesartan 8 – 16 mg + Open-label active antihypertensive therapy Vs Placebo + Open-label active antihypertensive therapy	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: unclear Assessors: yes Remarks on blinding method: central, computer-generated randomization balanced with respect to a number of likely prognostic variables FOLLOW-UP: Lost-to follow-up: 0.1% Drop-out and Exclusions: 0.4 % • Described: yes • Balanced across groups: yes
			Major cardiovascular events (PO) Composite endpoint (consisting off: CV death, non-fatal stroke, non-fatal myocardial infarction)	Candesartan: 242 / 2477 Placebo: 268 / 2460 Risk Reduction = 10.9% (95% CI: -6.0 to 25.1) P = 0.19 NS	
			Cardiovascular death	No significant difference Numbers not reported	
			Non-fatal stroke	Candesartan: 68/2477 Placebo: 93/2460 Risk Reduction = 27.8% (95% CI: 1.3 to 47.2) P = 0.04	
			All stroke	Candesartan: 89/2477 Placebo: 115 / 2460 Risk Reduction= 23.6% (95% CI: -0.7 to 42.1) P = 0.056	

	antihypertensive medication to HCT 12.5 mg - MMSE 24 or above on two consecutive occasions separated by at least 14 days Exclusion - SBP ≥ 180 mmHg - orthostatic hypotension - need of an antihypertensive treatment other than HCT during the run-in - stroke or myocardial infarction within 6 months - decompensated heart failure - serum AST or ALT > 3 times the upper normal limit - serum creatinine >180 µmol in men and >140 µmol in women - contra-indications for study drug or HCT		Non-fatal myocardial infarction	No significant difference Numbers not reported	ITT: No, some patients dropped due to concerns on data quality Patients who took no medication or placebo pill were dropped too SELECTIVE REPORTING: no The study consisted of an open run-in period of minimum 1 month, maximum 3 month followed by a double-blind treatment for 3-5 years. If a SBP > 160 mmHg or a DBP > 90 mmHg was observed during the study, in spite of 2 tablets o.d. of study drug, additional antihypertensive treatment was recommended. The recommendation was to start with HCT 12.5 mg once daily. Other drugs, except angiotensin-converting enzyme inhibitors (ACE-I) and AT1-receptor blockers (ARB), could be added later. Sponsor: Fully sponsored by Astra Zeneca
			Total mortality	No significant difference Numbers not reported	
			New-onset diabetes mellitus	Candesartan : 4.3% of patients Placebo: 5.3% of patients P = 0.09	
			Safety		
			Patient withdrawal due to severe adverse effect	Candesartan group: 15% Placebo group: 17% P = 0.07	

	- serious concomitant diseases affecting survival - alcoholism and drug abuse - Number of exclusion criteria related to the aim of studying cognitive function and dementia (dementia; treatment with antidementia drugs; conditions which preclude MMSE; vitamin B12 deficiency treated , 12 months; hypothyroidism treated, 12 months; neurosyphilis or AIDS; severe brain disorder which may interfere with cognitive function; certain mental disorders (e.g. severe depression within 12 months, history of recurrent				

	depression or psychotic disorder); and psycho-pharmacological treatment started within 6 months.)				

Table 204

4.3.1.6.2 Summary and conclusions

Angiotensin receptor blockers versus placebo in hypertension patients with or without additional risk factors			
Bibliography: Lithell 2003(91) SCOPE			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular events	4964 (1 study) 3.7 years	Risk Reduction = 10.9% (95% CI: -6.0 to 25.1) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Non-fatal stroke	4964 (1 study) 3.7 years	**Risk Reduction = 27.8% (95% CI: 1.3 to 47.2)** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	4964 (1 study) 3.7 years	Risk Reduction= 23.6% (95% CI: -0.7 to 42.1) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
New-onset diabetes mellitus	4964 (1 study) 3.7 years	Candesartan : 4.3% of patients Placebo: 5.3% of patients P = 0.09 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness:ok Imprecision: -1
Withdrawal due to severe adverse effects	4964 (1 study) 3.7 years	Candesartan group: 15% Placebo group: 17% P = 0.07 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: Directness: Imprecision: -1

Table 205

In this double blind RCT, 4964 elderly patients (70-89 years old) with mild to moderate hypertension (SBP <180 mmHg) were treated with either candesartan or placebo.

The paucity of the evidence limits our confidence in the results.

In patients with hypertension with or without additional risk factors, treatment with an angiotensin receptor blocker significantly decreases non-fatal stroke, compared to placebo.
GRADE: LOW quality of evidence

In patients with hypertension with or without additional risk factors, treatment with an angiotensin receptor blocker does not result in a statistically significant difference in cardiovascular events, total stroke, new-onset diabetes mellitus, or withdrawal due to adverse effects, compared to placebo.
GRADE: LOW quality of evidence

4.3.1.7 Chlortalidone versus hydrochlorothiazide

4.3.1.7.1 Summary and conclusions

Our search yielded no MA's or RCTs that directly evaluated this comparison in hypertension patients with or without additional risk factors.

We found one network-MA (Roush 2012(130)) that indirectly compared chlortalidone and hydrochlorothiazide. In this paper, chlortalidone was superior to hydrochlorothiazide in preventing cardiovascular events.

GRADE: LOW quality of evidence

4.3.1.8 Diuretics versus beta blockers

4.3.1.8.1 Clinical evidence profile

Meta-analysis: WIYSONGE 2012 (cochrane)

Inclusion criteria:
Studies: RCT with a duration of one year or more.
Participants: Men and non-pregnant women, aged 18 years and over, with hypertension as defined by cut-off points operating at the time of the study under consideration.
Intervention: The treatment groupmust have received a beta-blocker drug either as monotherapy or as a first-line drug in a stepped care approach. The control group could be a placebo, no treatment, or another anti-hypertensive drug (including a different beta-blocker or the same beta-blocker at a different dose).

Search strategy: On 08 May 2011, a comprehensive search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted and repeated on 02 December 2011. Reference list of relevant reviews were screened as were those of studies selected for inclusion in this review.

Assessment of quality of included trials: Yes, grade
ITT analysis: Yes

Table 206

Ref	Comparison	N/n	Outcomes	Result (RR, 95% CI)	Quality assessment (GRADE)
WIYSONGE 2012(126) Design: SR+MA Search date: dec	β-blockers versus diuretics	N = 5 n = 18241 (Berglund 1981, MRC 1985, HAPPHY 1987, MRCOA 1992, VA COOP 1982)	**Total Mortality**	RR: 1.04 [0.91, 1.19]	MODERATE (The two studies that contribute to the most weight of the pooled RR have high risk of bias (especially incomplete outcome reporting due to attrition bias): Rated

2011					down by 1.)
		N = 4 n = 18135 (VA COOP 1982, MRC 1985, HAPPHY 1987, MRCOA 1992)	**CHD**	RR: 1.12 [0.82, 1.54]	
		N = 4 n = 18135 (VA COOP 1982, HAPPHY 1987, MRCOA 1992, MRC 1985)	**Stroke**	1.17 [0.65, 2.09]	
		N = 3 n = 17452 (MRC 1985, HAPPHY 1987, MRCOA 1992)	**Cardiovascular mortality**	1.09 [0.90, 1.32]	
		N = 4 n = 18135 (VA COOP 1982, MRC 1985, HAPPHY 1987, MRCOA 1992)	**Cardiovascular disease**	1.13 [0.99, 1.28]	MODERATE (The two studies that contribute to the most weight of the pooled RR have high risk of bias (especially incomplete outcome reporting due to attrition bias): Rated down by 1.)
		N = 3 n = 11566 MRC 1985,	**Withdrawal due to adverse effects**	1.69 [0.95, 3.00]	

		MRCOA 1992, VACOOP 1982			

Table 207

* Characteristics of included studies: see below

Study	N	Intervention	Comparison	Follow-up	Methodology (Quality assessment by Wiysonge 2012)
Berglund 1981 (131)	106	β-blocker (propranolol)	Thiazide diuretic (bendroflumethiazide)	mean: 10 years	ALLOC CONC: unclear RANDO: unclear BLINDING: unblinded, but outcome (death) not likely influenced by blinding Loss to follow up: 7% 100% male population Not rated by JNC-8
MRC 1985 (124)	17354	β-blocker arm: Propranolol (up to 240 mg/d)	Diuretic arm: bendrofluazide (10 mg /d) Also placebo arm	Mean: 4.9 years	ALLOC Conc.: Unclear RANDO: Unclear BLINDING: Patients blinded, outcome assessors unblinded Loss to follow-up 19%. High risk of attrition bias Rated “Fair” by JNC-8
HAPPHY 1987 (132)	6569	β-blocker arm: atenolol or metoprolol or propranolol	Diuretic (bendroflumethiazide or hydrochlorothiazide)	Mean: 3.8 years	ALLOC Conc.: Unclear RANDO: Unclear BLINDING: Only outcome assessors Loss to follow-up: 1% 100% male population

					Rated “Fair” by JNC-8
MRCOA 1992 (125)	4396	β-blocker arm: Atenolol (50 to 100 mg/ d)	Diuretic arm: amiloride 2.5mg or 5 mg and hydrochlorothiazide 25 mg or 50 mg Also placebo arm	Mean: 5.8 years	ALLOC Conc.: Unclear RANDO: Unclear BLINDING: Patients blinded, providers not blinded, outcome assessors blinded Loss to follow-up 25, high risk of attrition bias Not rated by JNC-8
VA COOP 1982 (133)	683	β-blocker arm: propranolol 40 mg 2x/d	Diuretic arm: HCTZ up to 200 mg/d	Mean: 12 months	ALLOC. Conc.: unclear RANDO: unclear BLIINDING: adequate Loss to follow-up: 8% Not rated by JNC-8

Table 208

4.3.1.8.2 Summary and conclusions

Diuretics versus beta-blockers in hypertension patients with or without additional risk factors			
Bibliography: Wiysonge 2012(126), including Berglund 1981 (131), MRC 1985(124), HAPPHY 1987(132), MRCOA 1992(125), VA COOP 1982(133)			
Outcomes	N° of participants (studies) Follow up	Results (RR[95%CI])	Quality of the evidence (GRADE)
Mortality	18241 (5 studies) 1 to 10 years	1.04 [0.91, 1.19] In favour of diuretic NS	⨁⨁⨁⨀ **MODERATE** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: ok Directness: two studies 100% male Imprecision:ok
Coronary heart disease	18135 (4 studies) 1 to 5.8 years	1.12 [0.82, 1.54] In favour of diuretic NS	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: ok Directness: one study 100% male Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Stroke	18135 (4 studies) 1 to 5.8 years	1.17 [0.65, 2.09] In favour of diuretic NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: -1 heterogeneity I^2=73% Directness: one study 100% male Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular mortality	17452 (3 studies) 3.8 to 5.8 years	1.09 [0.90, 1.32] In favour of diuretic NS	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: ok Directness: one study 100% male Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular disease	18135 (4 studies) 1 to 5.8 years	1.13 [0.99, 1.28] In favour of diuretic NS	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: ok Directness: one study 100% male Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Withdrawal due to adverse effects	11566 (3 studies) 1 to 5.8 years	1.69 [0.95, 3.00] In favour of diuretic NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; unclear randomization and allocation concealment; 2 studies with high risk of attrition bias Consistency: -1; heterogeneity: I^2=95% Directness:ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Table 209

Note: in this MA the comparison was "beta-blocker versus diuretic". It is clarified whether a beta-blocker or a diuretic is favoured, even if the result was NS.

Wiysonge 2012{Wiysonge Charles, 2012 #686
In this Cochrane systematic review and meta-analysis, diuretics were compared to beta-blockers in hypertensive patients with or without additional risk factors. 5 RCT's were included, with follow-up ranging from 1 to 10 years. In two of the RCT's, only men were included. There were some methodological problems in all of the studies, such as unclear randomization and allocation concealment.

In hypertensive patients with or without additional risk factors, a treatment with diuretics, compared with beta-blockers, did not result in a statistically significant difference in mortality.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with diuretics, compared with beta-blockers, did not result in a statistically significant difference in coronary heart disease, cardiovascular mortality, or cardiovascular disease.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with diuretics, compared with beta-blockers, did not result in a statistically significant difference in stroke or withdrawal due to adverse effects.
GRADE: VERY LOW quality of evidence

4.3.1.9 Diuretics versus calcium channel blockers

1.1.1.1.1 Clinical evidence profile

Meta-analysis: NICE 2011

Inclusion criteria: SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 210

Ref	Comparison	N/n	Outcomes	Result
NICE 2011(3), Design: MA/SR Search date: Nov 2010	Chlorthalidone vs CCB	N= 3 n= 26922 (ALLHAT 2002, SHELL 2003, VHAS 1998)	**Overall mortality (follow-up 2 to 4.9 years)**	HR 1.03 (0.97 to 1.10)
		N= 2 n= 25040 (ALLHAT 2002, VHAS 1998)	**CHD events (follow-up 2 to 4.9 years)**	HR 0.94 (0.88 to 1.0)

		N= 3 n= 26922 (ALLHAT 2002, SHELL 2003, VHAS 1998)	**Stroke (follow-up 2 to 4.9 years)**	HR 0.94 (0.83 to 1.06)
		N= 1 n= 23626 (ALLHAT 1998)	**Cardiovascular events (follow-up mean 4.9 years)**	HR 0.96 (0.91 to 1.01)
		N= 1 n= 1882 (SHELL)	**Heart failure (follow-up mean 32 months)**	HR 0.83 (0.46 to 1.62)
		N= 1 n= 1882 (SHELL 2003)	**MI (follow-up mean 32 months)**	HR 1.17 (0.54 to 2.53)

Table 211

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
ALLHAT 2002 (134)	33357	Adults, ≥ 55 years of age with at least one additional risk factor for CHD	Mean 4.9 years	3 arms: CHL: Chlorthalidone: 12.5 to 25 mg/d LIS: Lisinopril: 10, 20, and 40 mg /d AML: Amlodipine: 2.5, 5, and 10 mg/d	Rated “good” by JNC-8
SHELL 2003 (135)	1882	Adults ≥ 60 years with isolated systolic HTN	Median 32 months	Two arms: CHL: Chlorthalidone: 12.5, 25 mg QD LAC: Lacidipine: 4, 6 mg QD	Rated “fair” by JNC-8

VHAS 1998 (136)	1414	Adults, ages 40-65 years, with HTN	2 years	CHL: Chlorthalidone: 25 mg QD VER: Verapamil: slow release 240 mg QD	Rated "Fair" by JNC-8

Table 212

Meta-analysis: NICE 2011

Inclusion criteria: SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 213

Ref	Comparison	N/n	Outcomes	Result
NICE 2011(3), Design: MA/SR Search date: Nov 2010	Hydrochlorothiazide versus calcium channel blockers	N= 3 n= Sareli 2001, MIDAS 1996, THAI 2005	**Overall mortality** **2-36 months**	HR 1.18 (0.48 to 2.90) NS
		N= 2 n= Sareli 2001, MIDAS 1996	**CHD events** **2-36 months**	HR 0.77 (0.37 to 1.57) NS

		N= 1 n= MIDAS 1996	**Stroke** **36 months**	HR 1.99 (0.5 to 7.97) NS
		N= 2 n= Sereli 2001, MIDAS 1996	**Cardiovascular events** **2 -36 months**	HR 1.8 (0.94 to 3.44) NS

Table 214

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Sareli 2001(137)	409	- black men and women between 18 and 70 years of age - free of significant cardiovascular or non-cardiovascular disorders - mean ambulatory daytime diastolic blood pressure between 90 and 114 mm Hg	13 months in total but 2 months for monotherapy data	HCTZ (12.5 mg/day) Versus CCB (nifedipine SR)(30 mg/day) or CCB (verapamil hydrochloride SR)(240 mg/day) or ACEi (enalapril maleate) (10 mg/day)	Trial did not provide adequate information on allocation concealment No ITT analysis
MIDAS 1996(138)	883	-Adults, ages ≥ 40 years, -without hyperlipidemia	36 months	HCTZ (25 – 50 mg/day) Versus CCB (isradipine) (2.5- 5mg/daily)	Trial did not provide adequate information on allocation concealment and attrition > 20%
THAI 2005(139)	200	Thai Elderly 60- 80 y Mild to moderate isolated systolic hypertension	18 months	HCTZ (25-50 mg/day) Versus CCB (amlodipine) (5-10 mg/day)	Trial did not provide adequate information on allocation concealment

Table 215

1.1.1.1.2 Summary and conclusions

Chlortalidone versus calcium channel blocker for hypertensive patients with or without additional risk factors			
Bibliography: NICE 2011(3), including ALLHAT 2002(134), SHELL 2003(135), VHAS 1998(136)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR (95%CI))**	**Quality of the evidence (GRADE)**
Mortality	26922 (3 studies) 2 to 4.9 years	1.03 (0.97 to 1.10) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1; Attrition was >20% in two trials. There was inadequate explanantion of allocation concealment in one trial Consistency: ok Directness: ok Imprecision: ok
Coronary heart disease events	25040 (2 studies) 2 to 4.9 years	0.94 (0.88 to 1.0) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; Attrition was >20% in two trials. There was inadequate explanantion of allocation concealment in one trial Consistency: ok Directness: ok Imprecision: ok
Stroke	26922 (3 studies) 2 to 4.9 years	0.94 (0.83 to 1.06) NS	⊕⊕⊖⊖ **LOW** Study quality:-1; Attrition was >20% in two trials. There was inadequate explanantion of allocation concealment in one trial Consistency: ok Directness: ok Imprecision: -1; 95%CI includes both no effect and appreciable benefit or harm
Cardiovascular events	23626 (1 study) 4.9 years	0.96 (0.91 to 1.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; Attrition>20% Consistency: ok Directness: ok Imprecision: ok
Heart failure	1882 (1 study) 32 months	0.83 (0.46 to 1.62) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1; Unclear allocation concealment Consistency: ok Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Myocardial infarction	1882 (1 study) 32 months	1.17 (0.54 to 2.53) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: Unclear allocation concealment Consistency: ok Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit

Table 216

NICE 2011 NICE 2011(3) conducted a systematic review and meta-analysis, evaluating treatment with chlortalidone versus calcium channel blockers in hypertensive patients with or without

additional risk factors. 3 RCT's were included in this MA. The follow-up in these RCT's ranged from 2 years to 4.9 years. One RCT included only patients with isolated systolic hypertension.

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared to treatment with a calcium channel blocker, did not result in a statistically significant difference in mortality, coronary heart disease, or cardiovascular events.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared to treatment with a calcium channel blocker, did not result in a statistically significant difference in stroke.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared to treatment with a calcium channel blocker, did not result in a statistically significant difference in heart failure, or myocardial infarction.
GRADE: VERY LOW quality of evidence

Hydrochlorothiazide versus calcium channel blocker for hypertensive patients with or without additional risk factors			
Bibliography: NICE 2011(3), Including Sareli 2001(137), MIDAS 1996(138), THAI 2005(139)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	1492 (3 studies) 2-36 months	HR 1.18 (0.48 to 2.90) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1; None of the trials provide adequate information on allocation concealment. One of the trials had attrition >20% and ITT analysis was not conducted on the data in the other trial Consistency: ok Directness: ok Imprecision: -2; 95%CI includes no effect and appreciable benefit and appreciable harm
Coronary heart disease events	1292 (2 studies) 2-36 months	HR 0.77 (0.37 to 1.57) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1; None of the trials provide adequate information on allocation concealment. One of the trials had attrition >20% and ITT analysis was not conducted on the data in the other trial Consistency: ok Directness: ok Imprecision: -2; 95%CI includes no effect and appreciable benefit and appreciable harm

Stroke	883 (1 studies) 36 months	HR 1.99 (0.5 to 7.97) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; Trial did not provide adequate information on allocation concealment and attrition > 20% Consistency: ok Directness: ok Imprecision: -2; 95%CI includes no effect and appreciable benefit and appreciable harm
Cardiovascular events	1292 (2 studies) 2-36 months	HR 1.8 (0.94 to 3.44) NS	⨁⨁⊖⊖ **LOW** Study quality: -1; Trial did not provide adequate information on allocation concealment and attrition > 20% Consistency: ok Directness: ok Imprecision: -1; 95% CI includes both no effect and appreciable benefit or appreciable harm

Table 217

NICE 2011 (3) conducted a systematic review and meta-analysis, evaluating treatment with hydrochlorothiazide versus calcium channel blockers in hypertensive patients with or without additional risk factors. 3 RCT's were included in this MA. The follow-up in these RCT's ranged from only 2 months to 3 years. One RCT included only elderly patients with isolated systolic hypertension.

In hypertensive patients with or without additional risk factors, treatment with hydrochlorothiazide, compared to treatment with a calcium channel blocker, did not result in a statistically significant difference in cardiovascular events.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with hydrochlorothiazide, compared to treatment with a calcium channel blocker, did not result in a statistically significant difference in mortality, coronary heart disease, or stroke.
GRADE: VERY LOW quality of evidence

4.3.1.10 Diuretics versus ACE-inhibitors

4.3.1.10.1 Clinical evidence profile

Meta-analysis: NICE 2011
Inclusion criteria:SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 218

Ref	Comparison	N/n	Outcomes	Result	Quality of evidence
NICE 2011(3) Design: MA/SR Search date: nov 2010	Chloorthalidone vs ACE-inhibitor	N= 2 n= 29695 (ALLHAT 2002, ANBP2 2003)	Overall mortality (follow-up 4.1 to 4.9 years	HR 1.00 (0.94 to 1.07)	MODERATE
		N= 2 n= 29695 (ALLHAT 2002, ANBP2 2003)	CHD events (follow-up 4.1 to 4.9 years	HR 0.97 (0.91 to 1.03)	MODERATE

		N= 2 n= 6081 (ALLHAT 2002, ANBP2 2003)	Stroke (follow-up 4.1 to 4.9 years)	**HR 0.88 (0.79 to 0.98)**	**LOW**
		N= 2 n= 6081 (ALLHAT 2002, ANBP2 2003)	Cardiovascular events (follow-up 4.1 to 4.9 years)	**HR 0.91 (0.86 to 0.96)**	**LOW**

Table 219

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
ALLHAT 2002 (134)	33357	- Adults, ≥ 55 years of age - stage 1 or stage 2 HT with at least 1 additional risk factor for CHD events (risk factors: previous (>6 mo) MI or stroke, LVH demonstrated by ECG or echocardiography, history of type 2 diabetes, current cigarette smoking, HDL cholesterol <35mg/dL (0.91mmol/L) or documentation of other atherosclerotic CVD) - 65% white population, 35% blacks <u>Exclusion criteria:</u> - history of hospitalized or treated symptomatic heart failure	Mean 4.9 years	3 arms: CHL: Chlorthalidone: 12.5 to 25 mg/d LIS: Lisinopril: 10, 20, and 40 mg /d AML: Amlodipine: 2.5, 5, and 10 mg/d + open label agents to achieve BP of less than 140/90mmHg	ALLOC. CONC.: concealed scheme, communicated centrally by telephone RANDO.: computer generated, stratified by center and blocked BLINDING: Participants: yes, assessors: unclear, states double blind Rated “good” by JNC-8

		- known left ventricular ejection fraction less than 35%			
ANBP2 2003 (140)	6083	Adults, ages 65 to 84, with absence of recent CV events - predominantly white	Mean 4.1 years	2 arms DIU: Diuretic: HCTZ recommended; dose not specified ACE: ACE Inhibitor: Enalapril recommended; dose not specified	ALLOC. CONC: Open label, communicated by telephone RANDO: unclear, mentions randomly assigned centrally BLINDING: Open label, assessment of endpoints blinded Rated "Fair" by JNC-8

Table 220

Meta-analysis:
: NICE 2011

Inclusion criteria: SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Table 221

Ref	Comparison	N/n	Outcomes	Result	Quality of evidence

NICE 2011(3) Design: MA/SR Search date: nov 2010	hydrochlorthiazide versus ACEi inhibitor	N= 1 n= 118 (Sareli 2001)	Overall mortality (follow-up mean 2 months)	HR 4.06 (0.08 to 204.37)	VERY LOW 95%CI includes both no effect and appreciable benefit and appreciable harm
		N= 1 n= 507 (PHYLLIS 2004)	CHD events (follow-up mean 2.6 years)	HR 3.02 (0.31 to 29.07)	VERY LOW 95%CI includes both no effect and appreciable benefit and appreciable harm
		N= 1 n= 507 (PHYLLIS 2004)	Stroke (follow-up mean 2.6 years)	HR 3.90 (0.08 to 196.36)	VERY LOW 95%CI includes both no effect and appreciable benefit and appreciable harm
		N = 1 n = 507 (PHYLLIS 2004)	Cardiovascular event (follow-up mean 2.6 years)	HR 3.90 (0.08 to 196.36)	VERY LOW 95%CI includes both no effect and appreciable benefit and appreciable harm

Table 222

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Sareli 2001(137)	118 (comparison) (409 in total study)	- black men and women between 18 and 70 years of age - free of significant cardiovascular or non-cardiovascular disorders - mean ambulatory daytime diastolic blood pressure between 90 and 114 mm Hg	13 months	4 arms: nifedipine gastrointestinal therapeutic system (30 mg/d, n = 233) sustained-release verapamil hydrochloride (240 mg/d, n = 58) hydrochlorothiazide (12.5	ALLOCATION CONC: unclear RANDO: unclear, merely states "randomized" BLINDING : Participants/personnel/assessors Adequate/inadequate/unclear ITT: no 2-week placebo run-in NICE 2011: No information on

				mg/d, n = 58) enalapril maleate (10 mg/d, n = 60	allocation concealment and attrition >20%
PHYLLIS 2004(141)	507	- men and postmenopausal women aged 45 to 70 years - with untreated or uncontrolled hypertension - hypercholesterolemic patiens with asymptomatic carotid atherosclerosis	2.6 years	4 arms: - Hydrochlorothiazide - Fosinopril - Hydrochlorothiazide plus pravastatin - Fosinopril plus pravastatin As well as low-lipid diet	ALLOC. CONC.: No information RANDOMISATION: Computer generated with a block size 4 BLINDING: patients and study personnel blinded NICE: No information on allocation concealment and unclear on attrition Not rated by JNC-8

Table 223

4.3.1.10.2 Summary and conclusions

Chlortalidone versus ACE-inhibitors in hypertensive patients with or without additional risk factors			
Bibliography: NICE 2011(3), including ALLHAT 2002(134), ANBP2 2003(140)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR (95%CI))**	**Quality of the evidence (GRADE)**
Mortality	29695 (2 studies) 4.1 to 4.9 years	1.00 (0.94 to 1.07) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1; Attrition >20% Consistency: ok Directness: ok Imprecision: ok
Coronary heart disease events	29695 (2 studies) 4.1 to 4.9 years	0.97 (0.91 to 1.03) NS	⊕⊕⊕⊖ **MODERATE** Study quality: 1; Attrition >20% Consistency: ok Directness: ok Imprecision: ok
Stroke	29695 (2 studies) 4.1 to 4.9 years	**0.88 (0.79 to 0.98)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: 1; Attrition >20% Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cardiovascular events	29695 (2 studies) 4.1 to 4.9 years	**0.91 (0.86 to 0.96)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: 1; Attrition >20% Consistency: ok Directness: ok Imprecision: ok

Table 224

NICE 2011 conducted a systematic review and meta-analysis that evaluated treatment with chlortalidone versus treatment with ACE-inhibitors in hypertensive patients with or without additional risk factors. Two RCT's with a follow-up of 4.1 to 4.9 years, was included in the MA.

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared with treatment with ACE-inhibitors, significantly decreased risk of stroke.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared with treatment with ACE-inhibitors, significantly decreased risk of cardiovascular events.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, treatment with chlortalidone, compared with treatment with ACE-inhibitors, did not result in a statistically significant difference in mortality or coronary heart disease events.
GRADE: MODERATE quality of evidence

Hydrochlorothiazide versus ACE-inhibitor in hypertensive patients with or without additional risk factors			
Bibliography: NICE 2011(3), including Sareli 2001(137), PHYLLIS 2004(141)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Coronary heart disease events	507 (1 study) 2.6 years	3.02 (0.31 to 29.07) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; No information on allocation concealment and unclear on attrition Consistency: ok Directness: ok Imprecision: -2; 95%CI includes both no effect and appreciable benefit and appreciable harm
Stroke	507 (1 study) 2.6 years	3.90 (0.08 to 196.36) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; No information on allocation concealment and unclear on attrition Consistency: ok Directness: ok Imprecision: -2; 95%CI includes both no effect and appreciable benefit and appreciable harm
Cardiovascular events	507 (1 study) 2.6 years	3.90 (0.08 to 196.36) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; No information on allocation concealment and unclear on attrition Consistency: ok Directness: ok Imprecision: -2; 95%CI includes both no effect and appreciable benefit and appreciable harm

Table 225

NICE 2011 conducted a systematic review and meta-analysis that evaluated treatment with hydrochlorothiazide versus treatment with ACE-inhibitors in hypertensive patients with or without additional risk factors. Two RCT's with a follow-up of 2 months to 2.6 years were included in the MA.

The trial with only two months of follow-up (Sareli 2001(137)) reported only on mortality and was the only trial to do so. We did not report the result as the follow-up is too short. There was only one RCT with methodological problems that reported on the other outcomes. Therefore, our confidence in the results is severely limited.

In hypertensive patients with or without additional risk factors, treatment with hydrochlorothiazide, compared to treatment with ACE-inhibitors, did not result in a statistically significant difference in coronary heart disease events, stroke rates, or cardiovascular events.
GRADE: VERY LOW quality of evidence

4.3.1.11 Diuretics versus ARB

Our search yielded no MA's or RCTs for this comparison that met our inclusion criteria.

4.3.1.12 Beta blockers versus ACE-inhibitors

4.3.1.12.1 Clinical evidence profile

1) JNC-8

In the general population 55 to 80 years of age with hypertension, initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with a beta blocker **decreases stroke and a primary composite endpoint** (consisting of CV death, MI, or stroke), but results in no difference in overall mortality, heart failure or MI.
Evidence Quality: Low

One trial contributed to this evidence statement: LIFE (Dahlöf 2002).

2) NICE 2011

One study (LIFE)176,222,507,618,619 was found comparing the angiotensin-II receptor antagonist (ARB) losartan with the beta-blocker atenolol as first-line antihypertensive therapy.
The study found no significant difference between the two treatments in terms of myocardial infarction, revascularisation procedures, heart failure or angina. However, the study did find ARBs to be associated with a:
- **reduced incidence of stroke (RR 0.75, 95% CI 0.63 to 0.88)**
- new-onset diabetes (RR 0.75, 95% CI 0.64 to 0.88)
- fewer study drug withdrawals (RR 0.86, 95% CI 0.82 to 0.91)

(all in favor of ARB)

Although mortality was lower in the ARB treatment group, this result was not statistically significant.

3) WIYSONGE 2012 Cochrane

B-blockers versus RAS-inhibitors

Meta-analysis: WIYSONGE 2012 (cochrane)

Inclusion criteria:
Studies: RCT with a duration of one year or more.
Participants: Men and non-pregnant women, aged 18 years and over, with hypertension as defined by cut-off points operating at the time of the study under consideration.
Intervention: The treatment group must have received a beta-blocker drug either as monotherapy or as a first-line drug in a stepped care approach. The control group could be a placebo, no treatment, or another anti-hypertensive drug (including a different beta-blocker or the same beta-blocker at a different dose).

Search strategy: On 08 May 2011, a comprehensive search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted and repeated on 02 December 2011. Reference list of relevant reviews were screened as were those of studies selected for inclusion in this review.

Assessment of quality of included trials: Yes, grade
ITT analysis: Yes

Table 226

Ref	Comparison	N/n	Outcomes	Result (RR, [95% CI])	Quality assessment (GRADE)
WIYSONGE 2012(126) Design: SR+MA	β-blockers versus RAS-inhibitors	N = 3 n = 10828 (AASK 2002, LIFE 2002, UKPDS-39-1998)	**Total Mortality ARB+ACEi**	1.10 [0.98, 1.24]	MODERATE (Only 3 hypertension trials comparing beta-blockers to RAS inhibitors have reported data on this outcome)
		N = 2	**CHD**	0.90 [0.76, 1.06]	

Search date: dec 2011		n = 9951 (LIFE 2002, UKPDS-39-1998)	ARB+ACEi		
		N = 2 n =9951 (LIFE 2002, UKPDS-39-1998)	**Stroke** ARB+ACEi	1.30 [1.11, 1.53]	
		N = 3 n = 10828 (AASK 2002, LIFE 2002, UKPDS-39-1998)	**Cardiovascular mortality** ARB+ACEi	1.09 [0.92, 1.29]	
			Cardiovascular disease		LOW (Inconsistent results across studies)
		N= 3 n = 108282 (AASK 2002, LIFE 2002, UKPDS-39-1998)	**ACE-inhibitor+ ARB** (compared to β-blocker)	1.00 [0.72, 1.38]	
		N = 2 n = 1635 (UKPDS-39-1998, AASK 2002)	**ACE-i** (compared to β-blocker)	0.81 [0.63, 1.04]	
		N = 1 n = 5093 (LIFE 2002)	**ARB** (compared to β-blocker)	1.16 [1.04, 1.30]	
		N = 2 n = 9951 (UKPDS-39-1998, LIFE 2002)	**Withdrawal due to adverse effect** **ARB + ACEi** (compared to β-blocker)	1.41 [1.29, 1.54]	

Table 227

* Characteristics of included studies: see below

AASK 2002 and UKPDS-39-1998 compare a β-blocker to an ACE-inhibitor, LIFE 2002 compares a β-blocker to an ARB (angiotensine-2 receptor blocker)

Study	N	Population	Intervention	Comparison	Follow-up	Methodology (Quality assessment by Wiysonge 2012)
AASK 2002 (109)	1094	- African Americans - aged 18 to 70 years (mean: 54.5) - with hypertensive renal disease (GFR 20-65 ml/min per 1.73m²) Exclusion criteria: - diastolic BP of less than 95 mmHg - known history of diabetes mellitus - urinary protein to creatinine ratio of more than 2.5 - accelerated or malignant hypertension within the last 6 months - secondary hypertension - non-BP related causes of kidney-disorders	β-blocker arm: metoprolol 50 to 200 mg/day Also: CCB arm: amlodipine 5 to 10 mg/d Halted in sept 2005 after which patients were switched to open-label medication due to safety Additional open-labeled AHT could be added if BP goal was not achieved	ACE-inhibitor Arm: Ramipril 2.5 to 10 mg/day	Mean: 4.1 years	ALLOC CONC.: unclear RANDO: unclear BLINDING: participants and investigators blinded to randomized drug but not BP goal Loss to follow-up: 0% Population 100% African-americans Rated “good” by JNC-8
LIFE 2002 (142)	9193	- aged 55-80 years (mean: 66.9) - with essential hypertension (BP 160-200 / 95-115 mm HG) - with LVH ascertained by ECG Exclusion criteria:	β-blocker arm: Atenolol 50 mg	ARB-arm: losartan 50 mg	Mean: 4.8 years	ALLOC. CONC.: unclear RANDO: adequate BLINDING: patients yes, providers yes, outcome assessors yes Loss to follow-up: 2% 2 week placebo run-in Rated “good” by JNC-8

		- secondary hypertension - myocardial infacrtion or stroke within the previous 6 months - angina pectoris requiring treatment with β-blockers or CCB - heart failure or LVEF of 40% or less - disorder that in the treating physician's opinion required treatment with losartan or another ARB, atenolol or another β-blocker				
UKPDS-39-1998 (129)	758 (only patients allocated to tight BP control)	- hypertensive patients with type 2 diabetes - mean age of 56 - Black population about 30 %	β-blocker arm: atenolol 50-100 mg/day	ACE-I arm: captopril 25-50 mg 2x/d	Mean: 8.4 years	ALLOC. CONC: adequate RANDO: adequate, not blocked BLINDING: patients not blinded, providers not blinded, assessors not blinded Loss to follow-up: 4% Not rated by JNC-8

Table 228

4.3.1.12.2 Summary and conclusions

Beta-blockers versus ACE-inhibitors for hypertensive patients with or without additional risk factors.			
Bibliography: Wiysonge 2012(126), including AASK(109) and UKPDS-39(129)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular disease	1635 (2)	Acei vs Beta-blockers 0.81 [0.63, 1.04]	⨁⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: ok Directness: -2 (population with 100% CKD or 100% diabetes) Imprecision: -1

Table 229

In this trial/meta-analysis, studies comparing ARB and ACEi with beta-blockers were included and pooled together. There was a separate analysis only for the endpoint ”cardiovascular disease”. For the two studies with ACE-inhibitors, all patients from the AASK study had hypertensive kidney disease and all patients from the UKPDS-39 study had type 2 diabetes, making the conclusions difficult to translate to the general population.

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with angiotensin converting enzyme inhibitor did not result in a statistically significant difference in cardiovascular disease.
GRADE: VERY LOW quality of evidence

4.3.1.13 Beta blockers versus angiotensin receptor blockers

4.3.1.13.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Dahlöf/ LIFE 2002(142) Design: RCT (SB DB OL) (PG CO) Duration of follow-up: 4.8 years	n= 9193 Mean age: 66.9 Hypertension: 100% Coronary heart disease: 16% Cerebrovascular disease:8 % Peripheral vascular disease:6 % Diabetes:13 % Smoking:16.5 % Age >80y: unknown <u>Inclusion</u> - aged 55-80 years (mean: 66.9) - with essential hypertension (BP 160-200 / 95-115 mm HG) - with LVH ascertained by ECG	β-blocker: Atenolol 50 mg Vs ARB: losartan 50 mg	Efficacy		RANDO: Adequate computer generated allocation schedule ALLOCATION CONC: Adequate BLINDING : Participants: yes, double dummy Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0.13 % Drop-out and Exclusions: 2% • Described: yes • Balanced across groups: yes ITT: no, 22 patients were excluded between randomization and analysis. However drop-outs and lost to follow up patients were
			Composite (cardiovascular death, myocardial infarction, stroke) and death (PO)	Losartan: 508/4605 Atenolol: 58/4588 **HR: 0.87 (0.77-0.98) SS** p:0.021	
			cardiovascular mortality	Losartan: 204/4605 Atenolol: 234/4588 HR: 0.89 (0.73-1.07) p:0.206	
			stroke	Losartan: 232/4605 Atenolol: 309/4588 **HR: 0.75 (0.63-0.89) SS** p: 0.001	
			myocardial infarction	Losartan: 198/4605 Atenolol: 188/4588 HR: 1.07 (0.88-1.31) p:0.128	
			Total mortality	Losartan:383 /4605 Atenolol: 431/4588 HR: 0.90 (0.78-1.03) p:0.128	
			Heart failure (with hospital	Losartan:153 /4605	

	<u>Exclusion</u> - secondary hypertension - myocardial infacrtion or stroke within the previous 6 months - angina pectoris requiring treatment with β-blockers or CCB - heart failure or LVEF of 40% or less - disorder that in the treating physician's opinion required treatment with losartan or another ARB, atenolol or another β-blocker		admission)	Atenolol: 161/4588 HR:1.16 (0.92-1.45) p:0.212	included. SELECTIVE REPORTING: no Sponsor: Merckx
			New onset diabetes	Losartan: 241/4605 Atenolol: 319/4588 **HR: 0.75 (0.63-0.88) SS** p: 0.001	
			Safety		
			Angio-oedema	Losartan: 6/4605 Atenolol: 11/4588 p:0.237	
			Bradycardia	Losartan: 66/4605 Atenolol:391/4588 p <0.0001	
			Cough	Losartan: 133/4605 Atenolol: 113/4588 p:0.220	
			Dizziness	Losartan: 771/4605 Atenolol:727/4588 p:0.247	
			Hypotension	Losartan: 121/4605 Atenolol: 75/4588 p:0.001	

Table 230

4.3.1.13.2 Summary and conclusions

Beta blockers versus angiotensin receptor blockers in hypertension patients			
Bibliography: Dahlöf/LIFE 2002(142) (reported by: Wiysonge 2012, NICE 2011, JNC-8 2014)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite (cardiovascular death, myocardial infarction, stroke) and death	9193 (1) 4.8 years	**HR: 0.87 (0.77-0.98)** **SS in favour of ARB**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1, all patients had LVH Imprecision: ok
Cardiovascular mortality	9193 (1) 4.8 years	HR: 0.89 (0.73-1.07) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision:ok
Stroke	9193 (1) 4.8 years	**HR: 0.75 (0.63-0.89)** **SS in favour of ARB**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Myocardial Infarction	9193 (1) 4.8 years	HR: 1.07 (0.88-1.31) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Total mortality	9193 (1) 4.8 years	HR: 0.90 (0.78-1.03) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
Heart failure (with hospital admission)	9193 (1) 4.8 years	HR: 1.16 (0.92-1.45) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: ok
New onset diabetes	9193 (1) 4.8 years	**HR: 0.75 (0.63-0.88)** **SS in favour of ARB**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: ok

Table 231

This RCT reports on the LIFE trial, comparing an angiotensin receptor blocker (losartan) against a beta-blocker (atenolol) in hypertensive patients with confirmed left ventricular hypertrophy . The trial is of good quality and industry-sponsored.

In a hypertensive population with and without additional risk factors, a treatment of angiotensin receptor blockers compared to a treatment with beta-blockers did result in a statistically significantly lower occurrence of stroke.
GRADE: MODERATE quality of evidence

In a hypertensive population with and without additional risk factors, a treatment of angiotensin receptor blockers compared to a treatment with beta-blockers did result in a statistically significantly lower occurrence of new onset diabetes.
GRADE: MODERATE quality of evidence

In a hypertensive population with and without additional risk factors, a treatment of angiotensin receptor blockers compared to a treatment with beta-blockers did result in a statistically significantly lower occurrence of events described by the composite endpoint of cardiovascular death, myocardial infarction and stroke.
GRADE: MODERATE quality of evidence

In a hypertensive population with and without additional risk factors, a treatment of angiotensin receptor blockers compared to a treatment with beta-blockers did not result in a statistically significant difference in cardiovascular mortality, myocardial infarction, total mortality or heart failure.
GRADE: MODERATE quality of evidence

4.3.1.14 Beta blockers versus calcium channel blockers

4.3.1.14.1 Clinical evidence profile

1) Conclusions from JNC-8

In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a beta blocker compared to initial antihypertensive drug therapy with a calcium channel blocker improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.
Evidence Quality: Unable to determine because there is insufficient evidence

Two trials contributed to this evidence statement: ASCOT (Dahlöf 2005) and ELSA (Zanchetti 2002).

2) WIYSONGE 2012 Cochrane

Meta-analysis: WIYSONGE 2012 (cochrane) Inclusion criteria: Studies: RCT with a duration of one year or more. Participants: Men and non-pregnant women, aged 18 years and over, with hypertension as defined by cut-off points operating at the time of the study under consideration. Intervention: The treatment group must have received a beta-blocker drug either as monotherapy or as a first-line drug in a stepped care approach. The control group could be a placebo, no treatment, or another anti-hypertensive drug (including a different beta-blocker or the same beta-blocker at a different dose). Search strategy: On 08 May 2011, a comprehensive search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted and repeated on 02 December 2011. Reference list of relevant reviews were screened as were those of studies selected for inclusion in this review. Assessment of quality of included trials: Yes, grade ITT analysis: Yes

Table 232

Ref	Comparison	N/n	Outcomes	Result (RR, 95% CI)	Quality assessment (GRADE) by Wiysonge
WIYSONGE 2012(126) Design: SR+MA Search date: dec 2011	β-blockers versus ccb	N = 4 n = 44825 (AASK 2002, ELSA 2002, INVEST 2003, ASCOT 2005)	**Total Mortality**	RR: 1.07 [1.00, 1.14] NS	MODERATE (RR is too close to 1 and could easily include 1 of more trials were added)
		N = 3 n = 44167 (ELSA 2002, INVEST 2003, ASCOT 2005)	**CHD**	RR: 1.05 [0.96, 1.15] NS	
		N = 3 n = 44167 (ELSA 2002, INVEST 2003, ASCOT 2005)	**Stroke**	**RR: 1.24 [1.11, 1.40] SS**	
		N = 4 n = 44825 (AASK 2002, ELSA 2002, INVEST 2003, ASCOT 2005)	**Cardiovascular mortality**	RR: 1.15 [0.92, 1.46] NS	
		N = 2 n = 19915 (AASK 2002, ASCOT 2005)	**Cardiovascular disease**	**RR: 1.18 [1.08, 1.29] SS**	MODERATE (the study that contributes more weight to the pooled risk ratio has a high risk of bias (open treatment).
		N = 2 n = 11591 (ASCOT 2005, ELSA 2002)	**Withdrawal due to adverse effects**	RR: 1.20 [0.71, 2.04] NS	

Table 233

* Characteristics of included studies: see below

Study	N	Population	Intervention	Comparison	Follow-up	Methodology (Quality assessment by Wiysonge 2012)
AASK 2002 (109)	1094	-Adult African-Americans - ages 18-70, mean: 54 - HTN and renal hypertensive disease GFRs of 20-65 ml/min per 1.73m², no diabetes - entry BP: DBP ≥95mmHg, mean 150/96mmHg Exclusion: - known history of diabetes mellitus - urinary protein/creatinine ratio >2.5 - secondary hypertension - non-BP related kidney disease - clinical congestive heart failure	β-blocker arm: metoprolol 50 to 200 mg/day Also: ACE-inhibitor Arm: Ramipril 2.5 to 10 mg/day Halted in sept 2005 after which patients were switched to open-label medication due to safety Additional open-labeled AHT could be added if BP goal was not achieved	CCB arm: amlodipine 5 to 10 mg/d	Mean: 4.1 years	ALLOC CONC.: unclear RANDO: unclear BLINDING: participants, providers and outcome assessors blinded Loss to follow-up: 0% Population 100% African-americans Rated “good” by JNC-8
ASCOT 2005 (143)	19257	- age 40-79 years, mean: 63 y - entry bp: sitting SBP ≥160 and DBP ≥100 mmHg for untreated;	β-blocker arm: atenolol-based regimen	CCB arm: amlodipine-based	Median: 5.5 years	ALLOC CONC.: adequate RANDO:adequate BLINDING: open treatment, blinded endpoint evaluation (PROBE design)

		SBP ≥140 mmHG and/or DBP ≥90mmHg for treated subjects - 3 CHD risk factors - smoking 33% - type 2 diabetes 27% - LVH 22%				Loss to follow-up: 0.3% Rated "Good" by JNC-8
ELSA 2002 (144)	2334	- age 45-75 years, mean: 56 - entry BP: sitting SBP of 150-210 mmHg and DBP of 91-115 mmHg - fasting serum cholesterol concentration ≤320 mg/dl, fasting serum TG ≤300mg/dl, serum creatinine concentration ≤1.7mg/dl - smoking: 20.5% - at least one plaque: 64%	β-blocker arm: atenolol, 50-100 mg/d	CCB-arm: lacidipine 4-6 mg/d	Mean: 3.75 years	ALLOC CONC.: unclear RANDO: adequate BLINDING: Participants and study personnel, excluding safety committee were blinded for study duration Loss to follow-up: 4% Rated "Fair" by JNC-8
INVEST 2003 (145)	22576	- age 50 or older, mean: 66.1 years - entry criteria: sitting BP > 140/90 mm HG and <u>documented coronary artery disease</u> - mean entry BP: 149.5/86.3 mmHg	β-blocker arm: atenolol 50 mg/d + (if needed) HCT,trandolapril	CCB: verapamil 240mg/d + if needed trandolapril, HCT	Mean: 2.7 years	ALLOC. CONC: Adequate RANDO: adequate BLINDING: patients unblinded, provider unblinded, assessor blinded (PROBE set up) Loss to follow-up: 2.5% Not rated by JNC-8

		- smokers 12.4% - hypercholesterolemia 55.8% - diabetes 28.3% - prior MI or abnormal angiogram 53.0%				

Table 234

4.3.1.14.2 Summary and conclusions

Beta-blockers versus calcium channel blockers in hypertensive patients with and without additional risk factors			
Bibliography: Wiysonge 2012(126), including: AASK 2002(109), ELSA 2002(144), INVEST 2003(145), ASCOT 2005(143)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Total mortality	44825 (4)	RR: 1.07 [1.00, 1.14] NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok
CHD	44167 (3)	RR: 1.05 [0.96, 1.15] NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok
Stroke	44167 (3)	**RR: 1.24 [1.11, 1.40]** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok
Cardiovascular mortality	44825 (4)	RR: 1.15 [0.92, 1.46] NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok
Cardiovascular disease	19915 (2)	**RR: 1.18 [1.08, 1.29]** **SS**	⊕⊕⊕⊖ **LOW** Study quality: -1, the study that contributes more weight to the pooled risk ratio has a high risk of bias (open treatment) Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok
Withdrawal due to adverse effects	11591 (2)	RR: 1.20 [0.71, 2.04] NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 for diverse population selection criteria Imprecision: ok

Table 235

In this meta-analysis, RCT's comparing beta-blockers to CCBs were pooled together. The studies were of good quality, but the two largest had unblinded treatment. The two smaller studies recruited younger people. Population selection criteria were diverse but generally selected high-risk population (with, for example, coronary heart disease or a number of risk factors).

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers did not result in a statistically significant difference in total mortality.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers did not result in a statistically significant difference in coronary heart disease.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers did not result in a statistically significant difference in stroke.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers did not result in a statistically significant difference in cardiovascular mortality.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers, did result in a statistically significant difference in cardiovascular disease.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with beta-blockers, compared with a treatment with calcium channel blockers did not result in a statistically significant difference in withdrawal from study drugs.
GRADE: MODERATE quality of evidence

4.3.1.15 ACE-inhibitors versus calcium channel blockers

4.3.1.15.1 Clinical evidence profile

1) ACEi versus CCB in JNC-8

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with an ACE inhibitor reduces the incidence of heart failure, but it has a similar effect on other cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, and overall mortality compared to initial antihypertensive drug therapy with a calcium channel blocker.
Evidence Quality: Moderate

Rationale/Comments: Three trials contributed to this evidence statement (ALLHAT, JMIC-B, and STOPHTN2) [Leenen 2006; Yui, 2004b; Hansson, 1999a]. In ALLHAT, the comparison of the ACE inhibitor and calcium channel blocker was a secondary comparison and was thus rated as Fair. JMIC-B was also rated as Fair, and STOP-HTN2 was rated as Good. All three trials had different primary outcomes: fatal CHD and nonfatal MI in ALLHAT, a composite of cardiac events in JMICB, and a composite of cardiovascular death in STOP-HTN2. In two of the three studies (ALLHAT and STOP-HTN2), heart failure events were reduced significantly with the use of an ACE inhibitor compared to the use of a calcium channel blocker. In ALLHAT, heart failure was reduced by 13% (95% CI, 0.78, 0.96; p=0.007). In STOP-HTN2, heart failure was reduced by 24% (95% CI, 0.63, 0.97; p=0.025). In JMIC-B and STOP-HTN2, there was no difference in stroke with the use of an ACE inhibitor compared to the use of a calcium channel blocker. In ALLHAT, stroke was higher by 23% in the ACE inhibitor group (95% CI, 1.08, 1.41; p=0.003). This difference was driven by a significant 51% increase in blacks, but there was no difference in stroke for non-blacks, which constituted 65% of the trial population (see Question 3, ACE Inhibitor Evidence Statement 2). None of the trials showed a difference in overall mortality or kidney outcomes. In STOP-HTN2, there was a significant 23% (95% CI, 0.61, 0.96; p=0.016) lower occurrence of myocardial infarction in the ACE inhibitor group compared to the calcium channel blocker group, but there was no significant difference in myocardial infarctions in the other two trials.
The primary composite cardiovascular outcomes in STOP-HTN2 and JMIC-B were also not significantly different between groups. However, combined cardiovascular disease in ALLHAT was higher by 6% (95% CI, 1.00, 1.12; p=0.047) in the ACE inhibitor group compared to the calcium channel blocker group, but it was only significant in blacks.

2) ACEi versus CCB in NICE

Meta-analysis: NICE 2011

Inclusion criteria:SRs/MAs and RCTs were included that compared the following TDs (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 236

Ref	Comparison	N/n	Outcomes	Result (HR [95%CI])	I^2
ref NICE 2011(3) Design: MA/SR Search date: nov 2010	ACE-inhibitor versus calcium channel blockers	N= 3 n= 23625** (ALLHAT 2002, JMIC-B 2004, STOP-H2 1999)	Mortality	1.04 [0.98 – 1.11]	0
		N= 3 n= 23619** (ALLHAT 2002, JMIC-B 2004, STOP-H2 1999)	Myocardial Infarction	0.94 [0.74 – 1.19]	69.3
		N= 3 n= 23619** (ALLHAT 2002, JMIC-B 2004, STOP-H2 1999)	Stroke	**1.14 [1.02 – 1.28]** **SS**	5.2
		N= 3 n= 23619** (ALLHAT 2002, JMIC-B 2004, STOP-H2 1999)	Heart Failure	**0.85 [0.78 – 0.93]** **SS**	0
		N= 2	New onset Diabetes	**0.85 [0.76 – 0.94]**	15.2

		n= 15501** (ALLHAT 202, STOP-H2 1999)		**SS**	

Table 237

* Characteristics of included studies: see below

** It is unclear how NICE investigators came to those numbers

Ref + design	n	Population	Duration	Comparison	Methodology
Leenen, ALLHAT 2002 (134)	33357	- Adults, ≥ 55 years of age - stage 1 or stage 2 HT with <u>at least 1 additional risk factor</u> for CHD events (risk factors: previous (>6 mo) MI or stroke, LVH demonstrated by ECG or echocardiography, history of type 2 diabetes, current cigarette smoking, HDL cholesterol <35mg/dL (0.91mmol/L) or documentation of other atherosclerotic CVD) - 65% white population, 35% blacks <u>Exclusion criteria:</u> - history of hospitalized or treated symptomatic heart failure - known left ventricular ejection fraction less than 35%	Mean 4.9 years	3 arms: CHL: Chlorthalidone: 12.5 to 25 mg/d LIS: Lisinopril: 10, 20, and 40 mg /d AML: Amlodipine: 2.5, 5, and 10 mg/d + open label agents to achieve BP of less than 140/90mmHg	ALLOC. CONC.: concealed scheme, communicated centrally by telephone RANDO.: computer generated, stratified by center and blocked BLINDING: Participants: yes, assessors: unclear, but states double blind Rated “good” by JNC-8

Hansson, STOP-H2 1999(146)	6614	- patients with hypertension - aged 70-84 years, mean: 76 - from Sweden	Mean F/U unclear; authors report study duration of 60 months; max BP measurement reported is 54 months, and Kaplan-Meier curves extend to 6 years	3 arms: ACE: ACE inhibitors: enalapril 10 mg, or lisinopril 10 mg CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5mg QD BB or DIUR: atenolol 50 mg, or metoprolol 100 mg, or pindolol 5 mg, or fixed ratio HCTZ 25 mg plus amiloride 2.5 mg	ALLOC. CONC.: unclear RANDOM.: states randomized, unclear BLINDING: patients: open; assessors: blinded (independent endpoint assessment committee) Open trial with masked endpoints Rated “Good” by JNC-8
Yui, JMIC-B 2004(147)	1650	- hypertensive patients with coronary heart disease (75% stenosis on coronary angiography) - Japanese - mean age: 64 - 23% diabetic patients	3 years	2 arms: nifedipine retard (a long-acting nifedipine formulation that is given at a dose of 20–40 mg/day in Japan) ACE inhibitor (enalapril 5–10 mg/day, imidapril 5–10 mg/day, or lisinopril 10–20 mg/day as recommended in Japan) concomitant treatment with a β-blocker or α-	ALLOC. CONC.: unclear RANDOM.: states randomized, unclear BLINDING: patients: open; assessors: blinded (independent endpoint assessment committee) (PROBE design) Rated “Fair” by JNC-8

				blocker was permitted if the BP reduction did not meet the target of <150/90mmHg	

Table 238

3) CCB versus ACE-inhibitor – Cochrane review Chen

Chen et al. from 2010 compares CCB versus ACEi inhibitors in a Cochrane review. Results are in line with those of NICE 2011. Chen 2010 includes other studies than NICE 2011 (ABCD and FACET with diabetic patients, and AASK with patients with chronic kidney disorder) but even so results and direction of the effect is maintained.

4.3.1.15.2 Summary and conclusions

Ace inhibitors versus CCB			
Bibliography: NICE 2001(3), including ALLHAT 2002(134), JMIC 2004(147), STOP-H2 1999(146)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	23625 (3)	1.04 [0.98 – 1.11] NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1, 2/3 open label Consistency: ok Directness: ok Imprecision: ok
Myocardial Infarction	23619 (3)	0.94 [0.74 – 1.19] NS	⊕⊕⊖⊖LOW Study quality: -1, 2/3 open label Consistency: -1, I^2: 69% Directness: ok Imprecision: ok
Stroke	23619 (3)	**1.15 [1.03 – 1.27]** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, 2/3 open label Consistency: ok Directness: ok Imprecision: ok
Heart failure	23619 (3)	**0.85 [0.78 – 0.93]** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, 2/3 open label Consistency: ok Directness: ok Imprecision: ok
New onset diabetes	15501 (2)	**0.85 [0.76 – 0.94]** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, one study open label Consistency: ok Directness: ok Imprecision: ok

Table 239

Nice 2011 compared 3 studies in a meta-analysis to evaluate the effect of ACE-inhibitors versus CCB in hypertension patients with and without additional risk factors. Two out of three included trials worked with an open label, blinded endpoint (PROBE) design. The largest trial stated that it was double blind but gave no details about the blinding. All selected populations were above 55 years of age.

In hypertensive patients with or without additional risk factors, treatment with ACE-inhibitors did not result in a statistically significant difference in mortality compared to calcium channel blockers.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, treatment with ACE-inhibitors did not result in a statistically significant difference in myocard infarction compared to calcium channel blockers.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with ACE-inhibitors significantly increases stroke compared to calcium channel blockers.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, treatment with ACE-inhibitors significantly decreases heart failure compared to calcium channel blockers.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, treatment with ACE-inhibitors significantly decreases new onset diabetes compared to calcium channel blockers.
GRADE: MODERATE quality of evidence

4.3.1.16 Angiotensin receptor blockers versus calcium channel blockers

4.3.1.16.1 Clinical evidence profile

ARB vs CCB

1) Jnc-8

In the general population 50 years of age or older with hypertension, initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with a calcium channel blocker resulted in a 3 to 5 percent absolute lower rate of new onset diabetes.
Evidence Quality: Low

Two studies contributed to this evidence statement (VALUE and CASE-J) [Julius,2004; Ogihara, 2008].
Value: See (2) NICE.

Also:
In the general population 50 years of age or older with hypertension, initial antihypertensive therapy with a calcium channel blocker compared to initial antihypertensive therapy with an angiotensin receptor blocker results in no difference in composite outcomes.
Evidence Quality: Low

Three trials contributed to this Evidence Statement (VALUE, CASE-J, and MOSES) [Julius, 2004; Ogihara, 2008, Schrader, 2005]. Each trial used a composite endpoint as the primary outcome. In VALUE, the primary outcome was a composite of time to first cardiac event that included sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary bypass graft, death due to heart failure, heart failure requiring hospitalization, nonfatal MI, or emergency procedures to prevent MI. The hazard ratio was 1.04 (95% CI, 0.94, 1.15) (p = 0.49). In CASE-J, the primary outcome was a composite that included sudden death, stroke, TIA, heart failure, MI, angina, a kidney event composite, dissecting aortic aneurism, and occlusion of a peripheral artery. The hazard ratio was 1.01 (95% CI, 0.79, 1.28) (p = 0.969). In MOSES, the primary outcome was a composite that included all-cause mortality, stroke, TIA, MI, and new heart failure. In MOSES the relative risk was 0.79 (95% CI, 0.66, 0.96) (p = 0.014) favoring eprosartan over nitrendipine.

Study criteria and characteristics	**Mortality outcomes**	**Coronary heart disease outcomes**	**Cerebrovascular outcomes**	**Heart Failure outcomes**	**Composite outcomes**	**Adverse events**
Ogihara CASE-J, 2009(148) Patients: Adults with high CVD risk AML: Amlodipine 2.5-10 mg/day CAN: Candesartan 4-12 mg/day N: 4,728 Mean 3.2 years Good	**All-cause death** 11.1 per 1000 p-y AML vs 9.4 per 1000 p-y CAN HR (95% CI): NR p = NS	**Acute MI** HR (95% CI) for CAN: 0.95 (0.49, 1.84) p = 0.870 **Sudden death** HR (95% CI) for CAN: 0.73 (0.34, 1.60) p = 0.434	**Cerebrovascular events** HR (95% CI) for CAN: 1.23 (0.85, 1.78) p = 0.282 **Stroke** HR (95% CI) for CAN: 1.28 (0.88, 1.88) p = 0.198 **TIA** HR (95% CI) for CAN: 0.50 (0.09, 2.73) p = 0.414	**Heart Failure** HR (95% CI) for CAN: 1.25 (0.65, 2.42) p = 0.498	**Primary composite endpoint** HR (95% CI) for CAN: 1.01 (0.79, 1.28) p = 0.969 **Peripheral vascular events** HR (95% CI) for CAN: 1.57 (0.61, 4.05) p = 0.348	**New onset diabetes** HR (95% CI) for CAN: 0.64 (0.43, 0.97) **p=0.033** **Hyperkalemia** 0.3% AML vs 1.0% CAN p = NR
Schrader , MOSES 2005(149) Adults with HTN and history of a cerebrovascular event NIT: Nitrendipine 10 mg/day EPR: Eprosartan 600 mg/day	**All cause death** HR (95% CI) for EPR: 1.07 (0.73, 1.56) p = 0.725		**Fatal and non-fatal** cerebrovascular events (including recurrent events) IDR (95% CI): 0.75 (0.58, 0.97) **p = 0.026** **First time occurrence of cerebrovascular event** HR (95% CI) for		**Primary combined endpoint: cerebrovascular and CV events and non-CV death (including recurrent events)** IDR (95% CI): 0.79 (0.66, 0.96) **p = 0.014** **Fatal and non-fatal**	**Dizziness /hypotension** 10.6% NIT vs 12.9% EPR p = NR **Metabolic disorder** 5.9% NIT vs 5.5% EPR p = NR

N: 1,405 Mean 2.5 years Fair Notes: IDR: incidence density ratio			EPR: 0.88 (0.65, 1.20) p = 0.425		**CV events (including recurrent events)** IDR (95% CI): 0.75 (0.55, 1.02) p = 0.061	

Table 240

2) NICE 2011

ARB (valsartan) versus CCB (amlodipine) – only the VALUE trial

Study details	n/Population	Comparison	Outcomes		Methodological
Julius / VALUE 2004(150) Design: RCT (DB) (PG)	n= 15245 Mean age: 67.3 Coronary heart disease: 45.8% % Peripheral arterial disease:13.9 % Stroke or TIA:19.8 % LVH with strain pattern: 6.0%	Valsartan 80 mg Vs amlodipine 5 mg Treatment stepped up as necessary in five steps, with higher dosage or with addition of hydrochlorothiazide to achieve BP	Efficacy		RANDO: Adequate, computer generated, using blocks ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: unclear Assessors: unclear states “double blind” rationale and design article behind paywall
			Cardiac event Composite (PO) (composite endpoint consisting of sudden cardiac death, death during or after PCI or CABG, death due to MI, non-fatal MI, fatal and non-fatal stroke, etc.)	Valsartan 810/7649 Amlodipine: 789/7596 Hr: 1.04(0.94-1.15) NS p: 0.49	
			cardiac mortality	Valsartan: 304/7649	

Duration of follow-up: 4-6 years	Diabetes: not given % CKD: not given % Smoking: not given % Age >80y: not given % <u>Inclusion</u> - 50 years or older - treated or untreated hypertension at baseline - for previously untreated patients: mean sitting SBP between 160 and 210 mmHg, mean sitting DBP <115mmHg - with predefined combinations of cardiovascular risk factors or disease according to an algorithm based on age and sex <u>Exclusion</u> - renal artery stenosis - pregnancy	control		Amlodipine: 304/7596 HR: 1.01 (0.86-1.18) p: 0.90	Remarks on blinding method: (vrij te omschrijven, schrappen als nvt) FOLLOW-UP: Lost-to follow-up: 0.6% Drop-out and Exclusions: 0.5% • Described: partially • Balanced across groups: unknown ITT: Yes/no (+'definitie auteurs') SELECTIVE REPORTING: yes/no (describe if yes) Other important methodological remarks (schrappen als nvt) (vb. placebo-run-in) Sponsor: Novartis
			cardiac morbidity	Valsartan: 586/7649 Amlodipine:578/7596 HR: 1.02 (0.91-1.15) p: 0.71	
			MI (fatal and non-fatal)	Valsartan: 369/7649 Amlodipine: 313/7596 **HR: 1.19 (1.02-1.38)** **p: 0.02** SS	
			Heart failure (fatal and not)	Valsartan: 354/7649 Amlodipine: 400/7596 HR: 0.89 (0.77 – 1.03) p: 0.12	
			Stroke	Valsartan: 322/7649 Amlodipine: 281/7596 HR: 1.15 (0.98-1.35) p: 0.08	
			All-cause death	Valsartan: 841/7649 Amlodipine: 818/7596 HR: 1.04 (0.94 – 1.14) p: 0.45	
			New onset diabetes (incidence rate based on patients without diabetes at baseline)	Valsartan: 690/7649 Amlodipine: 845/7596 OR:0.77 (0.69-0.86) **p: <0.0001** **SS**	

	- acute MI - percutaneous transluminal coronary angioplasty or coronary bypass graft in the past 3 months - clinically relevant valvular disease - CVA in the past 3 months - severe hepatic disease - sever chronic renal failure - congestive heart failure requiring ACE inhibitor therapy - patients on monotherapy with β-blockers for both coronary artery disease and hypertension		Safety	
			Peripheral oedema (prespecified)	Valsartan: 1135/7649 Amlodipine: 2492/7596 p<0.0001 Favours Valsartan
			Dizziness (prespecified)	Valsartan: 1257/7649 Amlodipine: 1083/7596 p<0.0001 Favours amlodipine
			Headache (prespecified)	Valsartan: 1120/7649 Amlodipine: 947/7596 p<0.0001 favours amlodipine
			Fatigue (prespecified)	Valsartan: 739/7649 Amlodipine: 674/7596 p:0.0750
			Diarrhea	Valsartan:670/7649 Amlodipine: 515/7596 p: <0.0001 favours amlodipine
			Angina pectoris	Valsartan: 708/7649 Amlodipine: 485/7596 p<0.0001 favours amlodipine
			oedema other	Valsartan: 243/7649 Amlodipine: 462/7596 p<0.0001 favours valsartan
			hypokalaemia	Valsartan: 266/7649

				Amlodipine: 469/7596 p<0.0001 favours valsartan	
			atrial fibrillation	Valsartan: 182/7649 Amlodipine: 151/7596 p: 0.1197	
			Syncope	Valsartan: 129/7649 Amlodipine: 75/7596 p<0.0001 favours amlodipine	

Table 241

4.3.1.16.2 Summary and conclusions

In JNC-8 2014(8) and NICE 2011(3), three studies in total were found that compared angiotensin receptor blockers to calcium channel blockers, but they were not included in a meta-analysis. All patients were high-risk patients, with cardiovascular risk factors or previous events.

Two of the studies reported a statistically significant lower amount of new onset diabetes with angiotensin receptor blockers (CASE-J 2008(148), VALUE 2004(150)).
One study (MOSES 2005(149)) reported a statistically significant difference, with less fatal and non-fatal cardiovascular events, and less events for their primary composite endpoint with angiotensin receptor blockers.
One other study (VALUE 2004(150)) reported a statistically significant lower amount of fatal and non-fatal myocard infarcts.

However, those results come from individual studies and not a meta-analysis, and thus we do not know if the effect would uphold when pooled together and cannot provide an evaluation of the quality of evidence.

4.3.1.17 ACE-inhibitors versus angiotensin receptor blockers in patients without comorbidity

4.3.1.17.1 Clinical evidence profile

Ace inhibitors versus ARBs

1) JNC-8

In the general population with hypertension, there are no randomized controlled trials of good or fair quality to determine whether initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with an angiotensin converting enzyme inhibitor improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

ONTARGET 2008 compared an angiotensin receptor blocker to an angiotensin converting enzyme inhibitor to a combination of the two drugs in participants with vascular disease or high-risk diabetes [ONTARGET 2008, 2008]. However, ONTARGET 2008 was not eligible for inclusion in our evidence review because the study was not designed to assess the effects of blood pressure lowering in hypertension and not all patients in the study were hypertensive. ONTARGET 2008 found no difference between the angiotensin receptor blocker and the angiotensin converting enzyme inhibitor for the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure (risk ratio 1.01, 95% CI 0.94, 1.09).

2) NICE 2011

Meta-analysis: NICE 2011 Inclusion criteria: The literature was reviewed from December 2005 onwards (this was the cut-off date of the previous NICE guidance on pharmalogical treatment of hypertension, CG34) for SR and RCTs comparing ACEi vs ARB for first line treatment in adults with primary hypertension RCTs were included if there was ≥12 months follow up, n≥200 and the population did not consist of people who were exclusively diabetic or had CKD. Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date. Assessment of quality of included trials: yes: GRADE ITT analysis: unclear

Table 242

Ref	Comparison	N/n	Outcomes	Result	Quality assessment (GRADE)
ref NICE 2011(3) Design: MA/SR Search date: nov 2010	ACEi vs ARB	N= 2 n= 20978 (CORDIB, ONTARGET 2008)	Mortality (all cause) (follow-up 12 - median 56 months)	HR 0.98 (0.9 to 1.07) NS	HIGH
		N= 2 n= 20978 (CORDIB 2009, ONTARGET 2008)	MI (fatal and non-fatal) (follow-up 12-56 months)	HR 1.07 (0.94 to 1.22) NS	MODERATE
		N= 2 n= 20978 (CORDIB 2009, ONTARGET 2008)	Stroke (fatal and non-fatal) (follow-up 12 - median 56 months)	HR 0.92 (0.8 to 1.06) NS	MODERATE Serious imprecision: 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
		N = 1 n = 17118 (ONTARGET 2008)	Hospitalisation for angina (follow-up median 56 months)	HR 1.04 (0.95 to 1.14) NS	MODERATE Serious imprecision: 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
		N = 1 n = 17118 (ONTARGET 2008)	Coronary revascularisation (follow-up median 56 months)	HR 1.02 (0.95 to 1.1) NS	HIGH
		N = 1 n = 17118 (ONTARGET 2008)	New onset diabetes (follow-up 12-56 months)	HR 1.12 (0.97 to 1.29) NS	MODERATE Serious imprecision: 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
		N = 1	Heart failure (follow-up median 56	HR 1.05 (0.93 to 1.19)	MODERATE

		n = 17118 (ONTARGET 2008)	months)		Serious imprecision: 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
		N = 1 n = 17118 (ONTARGET 2008)	Study drug withdrawal (follow-up 12 - median 56 months)	**HR 0.87 (0.81 to 0.92) SS**	LOW Patients who entered the trial had already been 'filtered' at run-in to exclude those with poor compliance or who did not perform well. 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm

Table 243

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
CORD IB 2009 Spinar J(151) Ref 552 in nice	3860	Article in Czech 100% hypertensive	12 months	ACEi Ramipril 5mg/day vs ARB losartan (50 mg/day) Treatment followed a stopped-dose adjustment and add-on therapy protocol	Article in Czech No problems with allocation concealment, randomization, blinding or attrition reported in NICE 2011.
ONTARGET 2008(152)	25620	- patients with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage - ≥55 years (mean age 66.4)	56 months	ACEi rampipril 5 mg /day vs ARB telmisartan (50 mg/day) vs	ALLOC. CONC.: unclear RANDOM.: randomized via a 24-hour service computerized voice-activated telephone call to a central

		- 69% of patients had hypertension - 37.8% of patients had diabetes - 12.7% of patients were current smokers		a combination of both drugs Treatment followed a stepped add-on therapy protocol	office BLINDING: states double blind, how unclear Single blind run-in period Not rated by JNC-8

Table 244

4.3.1.17.2 Summary and conclusions

Angiotensin converting enzyme inhibitor versus angiotensin receptor blocker			
Bibliography: Nice 2011(3), including: ONTARGET 2008(152), CORDIB 2009(151)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	20978 (2) 56 months	HR 0.98 (0.9 to 1.07) NS	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
MI (fatal and non-fatal)	20978 (2) 56 months	HR 1.07 (0.94 to 1.22) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision:-1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
Stroke (fatal and non-fatal)	20978 (2) 56 months	HR 0.92 (0.8 to 1.06) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
Coronary revascularisation	17118 (1) 56 months	HR 1.02 (0.95 to 1.1) NS	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
New onset diabetes	17118 (1) 56 months	HR 1.12 (0.97 to 1.29) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
Heart failure	17118 (1) 56 months	HR 1.05 (0.93 to 1.19) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
Study drug withdrawal	17118 (1) 56 months	**HR 0.87 (0.81 to 0.92)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1, Patients who entered the trial had already been 'filtered' at run-in to exclude those with poor compliance or who did not perform well Imprecision: -1, 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or

		harm and non-appreciable benefit or harm

Table 245

In this meta-analysis, NICE 2011(3), used two studies, ONTARGET 2008(152), and CORD IB 2009(151) which compared the use of angiotensin conversion enzyme inhibitor with angiotensin receptor blocker. The ONTARGET study was not selected by JNC-8 because not all patients were hypertensive (around 70%). NICE chose to include it and compared it with CORD IB 2009. The effects were similar between both studies. It is difficult to give more information on the CORD IB study since it was published in Czech and translation was not available to us.

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in mortality.
GRADE: HIGH quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in myocard infarct.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in stroke.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in coronary revascularization.
GRADE: HIGH quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in new onset diabetes.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did not result in a statistically significant difference in heart failure.
GRADE: MODERATE quality of evidence

In hypertensive patients with or without additional risk factors, a treatment with ACE-inhibitors compared with a treatment with ARB did result in a statistically significant difference in drug withdrawals.
GRADE: LOW quality of evidence

4.3.1.18 Calcium channel blocker + diuretic versus diuretic + placebo

4.3.1.18.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
LIU/ FEVER 2005(153) <u>Design:</u> RCT (DB) (PG) <u>Duration of follow-up:</u> Average of 40 months	n= 9800 <u>Mean age:</u> 61.5 <u>Previous CV event:</u> 100% (population selection criteria) LVH :11.0 % Diabetes:12.8 % Proteinuria: 2 % Smoking: 29.2% Age >80y:0% <u>Inclusion</u> - Chinese patients - aged 50-79 - if aged 60 or less: clinical evidence or a history of one cardiovascular event	HCT 12.5 mg/ day + felodipine 5mg/day Vs HCT 12.5 mg/day + placebo If BP not under control, added were: - another 12.5 HCT dose - other AHT drugs but not calcium antagonists	Efficacy (first time occurrence)		RANDO: Adequate, computer generated ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0.3 % Drop-out and Exclusions: % • Described: yes/no • Balanced across groups: yes/no ITT: NO some randomized patients excluded because the centers closed
			Stroke	Felodipine:177/4841 Placebo: 251/4870 **HR: 0.73 (0.60-0.89)** SS in favour of felodipine p: 0.0019	
			Fatal stroke	FDP: 33/4841 PL:50/4870 HR: 0.72 (0.45–1.13) NS, p:0.1516	
			Non-fatal stroke	FDP: 144/4841 PL: 201/4870 **HR: 0.74 (0.59 – 0.91)** **SS**, p: 0.0059	
			All CV events	FDP: 241/4841 PL: 334/4870 **HR: 0.73 (0.61 – 0.86)** **SS**, p: 0.0002	
			All cardiac events	FDP: 73/4841 PL: 105/4870 **HR:0.65 (0.47-0.89)** **SS**, p: 0.0074	

	(MI, stroke, … – beyond previous 6 months) OR presence of at least 2 CV risk factors (male sex, current smoking of more than 1 cigarette per day during at least 1 year etc.) - BP after switching to low dose HCT (12.5mg/d) was SBP: 140-180mmHg and DBP: 90-100mmHg <u>Exclusion</u> - stroke or MI during the previous 6 months - secondary hypertension - unstable angina - cardiomyopathy or significant valvular disease - serum creatinine greater than 178 µmol/L - gout - uncontrolled diabetes (fasting plasma glucose >10mmol/L, 180 mg/dl) - serious pulmonary or hepatic disease - known contraindications		Coronary events	FDP: 71/4841 PL: 99/4870 **HR: 0.68 (0.49 – 0.92)** **SS**, p:0.015	SELECTIVE REPORTING: yes/no (describe if yes) 6-week run in period with HCT 12.5 mg 85.9 remained on blinded treatment throughout the study Sponsor: Chinese ministry of health Chinese ministry of science
			Heart Failure	FDP: 18/4841 PL:27/4870 HR: 0.70 (0.37-1.30) NS, p: 0.2604	
			PTCA and CABG	FDP: 4/4841 PL: 11/4870 HR: 0.35 (0.11 – 1.11) NS, p:0.0757	
			All-cause death	FDP:112/4841 PL: 151/4870 **HR: 0.69 (0.54 – 0.89)** **SS**, p: 0.0053	
			Cardiovascular death	FDP: 73/4841 PL: 101/4870 **HR: 0.67 (0.48-0.91)** **SS**, p: 0.0112	
			New-onset diabetes	FDP: 177/4841 PL: 154/4870 HR:1.20 (0.76-1.90) NS, p: 0.4371	
			Renal Failure	FDP:10/4841 PL: 8/4870 HR: 1.38 (0.54-3.52) NS, p: 0.4994	
			Cancer	FDP: 42/4841	

	to study drugs			PL:62/4870 **HR: 0.64 (0.42-0.96)** **SS**, 0.0316
			Safety	
			Dizziness	FDP: 174/4841 PL:203/4870 p: 0.151
			Flushness	FDP: 66/4841 PL: 9/4870 **p <0.001**
			Headache	fDP:68/4841 PL:61/4870 p: 0.581
			Palpitation	FDP:56/4841 PL:49/4870 p: 0.544
			Fatigue	FDP: 31/4841 PL: 51/4870 **p: 0.037**
			Ankle oedema	FDP: 49/4841 PL:18/4870 **p < 0.001**

Table 246

4.3.1.18.2 Summary and conclusions

Diuretics + calcium channel blocker (felodipine) versus Diuretic plus placebo			
Bibliography: FEVER 2005 (153)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All cause death	9800 (1) 40 months	**HR: 0.69 (0.54 – 0.89)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
Cardiovascular death	9800 (1) 40 months	**HR: 0.67 (0.48-0.91)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
All cardiovascular events	9800 (1) 40 months	**HR: 0.73 (0.61 – 0.86)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
All cardiac events	9800 (1) 40 months	**HR:0.65 (0.47-0.89)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
Coronary events	9800 (1) 40 months	**HR: 0.68 (0.49 – 0.92)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
Heart Failure	9800 (1) 40 months	HR: 0.70 (0.37-1.30) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: -1 for large CI, includes both no effect and sizeable benefit and harm
Stroke (fatal and non-fatal)	9800 (1) 40 months	**HR: 0.73 (0.60-0.89)** SS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
Fatal Stroke	9800 (1) 40 months	HR: 0.72 (0.45–1.13) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: ok
Non-fatal stroke	9800 (1)	**HR: 0.74 (0.59 – 0.91)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA

	40 months		Directness: ok, but population with previous CV event Imprecision: ok
Renal failure	9800 (1) 40 months	HR: 1.38 (0.54-3.52) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: -1 for large CI
New onset diabetes	9800 (1) 40 months	HR:1.20 (0.76-1.90) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok, but population with previous CV event Imprecision: -1 for large CI

Table 247

We only found one randomized, double blind trial comparing a diuretic and calcium channel blocker with a diuretic and a placebo. The study was conducted on 9800 hypertensive Chinese patients (mean age >60) with a previous cardiovascular event. The study was of good quality.

In patients with hypertension, with or without additional risk factors, a treatment with diuretics and a calcium channel blocker, compared to a treatment with diuretics and a placebo, did result in a statistically significant lower occurrence of: death (all cause), cardiovascular death, cardiovascular events (all), cardiac events (all), coronary events, fatal and non-fatal stroke combined, and non-fatal stroke considered apart.
GRADE: MODERATE quality of evidence

In patients with hypertension, with or without additional risk factors, a treatment with diuretics and a calcium channel blocker, compared to a treatment with diuretics and a placebo did not result in a statistically significant difference in the occurrence of: heart failure, fatal stroke, renal failure and new onset diabetes.
GRADE: HIGH MODERATE LOW VERY LOW quality of evidence

4.3.1.19 Calcium channel blockers + ARB versus CCB + BB versus CCB + diuretics

4.3.1.19.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Matsuzaki / COPE 2011(154) Design: RCT (OL) (PG) PROBE design Duration of follow-up: median 3.61 years	n= 3501 Mean age: 63 Previous CV event: 12.3% Previous stroke:1.7 % MI: 0.6% Diabetes:14.3 % CKD: unknown% Smoking: 39.6% Age >80y:unknown % <u>Inclusion</u> - outpatients between 40 and 85 years - sitting SBP at least 140 mmHg, DBP at least 90mmHg whatever the treatment	CCB (Benidipine) + One of the following three: 1) ARB (n = 1167) Vs 2) β-blocker (n = 1166) vs 3) Thiazide diuretic (n = 1168)	Efficacy		RANDO: computer generated at TokioU data center, dynamic allocation Adequate/inadequate/unclear ALLOCATION CONC: concealed until investigators contacted data center BLINDING : Participants: no Personnel: no Assessors: yes (PROBE design) FOLLOW-UP: Lost-to follow-up: 6.3 % Drop-out and Exclusions: 8.3% • Described: yes • Balanced across groups: yes ITT: no, drop-outs & lost-to follow-up
			Cardiovascular hard composite endpoint (PO)	B+BB: 29/1166 B+ARB: 25/1167 B+TD: 14/1168 BB/ARB – HR: 1.21(0.71-2.06) ARB/TD – HR: 1.76(0.92-3.39) BB/TD – HR: 2.13(1.12-4.02)	
			All-cause mortality	B+BB: 23/1166 B+ARB: 25/1167 B+TD: 23/1168 BB/ARB – HR: 0.95 (0.54-1.67) NS ARB/TD – HR: 1.07 (0.61-1.89) NS BB/TD – HR:1.02 (0.57 – 1.82) NS	
			New-onset diabetes	B+BB: 37/1166 B+ARB: 21/1167 B+TD: 32/1168 BB/ARB – **HR: 1.85(1.08-3.16) SS**	

	Exclusion - SBP at least 200mmHG, DBP 120mmHG - secondary hypertension - type 1 diabetes or type 2 requiring insulin - history of cerebrovascular disorder - MI - angina pectoris - coronary angioplasty - coronary artery bypass graft within 6 months - heart failure (NYHA II-IV) - chronic atrial fibrillation or flutter - severe liver dysfunction - severe renal dysfunction - history or complicated or congenital rheumatic heart disease - history of malignancy within 5 years before			ARB/TD- HR: 0.64 (0.37 – 1.11) NS BB/TD – HR: 1.18 (0.74 – 1.90) NS	excluded SELECTIVE REPORTING: no run-in phase of 4-8 weeks (monotherapy of benidipine 4mg) Sponsor: Kyowa Hakko Kirin Co., Ltd

Table 248

Ogihara 2012(155): subgroup analysis ≥65 years	
Fatal and non-fatal stroke	CCB+BB vs CCB+ARB: 1.79 (0.80-4.01)
	CCB+ARB vs CCB+TD: 1.53 (0.55 – 4.31)
	CCB+BB vs CCB +TD: **2.74 (1.08 – 6.96) SS**
All-cause mortality	CCB+BB vs CCB+ARB: 0.99 (0.54-1.82)
	CCB+ARB vs CCB+TD: 1.36 (0.69-2.65)
	CCB+BB vs CCB +TD: 1.34 (0.69-2.60)
New onset diabetes	CCB+BB vs CCB+ARB: **2.47 (1.03 – 5.91) SS**
	CCB+ARB vs CCB+TD: 0.47 (0.19-1.15)
	CCB+BB vs CCB +TD: 1.16 (0.58-2.29)

Table 249

4.3.1.19.2 Summary and conclusions

Calcium channel blockers plus angiotensin receptor blockers versus calcium channel blockers plus beta-blockers versus calcium channel blockers plus diuretics in hypertension patients with and without additional risk factors			
Bibliography: COPE 2011(154); subgroup analysis Ogihara 2012(155)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	3501 (1) 3.6 years	CCB+BB vs CCB+ARB: HR: 0.95 (0.54-1.67) NS CCB+ARB vs CCB+TD: HR: 1.07 (0.61-1.89) NS CCB+BB vs CCB +TD: HR: 1.02 (0.57 – 1.82) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: NA Directness: ok Imprecision: ok
New onset diabetes	3501 (1) 3.6 years	CCB+BB vs CCB+ARB: **HR: 1.85(1.08-3.16) SS** CCB+ARB vs CCB+TD: 0.64 (0.37 – 1.11) NS CCB+BB vs CCB +TD: 1.18 (0.74 – 1.90) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, open label Consistency: NA Directness: ok Imprecision: ok
Fatal and non-fatal stroke **in subgroup ≥65y**	1533 (1) 3.6 years	CCB+BB vs CCB+ARB: 1.79 (0.80-4.01) CCB+ARB vs CCB+TD: 1.53 (0.55 – 4.31) CCB+BB vs CCB +TD: **2.74 (1.08 – 6.96) SS**	⊕⊖⊖⊖ **VERY LOW** Study quality: -1, open label, subgroup analysis Consistency: NA Directness: ok Imprecision: -1, large CI
All-cause mortality **in subgroup ≥65y**	1533 (1) 3.6 y	CCB+BB vs CCB+ARB: 0.99 (0.54-1.82) CCB+ARB vs CCB+TD: 1.36 (0.69-2.65) CCB+BB vs CCB +TD: 1.34 (0.69-2.60)	⊕⊖⊖⊖ **VERY LOW** Study quality: -1, open label, subgroup analysis Consistency: NA Directness: ok Imprecision: -1, large CI
New-onset diabetes	1533 (1) 3.6y	CCB+BB vs CCB+ARB: **2.47 (1.03 – 5.91) SS** CCB+ARB vs CCB+TD: 0.47 (0.19-1.15) CCB+BB vs CCB +TD: 1.16 (0.58-2.29)	⊕⊖⊖⊖ **VERY LOW** Study quality: -1, open label, subgroup analysis Consistency: NA Directness: ok Imprecision: -1, large CI

Table 250

The two trials providing the evidence are the original trial (COPE 2011) and a predefined subgroup analysis (Ogihara 2012). The trial was an open label, blinded endpoint design. Previous MI or cardiovascular intervention were exclusion criteria.

In hypertensive patients, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and an angiotensin receptor blocker, did not result in a statistically significant difference for mortality.
GRADE: LOW quality of evidence
In hypertensive patients, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and an angiotensin receptor blocker, did result in a statistically significant higher occurrence of new onset diabetes.
GRADE: LOW quality of evidence

In hypertensive patients over 65 years of age, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and an angiotensin receptor blocker, did not result in a statistically significant difference for fatal and non-fatal stroke or mortality.
GRADE: LOW quality of evidence

In hypertensive patients over 65 years of age, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and an angiotensin receptor blocker, did result in a statistically significant higher occurrence of new onset diabetes.
GRADE: VERY LOW quality of evidence

In hypertensive patients, with or without additional risk factors, a treatment with a calcium channel blocker and an angiotensin receptor blocker , compared to a treatment with a calcium channel blocker and a thiazide diuretic, did not result in a statistically significant difference for mortality or new onset diabetes.
GRADE: LOW quality of evidence

In hypertensive patients over 65 years of age, with or without additional risk factors, a treatment with a calcium channel blocker and an angiotensin receptor blocker , compared to a treatment with a calcium channel blocker and a thiazide diuretic, did not result in a statistically significant difference for fatal and non-fatal stroke, mortality or new onset diabetes.
GRADE: VERY LOW quality of evidence

In hypertensive patients, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and a thiazide diuretic, did not result in a statistically significant difference for mortality or new onset diabetes.
GRADE: LOW quality of evidence

In hypertensive patients over 65 years of age, with or without additional risk factors, a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and a thiazide diuretic, did result in a statistically significant higher occurrence of fatal and non-fatal stroke.
GRADE: VERY LOW quality of evidence

In hypertensive patients over 65 years of age, with or without additional risk factors a treatment with a calcium channel blocker and a beta-blocker, compared to a treatment with a calcium channel blocker and a thiazide diuretic, did not result in a statistically significant difference for mortality or new onset diabetes.
GRADE: VERY LOW quality of evidence

4.3.1.20 ACE-inhibitor + calcium channel blocker versus ACE-inhibitor + diuretic

4.3.1.20.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Jamerson 2008(156) (ACCOMPLISH) Design: RCT (DB) (PG) Duration of follow-up: 36 months	n= 11506 Mean age: 68.4 Previous MI 23.6: % Previous stroke: 13.0% Previous hospitalization for unstable angina:11.5 % Diabetes:60.2 % Estimated glomerular filtration rate >60: 18.1% % Smoking: 11.3% Age >65y: 66.4 % <u>Inclusion</u> - At least 55 years of age. - Previously untreated or treated hypertension. - For patients >= 60 years,	ACEi (benazepril) + CCB amlodipine (n = 5744) Vs ACEi (benazepril) + Diuretic (Hydrochlorothiazide) (n = 5762)	Efficacy		RANDO: unclear, no details ALLOCATION CONC: Adequate, assignments made centrally by telephone BLINDING : Participants: yes Investigators: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 1% Drop-out and Exclusions: 1.2 % • Described: partially • Balanced across groups: unclear ITT: Yes SELECTIVE REPORTING: no
			Composite of cv events and death from cv causes (PO)	CCB: 552/5744 DIU: 679/5762 **HR: 0.80 (0.72-0.90) SS** p: <0.0001	
			Death from CV causes	CCB: 107/5744 Diu: 134/5762 HR: 0.80 (0.62 – 1.03) NS p: 0.08	
			Fatal and non-fatal MI	CCB: 125/5744 DIU: 159/5762 **HR: 0.78 (0.62 – 0.99) SS** p: 0.04	
			Fatal and non-fatal stroke	CCB: 112 / 5744 DIU: 133/5762 HR: 0.84 (0.65 – 1.08) p: 0.17	
			Hospitalization for unstable angina	CCB: 44/5744 DIU: 59/5762 HR: 0.75 (0.50 – 1.10) p: 0.14	
			Coronary	CCB: 334/ 5744	

	evidence of at least one CV disease or target organ damage, or for patients 55-59 years evidence of at least two CV diseases or target organ damage from two different organ systems as defined in the protocol. <u>Exclusion</u> Allergy to any of the drugs administered in this trial. Current angina pectoris (ie, no anginal event requiring NTG within 1 month prior to Visit 1). Secondary hypertension. Refractory hypertension defined as SBP >= 180 mmHg and/or DBP >= 110 mmHg unresponsive to triple-drug regimens of sympatholytics, diuretics and vasodilators. History of symptomatic heart failure (NYHA classes II-IV) or ejection fraction < 40%.		revascularization procedure	DIU: 386/5762 HR: 0.86 (0.74 – 1.00) p: 0.04	Sponsor: Novartis The trial was terminated early after a mean follow-up of 36 months due to this difference favoring the benazepril–amlodipine group in the primary outcome. JNC-8 notes the following remarks: - criteria for event classification were not explicitly described other than being "standardized", - use of concomitant medications was reported at baseline but not at the end of follow-up, and adherence information was reported at six months and one year but not at the end of follow-up NICE reports only serious limitations on precision, seeing as some CI include both no effect and appreciable benefit/harm
			Resuscitation after cardiac arrest	CCB: 14/5744 DIU: 8/5762 HR: 1.75 (0.73 – 4.17) p: 0.20	
			SUBGROUPS		
			PO, ≥65 years	CCB: 386/3813 DIU: 474/3827 **HR: 0.81 (0.71 – 0.92) SS** p: 0.002	
			PO, ≥70 years	CCB: 260/2363 DIU: 323/2340 **HR: 0.79 (0.67 – 0.93) SS** p: 0.004	
			Safety		

	Myocardial infarction, coronary revascularization (CABG or PCI), unstable angina within one month of Visit 1. Stroke or transient ischemic event (TIA) within 3 months of Visit 1. Significant obstructive valvular cardiovascular disease or any valvular disease expected to lead to surgery during the course of the study. Evidence of hepatic disease (AST or ALT values >= 2 X upper limit of normal). Impaired renal function (serum creatinine >= 2.5 mg/dL (221 µmol/L)). Baseline serum potassium of > 5.2 meq/L not on potassium supplements. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the last 5 years.				

	History of clinically significant auto immune disorders such as Systemic Lupus Erythematosus. Significant non-cardiovascular illness or condition likely to result in death prior to trial completion, e.g., major organ transplant (life expectancy <5 years). Significant cardiovascular disease such as an aortic aneurysm ≥ 6 cm, likely requiring surgical intervention during the course of the study. Other protocol-defined exclusion criteria applied to the study.				

Table 251

4.3.1.20.2 Summary and conclusions

ACE-inhibitor + calcium channel blocker versus ACE-inhibitor + diuretic for hypertension			
Bibliography: ACCOMPLISH 2008 (156)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite of cv events and death from cv causes (PO)	11506 (1) 36 months	**HR: 0.80 (0.72-0.90) SS**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok Imprecision:-1; 95% confidence interval includes both 1) appreciable benefit or harm and 2) non-appreciable benefit or harm
Death from CV causes	11506 (1) 36 months	HR: 0.80 (0.62 – 1.03) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok Imprecision: -1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
Fatal and non-fatal MI	11506 (1) 36 months	**HR: 0.78 (0.62 – 0.99) SS**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok Imprecision: -1, 95% confidence interval includes both 1) appreciable benefit or harm and 2) non-appreciable benefit or harm
Fatal and non-fatal stroke	11506 (1) 36 months	HR: 0.84 (0.65 – 1.08)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: ok Imprecision: -1, 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm

Table 252

In this RCT, 11506 hypertensive patients older than 55, with a relatively high cardiovascular risk, were randomized to treatment with an ACE-inhibitor plus a calcium channel blocker or an ACE-inhibitor plus a diuretic (hydrochlorothiazide) and followed over 36 months. All patients were required to have at least symptoms of organ damage due to hypertension of one cardiovascular disease.

In hypertensive patients with or without additional risk factors, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, yielded a statistically significant lower occurrence of the primary composite endpoint (cardiovascular events and deaths from cardiovascular causes).
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, did not result in a statistically significant difference in death from cardiovascular causes.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, yielded a statistically significant lower occurrence if fatal and non-fatal myocard infarct.
GRADE: LOW quality of evidence

In hypertensive patients with or without additional risk factors, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, did not result in a statistically significant difference in fatal and non-fatal stroke.
GRADE: LOW quality of evidence

4.3.1.21 Resistant hypertension

Our search yielded no MA's or RCTs meeting our inclusion criteria.

4.3.2 Elderly patients >60 years

4.3.2.1 Thiazide diuretics versus placebo

4.3.2.1.1 Clinical evidence profile

Trial, year Population Sample size Trial duration Quality Rating	**Overall Mortality**	**Coronary Heart Disease** (includes non-fatal MI, fatal MI, sudden death or combination)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal or combination)	**Heart Failure** (includes fatal, non-fatal, or combination)
HYVET, 2008(63) Adults, ages ≥80 years, SBP ≥160 and DBP 90-109 at start of trial but relaxed later to <110 mmHg N = 3,845 Mean 2.1 years Good	**Death from any cause:** Unadj HR: 0.79 CI (0.65, 0.95) p =0.02 **study stopped early due to mortality reduction*	**Death from cardiac cause:** Unadj HR: 0.71 CI (0.42, 1.19) p = 0.19 **Fatal and non-fatal MI:** Unadj HR: 0.72 CI (0.30, 1.70) p = 0.45	**Death from stroke:** Unadj HR: 0.61 CI (0.38, 0.99) p = 0.046 **Fatal or non-fatal stroke:** Unadj HR: 0.70 CI (0.49, 1.01) p = 0.06	**Death from HF**: unadj HR: 0.48 CI (0.18, 1.28) p = 0.14 **Fatal or non-fatal HF:** Unadj HR: 0.36 CI (0.22, 0.58) p < 0.001

SHEP, 1991(157) Adults, ages ≥60 years, SBP 160-219 and DBP <90 mmHg N = 4,736 Mean 4.5 years Good Step1: chlortalidone 12.5-25mg/d or matching placebo Step 2: Atenolol 25-50mg/d or matching placebo	**Total deaths:** RR: 0.87 CI (0.73, 1.05) p = NR	**Non-fatal MI:** RR: 0.67 CI (0.47, 0.96) p = NR **Symptomatic MI** events**:** 63 vs 98 (txt vs control) p = 0 .005 **CHD** RR:0.75 CI (0.60, 0.94) p = NR **Non-fatal MI or CHD deaths** RR: 0.73 CI (0.57, 0.94) p = NR **MI deaths:** RR: 0.57 CI (0.30-1.08) p = NR **Total CHD deaths:** RR: 0.80 CI (0.57, 1.13) p = NR **Sudden death** (<1 hour)**:** RR: 1.00 CI (0.56, 1.78) p = NR **Rapid deaths** (1-24 hours)**:** RR: 0.87 CI (0.48, 1.56) p = NR	**Non-fatal plus fatal stroke:** RR: 0.64 (0.50, 0.82) p = 0.0003	**Fatal and non-fatal HF:** RR: 0.51 (0.37, 0.71) p < 0.001

Table 253

4.3.2.1.2 Summary and conclusions

Thiazide diuretic versus placebo in elderly hypertension patients			
Bibliography: SHEP 1991(157)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(958%CI))**	**Quality of the evidence (GRADE)**
Mortality	4736 (1 study) 4.5 years	0.87 (0.73, 1.05) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; attrition>20% Consistency: ok Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Coronary heart disease events	4736 (1 study) 4.5 years	**0.75 CI (0.60, 0.94)** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1; attrition>20% Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	4736 (1 study) 4.5 years	**0.64 (0.50, 0.82)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; attrition>20% Consistency: ok Directness: ok Imprecision: ok
Heart failure	4736 (1 study) 4.5 years	**0.51 (0.37, 0.71)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; attrition>20% Consistency: ok Directness: ok Imprecision: ok

Table 254

This RCT that included 4736 elderly (≥60 y) patients with isolated systolic hypertension, compared treatment with a thiazide diuretic (chlortalidone) to placebo. The mean follow-up was 4.5 years.

In elderly patients with isolated hypertension, treatment with a thiazide diuretic significantly decreased stroke and heart failure rates, compared to placebo.
GRADE: MODERATE quality of evidence

In elderly patients with isolated hypertension, treatment with a thiazide diuretic significantly decreased coronary heart disease events, compared to placebo.
GRADE: LOW quality of evidence

In elderly patients with isolated hypertension, treatment with a thiazide diuretic did not result in a statistically significant difference in mortality, compared to placebo.
GRADE: LOW quality of evidence

Thiazide diuretic versus placebo in elderly hypertension patients			
Bibliography: HYVET 2008(63)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	3845 (1 study) 1.8 years	**0.79 (0.65 to 0.95)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; attrition>20%, allocation concealment unclear Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	3845 (1 study) 1.8 years	0.70 (0.49 to 1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; attrition>20%, allocation concealment unclear Consistency: ok Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular death	3845 (1 study) 1.8 years	0.77 (0.60 to 1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; attrition>20%, allocation concealment unclear Consistency: ok Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Stroke mortality	3845 (1 study) 1.8 years	**0.61 (0.38 to 0.99)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; attrition>20%, allocation concealment unclear Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Serious adverse events	3845 (1 study) 1.8 years	**indapamide: 358/1933** **placebo: 448/1912** **P: 0.001 in favour of indapamide**	⊕⊕⊖⊖ **LOW** Study quality: -1; attrition>20%, allocation concealment unclear Consistency: ok Directness: ok Imprecision: -1; no CI

Table 255

This RCT that included 3845 very elderly (≥80 y) patients with hypertension, compared treatment with a thiazide diuretic (indapamide) to placebo. The mean follow-up was 1.8 years.

In elderly patients hypertension, treatment with a thiazide diuretic significantly decreased **mortality**, **stroke mortality**, and **serious adverse events**, compared to placebo.
GRADE: LOW quality of evidence

In elderly patients with isolated hypertension, treatment with a thiazide diuretic did not result in a statistically significant difference in **stroke**, or **cardiovascular death**, compared to placebo.
GRADE: LOW quality of evidence

4.3.2.2 Beta blockers versus placebo

4.3.2.2.1 Clinical evidence profile

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
STOP, 1991(61) Adults, ages 70 to 84 years, treated or untreated for hypertension, with SBPs of 180 to 230 and DBP ≥ 90 or DBPs of 105 to 120 irrespective of SBP during run-in N = 1,627 Mean 25 months Fair	SBP/DBP Goal: <160/95 mmHg <u>At start of trial</u> Baseline SBP/DBP, mmHg (SD): Txt: 195/102 (14/7) Control: 195/102 (14/7) <u>At 4 years followup</u> Achieved SBP/DBP (SD) Txt: 166/85 (21/10) Placebo: 193/95 (20/11) p = NR SBP/DBP change from baseline Txt: -29/-17 Placebo: -2/-7	**Total deaths** (irrespective of preceding non-fatal endpoint)**:** RR (CI): 0.57 (0.37, 0.87)	**All MI** (first endpoint)**:** RR (CI): 0.87 (0.49,1.56) **Fatal MI** (first endpoint)**:** RR (CI): 0.98 (0.26, 3.66)	**All stroke** (first endpoint)**:** RR (CI): 0.53 (0.33, 0.86) **Fatal stroke** (first endpoint)**:** RR (CI): 0.24 (0.04, 0.91)	**CHF endpoints**: 19 vs. 39 (txt vs placebo) p = NR	**Total primary endpoint** [stroke, MI, other CV death] (first to happen)**:** RR (CI): 0.60 (0.43, 0.85)

Table 256

Trial, year Sample characteristics Sample size Duration Quality Rating	**BP Goal Achieved BP Differences between groups**	**Overall Mortality**	**Coronary Heart Disease** (includes fatal MI, non-fatal MI, sudden death, or combinations)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal, or combination)	**Heart Failure** (includes fatal, non-fatal or combination)
Coope and Warrender, 1986 (60) Adults, age 60 to 79, SBPs ≥ 170 or DBP ≥ 105 mmHg N = 884 Mean 4.4 years Good	Goal: Not explicitly stated, however additional therapy added if at the end of 3 months, SBP > 170 or DBP >105 mmHg <u>At start of trial</u> Baseline SBP/DBP, mmHg (SD): Txt: 196.2/99.7 (16.7/12.0) Control: 196.1/98.0 (15.6/11.8) <u>During follow-up:</u> Achieved SBP: NR SBP/DBP achieved differences between groups, mmHg 18/11 p = NR Reduction in SBP/DBP mmHg Txt: NR	**All deaths** Rate of txt/rate of control (95% CI): 0.97 (0.70, 1.42) p = NS	**Fatal coronary attacks** Rate of txt/rate of control (95% CI): 1.00 (0.58, 1.71) p = NS **Non-fatal coronary attacks** Rate of txt/rate of control (95% CI): 1.11 (0.46, 2.68) p = NS **All coronary attacks** Rate of txt/rate of control (95% CI): 1.03 (0.63, 1.63) p = NS	**Fatal stroke** Rate of txt/rate of control (95% CI): 0.30 (0.11, 0.84) p < 0.025 **All stroke** Rate of txt/rate of control (95% CI): 0.58 (0.35, 0.96) p < 0.03	**Fatal ventricular failure** Rate of txt/rate of control (95% CI): 1.11 (0.28, 4.45) p = NS **Non-fatal ventricular failure** Rate of txt/rate of control (95% CI): 0.63 (0.35, 1.11) p = NS

	Control: 16/10 p = NR <u>At 1 year</u> % of patients at or below SBP 170 mmHg Txt: 36% Control: 20% p = NR <u>At 8 years</u> % of patients at or below SBP 170 mmHg Txt: 62% Control: 31% p = NR				

Table 257

4.3.2.2.2 Summary and conclusions

Beta-blocker versus placebo for hypertension in the elderly			
Bibliography: Coope-Warrender 1986(60)			
Outcomes	**N° of participants (studies) Follow up**	**Results (Rate of treatment/rate of control (95%CI))**	**Quality of the evidence (GRADE)**
Mortality	884 (1 study) 4.4 years	0.97 (0.70 to 1.42) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; no placebo Consistency: ok Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Coronary attacks	884 (1 study) 4.4 years	1.03 (0.63, 1.63) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; no placebo Consistency: ok Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Stroke	884 (1 study) 4.4 years	**0.58 (0.35, 0.96)** **SS**	⨁⨁⊖⊖ **LOW** Study quality: -1; no placebo Consistency: ok Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 258

In this RCT in 884 elderly (60 to 79y) hypertensive patients, treatment with a beta-blocker was compared to no treatment. The follow-up was 4.4 years.

In elderly hypertension patients, treatment with a beta-blocker, compared to no treatment, resulted in a significant decrease of stroke rate.
GRADE: LOW quality of evidence

In elderly hypertension patients, treatment with a beta-blocker, compared to no treatment, did not result in a statistically significant difference in mortality or coronary attack rate.
GRADE: VERY LOW quality of evidence

Beta-blocker versus placebo for hypertension in the elderly			
Bibliography: STOP 1991(61)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	1627 (1 study) 25 months	**0.57 (0.37 to 0.87)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok
Stroke	1627 (1 study) 25 months	**0.53 (0.33, 0.86)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok
Myocardial infarction	1627 (1 study) 25 months	0.87 (0.49,1.56) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Stroke, myocardial infarction, other cardiovascular death (composite)	1627 (1 study) 25 months	**0.60 (0.43, 0.85)** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; unclear randomization and allocation concealment Consistency: ok Directness: ok Imprecision: ok

Table 259

In this RCT in 1627 elderly (70 to 84y) hypertensive patients, treatment with a beta-blocker was compared to placebo. The follow-up was 4.4 years.

In elderly hypertension patients, treatment with a beta-blocker, compared to placebo, resulted in a statistically significant decrease in mortality, stroke, and a composite of stroke, myocardial infarction, and cardiovascular death.
GRADE: MODERATE quality of evidence

In elderly hypertension patients, treatment with a beta-blocker, compared to placebo, did not result in a statistically significant difference in myocardial infarction rate.
GRADE: VERY LOW quality of evidence

4.3.2.3 Calcium channel blockers versus placebo

4.3.2.3.1 Clinical evidence profile

Trial, year Sample characteristics Sample size Duration Quality Rating	**Intervention**	**Overall Mortality**	**Coronary Heart Disease** (includes fatal MI, non-fatal MI, sudden death, or combinations)	**Cerebrovascular morbidity and mortality** (includes fatal, non-fatal, or combination)	**Heart Failure** (includes fatal, non-fatal or combination)
Syst-Eur, 1997(52) Adults, ages ≥ 60 years, SBPs 160-219 and DBPs of < 95 mmHg N = 4,695 Median 24 months Good	Nitrendipine 10–40 mg daily, with the possible addition of enalapril 5–20 mg daily and hydrochlorothiazide 12·5–25·0 mg daily, or matching placebos.	**Total mortality:** adj HR: 0.86 CI (0.67, 1.10) p = NR	**Fatal and non-fatal cardiac endpoints:** adj HR: 0.71 CI (0.54, 0.95) p < 0.05 **Fatal MI** Rate per 1000 py: in txt group CI (-82, 9) p =0.08 **Non-fatal MI:** Rate per 1000 py: 20% ↓ in txt group CI (-53, 34) p = 0.40 **Coronary mortality:** Rate per 1000 py: 27% ↓ in txt group CI (-54, 15) p = 0.17 **Sudden death:** Rate per 1000 py: 12% ↓ in txt group CI (-49, 52) p =0.65	**Non-fatal stroke:** Rate per 1000 py: 44% ↓ in txt group CI (-63,-14) p = 0.007 **Death due to stroke:** Rate per 1000 py: 27% ↓ in txt group CI (-62, 39) p = 0.33 **Fatal and non-fatal stroke combined** adj HR: 0.59 CI (0.38, 0.79) p < 0.01	**Non-fatal HF:** Rate per 1000 py: 36% ↓ in txt group CI (-60, 2) p = 0.06 **Fatal HF:** Rate per 1000 py: 24% ↓ in txt group CI (-70, 93) p = 0.57 **Fatal and non-fatal HF** Rate per 1000 py: 29% ↓ in txt group CI (-53, 10) p =0.12

			Fatal and non-fatal MI: Rate per 1000 py: 30% ↓ in txt group CI (-56, 9) p = 0.12		

Table 260

4.3.2.3.2 Summary and conclusions

Calcium channel blockers versus placebo in elderly hypertension patients			
Bibliography: Syst-Eur 1997(52)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	4695 (1 study) 2 years	0.86 CI (0.67, 1.10) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment Consistency: only one study Directness:ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Fatal and non-fatal cardiac endpoints	4695 (1 study) 2 years	**0.71 CI (0.54, 0.95)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	4695 (1 study) 2 years	**0.59 CI (0.38, 0.79)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment Consistency: only one study Directness: ok Imprecision: ok
Heart failure	4695 (1 study) 2 years	Rate per 1000 py: 29% ↓ in txt group CI (-53, 10) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Table 261

This RCT in 4695 elderly (>60y) patients with isolated systolic hypertension , a calcium channel blocker was compared to placebo. The median follow-up was 24 months.

In elderly patients with isolated systolic hypertension, treatment with a calcium channel blocker, compared to placebo, resulted in a significant decrease of **stroke** rate.
GRADE: MODERATE quality of evidence

In elderly patients with isolated systolic hypertension, treatment with a calcium channel blocker, compared to placebo, resulted in a significant decrease of **cardiac endpoints**.
GRADE: LOW quality of evidence

In elderly patients with isolated systolic hypertension, treatment with a calcium channel blocker, compared to placebo, did not result in a statistically significant difference in **mortality** or **heart failure** rates.
GRADE: LOW quality of evidence

4.3.2.4 Angiotensin receptor blockers versus placebo

4.3.2.4.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Lithell 2003(91) Design: RCT (DB) (PG) Duration of follow-up: Mean: 3.7 years	n= 4964 Mean age: 76.4 Previous CV event: 4.5% Previous stroke:3.9 % Heart failure: not given Diabetes: 12.8 % CKD: not given Smoking: 8.7% Age >80y: 21.3% Inclusion - age between 70 and 89 years - SBP 160-179 mmHg, DBP 90-99 mmHg after standardization of	Candesartan 8 – 16 mg + Open-label active antihypertensive therapy Vs Placebo + Open-label active antihypertensive therapy	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: unclear Assessors: yes Remarks on blinding method: central, computer-generated randomization balanced with respect to a number of likely prognostic variables FOLLOW-UP: Lost-to follow-up: 0.1% Drop-out and Exclusions: 0.4 % • Described: yes • Balanced across groups: yes
			Major cardiovascular events (PO) Composite endpoint (consisting off: CV death, non-fatal stroke, non-fatal myocardial infarction)	Candesartan: 242 / 2477 Placebo: 268 / 2460 Risk Reduction = 10.9% (95% CI: -6.0 to 25.1) P = 0.19 NS	
			Cardiovascular death	No significant difference Numbers not reported	
			Non-fatal stroke	Candesartan: 68/2477 Placebo: 93/2460 Risk Reduction = 27.8% (95% CI: 1.3 to 47.2) P = 0.04	
			All stroke	Candesartan: 89/2477 Placebo: 115 / 2460 Risk Reduction= 23.6% (95% CI: -0.7 to 42.1)	

	previous antihypertensive medication to HCT 12.5 mg - MMSE 24 or above on two consecutive occasions separated by at least 14 days Exclusion - SBP ≥ 180 mmHg - orthostatic hypotension - need of an antihypertensive treatment other than HCT during the run-in - stroke or myocardial infarction within 6 months - decompensated heart failure - serum AST or ALT > 3 times the upper normal limit - serum creatinine >180 µmol in men and >140 µmol in women - contra-indications for			P = 0.056	
			Non-fatal myocardial infarction	No significant difference Numbers not reported	ITT: No, some patients dropped due to concerns on data quality Patients who took no medication or placebo pill were dropped too SELECTIVE REPORTING: no The study consisted of an open run-in period of minimum 1 month, maximum 3 month followed by a double-blind treatment for 3-5 years. If a SBP > 160 mmHg or a DBP > 90 mmHg was observed during the study, in spite of 2 tablets o.d. of study drug, additional antihypertensive treatment was recommended. The recommendation was to start with HCT 12.5 mg once daily. Other drugs, except angiotensin-converting enzyme inhibitors (ACE-I) and AT1-receptor blockers (ARB), could be added later. Sponsor:
			Total mortality	No significant difference Numbers not reported	
			New-onset diabetes mellitus	Candesartan : 4.3% of patients Placebo: 5.3% of patients P = 0.09	
			Safety		
			Patient withdrawal due to severe adverse effect	Candesartan group: 15% Placebo group: 17% P = 0.07	

	study drug or HCT - serious concomitant diseases affecting survival - alcoholism and drug abuse - Number of exclusion criteria related to the aim of studying cognitive function and dementia (dementia; treatment with antidementia drugs; conditions which preclude MMSE; vitamin B12 deficiency treated , 12 months; hypothyroidism treated, 12 months; neurosyphilis or AIDS; severe brain disorder which may interfere with cognitive function; certain mental disorders (e.g. severe depression within 12 months,				Fully sponsored by Astra Zeneca

	history of recurrent depression or psychotic disorder); and psycho-pharmacological treatment started within 6 months.)				

Table 262

4.3.2.4.2 Summary and conclusions

Angiotensin receptor blockers versus placebo in elderly hypertension patients			
Bibliography: Lithell 2003(91)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular events	4964 (1 study) 3.7 years	Risk Reduction = 10.9% (95% CI: -6.0 to 25.1) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Non-fatal stroke	4964 (1 study) 3.7 years	**Risk Reduction = 27.8% (95% CI: 1.3 to 47.2)** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	4964 (1 study) 3.7 years	Risk Reduction= 23.6% (95% CI: -0.7 to 42.1) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
New-onset diabetes mellitus	4964 (1 study) 3.7 years	Candesartan : 4.3% of patients Placebo: 5.3% of patients P = 0.09 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: only one study Directness:ok Imprecision: -1
Withdrawal due to severe adverse effects	4964 (1 study) 3.7 years	Candesartan group: 15% Placebo group: 17% P = 0.07 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; Unclear blinding, no ITT, industry-sponsored Consistency: Directness: Imprecision: -1

Table 263

In this double blind RCT, 4964 elderly patients (70-89 years old) with mild to moderate hypertension (SBP <180 mmHg) were treated with either candesartan or placebo and followed over 3.7 years.

The paucity of the evidence limits our confidence in the results.

In elderly patients with hypertension, treatment with an angiotensin receptor blocker significantly decreases non-fatal stroke, compared to placebo.
GRADE: LOW quality of evidence

In elderly patients with hypertension, treatment with an angiotensin receptor blocker does not result in a statistically significant difference in cardiovascular events, total stroke, new-onset diabetes mellitus, or withdrawal due to adverse effects, compared to placebo.
GRADE: LOW quality of evidence

4.3.2.5 ACE-inhibitors versus diuretics

4.3.2.5.1 Clinical evidence profile

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes
ANBP2, 2003(140) Adults, ages 65 to 84, with absence of recent CV events DIU: Diuretic: HCTZ recommended; dose not specified ACE: ACE Inhibitor: Enalapril recommended; dose not specified N: 6,083 Median 4.1 years Fair Open-label RCT	**Death from any cause** HR (95% CI): 0.90 (0.75, 1.09) p = 0.27	**Non-fatal MI** 5.8 per 1000 py DIUR vs 4.1 per 1000 py ACE HR (95% CI): 0.68 (0.47, 0.99) p = 0.05 **MI** 6.7 per 1000 py DIUR vs 4.7 per 1000 py ACE HR (95% CI):0.68 (0.47, 0.98) p = 0.04 **Coronary event** HR (95% CI): 0.86 (0.70, 1.06) p = 0.16 **Fatal MI events** HR (95% CI): 0.79 (0.31, 1.99) p = 0.61 **Fatal coronary events** HR (95% CI): 0.74 (0.49, 1.11) p = 0.14	**Non-fatal Stroke** HR (95% CI): 0.93 (0.70, 1.26) p = 0.65 **Stroke** HR (95% CI): 1.02 (0.78, 1.33) p = 0.91 **Cerebrovascular event** HR (95% CI): 0.90 (0.73, 1.12) p = 0.35 **Fatal stroke events** 1.2 per 1000 py DIUR vs 2.3 per 1000 py ACE HR (95% CI): 1.91 (1.04, 3.50) p = 0.04	**Non-fatal HF** HR (95% CI): 0.85 (0.62, 1.17) p = 0.32 **HF** HR (95% CI): 0.85 (0.62, 1.18) p = 0.33 **Fatal HF events** HR (95% CI): 0.24 (0.03, 1.94) p = 0.18	**Non-fatal CV event** 32.8 per 1000 py DIUR vs 28.9 per 1000 py ACE HR (95% CI):0.86 (0.74, 0.99) p = 0.03 **Non-fatal other CV** HR (95% CI):0.84 (0.66, 1.07) p = 0.17 **All CV events or death from any cause (PO)** 59.8 per 1000 py DIUR vs 56.1 per 1000 py ACE HR (95% CI):0.89 (0.79, 1.00) p = 0.05 **First CV event or death from any cause** 45.7 per 1000 py DIUR vs 41.9 per 1000 py ACE HR (95% CI):0.89 (0.79, 1.01) p = 0.06 **First CV event** 37.1 per 1000 py DIUR vs 33.7 per 1000 py ACE

					HR (95% CI):0.88 (0.77, 1.01) p = 0.07 **Other CV event** HR (95% CI):0.90 (0.71, 1.14) p = 0.36 **Fatal CV events** HR (95% CI):0.99 (0.72, 1.35) p = 0.94 **Other fatal CV events** HR (95% CI):0.95 (0.46, 1.96) p = 0.89

Table 264

4.3.2.5.2 Summary and conclusions

Diuretic (hydrochlorothiazide) versus ACE-inhibitor in elderly hypertensive patients.			
Bibliography: ANBP2(140)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	6,083 (1 study) 4.1 years	0.90 (0.75, 1.09) NS	⊕⊕⊖⊖ **LOW** Study quality:-1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
All cardiovascular events or all-cause mortality (composite)	6,083 (1 study) 4.1 years	0.89 (0.79, 1.00) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1; open-label Consistency: only one study Directness: ok Imprecision: ok
Myocardial infarction	6,083 (1 study) 4.1 years	**0.68 (0.47, 0.98)** **SS**	⊕⊕⊖⊖ **LOW** Study quality:-1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Stroke	6,083 (1 study) 4.1 years	1.02 (0.78, 1.33) NS	⊕⊕⊖⊖ **LOW** Study quality:-1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Heart failure	6,083 (1 study) 4.1 years	0.85 (0.62, 1.18) NS	⊕⊕⊖⊖ **LOW** Study quality:-1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Table 265

This open-label RCT in 6083 elderly (65 to 84 y) hypertension patients compared treatment with a hydrochlorothiazide diuretic to treatment with an ACE-inhibitor. The median follow-up was 4.1 years.

In elderly hypertension patients, treatment with a hydrochlorothiazide diuretic, compared to treatment with an ACE-inhibitor, significantly decreases myocardial infarction rate.
GRADE: LOW quality of evidence

In elderly hypertension patients, treatment with a hydrochlorothiazide diuretic, compared to treatment with an ACE-inhibitor, does not result in a statistically significant difference in a composite of all cardiovascular events and all-cause mortality.

GRADE: MODERATE quality of evidence

In elderly hypertension patients, treatment with a hydrochlorothiazide diuretic, compared to treatment with an ACE-inhibitor, does not result in a statistically significant difference in mortality, stroke, or heart failure rates.
GRADE: LOW quality of evidence

4.3.2.6 Angiotensin receptor blockers versus ACE-inhibitors

4.3.2.6.1 Summary and conclusions

The ONTARGET 2008 study(158), see also 4.3.4.3,was a double blind RCT that compared an ACE-inhibitor to an angiotensin receptor blocker, and to a combination of both drugs, in 25620 patients with vascular disease or high-risk diabetes without heart failure, with a follow-up of 56 months.

The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

There was no statistically significant difference of risk of developing this primary outcome with an ACE-inhibitor, compared to an angiotensin receptor blocker.

There was a statistically significant increase of total number of discontinuations, and of cough, with an ACE-inhibitor, compared to an angiotensin receptor blocker.

There was a statistically significant decrease of hypotensive symptoms with an ACE-inhibitor, compared to an angiotensin receptor blocker.

In the subgroup analyses by systolic blood pressure, the participants with hypertension did not show a statistically significant difference of risk for the primary outcome.

4.3.2.7 ACE-inhibitors + Calcium channel blockers versus ACE-inhibitors + diuretics

4.3.2.7.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Jamerson 2008(156) (ACCOMPLISH) Design: RCT (DB) (PG) Duration of follow-up: 36 months	n= 11506 Mean age: 68.4 Previous MI 23.6: % Previous stroke: 13.0% Previous hospitalization for unstable angina:11.5 % Diabetes:60.2 % Estimated glomerular filtration rate >60: 18.1% % Smoking: 11.3% Age >65y: 66.4 % <u>Inclusion</u> - At least 55 years of age. - Previously untreated	ACEi(benazepril) + CCB amlodipine (n = 5744) Vs ACEi (benazepril) + Diuretic (Hydrochloro-thiazide) (n = 5762)	Efficacy		RANDO: unclear, no details ALLOCATION CONC: Adequate, assignments made centrally by telephone BLINDING : Participants: yes Investigators: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 1% Drop-out and Exclusions: 1.2 % • Described: partially • Balanced across groups: unclear ITT: Yes SELECTIVE REPORTING: no
			Composite of cv events and death from cv causes (PO)	CCB: 552/5744 DIU: 679/5762 **HR: 0.80 (0.72-0.90) SS** p: <0.0001	
			Death from CV causes	CCB: 107/5744 Diu: 134/5762 HR: 0.80 (0.62 – 1.03) NS p: 0.08	
			Fatal and non-fatal MI	CCB: 125/5744 DIU: 159/5762 **HR: 0.78 (0.62 – 0.99) SS** p: 0.04	
			Fatal and non-fatal stroke	CCB: 112 / 5744 DIU: 133/5762 HR: 0.84 (0.65 – 1.08) p: 0.17	
			Hospitalization for unstable angina	CCB: 44/5744 DIU: 59/5762 HR: 0.75 (0.50 – 1.10) p: 0.14	
			Coronary revascularization	CCB: 334/ 5744 DIU: 386/5762	

	or treated hypertension. - For patients >= 60 years, evidence of at least one CV disease or target organ damage, or for patients 55-59 years evidence of at least two CV diseases or target organ damage from two different organ systems as defined in the protocol. <u>Exclusion</u> Allergy to any of the drugs administered in this trial. Current angina pectoris (ie, no anginal event requiring NTG within 1 month prior to Visit 1). Secondary hypertension. Refractory hypertension defined as SBP >= 180 mmHg and/or DBP >= 110 mmHg unresponsive to triple-		procedure	HR: 0.86 (0.74 – 1.00) p: 0.04	Sponsor: Novartis The trial was terminated early after a mean follow-up of 36 months due to this difference favoring the benazepril–amlodipine group in the primary outcome. JNC-8 notes the following remarks: - criteria for event classification were not explicitly described other than being "standardized", - use of concomitant medications was reported at baseline but not at the end of follow-up, and adherence information was reported at six months and one year but not at the end of follow-up NICE reports only serious limitations on precision, seeing as some CI include both no effect and appreciable benefit/harm
			Resuscitation after cardiac arrest	CCB: 14/5744 DIU: 8/5762 HR: 1.75 (0.73 – 4.17) p: 0.20	
			SUBGROUPS		
			PO, ≥65 years	CCB: 386/3813 DIU: 474/3827 **HR: 0.81 (0.71 – 0.92) SS** p: 0.002	
			PO, ≥70 years	CCB: 260/2363 DIU: 323/2340 **HR: 0.79 (0.67 – 0.93) SS** p: 0.004	

	drug regimens of sympatholytics, diuretics and vasodilators. History of symptomatic heart failure (NYHA classes II-IV) or ejection fraction < 40%. Myocardial infarction, coronary revascularization (CABG or PCI), unstable angina within one month of Visit 1. Stroke or transient ischemic event (TIA) within 3 months of Visit 1. Significant obstructive valvular cardiovascular disease or any valvular disease expected to lead to surgery during the course of the study. Evidence of hepatic disease (AST or ALT values >= 2 X upper limit of normal). Impaired renal function				

	(serum creatinine >= 2.5 mg/dL (221 µmol/L)). Baseline serum potassium of > 5.2 meq/L not on potassium supplements. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the last 5 years. History of clinically significant auto immune disorders such as Systemic Lupus Erythematosus. Significant non-cardiovascular illness or condition likely to result in death prior to trial completion, e.g., major organ transplant (life expectancy <5 years). Significant cardiovascular disease such as an aortic aneurysm ≥ 6 cm, likely				

	requiring surgical intervention during the course of the study. Other protocol-defined exclusion criteria applied to the study.				

Table 266

4.3.2.7.2 Summary and conclusions

ACE-inhibitor + calcium channel blocker versus ACE-inhibitor + diuretic for hypertension in the elderly ≥65			
Bibliography: Jamerson 2008 (ACCOMPLISH)(156)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular events and cardiovascular mortality (composite)	7640 (1 study) 36 months	**HR: 0.81 (0.71 – 0.92)** **SS**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; subgroup analysis, unclear randomization, unblinded investigators Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 267

ACE-inhibitor + calcium channel blocker versus ACE-inhibitor + diuretic for hypertension in the elderly ≥70			
Bibliography: Jamerson 2008 (ACCOMPLISH)(156)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular events and cardiovascular mortality (composite)	4703 (1 study) 36 months	**HR: 0.79 (0.67 – 0.93)** **SS**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; subgroup analysis, unclear randomization, unblinded investigators Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 268

In this RCT, 11506 hypertensive patients older than 55, with a relatively high cardiovascular risk, were randomized to treatment with an ACE-inhibitor plus a calcium channel blocker or an ACE-inhibitor plus a diuretic (hydrochlorothiazide) and followed over 36 months. There were two subgroup analyses in elderly people, one in all participants over 65 years of age, and one in all participants over 70 years of age. As it concerns a subgroup analysis of a single study, our confidence in these results is limited.

In elderly people (>60y) with hypertension, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, resulted in a statistically significant reduction of a composite of cardiovascular events and cardiovascular mortality.
GRADE: VERY LOW quality of evidence

4.3.2.8 Angiotensin receptor blockers + calcium channel blockers versus angiotensin receptor blockers + diuretics

4.3.2.8.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ogihara 2014(159) Design: RCT (SB) (PG) Duration of follow-up: 3 to 4.5 years	n= 5141 Mean age: ±73.6 Ischaemic heart disease: 10.9% Previous stroke: 14.6 % Diabetes: ±26.5% CKD: % Smoking: ±25.3% Age ≥75y: 43.2 % <u>Inclusion</u> - at least 65 and less than 85 years - history of cardiovascular disease or risk	Olmesartan (4-40 mg/day) + CCB: Amlodipine (2.5 or 5 mg/day) OR Azelnidipine (8 or 16 mg/day) Vs Olmesartan (4-40mg/day) + Low-dose diuretic: Trichlormethiazide ≤1mg, hydrochlorothiazide ≤12.5mg,	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 2.3 % Drop-out and Exclusions: 3.5 % • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no
			Primary endpoint		
			Composite of fatal and non-fatal cardiovascular events (including sudden death, new or reoccurring cerebral infarction, cerebral haemorrhage, MI, TIA, hospitalization, renal events)	Olmesartan + CCB: 116/2568 Olmesartan + diuretic: 135/2573 Hazard ratio: 0.83 (95% CI: 0.65 to 1.07) P = 0.16 NS	
			Secondary endpoints		
			All-cause mortality	Olmesartan + CCB: 64/2568 Olmesartan + diuretic: 76/2573 Hazard ration: 0.83 (95% CI: 0.59 to 1.15) P = 0.27 NS	
			Composite of hard endpoints	Olmesartan + CCB: 72 / 2568 Olmesartan+diuretic: 88/2573	

	- SBP at least 140 mmHg and/or DBP at least 90 mmHG during treatment with one or more antihypertensive drugs at enrolment, or SBP at least 160mmHG and/or DBP at least 100mmHg without antihypertensive treatment <u>Exclusion</u> - Secondary hypertension or malignant hypertension - History of cerebrovascular accident (including TIA) or myocardial infarction within 6 months before registration - PCI or CABG within 6 months before registration or	indapamide ≤1mg		HR: 0.80 (95% CI: 0.58 to 1.09) P=0.16 NS	Other important methodological remarks: If the target BP was not achieved with maximal doses of the allocated drug, another class of antihypertensive drug was added Sponsor: Grant from the Japan Heart Foundation
			Cardiovascular death	Olmesartan+CCB : 13/2568 Olmesartan + diuretic: 18/2573 HR: 0.70 (95% CI: 0.34 to 1.43) P= 0.33 NS	
			Non-fatal stroke	Olmesartan+CCB: 60/2568 Olmesartan+diuretic:62/2573 HR: 0.95 (95% CI: 0.66 to 1.35) P=0.78 NS	
			Non-fatal MI	Olmesartan+CCB: 9/2568 Olmesartan+diuretic: 16/2573 HR: 0.55 (95 CI: 0.24 to 1.24) p = 0.14 NS	
			Atrial Fibrillation	Olmesartan+ccb: 43/2568 Olmesartan+diuretic: 32/2573 HR: 1.33 (95% CI: 0.84 to 2.10) P = 0.21 NS	
			Subgroup analysis for primary endpoint		
			Age - <75 years old - ≥75 years old	 HR: 1.03 (95% CI: 0.71 to 1.49) **HR: 0.70 (95% CI: 0.50 to 0.99)**	
			Safety		
			Withdrawal because of	Olmesartan + CCB: 77/2568	

	scheduled - History of hospitalization for angina pectoris or heart failure within 6 months before registration - Severe heart failure (NYHA] functional class III or more severe) - Complications of atrial fibrillation, atrial flutter or severe arrhythmia - Severe hepatic or renal dysfunction (including current treatment of dialysis or renal dysfunction with serum creatinine ≥ 2.0mg/dL) - Not appropriate for change to the study drugs from current therapy for concurrent disease including coronary diseases (i.e. calcium		SAE	Olmesartan + diuretic: 253/2573 **P<0.001**	
			Malignancy	Olmesartan + CCB: 2.5% Olmesartan + diuretics: 3.1% P=0.17	
			Hyperuricemia	Olmesartan+CCB: 6.5% Olmesartan+diuretics: 2.6% **P<0.001**	

	channel blockers, diuretics, etc) - History of serious side effect from study drugs (AT1 subtype angiotensin II receptor antagonist, calcium channel blocker, diuretic) - Life threatening condition (malignant tumor, etc) - Not suited to be study subject judged by a study physician				

Table 269

Study details	n/Population	Comparison	Outcomes		Methodological
Saruta 2015(160) Design based on Ogihara 2014 (RCT (SB) (PG)) Duration of follow-up: 3 to 4.5 years	n= 5141 Mean age: ±73.6 Ischaemic heart disease: 10.9% Previous stroke: 14.6 % Diabetes: ±26.5% CKD: % Smoking: ±25.3% Age ≥75y: 43.2 % <u>Inclusion</u> - at least 65 and less than 85 years - history of cardiovascular disease or risk - SBP at least 140 mmHg and/or DBP at least 90 mmHG during treatment with one or more antihypertensive drugs at enrolment, or	Olmesartan (4-40 mg/day) + CCB: Amlodipine (2.5 or 5 mg/day) OR Azelnidipine (8 or 16 mg/day) Vs Olmesartan (4-40mg/day) + Low-dose diuretic: Trichlormethiazide ≤1mg, hydrochlorothiazide ≤12.5mg, indapamide ≤1mg	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 2.3 % Drop-out and Exclusions: 3.5 % • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no Other important methodological remarks: If the target BP was not achieved with maximal doses of the allocated drug, another class of antihypertensive drug was added
			See Ogihara 2014 for results See Ogihara 2015 for subgroup analyses		
			Safety		
			Arrhythmia	Olmesartan+CCB: 16/2568 Olmesartan+diuretic: 18/2573 P= 0.86	
			Death of unknown causes (except sudden death)	Olmesartan+CCB: 9/2568 Olmesartan+diuretic: 12/2573 P= 0.66	
			Renal dysfunction	Olmesartan+CCB: 11/2568 Olmesartan+diuretic: 7/2573 P= 0.35	
			Total	Olmesartan+CCB: 211/2568 Olmesartan+diuretic: 253/2573 **P= 0.029**	

	SBP at least 160mmHG and/or DBP at least 100mmHg without antihypertensive treatment <u>Exclusion</u> - Secondary hypertension or malignant hypertension - History of cerebrovascular accident (including TIA) or myocardial infarction within 6 months before registration - PCI or CABG within 6 months before registration or scheduled - History of hospitalization for angina pectoris or heart failure within 6 months before registration				Sponsor: Grant from the Japan Heart Foundation

	- Severe heart failure				

Table 270

Study details	n/Population	Comparison	Outcomes		Methodological
Ogihara 2015(161) Design: Prespecified subgroup analysis (data from RCT (SB) (PG)) Duration of follow-up: 3 to 4.5 years	n= 5141 Mean age: ±73.6 Ischaemic heart disease: 10.9% Previous stroke: 14.6 % Diabetes: ±26.5% CKD: % Smoking: ±25.3% Age ≥75y: 43.2 % <u>Inclusion</u> - at least 65 and less than 85 years - history of cardiovascular disease or risk - SBP at least 140 mmHg and/or DBP at least 90 mmHG during treatment with one or more antihypertensive	Olmesartan (4-40 mg/day) + CCB: Amlodipine (2.5 or 5 mg/day) OR Azelnidipine (8 or 16 mg/day) Vs Olmesartan (4-40mg/day) + Low-dose diuretic: Trichlormethiazide ≤1mg, hydrochlorothiazide ≤12.5mg, indapamide ≤1mg	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 2.3 % Drop-out and Exclusions: 3.5 % • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no Other important methodological remarks: If the target BP was not achieved with maximal doses of the allocated drug, another class of antihypertensive drug was added
			Primary composite endpoint (sudden death, stroke, cardiac events, renal events)		
			< 75 years	**≥75 years**	
			OS+CCB: 58/1459 OS+diuretic: 55/1459 HR: 1.04 (95% CI: 0.72 to 1.50)	OS+CCB: 58/1109 OS+diuretic: 80/1114 **HR: 0.71 (95% CI 0.51 to 0.99)**	
			Sudden death		
			HR:0.33 95% CI: 0.03 to 3.12)	HR: 0.62 (95% CI: 0.20 to 1.89)	
			Stroke (fatal and non-fatal)		
			HR: 1.48 (95% CI: 0.88 to 2.48)	HR: 0.63 (95% CI: 0.39 to 1.02)	
			Cardiac events (fatal and not)		
			HR: 0.71 (95% CI: 0.37 to 1.35)	HR: 0.83 (95% CI: 0.46 to 1.48)	
			Renal events		
			HR: 1.12 (95% CI: 0.41 to 3.08)	HR: 0.85 (95% CI: 0.28 to 2.52)	
			Secondary endpoints		
			All-cause mortality		
			HR: 0.95 (95% CI: 0.57 to 1.67)	HR: 0.74 (95% CI: 0.48 to 1.14)	
			Composite of hard endpoints		
			OS+CCB: 36/1459 OS+diuretics: 33/1459 HR: 1.07 (95% CI: 0.67 to 1.72)	OS+CCB: 36/1109 OS+diuretics: 49 / 1114 **HR: 0.64 (95% CI: 0.42 to 0.98) SS**	

	drugs at enrolment, or SBP at least 160mmHG and/or DBP at least 100mmHg without antihypertensive treatment <u>Exclusion</u> - Secondary hypertension or malignant hypertension - History of cerebrovascular accident (including TIA) or myocardial infarction within 6 months before registration - PCI or CABG within 6 months before registration or scheduled - History of hospitalization for angina pectoris or heart failure within 6 months before		Cardiovascular death		Sponsor: Grant from the Japan Heart Foundation
			HR:0.73 (95% CI: 0.16 to 3.27)	HR: 0.71 (95% CI: 0.31 to 1.59)	
			Safety		
			(see Saruta 2015)		

	registration - Severe heart failure				

Table 271

4.3.2.8.2 Summary and conclusions

Angiotensin receptor blocker plus calcium channel blocker versus angiotensin receptor blocker plus diuretic in elderly patients			
Bibliography: Ogihara 2014(159), Saruta 2015(160)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5141 (1 study) 3 to 4.5 years	HR: 0.83 (95% CI: 0.59 to 1.15) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular events	5141 (1 study) 3 to 4.5 years	HR: 0.83 (95% CI: 0.65 to 1.07) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular mortality	5141 (1 study) 3 to 4.5 years	HR: 0.70 (95% CI: 0.34 to 1.43) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm or and appreciable benefit
Non-fatal stroke	5141 (1 study) 3 to 4.5 years	HR: 0.95 (95% CI: 0.66 to 1.35) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm or and appreciable benefit
Non-fatal myocardial infarction	5141 (1 study) 3 to 4.5 years	HR: 0.55 (95 CI: 0.24 to 1.24) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -2; 95%CI crosses both no effect and appreciable harm or and appreciable benefit
Withdrawal because of severe adverse effects	5141 (1 study) 3 to 4.5 years)	**ARB + CCB: 77/2568** **ARB + diuretic: 131/2573** **P<0.001** **Favours ARB+CCB** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Malignancy	5141 (1 study) 3 to 4.5 years)	ARB + CCB: 2.5% ARB + diuretics: 3.1% P=0.17 NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Hyperuricemia	5141 (1 study) 3 to 4.5 years)	**ARB+CCB: 2.6%** **ARB+diuretics: 6.5%** **P<0.001**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok

		Favours ARB+CCB **SS**	Imprecision: -1; no CI
Arrhythmia	5141 (1 study) 3 to 4.5 years	ARB+CCB: 16/2568 ARB+diuretic: 18/2573 P= 0.86 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Death of unknown causes (except sudden death)	5141 (1 study) 3 to 4.5 years	ARB+CCB: 9/2568 ARB+diuretic: 12/2573 P= 0.66 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Renal dysfunction	5141 (1 study) 3 to 4.5 years	ARB+CCB: 11/2568 ARB+diuretic: 7/2573 P= 0.35 NS	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Total serious adverse events	5141 (1 study) 3 to 4.5 years	**ARB+CCB: 211/2568** **ARB+diuretic: 253/2573** **P= 0.029** **Favours ARB+CCB** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI

Table 272

This open-label RCT (Ogihara 2014(159)) in 5141 Japanese elderly (65-85y) hypertension patients with high cardiovascular risk, compared treatment with an angiotensin receptor blocker plus a calcium channel blocker with treatment with an angiotensin receptor blocker plus a diuretic. The follow-up in this study was 3 to 4.5 years. A second publication (Saruta 2015(160)) evaluated safety outcomes in these patients.

In elderly hypertension patients, treatment with an angiotensin receptor blocker plus a calcium channel blocker, compared with treatment with an angiotensin receptor blocker plus a diuretic, did not result in a statistically significant difference in **mortality** and **cardiovascular events**.
GRADE: LOW quality of evidence

In elderly hypertension patients, treatment with an angiotensin receptor blocker plus a calcium channel blocker, compared with treatment with an angiotensin receptor blocker plus a diuretic, did not result in a statistically significant difference in **cardiovascular mortality**, **non-fatal stroke**, **or non-fatal myocardial infarction**.
GRADE: VERY LOW quality of evidence

In elderly hypertension patients, treated with an angiotensin receptor blocker plus a calcium channel blocker, compared with those treated with an angiotensin receptor blocker plus a diuretic, there were significantly fewer **serious adverse events**, **withdrawals because of severe adverse effects** and **hyperuricemia** cases.
GRADE: LOW quality of evidence

In elderly hypertension patients, treated with an angiotensin receptor blocker plus a calcium channel blocker, compared with those treated with an angiotensin receptor blocker plus a diuretic, there was

no statistically significant difference in rates of **malignancy**, **arrhythmia**, **death of unknown causes**, or **renal dysfunction**.
GRADE: LOW quality of evidence

A subgroup analysis of this RCT (Ogihara 2015(161)) evaluated outcomes in patients aged <75 and ≥75. In this subgroup analysis, there was a statistically significant reduction of **cardiovascular events** in the ≥75 years group but not in the <75 years group, when treated with an ARB+ CCB compared to an ARB+ a diuretic.
GRADE: VERY LOW quality of evidence

4.3.2.9 Higher dose angiotensin receptor blocker versus angiotensin receptor blocker + calcium channel blocker

4.3.2.9.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ogawa 2012(162) Design: RCT (SB, 2-armed, PG) Duration of follow-up: 3 years	n= 1217 Mean age: ±73.6 Previous CV event:unknown % Previous stroke: unknown % Heart failure: unknown % Diabetes: 37 % CKD: unknown% Smoking: ±57.5% Age >80y: unknown <u>Inclusion</u> - taking olmesartan 20mg/d alone and target blood pressure	Olmesartan 20 mg / d + olmesartan 20 mg /d Vs Olmesartan 20 mg / d + CCB (amlodipine 2.5 or 5 mg/d OR azelnidipine 8 or 16 mg/d)	Efficacy		RANDO: Adequate, with minimization method ALLOCATION CONC: unclear BLINDING : Participants: no (SB) Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: 7.4% Drop-outs and Exclusions: 4.8% • Described: yes • Balanced across groups: yes ITT: no, patients who did not take any medication were excluded from analysis
			Composite endpoint of fatal and non-fatal CV events (PO) (cerebrovascular disease, coronary artery disease, heart failure, other arteriosclerotic disease, diabetic complications, deterioration of renal function)	High dose ARB: 58/578 ARB+CCB: 48/586 HR: 1.31 (95% CI: 0.89 to 1.96) p = 0.17 NS	
			Cerebrovascular disease	High dose ARB: 24 / 578 ARB+CCB: 15/586 HR: 1.75 (95% CI: 0.92 to 3.35) P = 0.08 NS	
			Coronary artery disease	High dose ARB: 6/578 ARB+CCB: 7/578 HR: 0.92 (95% CI: 0.31 to 2.75) P = 0.88	

	control not achieved - Aged 65 to 84 years - Sitting SBP ≥140 mmHg or sitting DBP ≥80 mm Hg - Having type II diabetes or a CV disease (cerebrovascular disease, cardiac disease, vascular disease or renal dysfunction) <u>Exclusion:</u> - Secondary hypertension or malignant hypertension - Heart Failure (NYHA III or IV) - Required treatment for malignant tumor - Serious liver or renal dysfunction - Changes to test drugs not appropriate - History of serious adverse drug reactions			NS	
			Heart failure	High dose ARB: 12/578 ARB+CCB: 8/586 HR: 1.56 (95% CI: 0.64 to 3.83) P = 0.33 NS	SELECTIVE REPORTING: yes, no reporting for all cause mortality Other important methodological remarks: Study done with a two-step process. Patients were first switched to olmesartan 20 mg/day If further additional antihypertensive treatment was allowed to achieve target blood pressure, other antihypertensive drugs (diuretics and beta-blockers for ex.) could be added but not ACEI, other ARB or other CCB. Sponsor: Japan heart foundation. First and second author declare some conflicts of interest
			Diabetic complications	High dose ARB: 2/578 ARB+CCB: 4/586 HR: 0.54 (95% CI: 0.10 to 2.94) P = 0.47 NS	
			Deterioration of renal function	High dose ARB: 2/578 ARB+CCB: 1/586 HR: 2.39 (95% CI: 0.21 to 26.71) P = 0.47 NS	
			Non-cardiovascular death	High dose ARB: 9/578 ARB+CCB: 11/586 HR: 0.85 (95% CI: 0.35 to 2.06) P = 0.72 NS	
			Subgroups		
			Primary endpoint		
			Patients with cardiovascular disease	High dose ARB: 51 / 405 ARB+CCB: 34 / 407 HR: 1.63 (95% CI: 1.06 to 2.52) P = 0.03 **S**	
			Patients without	High dose ARB: 7 / 173	

	to ARB		cardiovascular disease (/patients with diabetes only)	ARB+CCB: 14/179 HR: 0.52 (95% CI: 0.21 to 1.28) P = 0.14 NS	
			Safety		
			Serious adverse events (other than primary outcome events)	High dose ARB: 47 / 578 ARB+CCB: 51 / 586 P = 0.75 NS	

Table 273

4.3.2.9.2 Summary and conclusions

Higher dose angiotensin receptor blocker versus angiotensin receptor blocker plus calcium channel blocker in elderly hypertension patients			
Bibliography: Ogawa 2012(162) (OSCAR)			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Cardiovascular events	1217 (1 studies) 3 years	1.31 (95% CI: 0.89 to 1.96) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cerebrovascular disease	1217 (1 studies) 3 years	1.75 (95% CI: 0.92 to 3.35) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Coronary artery disease	1217 (1 studies) 3 years	0.92 (95% CI: 0.31 to 2.75) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Heart failure	1217 (1 studies) 3 years	1.56 (95% CI: 0.64 to 3.83) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Deterioration of renal function	1217 (1 studies) 3 years	2.39 (95% CI: 0.21 to 26.71) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Non-cardiovascular death	1217 (1 studies) 3 years	0.85 (95% CI: 0.35 to 2.06) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study

			Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Serious adverse effects	1217 (1 studies) 3 years	High dose ARB: 47 / 578 ARB+CCB: 51 / 586 P = 0.75 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; open-label, unclear allocation concealment, no ITT, selective reporting Consistency: only one study Directness: Japanese Imprecision: -1; no CI

Table 274

In this open-label RCT, 1217 elderly (65-84 years old) Japanese hypertension patients with high cardiovascular risk, whose blood pressure was not controlled when taking an angiotensin receptor blocker alone (olmesartan 20 mg/d), were randomized to a higher dose of the ARB (40 mg/d) or the ARB (20 mg/d) plus a calcium channel blocker. The follow-up in this study was 3 years.

As this is the only study for this comparison, and it has some serious methodological flaws that could lead to bias (no blinding, no intention-to-treat analysis, unclear allocation concealment), our confidence in its results are severely limited.

In elderly hypertension patients, treatment with higher dose of an angiotensin receptor blocker, compared with a standard-dose angiotensin receptor blocker plus a calcium channel blocker, does not result in a statistically significant difference in **cardiovascular events**, **cerebrovascular disease**, **coronary artery disease**, **heart failure**, **deterioration of renal function**, **non-cardiovascular death**, or **serious adverse effects**.
GRADE: VERY LOW quality of evidence

4.3.3 Elderly patients >80 years

4.3.3.1 Antihypertensive treatment versus placebo

4.3.3.1.1 Clinical evidence profile

Meta-analysis: NICE 2011

Inclusion criteria:SRs/MAs and RCTs were included that compared the following TDs (hydrochlorothiazide plus triamterene or amiloride; chlorthalidone; indapamide: atenolol or metoprolol or pindolol, nitrendipine) with either placebo or other classes of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease. Data from patients >80 years old was extracted.

Search strategy: All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Assessment of quality of included trials: yes: GRADE
ITT analysis: unclear

Table 275

Ref	Comparison	N/n	Outcomes	Result
NICE 2011 Design: SR/MA Search date:	Antihypertensive treatment Versus placebo	N= 8 / n= 6701 (SHEP-Pilot 1989; SHEP 1991; EWPHE 1985; Coope 1986; STOP	**All-cause mortality (follow-up 0-11.6 years)**	RR: 1.06 (95% CI: 0.89 to 1.25)

Nov 2010		1991; Syst-Eur 1997;HYVET-pilot 2003; HYVET 2008)		
		N= 6 n= not given	**Coronary events (follow-up 0-11.6 years)**	RR: 0.83 (95% CI: 0.56 to 1.22)
		N= 7 n= not given	**Stroke (follow-up 0-11.6 years)**	**RR: 0.65 (95% CI 0.52 to 0.83) SS**
		N = 6 n= not given	**CV events (follow-up 0-11.6 years)**	**RR: 0.73 (95% CI: 0.62 to 0.86) SS**
		N = 6 N= not given	**Heart failure (follow-up 0-11.6 years)**	**RR: 0.50 (95% CI: 0.33 to 0.76) SS**
		N=7 n= not given	**coronary death (follow-up 0-11.6 years)**	RR: 0.99 (95% CI: 0.69, 1.41) NS
		N = 8 n = 6701	**Stroke death (follow-up 0-11.6 years)**	RR: 0.80 (95% CI: 0.80, 1.11) NS
		N = 8 n = 6701	**CV death (follow-up 0-11.6 years)**	RR: 0.98 (95% CI: 0.83, 1.15) NS

Table 276

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Intervention	Comparison	Results	Methodology (quality assessment by NICE 2011 and JNC8 2014)
SHEP (group, 1991)	4736	Adults, ages ≥60 years, SBP 160-219 and DBP <90 mmHg	Mean: 4.5 years	For step 1 of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was	placebo	Statistically significant reduction with treatment of: Non-fatal plus fatal	JNC8 gives a good rating to 4 studies out of 6 evaluated (SHEP 1991, Syst-Eur 1997, Coope and warrender 1986, HYVET 2003) and a fair rating to the other 2 (EWPHE 1985, STOP

		Subgroup selected for MA: Adults >80 years of age (n=650)		25 mg/d. For step 2, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d		stroke: RR: 0.64 (0.50, 0.82) p = 0.0003 Fatal and non-fatal HF: RR: 0.51 (0.37, 0.71) p < 0.001	1991). NICE does not mention any serious limitations or inconsistence, safe for the outcome "CV death", where there is significant heterogeneity. NICE does not mention any problems with indirectness. NICE mentions serious imprecision for outcomes "mortality" and "stroke death" (95% confidence interval includes both 1) no effect and 2) the MID (appreciable benefit or appreciable harm); or only just crosses the MID) NICE mentions very serious imprecision for the outcomes "coronary death" and "CV death" (95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm)
SHEP pilot (Perry, 1989)	551	Adults, ages ≥60 years SBP 160-219 and DBP <90 mmHg	Mean: 34 months	Step 1: chlortalidone 25 to 50 mg/d Step 2: Another medication was added if BP was not under control (hydralazine, reserpine, meoprolol)	placebo	Significant differences between groups for SBP and DBP but not for stroke or death rates	
EWPHE (group, 1985)	840	Adults, ages ≥60 years, SBP 160-239 and DBP 90-119 mmHg	Mean: 4.6 years	Hydrochlorothiazide + triamterene Methyldopa added if BP was not under control with first medication	placebo	Significant reduction of cardiac mortality in treatment group Significant reduction of non-fatal cerebrovascular events in treatment group Significant reduction of deaths from myocardial infarction	
Coope and	884	Adults, age	Mean:	Atenolol &	placebo	Statistically	

Warrender, 1986		60 to 79, SBPs ≥ 170 or DBP ≥ 105 mmHg	4.4 years	Bendrofluazide		significant reduction for: Fatal stroke Rate of txt/rate of control (95% CI): 0.30 (0.11, 0.84) p < 0.025 All stroke Rate of txt/rate of control (95% CI): 0.58 (0.35, 0.96) p < 0.03	
STOP (group, 1991)	1627	Adults, ages 70 to 84 years, treated or untreated for hypertension, with SBPs of 180 to 230 and DBP ≥ 90 or DBPs of 105 to 120 irrespective of SBP during run-in	Mean 25 months	Atenolol 50 mg, hydrochlorothiazide 25 mg plus amiloride 2-5 mg, metoprolol 100 mg, or pindolol 5 mg.	placebo	Statistically significant reductions for: All stroke (first endpoint): RR (CI): 0.53 (0.33, 0.86) Fatal stroke (first endpoint): RR (CI): 0.24 (0.04, 0.91) Total primary endpoint [stroke, MI, other CV death] (first to	

						happen): RR (CI): 0.60 (0.43, 0.85)	
Syst-Eur, 1997	4695	Adults, ages ≥ 60 years, SBP 160-219 and DBP <95 mmHg	Median 24 months	Nitrendipine 10-40 mg daily, with the possible addition of enalapril 5-20 mg daily and hydrochlorothiazide 12.5-25.0 mg daily	placebo	Statistically significant reduction for: Fatal and non-fatal cardiac endpoints: Adj HR: 0.71 CI (0.54, 0.94) p < 0.05 Non-fatal stroke: 44% decrease in active (rate/1000 py) CI (-63, -14), p = 0.007 Fatal and non-fatal stroke combined: Adj HR: 0.59 (0.38, 0.79) p < 0.01	
HYVET-pilot (Bulpitt, 2003)	1283	Adults ≥80 years, SBP of 160-219/90-109 mmHg	Mean 13 months	A diuretic-based regimen (usually bendroflumethiazide; n = 426), an angiotensin-converting enzyme inhibitor regimen (usually lisinopril; n = 431)	No treatment	Statistically significant reduction in stroke events relative hazard rate (RHR) was 0.47 [95% confidence interval (CI) 0.24 to 0.93] and the reduction in stroke mortality	

						RHR was 0.57 (95% CI 0.25 to 1.32) Total mortality: (RHR 1.23, 95% CI 0.75 to 2.01)	
HYVET (group,2008)	3845	Adults, ages ≥ 80 yrs, SBP ≥ 160 and DBP 90-109 at start of trial but relaxed later to <110 mmHg	Mean 2.1 years	Indapamide sr 1.5mg/day	No treatment	Statistically significant reduction of: Death from stroke: Unadj HR: 0.61 CI (0.38, 0.99) p = 0.046 Fatal or non-fatal HF: Unadj HR: 0.36 CI (0.22, 0.58) p < 0.001	

Table 277

Study details	n/Population	Comparison	Outcomes		Methodological
Beckett, 2008 (63) HYVET Design: RCT (DB, PG) Duration of follow-up: median 1.8 y	n= 3845 AT= 1933 PL=1912 Mean age: 83.6 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1% Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 % Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg).	Indapamide (sustained release, 1.5mg) Vs Placebo *At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.* Target: SBP <150 mmHg DBP <80 mmHg	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: 33.7 % • Described: yes • Balanced across groups: yes ITT: Yes Data from patients were analyzed for the groups to which the patients were assigned,
			Stroke (fatal and non-fatal) (PO)	AT: 51/1000 patient-years (12.4%) PL: 69/1000 patient-years (17.7%) HR: 0.70 (95%CI 0.49 to 1.01) NS p 0.06	
			Death from any cause (SO)	**AT: 196/1000 patient-years (47.2%)** **PL: 235/1000 patient-years (59.6%)** **HR:0.79 (95%CI 0.65 to 0.95)** **SS** **P: 0.02 in favour of AT**	
			Death from cardiovascular causes (SO)	AT: 99/1000 patient-years (23.9%) PL: 121/1000 patient-years (30.7%) HR: 0.77 (95%CI 0.60 to 1.01) NS P: 0.06	
			Death from cardiac causes (SO)	AT: 25/1000 patient-years (6.0%) PL: 33/1000 patient-years (8.4%) HR: 0.71 (95%CI 0.42 to 1.19) NS P: 0.19	
			Death from stroke (SO)	**AT: 27/1000 patient-years (6.5%)** **PL: 42/1000 patient-years (10.7%)** **HR: 0.61 (95%CI 0.38 to 0.99)** **SS** **P: 0.046 in favour of AT**	
			Safety		
			Serious adverse events	**AT: 358/1933**	

	(At the start of the trial in 2000, the mean diastolic blood pressure while seated had to be 90 to 109 mm Hg, but in 2003 a protocol amendment relaxed this criterion to be under 110 mm Hg, allowing for the inclusion of patients with isolated systolic hypertension <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive			**PL: 448/1912** **P: 0.001 in favour of AT**	regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available. SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that these centers failed to provide complete and accurate data.
			Serious adverse events possibly due to trial medication	AT: 2 PL: 3	

	medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.				Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.

Table 278

Study details	n/Population	Comparison	Outcomes subgroup analyses		Methodological
Beckett, 2014 (64) HYVET Design: Prespecified subgroup analysis (data from RCT (DB, PG)) Duration of follow-up: median 1.8 y	n= 3845 AT= 1933 PL=1912 Mean age: 83.5±3.2 y Age ≥80y: 100% CV disease: ±11.8% Myocardial infarction: ±3.1% Previous stroke:± 6.8 % Heart failure: ±2.9% Diabetes: ±6.8% Smoking:± 6.5 % Serum creatinine: ±88.9 µmol/L <u>Inclusion</u> Patients had to be 80 years of age or older (confirmed by national documentation) with persistent hypertension (defined as a sustained systolic blood pressure of 160	Indapamide (sustained release, 1.5mg) Vs Placebo *At each visit (or at the discretion of the investigator), if needed to reach the target blood pressure, perindopril (2 mg or 4 mg) or matching placebo could be added.* Target: SBP <150 mmHg DBP <80 mmHg	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: not reported BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol FOLLOW-UP: Lost-to follow-up: 0.4 % Drop-out and Exclusions: 33.7 % • Described: yes • Balanced across groups: yes ITT: Yes Data from patients were analyzed for the groups to which the patients were assigned,
			Total mortality	Hazard ratio	
			Age • 80-84.9y • ≥85y	 **0.76 (95%CI 0.60 to 0.97)** 0.88 (95%CI 0.64 to 1.20)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.82 (95%CI 0.60 to 1.11) 0.83 (95%CI 0.62 to 1.12) 0.69 (95%CI 0.45 to 1.04)	
			Previous CVD • History of CVD • No history of CVD	 0.76 (95%CI 0.48 to 1.21) **0.81 (95%CI 0.66 to 0.99)**	
			Cardiovascular mortality		
			Age • 80-84.9y • ≥85y	 0.75 (95%CI 0.55 to 1.05) 0.82 (95%CI 0.53 to 1.32)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 0.73 (95%CI 0.47 to 1.15) 0.93 (95%CI 0.62 to 1.45) 0.61 (95%CI 0.36 to 1.04)	
			Previous CVD • History of CVD • No history of CVD	 0.64 (95%CI 0.33 to 1.24) 0.81 (95%CI 0.61 to 1.09)	
			Stroke (PO)		
			Age • 80-84.9y • ≥85y	 0.70 (95%CI 0.46 to 1.06) 0.59 (95%CI 0.27 to 1.29)	

	mm Hg). <u>Exclusion</u> Exclusion criteria included a contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 µmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and		Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	0.82 (95%CI 0.46 to 1.48) 0.63 (95%CI 0.36 to 1.12) 0.54 (95%CI 0.24 to 1.22)	regardless of which study drugs (or which doses) the patients actually received and regardless of other protocol irregularities. Patients from closed centers were included in the intention-to-treat population and contributed person-years and events up to the date of closure of the center, after which no further information was available. SELECTIVE REPORTING: no Other important methodological remarks: Patients were instructed to stop all antihypertensive treatment and to take a single placebo tablet daily for at least 2 months (placebo-run-in) On the basis of the committee's recommendations, four centers were closed after the first year of the trial because of concerns that these centers failed to provide
			Previous CVD • History of CVD • No history of CVD	 0.76 (95%CI 0.33 to 1.78) 0.67 (95%CI 0.45 to 1.01)	
			Heart failure		
			Age • 80-84.9y • ≥85y	 **0.28 (95%CI 0.15 to 0.51)** 0.62 (95%CI 0.26 to 1.49)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 **0.21 (95%CI 0.09 to 0.51)** **0.46 (95%CI 0.22 to 0.97)** 0.59 (95%CI 0.19 to 1.79)	
			Previous CVD • History of CVD • No history of CVD	 0.45 (95%CI 0.14 to 1.43) **0.34 (95%CI 0.20 to 0.59)**	
			Cardiovascular events		
			Age • 80-84.9y • ≥85y	 **0.64 (95%CI 0.49 to 0.83)** 0.75 (95%CI 0.50 to 1.12)	
			Initial SBP • 160-169 mmHg • 170-179 mmHg • ≥180 mmHg	 **0.65 (95%CI 0.46 to 0.93)** 0.75 (95%CI 0.53 to 1.06) **0.58 (95%CI 0.36 to 0.94)**	

	a requirement of nursing care.		Previous CVD • History of CVD • No history of CVD	0.75 (95%CI 0.44 to 1.25) **0.66 (95%CI 0.52 to 0.84)**	complete and accurate data. Sponsor: HYVET was funded by grants from the British Heart Foundation and the Institut de Recherches Internationales Servier.

Table 279

4.3.3.1.2 Summary and conclusions

Antihypertensive treatment versus no treatment in hypertensives ≥80 years.			
Bibliography: Bejan-Angoulvant 2010(58), HYVET 2008(63)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	6701 (8 studies) 13m- 4.6y	RR: 1.06 (95% CI: 0.89 to 1.25) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:OK(heterogeneity NS when HYVET removed) Directness:OK Imprecision: -1 95% confidence interval includes both 1) no effect and 2) the MID (appreciable benefit or appreciable harm); or only just crosses the MID
*HYVET 2008		* **HR:0.79 (95%CI 0.65 to 0.95)** **SS**	
CV death	6701 (8 studies) 13m- 4.6y	RR: 0.98 (95% CI: 0.83 to 1.15) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: ok Consistency:-1 significant heterogeneity Directness: ok Imprecision: 2 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
*HYVET 2008		*HR: 0.77 (95%CI 0.60 to 1.01)	
CV events	NR (6 studies) 13m- 4.6y	**RR: 0.73 (95% CI: 0.62 to 0.86)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
Coronary events	NR (6 studies) 13m- 4.6y	RR: 0.83 (95% CI: 0.56 to 1.22) NS	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:OK Directness:OK Imprecision:-2 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
Stroke	NR (7 studies) 13m- 4.6y	**RR: 0.65 (95% CI 0.52 to 0.83)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
*HYVET 2008		*HR: 0.70 (95%CI 0.49 to 1.01)	
Heart failure	NR (6 studies) 13m- 4.6y	**RR: 0.50 (95% CI: 0.33 to 0.76)** **SS**	⊕⊕⊕⊕ **HIGH** Study quality:ok Consistency:ok Directness:ok Imprecision:ok
Serious adverse events	3845 (1 study) 1.8y	**Treatment: 358/1933** **Placebo: 448/1912** **p: 0.001 in favour of treatment** **SS**	⊕⊕⊖⊖ **LOW** Study quality:ok Consistency:na Directness:-2 Imprecision:ok
*HYVET 2008			

Table 280

In this meta-analysis of 8 RCT's, antihypertensive treatment versus placebo or no treatment was evaluated in hypertensive patients (3 trials with isolated systolic hypertension SBP ≥ 160mmHg, 2 trials with systolic and diastolic hypertension (SBP ≥ 160mmHg DBP ≥ 90mmHg), 3 trials with mixed systolic and/or diastolic hypertension). The data concerning patients ≥80 years of age was extracted from these RCT's. The mean follow-up ranged from 13 months to 4.6 years. Two of these RCT's (HYVET-pilot and HYVET) included only patients ≥80 years old.
Results from the HYVET trial are also shown in the table above.

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, did not result in a statistically significant difference in **mortality** rates compared to placebo or no treatment.
GRADE: MODERATE quality of evidence

Nor did not result in a statistically significant difference in **cardiovascular death** compared to placebo or no treatment.
GRADE: VERY LOW quality of evidence

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, decrease risk of **cardiovascular events**, of **stroke** and of **heart failure**.
GRADE: HIGH quality of evidence

Antihypertensive treatment in a people aged ≥80 years with either systolic hypertension, diastolic hypertension, or both, did not result in a statistically significant difference in **coronary events** compared to placebo or no treatment.
GRADE: LOW quality of evidence

We do not have a lot of information on adverse events

The HYVET trial included 3845 patients aged ≥80 years, with a sustained SBP ≥ 160mmHg. (Inclusion criteria for diastolic blood pressure were modified during recruitment admitting also patients with isolated systolic hypertension). Patients were given indapamide or placebo and were followed for a median of 1.8years, to a target of SBP <150 mmHg and DBP <80 mmHg.
The primary endpoint was stroke (fatal and non-fatal), which did not yield a statistically significant difference between treatment and placebo-group.
In this trial, all-cause mortality (which was a secondary endpoint) is statistically significantly lower with treatment compared to placebo.

Information from a prespecified subgroup analysis from the HYVET trial (Beckett 2014(64)) suggests that for ages ≥85y, compared to ≥80 years, the benefit of treatment on total mortality, heart failure and cardiovascular events may be attenuated. Lack of statistical power diminishes the reliability of these results.

4.3.4 Type 2 diabetes

4.3.4.1 Medication class versus all other classes of antihypertensive drugs

4.3.4.1.1 Clinical evidence profile

Meta-analysis of head to head comparison between different medication regimens.

Meta-analysis: Emdin 2015

Inclusion criteria: Randomized controlled trials of BP-lowering treatment in which the entire trial population is comprised of patients with diabetes or in which the results of a diabetic subgroup were able to be obtained. More than 1000 patient-years in each randomized group
Search strategy: Systematic review and MA according to PRISMA approach (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).
Relevant studies were identified using the following search terms: anti-hypertensive agents or hypertension or diuretics, thiazide or angiotensin-converting enzyme or receptors, angiotensin/antagonists & inhibitors or tetrazoles or calcium channel blockers or vasodilator agents or the names of all BP-lowering drugs listed in the British National Formulary as keywords or text words or the MeSH (Medical Subject Headings [of the US National Library of Medicine]) term blood pressure/drug effects. We used this existing strategy to identify BP-lowering trials published on MEDLINE, from January 1, 1966, to October 28, 2014, restricted to those published in MEDLINE-defined core clinical journals.
Studies were restricted to clinical trials, controlled clinical trials, randomized controlled trials, or meta-analyses.
Bibliographies of included studies and bibliographies of identified meta-analyses were searched by hand. We then manually examined whether each trial included patients with diabetes and searched for any reporting of results for the diabetic subgroup.
Assessment of quality of included trials: yes, Cochrane tool but evaluations not given
ITT analysis: yes/no
Other methodological remarks:

Table 281

Ref	Outcome	N/n	comparison	Result
Emdin 2015(65) Design: MA	Mortality	N= 11 n= 34264 (Ostergen 2008, ALLHAT 2002, Ruggenenti 2004, Lewis 2001,Berl 2003, Weber 2010, Mancia 2003, Bakris 2004, Hansson 2000, Lindholm 2000, Estacio 1998,	CCB vs all other classes of hypertensives	RR: 0.98 (95% CI: 0.92 to 1.05) NS

Search date: (October 2014)		Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)		
		N= 6 n= 11771 (ALLHAT 2002, Ruggenenti 2004, UKPDS 39 1998, Lindholm 2000, Estacio 1998, Schrier 200, Estacio 2000, Schrier 2007, Schrier 2002)	ACEi vs all other classes of hypertensives	RR: 0.98 (95% CI: 0.93 to 1.03) NS
		N= 3 n= 16988 (ALLHAT 2002, Weber 2010, Mancia 2003)	Diuretics versus all other classes of hypertensives	RR: 1.00 (05% CI: 0.91 to 1.10) NS
		N= 4 n=13470 (Ostergren 2008, UKPDS 1998, Bakris 2004, Lindholm 2002)	β-blockers vs all other classes	RR: 1.02 (95% CI: 0.92 to 1.13) NS
		N= 2 n=2341 (Lewis 2001, Berl 2003, Lindholm 2002)	ARB vs all other classes	**RR: 0.81 (95% CI: 0.66 to 0.99)** **SS**
	Cardiovascular disease	N= 10 n= 32178 (Ostergen 2008, ALLHAT 2002, Lewis 2001, Berl 2003, Weber 2010; Mancia 2003, Bakris 2004, Hansson 2000, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	CCB vs all other classes of hypertensives	RR: 0.98 (95% CI: 0.93 to 1.03) NS
		N=4 n=10409 (ALLHAT 2002, Lindholm 2000, Estacio 1998, Schrier 2000,	ACE vs all other classes of hypertensives	RR: 1.06 (95% CI: 0.99 to 1.15) NS

		Estacio 2000, Schrier 2007, Schrier 2002)		
		N= 3 n=16988 (ALLHAT 2002, Weber 2010, Mancia 2003)	Diuretics versus all other classes	RR: 0.98 (95% CI: 0.85 to 1.12) NS
		N= 3 n=12732 (Ostergen 2008, Bakris 2004, Lindholm 2002)	β-blockers vs all other classes	RR: 1.24 (95% CI: 0.94 to 1.62) NS
		N=2 n=2341 (Lewis 2001, Berl 2003,Lindholm 2002)	ARB vs all other classes	RR: 0.93 (95% CI: 0.80 to 1.08) NS
	Coronary heart disease	N= 10 n= 32178 (Ostergen 2008, ALLHAT 2002, Lewis 2001, Berl 2003, Weber 2010; Mancia 2003, Bakris 2004, Hansson 2000, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	CCB vs all other classes of hypertensives	RR: 1.00 (95% CI: 0.91 to 1.09) NS
		N=5 n=11167 (ALLHAT 2002, UKPDS 1998, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	ACE vs all other classes of hypertensives	RR: 0.96 (95% CI: 0.85 to 1.08) NS
		N= 3 n=16988 (ALLHAT 2002, Weber 2010, Mancia 2003)	Diuretics versus all other classes	RR: 1.02 (95% CI: 0.90 to 1.15) NS
		N=4 n=13490 (Ostegren 2008, UKPDS 1998,	β-blockers vs all other classes	RR: 1.03 (95% CI: 0.87 to 1.20) NS

		Bakris 2004, Lindholm 2002)		
		N=2 n=2341 (Lewis 2001, Berl 2003,Lindholm 2002)	ARB vs all other classes	RR: 1.09 (95% CI: 0.80 to 1.48) NS
	Stroke	N= 10 n= 32178 (Ostergen 2008, ALLHAT 2002, Lewis 2001, Berl 2003, Weber 2010; Mancia 2003, Bakris 2004, Hansson 2000, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	CCB vs all other classes of hypertensives	**RR: 0.86 (95% CI: 0.77 to 0.97)** **SS**
		N= 5 n=11167 (ALLHAT 2002, UKPDS 1998, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	ACE vs all other classes of hypertensives	RR: 1.03 (95% CI: 0.89 to 1.20) NS
		N=3 n=16988 (ALLHAT 2002, Weber 2010, Mancia 2003)	Diuretics versus all other classes	RR: 0.98 (95% CI: 0.84 – 1.14) NS
		N=4 n=13490 (Ostegren 2008, UKPDS 1998, Bakris 2004, Lindholm 2002)	β-blockers vs all other classes	**RR: 1.25 (95% CI: 1.05 to 1.50)** **SS**
		N=2 n=2341 (Lewis 2001, Berl 2003,Lindholm 2002)	ARB vs all other classes	RR: 0.98 (95% CI: 0.71 to 1.34) NS
	Heart Failure	N=9 n=25778 (Ostergen 2008, ALLHAT 2002, Lewis 2001, Berl 2003, Weber	CCB vs all other classes of hypertensives	**RR: 1.32 (95% CI: 1.18 to 1.47)** **SS**

		2010, Mancia 2003, Hansson 2000, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)		
		N=5 n= 11167 (ALLHAt 2002, UKPDS 1998, Lindholm 2000, Estacio 1998, Schrier 2000, Estacio 2000, Schrier 2007, Schrier 2002)	ACE vs all other classes of hypertensives	**RR: 1.17 (95% CI: 1.02 to 1.35)** **SS**
		N=3 n= 16988 (ALLHAT 2002, Weber 2010, Mancia 2003)	Diuretics versus all other classes	**RR: 0.83 (95% CI: 0.72 to 0.95)** **SS**
		N=3 n=13490 (Ostegren 2008, UKPDS 1998, Bakris 2004, Lindholm 2002)	β-blockers vs all other classes	RR: 1.20 (95% CI: 0.92 to 1.56) NS
		N=2 n=2341 (Lewis 2001, Berl 2003,Lindholm 2002)	ARB vs all other classes	**RR: 0.61 (95% CI: 0.48 to 0.78)** **SS**

Table 282

* Characteristics of included studies: see below

Ref + design	n (number of patients with diabetes)	Population	Duration of follow-up	Comparison	Methodology
Ostergren 2008(163) Data from trial: ASCOT 2008	5137	Main inclusion criteria: Hypertension + 3 cardiovascular risk factors Mean age: 63	Mean: 5.5 years	CCB (amlodipine) vs β-blocker (atenolol)	ALLOCATION CONC: Open label RANDO: Open label BLINDING : Open label Rated “Good” by JNC8

RCT OL					
ALLHAT 2002(164) RCT DB	8851	Main inclusion criteria: men and women aged 55 years or older Hypertension + cardiovascular risk factor mean age: 67	Mean: 4.9 years	CCB (amlodipine) vs Diuretic (chlorthalidone) AND ACE (Lisinopril) vs diuretic (chlorthalidone)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING: Adequate Rated "Fair" by JNC8 NICE mentions serious limitations (attrition >20%).
Ruggenenti 2004(165) data from trial BENEDICT 2004 DB RCT	n = 600 (ACE+CCB vs placebo) n = 604 (ACE vs CCB)	Main inclusion criteria: Diabetes mellitus without microalbuminuria - 40 years of age or older and had hypertension and a known history of type 2 diabetes mellitus not exceeding 25 years Mean age: 63	Mean: 3.6 years	ACE (trandolapril)+CCB (verapamil) vs placebo AND ACE (trandolapril) vs CCB (verapamil)	ALLOCATION CONC: Unclear RANDO: Mentions randomized, method unclear BLINDING: Unclear The use of potassium-sparing diuretics, inhibitors of the renin–angiotensin system, and non-dihydropyridine calcium-channel blockers different from the study drugs was not allowed Quality not evaluated by NICE or JNC-8
Lewis 2001(166) data from trial IDNT 2001 DB RCT	n = 1715	Main inclusion criteria: Diabetes mellitus with diabetic nephropathy and proteinuria Mean age: 59	Mean: 2.6 years	ARB (irbesartan) vs placebo CCB (amlodipine) vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING: Adequate Rated as "fair" by JNC-8
Weber 2010(167) data from trial ACCOMPLISH 2010	n = 6946	Main inclusion criteria: hypertension and diabetes mellitus, including a subgroup of patients (n= 2842) with previous stroke or cv events)	24 months	RAB (benazepril) + CCB (amlodipine) VS RAB (benazepril) + diuretic (hydrochlorthiazide)	ALLOCATION CONC: Adequate RANDO: Unclear, only mentions "randomly assigned" BLINDING: Adequate

DB RCT		Mean age: 68			Quality reported by NICE as "moderate", with mention of serious imprecision Rated as "fair" by JNC-8 due to limitations of subgroup analyses
Mancia 2003(168) data from trial INSIGHT 2003 DB RCT	n = 1302	Main inclusion criteria: hypertension + cardiovascular risk factor Mean age: 66 years	Mean: 4 years	CCB (nifedipine) vs diuretic (co-amiloride)	ALLOCATION CONC: Unclear RANDO: Adequate BLINDING: Unclear Original study rated as "good" by JNC-8
Bakris 2004(169) data from trial INVEST 2004 OL RCT	n= 6400	Main inclusion criteria: coronary artery disease with hypertension Mean age: 66 years	Mean: 2.7 years	CCB (verapamil) vs β-blocker (atenolol and trandolapril/hydrocholothiazide if needed)	ALLOCATION CONC: Open label RANDO: Adequate BLINDING: No, open label Quality not evaluated by NICE or JNC-8
Hansson 2000(170) data from trial NORDIL 2000 OL RCT	n = 727	Main inclusion criteria: hypertension, aged 50–69 years (extended to 74 years during the trial), were previously untreated Mean age: 60 years	Mean: 4.5 years	CCB (diltiazem) vs Diuretic/β-blocker	ALLOCATION CONC: Open label RANDO: Adequate BLINDING: No, open label Quality not evaluated by NICE or JNC-8
Lindholm 2000(171) data from trial STOP Hypertension-2 OL RCT	n = 719	Main inclusion criteria: elderly patients with systolic hypertension Mean age: 76 years	Mean: 4 years	Conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2·5 mg daily) vs ACE-inhibitors(enalapril 10 mg or lisinopril 10 mg vs	ALLOCATION CONC.: Open label RANDO: class of drug was randomized, choice of drugs wasn't BLINDING: open label Rated "Good" by JNC-8

				Calcium antagonists (felodipine 2·5 mg or isradipine 2–5 mg daily)	
Estacio 1998(95) Data from trial ABCD 1998 Single Blind RCT	n = (normotensive + diabetes) 470 N = (hypertensive + diabetes) 480	Main inclusion criteria: Diabetes mellitus + hypertension (DBP>90 mmHg) Mean age: 57	Mean: 5 years	One normotensive arm with randomly assigned either: placebo (50%), nisoldipine (25%), enalapril (25%) One hypertensive group with randomly assigned nisoldipine (50%) or enalapril (50%) On top of that patients were also randomized to either intense treatment (target of 75 mmHg) or usual treatment (80-90mmHg)	ALLOCATION CONC.: unclear RANDO: unclear, merely mentions "randomly assigned" BLINDING: participants yes, assessors no Rated "fair" by JNC-8
Schrier 2000(172) Data from trial ABCD 1998 (see above)					
Estacio 2000(173) Data from trial ABCD 1998 (see above)					
Schrier 2007(174) Data from trial ABCD 1998 (see above)					
Schrier 2002(96) Data from trial ABCD 1998 (see above)					

UKPDS (38-39) 1998(101, 129) Data from UKPDS 1998	n= 1148	Main inclusion criteria: diabetes mellitus with hypertension Mean age: 56	Mean: 8.4 years	β-blocker (atenolol) vs ACE (captopril) vs other treatment not β-blocker or ACE	Rated as “Fair” by JNC-8
Berl 2003(175) Data from IDNT trial 2001	n= 1715	- Patients 30 to 70 years with overt diabetic nephropathy and proteinuria (excretion of 900mg/d or more) Mean age: 59 y	Mean: 2.6 years	ARB (irbesartan) vs calcium channel blocker (amlodipine) vs placebo	ALLOC. CONC.: unclear RANDOM.: by computer, blocked by center BLINDING: patients yes, investigators unclear, assessors yes Rated “Fair” by JNC-8
Lindholm 2002(176) Data from trial LIFE 2002	n = 1195	Main inclusion criteria: hypertension + left ventricular hypertrophy Mean age: 67	Mean: 4.7 years	ARB (losartan) vs β-blocker (atenolol) vs placebo	ALLOCATION CONC.: Unclear RANDO: unclear, states “randomized” BLINDING: unclear, states “double blind” Rated as “good” by jnc-8

Table 283

4.3.4.1.2 Summary and conclusions

Head to head comparison of different drug regimens **First comparison: Calcium channel Blockers versus all other classes**			
Bibliography: Emdin 2015(65) (Ostergren 2008(163), ALLHAT 2002(164), Ruggenenti 2004(165), Lewis 2001(166), Weber 2010(167), Mancia 2003(168), Bakris 2004(169), Hansson 2000(170), STOP-H2 2000(171), ABCD 1998(95, UKPDS 38-39 1998{UK Prospective Diabetes Study Group, 1998 #2587, 96, 101, 172-174) , Life 2002(176))			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	34264 (11) Mean 4.9 years	RR: 0.98 (95% CI: 0.92 to 1.05) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Cardiovascular diseases	32178 (10) Mean 4.9 years	RR: 0.98 (95% CI: 0.93 to 1.03) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Coronary Heart Diseases	32178 (10) Mean 4.9 years	RR: 1.00 (95% CI: 0.91 to 1.09) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Stroke	32178 (10) Mean 4.9 years	**RR: 0.86 (95% CI: 0.77 to 0.97)** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Heart failure	25778 (9) Mean 4.9 years	**RR: 1.32 (95% CI: 1.18 to 1.47)** **SS**	⨁⨁⨀⨀ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok

Table 284

In this meta-analysis, RCTs of BP-lowering treatment with a population or a subgroup of diabetic patients were included. One class of medication was compared against all the others together.
In all studies, the mean age was over 55. All patients had diabetes but differed on whether or not they had overt nephropathy, risk factors or previous events.

In diabetic and hypertensive patients, a treatment with calcium channel blockers, compared with all other treatments did not result in a statistically significant difference for: mortality, cardiovascular diseases or coronary heart diseases.
GRADE: LOW quality of evidence

In diabetic and hypertensive patients, a treatment with calcium channel blockers, compared with all other treatments did result in a statistically significant lower occurrence of stroke.
GRADE: LOW quality of evidence

In diabetic and hypertensive patients, a treatment with calcium channel blockers, compared with all other treatments did result in a statistically significant higher occurrence of heart failure.
GRADE: LOW quality of evidence

Head to head comparison of different drug regimens
2nd comparison: Angiotensin converting enzyme inhibitor versus all other classes

Bibliography: Emdin 2015(65) (Ostergren 2008(163), ALLHAT 2002(164), Ruggenenti 2004(165), Lewis 2001(166), Weber 2010(167), Mancia 2003(168), Bakris 2004(169), Hansson 2000(170), STOP-H2 2000(171), ABCD 1998(95, UKPDS 38-39 1998{UK Prospective Diabetes Study Group, 1998 #2587, 96, 101, 172-174)
, Life 2002(176))

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Mortality	11771 (6) Mean: 5.2 years	RR: 0.98 (95% CI: 0.93 to 1.03) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Cardiovascular diseases	10409 (4) Mean: 4.6	RR: 1.06 (95% CI: 0.99 to 1.15) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Coronary Heart Diseases	11167 (5) Mean: 5.2 y	RR: 0.96 (95% CI: 0.85 to 1.08) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials

			Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Stroke	11167 (5) Mean: 5.2 y	RR: 1.03 (95% CI: 0.89 to 1.20) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok
Heart failure	11167 (5) Mean: 5.2 y	**RR: 1.17 (95% CI: 1.02 to 1.35)** **SS**	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without over nephropathy, previous events or risk factors Imprecision: ok

Table 285

In this meta-analysis, RCTs of BP-lowering treatment with a population or a subgroup of diabetic patients were included. One class of medication was compared against all the others together.
In all studies, the mean age was over 55. All patients had diabetes but differed on whether or not they had overt nephropathy, risk factors or previous events.

In diabetic and hypertensive patients, a treatment with angiotensin converting enzyme inhibitor, compared with all other treatments did not result in a statistically significant difference for: mortality, cardiovascular diseases, coronary heart diseases or stroke.
GRADE: LOW quality of evidence

In diabetic and hypertensive patients, a treatment with angiotensin converting enzyme inhibitor, compared with all other treatments did result in a statistically significant higher occurrence of heart failure.
GRADE: LOW quality of evidence

Head to head comparison of different drug regimens **3rd comparison: Diuretics versus all other classes**			
Bibliography: : Emdin 2015(65) (including ALLHATT 2002 ALLHAT 2002(164), Weber 2010(167), Mancia 2003(168))			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	16988 (3) Mean: 3.6 years	RR: 1.00 (05% CI: 0.91 to 1.10)	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label

		NS	trials Consistency: ok Directness: -1, diabetes with or without overt nephropathy, previous events or risk factors Imprecision: ok
Cardiovascular diseases	16988 (3) Mean: 3.6 years	RR: 0.98 (95% CI: 0.85 to 1.12) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without overt nephropathy, previous events or risk factors Imprecision: ok
Coronary Heart Diseases	16988 (3) Mean: 3.6 years	RR: 1.02 (95% CI: 0.90 to 1.15) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without overt nephropathy, previous events or risk factors Imprecision: ok
Stroke	16988 (3) Mean: 3.6 years	RR: 0.98 (95% CI: 0.84 – 1.14) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without overt nephropathy, previous events or risk factors Imprecision: ok
Heart failure	16988 (3) Mean: 3.6 years	**RR: 0.83 (95% CI: 0.72 to 0.95)** **SS**	⨁⨁⊖⊖ **LOW** Study quality: -1 for subgroup analysis and large open label trials Consistency: ok Directness: -1, diabetes with or without overt nephropathy, previous events or risk factors Imprecision: ok

Table 286

In this meta-analysis, RCTs of BP-lowering treatment with a population or a subgroup of diabetic patients were included. One class of medication was compared against all the others together.
In all studies, the mean age was over 55. All patients had diabetes but differed on whether or not they had overt nephropathy, risk factors or previous events.

In diabetic and hypertensive patients, a treatment with a diuretic compared with all other treatments did not result in a statistically significant difference for: mortality, cardiovascular diseases, coronary heart diseases or stroke.
GRADE: LOW quality of evidence

In diabetic and hypertensive patients , a treatment with a diuretic, compared with all other treatments, did result in a statistically significant lower occurrence of heart failure.
GRADE: LOW quality of evidence

Head to head comparison of different drug regimens **4th comparison: Beta-blockers versus all other classes**			
Bibliography: Emdin 2015(65) (Ostergren 2008(163), Bakris 2004(169), UKPDS 38-39 1998(101, 129), Life 2002(176))			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	13470 (4) Mean: 5.3 years	RR: 1.02 (95% CI: 0.92 to 1.13) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: - 2 for subgroup and majority of patients from open label trials Consistency: ok Directness: -1, patients selection differs between studies Imprecision: ok
Cardiovascular diseases	12732 (3) Mean: 4.3	RR: 1.24 (95% CI: 0.94 to 1.62) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: - 2 for subgroup and majority of patients from open label trials Consistency: ok Directness: -1, patients selection differs between studies Imprecision: ok
Coronary Heart Diseases	13470 (4) Mean: 5.3 years	RR: 1.03 (95% CI: 0.87 to 1.20) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: - 2 for subgroup and majority of patients from open label trials Consistency: ok Directness: -1, patients selection differs between studies Imprecision: ok
Stroke	13470 (4) Mean: 5.3 years	**RR: 1.25 (95% CI: 1.05 to 1.50)** **SS**	⨁⊖⊖⊖ **VERY LOW** Study quality: - 2 for subgroup and majority of patients from open label trials Consistency: ok Directness: -1, patients selection differs between studies Imprecision: ok
Heart failure	13470 (4) Mean: 5.3 years	RR: 1.20 (95% CI: 0.92 to 1.56) NS	⨁⨁⨁⨁ **HIGH** ⨁⊖⊖⊖ **VERY LOW** Study quality: - 2 for subgroup and majority of patients from open label trials Consistency: ok Directness: -1, patients selection differs between studies Imprecision: ok

Table 287

In this meta-analysis, RCTs of BP-lowering treatment with a population or a subgroup of diabetic patients were included. One class of medication was compared against all the others together.
In all studies, the mean age was over 55. All patients had diabetes but differed on whether or not they had overt nephropathy, risk factors or previous events.

In diabetic and hypertensive patients, a treatment with a beta-blocker compared with all other treatments did not result in a statistically significant difference for: mortality, cardiovascular diseases, coronary heart diseases or heart failure.
GRADE: VERY LOW quality of evidence

In diabetic and hypertensive patients , a treatment with a diuretic, compared with all other treatments, did result in a statistically significant higher occurrence of stroke.
GRADE: VERY LOW quality of evidence

Head to head comparison of different drug regimens **5th comparison: Angiotensin receptor blocker versus all other classes**			
Bibliography: Emdin 2015(65) (Lewis 2001(166), , Life 2002(176), Berl 2003(175))			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2341 (2) Mean: 3.6	**RR: 0.81 (95% CI: 0.66 to 0.99)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis Consistency: ok Directness: -1, one trial selected with overt diabetic nephropathy, the other patients with HT and LVH Imprecision: ok
Cardiovascular diseases	2341 (2) Mean: 3.6	RR: 0.93 (95% CI: 0.80 to 1.08) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis Consistency: ok Directness: -1, one trial selected with overt diabetic nephropathy, the other patients with HT and LVH Imprecision: ok
Coronary Heart Diseases	2341 (2) Mean: 3.6	RR: 1.09 (95% CI: 0.80 to 1.48) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis Consistency: ok Directness: -1, one trial selected with overt diabetic nephropathy, the other patients with HT and LVH Imprecision: ok
Stroke	2341 (2) Mean: 3.6	RR: 0.98 (95% CI: 0.71 to 1.34) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for subgroup analysis Consistency: ok Directness: -1, one trial selected with overt diabetic nephropathy, the other patients with HT and LVH Imprecision: ok
Heart failure	2341	**RR: 0.61 (95% CI: 0.48 to**	⊕⊕⊖⊖ **LOW**

	(2) Mean: 3.6	**0.78)** **SS**	Study quality: -1 for subgroup analysis Consistency: ok Directness: -1, one trial selected with overt diabetic nephropathy, the other patients with HT and LVH Imprecision: ok

Table 288

In this meta-analysis, RCTs of BP-lowering treatment with a population or a subgroup of diabetic patients were included. One class of medication was compared against all the others together.
In all studies, the mean age was over 55. All patients had diabetes but differed on whether or not they had overt nephropathy, risk factors or previous events.

In diabetic and hypertensive patients, a treatment with an angiotensin receptor blocker compared with all other treatments did not result in a statistically significant difference for: cardiovascular diseases, coronary heart diseases or stroke.
GRADE: LOW quality of evidence

In diabetic and hypertensive patients, a treatment with an angiotensin receptor blocker compared with all other treatments did result in a statistically significant lower occurrence of death (all-cause mortality).
GRADE: LOW quality of evidence

In diabetic and hypertensive patients, a treatment with an angiotensin receptor blocker compared with all other treatments did result in a statistically significant lower occurrence of heart failure.
GRADE: LOW quality of evidence

4.3.4.2 ACE-inhibitors versus placebo or ARB versus placebo or ACE-inhibitor versus calcium channel blocker for preventing diabetic kidney disease

4.3.4.2.1 Summary and conclusions

The LV 2012(177) meta-analysis was a systematic review of RCTs that compared ACEIs, ARBs and CCB in hypertensive or normotensive patients with diabetes and no kidney disease, with a follow-up ranging from 6 to 72 months. Because this is a mixed population, a table of this study is not included. The reported outcomes were new onset microalbuminuria, macroalbuminuria or both, all-cause mortality, doubling of SCr, ESKD, adverse events and blood pressure.

Participants were selected on the presence of diabetes, not hypertension. A subgroup analysis in the participants with hypertension compared ACEis, ARBs and CCBs for preventin diabetic kidney disease.

There was a statistically significant lower risk of developing diabetic kidney disease with ACEi compared to placebo. (RR: 0.64, 95% CI: 0.43-0.96).

There was a statistically significant lower risk of developing diabetic kidney disease with ARB compared to placebo. (RR: 0.84, 95% CI: 0.75-0.95).

There was a statistically significant lower risk of developing diabetic kidney disease with ACEi compared to calcium channel blockers. (RR: 0.60, 95% CI: 0.42-0.85).

4.3.4.3 ACE-inhibitors versus angiotensin receptor blocker

4.3.4.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Yusuf / ONTARGET 2008(152) Design: RCT (SB DB OL) (PG CO) Duration of follow-up: median 56 months	n= 25620 Mean age: 66.4 **<u>Hypertension:68.7%</u>** Coronary artery disease:74.5 % Previous MI: 48.8 % Previous stroke or TIA: 20.8% LVH:12.8 % Diabetes: 37.5% Microalbuminuria:13.2 % Smoking: 12.6% Age >80y: unknown <u>Inclusion:</u> - 55 and older - one of the following risk factors: Coronary Artery Disease:	Telmisartan (80mg once daily) Vs Ramipril (5 mg once daily or 10 mg once daily) vs Ramipril+telmisartan once daily	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up, drop-out and exclusions: 0.2%Described: no • Balanced across groups: unknown Discontinuation of one or both study drugs: 22.5% ITT: Yes, all randomized patients included
			Composite outcome (PO) of death from CV causes, MI, stroke, or hospitalization for heart failure	Ramipril:1412/8576 Telmisartan:1423/8542 Combination:1386/8502 Telmisartan vs ramipril : 1.01 (0.94 – 1.09) NS Combination vs Ramipril: 0.99 (0.92 – 1.07) NS	
			Death from CV causes, myocardial infarction, or stroke	Ramipril: 1210/8576 Telmisartan: 1190/8542 Combination:1200/8502 Telmisartan vs ramipril: 0.99 (0.91-1.07) NS Combination vs Ramipril: 1.00 (0.93-1.09) NS	
			MI	Ramipril:413/8576 Telmisartan:440/8542 Combination:438/8502 Telmisartan vs ramipril: 1.07 (0.94-1.22) NS	

	Previous Myocardial infarction(> 2 days prior to informed consent), or stable or previous unstable angina (> 30 days prior to informed consent) with documented multivessel coronary artery disease or a positive stress test, or multivessel PTCA (> 30 days prior to informed consent), or previous multivessel Coronary Artery Bypass Grafting without angina (if surgery performed > 4 years prior to informed consent) or with recurrent angina after surgery - Other high risk: PAD, previous stroke, TIA >7 days and <1 year prior to informed consent, diabetes mellitus type I or II			Combination vs Ramipril: 1.08(0.94-1.23) NS	SELECTIVE REPORTING: yes/no (describe if yes) 3 week single-blind run-in Sponsor: Boehringer Ingelheim
			Stroke	Ramipril:405/8576 Telmisartan:369/8542 Combination:373/8502 Telmisartan vs ramipril: 0.91 (0.79-1.05) NS Combination vs Ramipril: 0.93 (0.81-1.07) NS	
			Death from CV causes	Ramipril:603/8576 Telmisartan:598/8542 Combination:620/8502 Telmisartan vs ramipril :1.00(0.89-1.12) NS Combination vs Ramipril:1.04 (0.93-1.17) NS	
			Death from non-CV causes	Ramipril:411/8576 Telmisartan:391/8542 Combination:445/8502 Telmisartan vs ramipril :0.96 (0.83-1.10) NS Combination vs Ramipril:1.10 (0.96-1.26) NS	
			Any heart failure	Ramipril:514/8576 Telmisartan:537/8542 Combination:478/8502	

	Exclusion: - Medication exclusion: inability to discontinue ACEi or AIIRA, known hypersensitivity or intolerance to ARB or ACEi - Cardiac disease exclusion: symptomatic congestive heart failure, hemodynamically significant primary valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 months, uncontrolled HT (BP >160/100 mm Hg), heart transplant recipient, strokes due			Telmisartan vs ramipril :1.05(0.93-1.19) NS Combination vs Ramipril:0.94 (0.83-1.07) NS	
			Diabetes Mellitus(new diagnosis)	Ramipril: 366/8576 Telmisartan:399/8542 Combination:323/8502 Telmisartan vs ramipril :1.12 (0.97-1.29) NS Combination vs Ramipril:0.91 (0.78-1.06) NS	
			Death from any cause	Ramipril:1014/8576 Telmisartan:989/8542 Combination:1065/8502 Telmisartan vs ramipril :0.98 (0.90-1.07) NS Combination vs Ramipril:1.07(0.98-1.16) NS	
			Subgroup: Patients with BP >150 mmHg		
			Composite outcome (PO) of death from CV causes, MI, stroke, or hospitalization for heart failure	data not given, see forest plots	
			Subgroup : patients with diabetes		

	to subarachnoidal hemorrhage - Other disease exclusion: significant renal disease, hepatic dysfunction, volume or sodium depletion, primary aldosteronism, fructose intolerance, any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation		**Composite outcome** (PO) of death from CV causes, MI, stroke, or hospitalization for heart failure	data not given, see forest plots	
			Subgroup : patients ≥75 years		
			Composite outcome (PO) of death from CV causes, MI, stroke, or hospitalization for heart failure	data not given, see forest plots	

Table 289

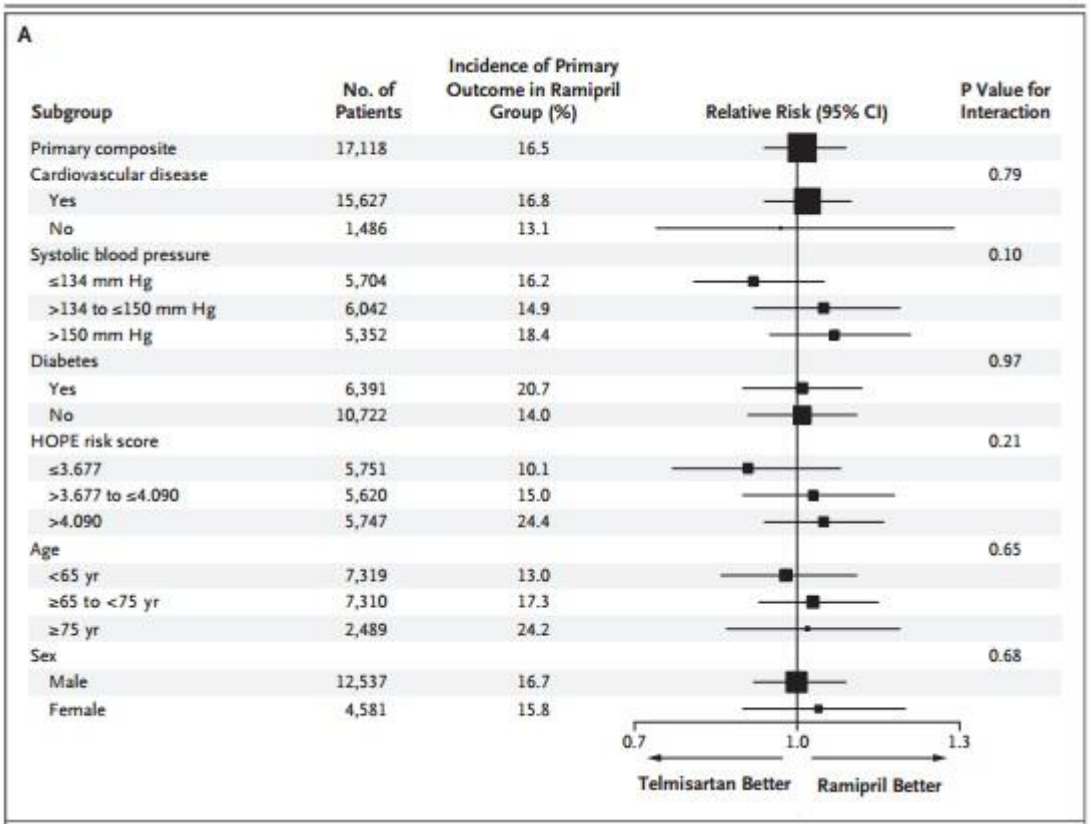


Figure 8: Relative risks in prespecified subgroups: comparison between telmisartan group and Ramipril group

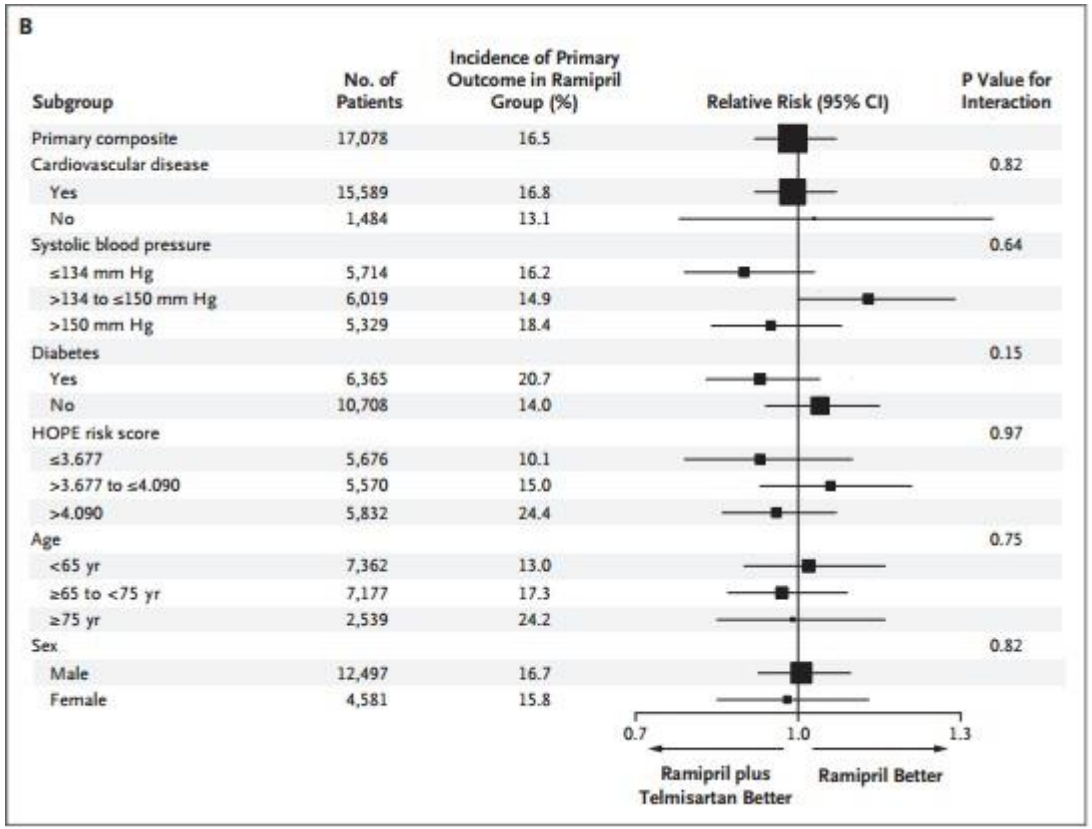


Figure 9: Relative risks in prespecified subgroups: comparison between combination-therapy (telmisartan plus ramipril) group and ramipril group

4.3.4.3.2 Summary and conclusions

ONTARGET 2008(152), see also 4.3.4.3, was a randomized, double blind trial that compared the Ace inhibitor Ramipril, the ARB telmisartan and a combination of both, in 25620 patients with vascular disease or high-risk diabetes, with a median follow up of 56 months. The primary outcome was a composite including death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure. Not all patients had hypertension, though 69% of them did.

There was no statistically significant difference of risk of developing this primary outcome with ACEi vs ARB or with the combination versus ACEi.
None of the secondary outcomes showed a statistically significant risk.

A subgroup analysis in the participants with hypertension was only shown in forests plots. However the results are not consistent.

4.3.4.4 CKD and diabetes: network meta-analysis

4.3.4.4.1 Summary and conclusions

Palmer 2015(178) was a network meta-analysis that compared all pharmacological agents to lower blood pressure in adults with diabetes and kidney disease. The primary outcomes were all-cause mortality and end-stage kidney disease.

This meta-analysis was not included in our search for it was not in line with several of the quality criteria we had. Studies with <100 patients were included in the meta-analysis, studies with follow up of <1 year as well. Population selected had both CKD and diabetes and all ages were present (ranging from 18+ to elderly patients). We will not give an in-depth discussion of this meta-analysis.

None of the medication comparisons found a statistically significant difference in mortality rates.

4.3.4.5 ACE-inhibitor + calcium channel blocker versus ACE-inhibitor + diuretic

4.3.4.5.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Jamerson 2008(156) (ACCOMPLISH) Design: RCT (DB) (PG) Duration of follow-up: 36 months	n= 11506 Mean age: 68.4 Previous MI 23.6: % Previous stroke: 13.0% Previous hospitalization for unstable angina:11.5 % Diabetes:60.2 % Estimated glomerular filtration rate >60: 18.1% % Smoking: 11.3% Age >65y: 66.4 % <u>Inclusion</u> - At least 55 years of age. - Previously untreated or treated hypertension.	ACEi(benazepril) + CCB amlodipine (n = 5744) Vs ACEi (benazepril) + Diuretic (Hydrochlorothiazide) (n = 5762)	Efficacy		RANDO: unclear, no details ALLOCATION CONC: Adequate, assignments made centrally by telephone BLINDING : Participants: yes Investigators: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 1% Drop-out and Exclusions: 1.2 % • Described: partially • Balanced across groups: unclear ITT: Yes SELECTIVE REPORTING: no
			Cardiovascular events and cardiovascular mortality (composite) (PO)	CCB: 552/5744 DIU: 679/5762 **HR: 0.80 (0.72-0.90) SS** p: <0.0001	
			Death from CV causes	CCB: 107/5744 Diu: 134/5762 HR: 0.80 (0.62 – 1.03) NS p: 0.08	
			Fatal and non-fatal MI	CCB: 125/5744 DIU: 159/5762 **HR: 0.78 (0.62 – 0.99) SS** p: 0.04	
			Fatal and non-fatal stroke	CCB: 112 / 5744 DIU: 133/5762 HR: 0.84 (0.65 – 1.08) p: 0.17	
			Hospitalization for unstable angina	CCB: 44/5744 DIU: 59/5762 HR: 0.75 (0.50 – 1.10) p: 0.14	
			Coronary	CCB: 334/ 5744	

	- For patients >= 60 years, evidence of at least one CV disease or target organ damage, or for patients 55-59 years evidence of at least two CV diseases or target organ damage from two different organ systems as defined in the protocol. <u>Exclusion</u> Allergy to any of the drugs administered in this trial. Current angina pectoris (ie, no anginal event requiring NTG within 1 month prior to Visit 1). Secondary hypertension. Refractory hypertension defined as SBP >= 180 mmHg and/or DBP >= 110 mmHg unresponsive		revascularization procedure	DIU: 386/5762 HR: 0.86 (0.74 – 1.00) p: 0.04	Sponsor: Novartis The trial was terminated early after a mean follow-up of 36 months due to this difference favoring the benazepril–amlodipine group in the primary outcome. JNC-8 notes the following remarks: - criteria for event classification were not explicitly described other than being "standardized", - use of concomitant medications was reported at baseline but not at the end of follow-up, and adherence information was reported at six months and one year but not at the end of follow-up NICE reports only serious limitations on precision, seeing
			Resuscitation after cardiac arrest	CCB: 14/5744 DIU: 8/5762 HR: 1.75 (0.73 – 4.17) p: 0.20	
			SUBGROUPS : age		
			PO, ≥65 years	CCB: 386/3813 DIU: 474/3827 **HR: 0.81 (0.71 – 0.92) SS** p: 0.002	
			PO, ≥70 years	CCB: 260/2363 DIU: 323/2340 **HR: 0.79 (0.67 – 0.93) SS** p: 0.004	
			SUBGROUPS: diabetes		
			PO, presence of diabetes	CCB: 307/3478 DIU: 383/3468 **HR: 0.79 (0.68-0.92) SS** p: 0.003	
			PO, absence of diabetes	CCB: 245/2266 DIU: 296/2294 **HR: 0.82 (0.69-0.97) SS** p: 0.02	

	to triple-drug regimens of sympatholytics, diuretics and vasodilators. History of symptomatic heart failure (NYHA classes II-IV) or ejection fraction < 40%. Myocardial infarction, coronary revascularization (CABG or PCI), unstable angina within one month of Visit 1. Stroke or transient ischemic event (TIA) within 3 months of Visit 1. Significant obstructive valvular cardiovascular disease or any valvular disease expected to lead to surgery during the course of the study. Evidence of hepatic disease (AST or ALT values >= 2 X upper limit of normal). Impaired renal function				as some CI include both no effect and appreciable benefit/harm

	(serum creatinine >= 2.5 mg/dL (221 µmol/L)). Baseline serum potassium of > 5.2 meq/L not on potassium supplements. History of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the last 5 years. History of clinically significant auto immune disorders such as Systemic Lupus Erythematosus. Significant non-cardiovascular illness or condition likely to result in death prior to trial completion, e.g., major organ transplant (life expectancy <5 years). Significant cardiovascular disease such as an aortic aneurysm ≥ 6 cm, likely requiring surgical intervention during the course of the study.				

	Other protocol-defined exclusion criteria applied to the study.				

Table 290

4.3.4.5.2 Summary and conclusions

Angiotensin converting enzyme inhibitor plus calcium channel blocker versus angiotensin converting enzyme inhibitor plus diuretic in hypertensive patients with diabetes			
Bibliography: Jamerson 2008 (ACCOMPLISH) {Jamerson, 2008 #296			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Cardiovascular events and cardiovascular mortality (composite)	11506 (1) 36 months	**HR: 0.79 (0.68-0.92)** **SS**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; subgroup analysis, unclear randomization, unblinded investigators Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 291

Angiotensin converting enzyme inhibitor plus calcium channel blocker versus angiotensin converting enzyme inhibitor plus diuretic in hypertensive patients without diabetes			
Bibliography: Jamerson 2008 (ACCOMPLISH) {Jamerson, 2008 #296			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Cardiovascular events and cardiovascular mortality (composite)	11506 (1) 36 months	**HR: 0.82 (0.69-0.97)** **SS**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; subgroup analysis, unclear randomization, unblinded investigators Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 292

In this RCT, 11506 hypertensive patients older than 55, with a relatively high cardiovascular risk, were randomized to treatment with an ACE-inhibitor plus a calcium channel blocker or an ACE-inhibitor plus a diuretic (hydrochlorothiazide) and followed over 36 months. There was a subgroup analysis for the primary composite endpoint for people with and people without diabetes. As it concerns a subgroup analysis of a single study, our confidence in these results is limited.

In diabetic patients with hypertension, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, resulted in a statistically significant reduction of a composite of cardiovascular events and cardiovascular mortality.
GRADE: VERY LOW quality of evidence

In non-diabetic patients with hypertension, treatment with an ACE-inhibitor plus a calcium channel blocker, compared to an ACE-inhibitor plus a diuretic, resulted in a statistically significant reduction of a composite of cardiovascular events and cardiovascular mortality.
GRADE: VERY LOW quality of evidence

4.3.5 Chronic kidney disease

4.3.5.1 Results from the consensus conference chronic kidney disease 2014

4.3.5.1.1 Antihypertensive treatment versus placebo

4.3.5.1.1.1 Clinical evidence profile

ACEI versus placebo

Clinical evidence profile

Ref	Comparison	Results		
AHRQ-CER37(105)	ACEI vs placebo (N=16) /no treatment (N=1) **N=17, n=11661**	**ACEI** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Perkovic 2007(179) Asselberghs 2004(180), Marre 2004(181), Katayama 2002(182), Bojestig 2001(183), Gerstein 2001(184), O'Hare 2000(185), Muirhead 1999(186), Ruggenenti 1999(187), Crepaldi 1998(188), GISEN Group 1997(189), Maschio 1996(190), Laffel 1995(191), Sano 1994(192), Lewis 1993(193), Ravid 1993(194)		Total (N=16)		
		ACEI= 667/5786 (11.5%)	Pla= 686/5750 (11.9%)	RR=0.94 (0.80-1.12) NS I^2:33%
		Diabetic nephropathy (N=11)		
		ACEI= 439/3584	Pla= 460/3580	RR=0.91 (0.70-1.18) NS I^2:38%
		Non-diabetic or mixed nephropathy (N=5)		
		ACEI= 228/2202	Pla= 226/2170	RR=1.01 (0.72-1.43) NS I^2:40%
Cardiovascular mortality				
Perkovic 2007, Asselberghs 2004, Marre 2004		Total (N=3)		

	ACEI= 231/3769 (6.1%)	Pla= 222/3764 (5.9%)	RR=1.03 (0.86-1.23) NS I^2:0%
	Diabetic nephropathy (N=1)		
	ACEI= 141/2443	Pla= 133/2469	RR=1.07 (0.85-1.35) NS
	Non-diabetic or mixed nephropathy (N=2)		
	ACEI= 90/1326	Pla= 89/1295	RR=0.97 (0.74-1.29) NS I^2:0%
CV events: MI (any)			
Marre 2004, Crepaldi 1998, Trevisan 1995(195)	Total = Diabetic nephropathy (N=3)		
	ACEI= 62/2535 (2.4%)	Pla= 80/2565 (3.1%)	RR=0.79 (0.57-1.09) NS I^2:0%
CV events: stroke (any)			
Perkovic 2007, Asselbergs 2004, Marre 2004, REIN 1999	Total (N=4)		
	ACEI= 232/3868 (6.0%)	Pla= 278/3851 (7.2%)	RR=0.80 (0.52-1.23) NS I^2:68%
	Diabetic nephropathy (N=1)		
	ACEI= 118/2443	Pla= 116/2469	RR=1.03 (0.80-1.32) NS
	Non-diabetic or mixed nephropathy (N=3)		
	ACEI= 114/1425	Pla= 162/1382	RR=0.51 (0.13-2.09) NS I^2:52%
Doubling of sCr			
Marre 2004, Katayama 2002, Gerstein 2001, REIN 1997, Maschio 1996, Lewis 1993, Ravid 1993	Total (N=7)		
	ACEI= 129/3682	Pla= 202/3710 (5.5%)	**RR=0.60**

	(3.5%)		**(0.40-0.89) SS I^2: 58%**
	Diabetic nephropathy (N=5)		
	ACEI= 98/3304	Pla= 135/3330	RR=0.69 (0.44-1.09) NS I^2:55%
	Non-diabetic or mixed nephropathy (N=2)		
	ACEI= 31/378	Pla= 67/371	RR=0.31 (0.07-1.35) NS I^2:58%
End-stage renal disease			
Marre 2004, Gerstein 2001, REIN 1999, REIN 1997, Maschio 1996, Lewis 1993, Ravid 1993	Total (N=7)		
	ACEI= 63/3729 (1.7%)	Pla= 97/3761 (2.6%)	**RR=0.65 (0.49-0.88) SS better with ACEI I^2:0%**
	Diabetic nephropathy (N=4)		
	ACEI= 36/3252 (1.1%)	Pla= 49/3303 (1.4%)	RR=0.73 (0.48-1.10) NS I^2:0%
	Non-diabetic or mixed nephropathy (N=3)		
	ACEI= 27/477	Pla= 48/458	**RR=0.59 (0.39-0.89) SS I^2:0%**
Progression from micro-to macroalbuminuria			
Bojestig 2001, Gerstein 2001, O'Hare 2000, Muirhead 1999, Crepaldi 1998, Laffel 1995, Ravid 1993	Total (N=7)		
	ACEI= 123/855 (13.9%)	Pla= 174/827 (21.4%)	**RR=0.48 (0.27-0.85) SS better with ACEI**

Blood pressure			
NR			
Any or serious adverse events leading to study withdrawal			
Asselberghs 2004, Marre 2004, Katayama 2002, Bojestig 2001, Gerstein 2001, O'Hare 2000, Muirhead 1999, REIN 1999, Crepaldi 1998, REIN 1997, Maschio 1996, Trevisan 1995, Laffel 1995, ,Ravid 1993	Total (N=14; n=7.336)		
	ACEI= 20.7%	Pla= 18.7%	**RR=1.12 (1.02-1.23) SS more frequent with ACEI**
Renal adverse events leading to study withdrawal			
REIN 1999, Crepaldi 1998, REIN 1997, Maschio 1996	Total (N= 4; n=1.001)		
	ACEI= 0.8%	Pla= 1.7%	NT
Cough			
Marre 2004, Bojestig 2001, Gerstein 2001, Muirhead 1999, REIN 1999, Maschio 1996, Trevisan 1995, Laffel 1995, Sano 1994, Ravid 1993	Total (N= 10; n=7.361)		
	ACEI= 4.7%	Pla= 1.8%	**RR=2.33 (1.49-3.63) SS more frequent with ACEI**
Hyperkalemia			
REIN 1999, REIN 1997, Maschio 1996, Laffel 1995, Sano 1994 Lewis 1993	Total (N=8; n= 2.758)		
	1.3%	0.9%	RR=1.08 (0.53-2.23) NS

Table 293

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality

Perkovic 2007(179) PROGRESS Multinational (Europe, Asia, Australia) Followup period: mean 4 years	Inclusion criteria - history of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 years. Exclusion criteria not described.	N=1757 patients with CKD (Baseline GFR <60 ml/min/ 1.73m2) of 6105 randomized. Age (yr): 70 Gender (Male %): 55 Race/Ethnicity (%): Asian 37 BP (mm Hg): 149/84 Serum creatinine (mg/dL): 1.2 Creatinine clearance 50 ml/min/1.73m2 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 11	Perindopril 4 mg/d (n=895) vs Placebo (n=862)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Study withdrawals (%): NR **post hoc analysis** Funding Source: industry and other
Asselbergs 2004(180) PREVEND IT The Netherlands Followup period: mean 3.8 years	Inclusion criteria - persistent microalbuminuria - BP <160/100 mm Hg and no use of antihypertensive medication Exclusion criteria - creatinine clearance <60% of the normal age adjusted value - use of ACEI or ARB antagonists.	N=864 Age (yr): 51 Gender (Male %): 65 Race/Ethnicity (%): white 96 BP (mm Hg): 130/76 Albuminuria (mg/24 h): 23 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 2.5	Fosinopril 20 mg/d (n=431) Placebo (n=433)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 28 Note: 2 x 2 factorial design with pravastatin Funding Source: Industry
Marre 2004(181) DIABHYCAR	Inclusion criteria - persistent microalbuminuria or proteinuria	N=4,912 Age (yr): 65	Ramipril 1.25 mg/d (n=2443) Placebo (n=2469)	- Allocation Concealment: Adequate - Blinding: double

Multinational (Europe and North Africa) Followup period: median 4 years	- <50 years of age - type 2 diabetes <u>Exclusion criteria</u> - serum creatinine concentration >150 mmol/L - treatment with insulin, an ACEI or ARB blocker - recent AMI intolerance to an ACE inhibitor.	Gender (Male %): 70 Race/Ethnicity (%): NR BP (mm Hg): 145/82 Microalbuminuria (%): 74 Proteinuria (%): 26 Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100		- Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 17 Funding Source: Industry
Katayama 2002(182) JAPAN-IDDM Sarafidis review Japan Followup period: mean 1.5 years	<u>Inclusion criteria</u> - UAE >30 mg/24 h - onset of type 1 diabetes before 20 year - aged between 20 and 50 years <u>Exclusion criteria</u> none stated.	N=53 (imdapril arm excluded) Age (yr): 33 Gender (Male %): 35 Race/Ethnicity (%): NR SBP (mm Hg): 127/78 Albumin excretion rate (mg/day): 711 Serum creatinine (mg/dL): 0.76 Creatinine clearance (ml/min): 98.4 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Captopril 37.5 mg (n=26) vs Placebo (n=27)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 30 Funding Source: Other
Bojestig 2001(183) Sarafidis review Sweden	<u>Inclusion criteria</u> - microalbuminuria - type 1 diabetes - normotensive	N=55 Age (yr): 40 Gender (Male %): 75 Race/Ethnicity (%): NR	Ramipril 1.25 mg/d (n=19) Ramipril 15 mg/d (n=18) Placebo (n=18)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes

Followup period: 2 years	Exclusion criteria - Patients treated with any form of hypertensive medication.	Systolic BP (mm Hg): 126 (clinic) Diastolic BP (mm Hg): NR Albumin excretion rate (µg/min): median 69-103 Estimated GFR (ml/min/1.73m2): median 100-108 Diabetes (%): 100		- Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 7 Funding Source: Industry
Gerstein 2001(184) HOPE Multinational (North and South America and in Europe) Followup period: median 4.5 years	Inclusion criteria - ≥55 years of age; - history of CV disease - history of DM; - plus at least one other CV risk factor (total cholesterol >200 mg/dL, high-density lipoprotein cholesterol ≤35mg/dL, HTN, known microalbuminaria, or current smoker. Exclusion criteria - heart failure; - serum creatinine concentration >200 mmol/L (2.3 mg/dL) - dipstick-positive proteinuria (>+1)	N=1.140 patients with diabetes and microalbuminuria from the larger HOPE trial. Patient characteristics not described for microalbuminuric subjects	Ramipril 10 mg/d (n=553) Placebo (n=587)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Study withdrawals (%): NR Note: 2 x 2 factorial design with vitamin E. **post hoc analysis** Funding Source: Industry
O'Hare 2000(185) ATLANTIS UK and Ireland Followup period:	Inclusion criteria - microalbuminuria - type 1 diabetes - untreated blood pressure <150/90 mmHg for patients <50 years of age and <165/90 mmHg for	N=140 Age (yr): 40 Gender (Male %): 71 Race/Ethnicity (%): NR	Ramipril 1.25 mg/d (n=47) Ramipril 5 mg/d (n=45) Placebo (n=48)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts

2 years	patients 50–65 years of age. Exclusion criteria - other known renal diseases or raised creatinine levels (>120 µmol/L) - liver function twice that of normal on repeat testing	BP (mm Hg): 132/76 Diastolic BP (mm Hg): 76 Albumin excretion rate (µg/min): 53 Estimated GFR (ml/min/1.73m2): 104 Diabetes (%): 100		adequately described: yes - Study withdrawals (%): 30 Funding Source: Industry
Muirhead 1999(186) Kunz review Canada Follow-up period: 1 year	Inclusion criteria - incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m2 - aged ≥18 years - type 2 DM Exclusion criteria - "brittle" diabetes (increased risk of hypoglycemia	N=60 (excluding valsartan arms) Age (yr): 56 Gender (Male %): 82 Race/Ethnicity (%): white 87 BP (mm Hg): 136/84 Serum creatinine (mg/dL): NR Albumin excretion rate (µg/min): 53.4 Estimated GFR (ml/min/1.73m2): 87 Diabetes (%): 100	Captopril 75 mg/d (n=29) Placebo (n=31)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 18 Funding Source: Industry
Ruggenenti 1999(187) REIN, proteinuria stratum 1: ≥1 g to <3g/24 h Italy Followup period: median 2.6 years	Inclusion criteria - chronic nephropathy - persistent proteinuria (≥1 g to <3g) - aged 18 to 70 years Exclusion criteria - treatment with corticosteroids, NSAIDs or immunosuppressive drugs; - recent AMI or cerebrovascular accident - severe uncontrolled hypertension - renovascular disease - type 1 diabetes	N=186 Age (yr): 50 Gender (Male %): 75 Race/Ethnicity (%): NR BP (mm Hg): 143/89 Urinary protein excretion (g/day): 1.7 Serum creatinine (mg/dL): 2.0 Creatinine clearance (ml/min/1.73m2): 52 Estimated GFR (ml/min/1.73m2): 46	Ramipril 1.25 mg/d (n=99) Placebo (n=87)	- Allocation Concealment: adequate - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 22 Funding Source: Industry

		Diabetes (%): NR		
Crepaldi 1998(188) Sarafidis review Italy Followup period: 3 years	Inclusion criteria - overt albuminuria - GFR ≥80 ml/min/1.73m2 - aged 18 to 70 years - onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis - standing systolic BP ≥115 and ≤145 mmHg and diastolic BP ≥75 and ≤90 mmHg. Exclusion criteria - impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min - nondiabetic renal disease - clinically significant liver or hematological disease - arrhythmias; unstable angina; recent AMI - hyperkalemia	N=96 (66 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Gender (Male %): 67 Race/Ethnicity (%): NR BP (mm Hg): 128/83 Albumin excretion rate (µg/min): 71.5 Serum creatinine (mg/dL): 0.98 Creatinine clearance (ml/min/1.73m2): 114 Estimated GFR (ml/min/1.73m2): 114 Diabetes (%): 100	Lisinoprol 2.5-20 mg/d (n=47) Placebo (n=49)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 32 Funding Source: None stated
The GISEN Group 1997(189) REIN proteinuria stratum 2: ≥3 g/ 24 h Italy Followup period:	Inclusion criteria - chronic nephropathy - persistent proteinuria (≥3 g) - aged 18 to 70 years Exclusion criteria - recent AMI or cerebrovascular accident - severe uncontrolled hypertension	N=166 Age (yr): 49 Gender (Male %): 78 Race/Ethnicity (%): NR BP (mm Hg): 149/92 Urinary protein excretion (g/day):	Ramipril 1.25 mg/d (n=78) Placebo (n=88)	- Allocation Concealment: Adequate - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 21

mean 1.3 years	- renovascular disease - type 1 diabetes - cancer, higher serum aminotransferase concentrations, or chronic cough	5.3 Serum creatinine (mg/dL): 2.4 Creatinine clearance (ml/min/1.73m2): 45 Estimated GFR (ml/min/1.73m2): 39 Diabetes (%): NR		Funding Source: Industry
Maschio 1996(190) Europe Followup period: median 3 years	Inclusion criteria - chronic renal insufficiency caused by various - aged 18 to 70 years -serum creatinine concentration of 1.5 to 4.0 mg/dL and a 24-hour estimated creatinine clearance of 30 to 60 ml/min Exclusion criteria - therapy-resistant oedema - treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; - urinary protein excretion over 10 g/24 h and serum albumin under 25 g/L - renovascular hypertension - cardiovascular disease; congestive heart failure - insulin-dependent DM	N=583 Age (yr): 51 Gender (Male %): 72 Race/Ethnicity (%): NR BP (mm Hg): 143-87 Urinary protein excretion (g/day): 1.8 Serum creatinine (mg/dL): 2.1 Creatinine clearance (ml/min): 43 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 4 (n=21) have diabetic Nephropathy Severity of renal dysfunction: Creatinine clearance 46 to 60 ml/min) (%): 39 Creatinine clearance 30 to 45 ml/min) (%): 61	Benazepril 10 mg/d (n=300) Placebo (n=283)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 23 Funding Source: Industry
Trevisan 1995(195)	Inclusion criteria - persistent microalbuminuria - aged 18 to 65 years	N=122 Age (yr): 57	Ramipril 1.25 mg/d (n=60) Placebo (n=62)	- Allocation Concealment: Unclear - Blinding: double

Italy Followup period: 6 months	- stable type 2 diabetes <u>Exclusion criteria</u> - systolic blood pressure was ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg - unstable angina, heart failure serum creatinine >1.5 mg/dL - high serum potassium levels (>5.5 mEq/L - liver, gastrointestinal, and connective tissue diseases.	Gender (Male %): 77 Race/Ethnicity: NR Systolic BP (mm Hg): 149 Diastolic BP (mm Hg): 91 Albumin excretion rate (µg/min): 67 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100		- Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 11 Funding Source: Industry
Laffel 1995(191) North American Microalbuminuria Study Sarafidis review USA and Canada Followup period: 2 years	<u>Inclusion criteria</u> - microalbuminaria - aged 14 to 57 years - at least 4 years insulin-dependent DM - normotensive <u>Exclusion criteria</u> - HbA1c ≥11.5%; - serum creatinine and potassium levels beyond normal ranges - antihypertensive therapy; - histories of renal, cardiac, hepatic, gastrointestinal, or autoimmune diseases.	N=143 Age (yr): 33 Gender (Male %): 50 Race/Ethnicity (%): white 92 BP (mm Hg): 140/90 Albumin excretion rate (µg/min): 62 Serum creatinine (mg/dL): 1.1 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min/1.73m2): 80 Diabetes (%): 100	Captopril 100 mg (n=70) Placebo (n=73)	-Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 30 Funding Source: Industry
Sano 1994(192) Sarafidis review	<u>Inclusion criteria</u> - noninsulin dependent DM - persistent microalbuminuria - aged 50 to 76 years	N=52 (48 included in the baseline characteristics) Age (yr): 64	Enalapril (n=26) No enalapril (n=26)	- Allocation Concealment: Unclear - Blinding: no

Japan Followup period: 2 years	- serum creatinine <1.2 mg/dL; systolic BP <150 mmHg and diastolic <90 mmHg - no history of nondiabetic renal disease <u>Exclusion criteria</u> none stated.	Gender (Male %): NR Race/Ethnicity (%): NR BP (mm Hg): 136/74 Albumin excretion rate (mg/day): 72 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min): 90 Diabetes (%): 100		- Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 8 Funding Source: none stated
Lewis 1993(193) USA Followup period: median 3 years	<u>Inclusion criteria</u> - urinary protein excretion of ≥ 500 mg/24 h - serum creatinine concentration of ≤ 2.5 mg/dL - aged 18 to 49 years - insulin-dependent - diabetic retinopathy; <u>Exclusion Criteria</u> - CHF NYHA class III or worse - serum potassium ≥6 mmol/L.	N=409 Age (yr): 35 Gender (Male %): 53 Race/Ethnicity (%): white 89; black 7 BP (mm Hg): 138/85 Urinary protein excretion (g/day): 2.7 Serum creatinine (mg/dL): 1.3 Estimated GFR (ml/min/1.73m2): NR Creatinine clearance (ml/min): 82 HbA1c (%): 11.7 Diabetes (%): 100	Captopril 75 mg (n=207) Placebo (n=202)	- Allocation Concealment: Unclear - Blinding: double - Intention to Treat Analysis: yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 26 Funding Source: Industry and Other
Ravid 1993(194) Sarafidis review	<u>Inclusion criteria</u> - microalbuminuria - type 1 diabetes <10 years	N=108 (94 included in the baseline characteristics)	Enalapril 10 mg (n=56) Placebo (n=52)	- Allocation Concealment: Unclear - Blinding: double

Israel Followup period: 5 years	- no evidence of systemic, renal, cardiac, or hepatic disease - age <50 years; BMI <27 - normal BP <u>Exclusion criteria</u> none stated.	Age (yr): 44 Gender (Male %): 45 Race/Ethnicity (%): NR Mean BP (mm Hg): 98 Proteinuria (mg/day): 133 Serum creatinine (mg/dL): 1.2 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100		- Intention to Treat Analysis: no - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 13 Funding Source: other

Table 294

Clinical evidence profile: ARB versus Placebo

Ref	Comparison	Results		
AHRQ-CER37(105) MA	Angiotensin II receptor blockers (ARB) versus placebo All patients have diabetes	**ARB** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Tobe 2011 (TRANSCEND(196), Brenner 2001 (RENAAL(197), Parving 2001 (IRMA-2(198), Lewis 2001 (IDNT(166)		Total (N=4; n=5242)		
		ARB=432/2711 (15.9%)	Pla=415/2531 (16.4%)	RR=1.04 (0.92-1.18) NS I^2:0%
Cardiovascular mortality				
Tobe 2011 (TRANSCEND)(196)		Total (N=1; n=1991)		
		ARB=114/992 (11.5%)	Pla=112/999 (11.2%)	RR=1.03 (0.80-1.31) NS
CV events: MI (any)				
Brenner 2001 (RENAAL)(197)		Total (N=1; n=1513)		
		ARB=50/751	Pla=68/762	RR= 0.75 (0.53-

	(6.7%)	(8.9%)	1.06) NS
CV events: stroke (any)			
	NR		
Doubling of sCr			
Tobe 2011 (TRANSCEND)(196), Brenner 2001 (RENAAL)(197), Lewis 2001 (IDNT)(166)	Total (N=3; n= 4652)		
	ARB=275/2322 (11.8%)	Pla=354/2330 (15.2%)	**RR=0.78 (0.68-0.90) SS SS I^2:1%**
End-stage renal disease			
Tobe 2011 (TRANSCEND)(196), Brenner 2001 (RENAAL)(197), Lewis 2001 (IDNT)(193)	Total (N=3; n=4652)		
	ARB=232/2322 (10.0%)	Pla=301/2330 (12.9%)	**RR=0.77 (0.66-0.90) SS I^2:0%**
Progression from micro-to macroalbuminuria			
Makino 2007(199), Parving 2001 (IRMA-2)(198)	Total (N= 2; n=1104)		
	ARB=96/729 (13.2%)	Pla=117/375 (31.2%)	**RR=0.42 (0.33-0.52) SS I^2:0%**
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
	NR		
Renal adverse events leading to study withdrawal			
	NR		
Hyperkalemia necessitating discontinuation of study medication			
	Total (N=3; n=4652)		
	ARB=3.2%	Pla= 1.3%	**RR=2.38 (1.57-3.61) SS**

Table 295

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Tobe, 2011 TRANSCEND(196) Location Multinational Study duration: median 4.7 years (all subjects)	<u>Inclusion criteria</u> - patients intolerant to ACEI - coronary artery, peripheral vascular or CVD - diabetes with endorgan damage. <u>Exclusion criteria</u> - heart failure, - valvular or cardiac outflow tract obstruction - systolic BP >160 mm Hg - creatinine levels >265 µmol/L - proteinuria - hepatic dysfunction.	(N=5926 total were randomized, 1480 had a GFR <60 ml/min/1.73m2 and an additional 511 had micro or macroalbuminuria with a GFR ≥60 ml/min/ 1.73m2 (n=1991). N=1991 Age (yr): 68.7 Gender (Male %): 51 Race/Ethnicity (%): European 59, Asian 23 BP (mm Hg): 143/82 Albuminuria-to-creatinine ratio (ACR): 6.8 Serum creatinine (mg/dL): 1.2 Estimated GFR (ml/min/1.73m2): 57. Diabetes (%): 41	Telmisartan 80mg/day vs placebo	- Allocation Concealment : adequate - Blinding: double - Intention to Treat Analysis (ITT): yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 24% Note: Post-hoc analysis
Makino 2007(199) Location Japan Followup period: median 1.3 +/- 0.5 years	<u>Inclusion criteria</u> - Age 30 to 74 - type 2 DM - urinary albumin-to-creatinine ratio 100-300 mg/g - serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). <u>Exclusion criteria</u> - DM type 1	N=527 Age (yr): 61.7 Gender (Male %): NR Race/Ethnicity (%): NR BP (mm Hg): 137/77 Albuminuria: see Inc. criteria Serum creatinine (mg/dL): see Inc.	n= 168 to Telmisartan 80mg/day n= 172 to Telmisartan 40mg/day n= 174 to placebo	- Allocation Concealment Unclear - Blinding: Double blinded - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: Yes - Study withdrawals:2.4%

	- hypertension - definable chronic kidney disease other than diabetic nephropathy	criteria Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100		Funding Source: NR
Brenner 2001(197) RENAAL Location Multinational Followup period: median 3.4 years	<u>Inclusion criteria</u> - Age 31 to 70 years - type 2 DM -nephropathy <u>Exclusion criteria</u> - Type 1 DM or nondiabetic renal disease including renal-artery stenosis. - recent MI , CABG, CVA or TIA	N=1513 Age (yr): 60 Gender (Male %): 63.2 Race/Ethnicity (%): 50% white, 18% BP (mm Hg): 153/82 Albuminuria: Median Urine Alb/Cr: 1250 mg/g Serum creatinine (mg/dL): 1.9 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100	Losartan 50-100 mg/day Vs Placebo	- Allocation Concealment Adequate - Blinding: Double blind - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 7.8 Funding Source Industry
Parving 2001(198) IRMA-2 Location: 96 centers Worldwide Followup period: median 2 years	<u>Inclusion criteria</u> - hypertension - age 30 to 70 - type 2 DM - persistent microalbuminuria <u>Exclusion criteria</u> - Nondiabetic kidney Disease - cancer, life-threatening disease	N=590 Age (yr): 58 Gender (Male %): 68.5 Race/Ethnicity (%): White: 97.3, BP (mm Hg): 153/90 Diastolic BP (mm Hg): 90 Albuminuria: 55.5 µg/min Serum creatinine (mg/dL): 1.18 Estimated GFR (ml/min/1.73m2):NR Diabetes (%): 100	n= 201 placebo n= 195 Irbesartan 150mg n= 194 Irbesartan 300mg	- Allocation Concealment: unclear - Blinding: Double blind - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 13 Funding Source Industry
Lewis, 2001(166) IDNT	<u>Inclusion criteria</u> - Age 30 – 70 - type 2 DM,	N=1.148 Age (yr): 59	n= 579 Irbesartan 300 n= 569 Placebo	- Allocation Concealment : Adequate - Blinding: Patients,

Location USA Followup period: median 2.6 years	- hypertension - proteinuria (urinary protein excretion > 900 mg per 24 hours) - serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men <u>Exclusion criteria</u> None stated	Gender (Male %): 68 Race/Ethnicity (%): White 74.3 BP (mm Hg): 159/87 Albuminuria: NR Median Urine Protein Excretion 2.9 g/24hr Median Urine Albumin Excretion 1.9 g/24hr Serum creatinine (mg/dL): 1.68 Estimated GFR (ml/min/1.73m2): NR Diabetes (%): 100%	Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.	investigators, and assessors - Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: yes - Study withdrawals (%): 0.8 Funding Source: Industry

Table 296

3. Characteristics of extra studies in the evidence profile, not reported in a meta-analysis

Study details	n/Population	Comparison	Outcomes		Methodological
Imai 2011(200) Design: RCT Duration of follow-up: mean 3.2 years	n= 577 (Japanese and Chinese) Mean age: 59 y CV disease: 85% Hypertension: 94% Diabetes: 100% Smoking: 25% <u>Inclusion</u> - Type 2 diabetes - UACR >33.9 g/mmol) - SCr concentration	10-40 mg 1x/d Vs Placebo Added to existing background antihypertensive therapy	Efficacy		- RANDO: Adequate - ALLOCATION CONC: Adequate - BLINDING : Adequate - FOLLOW-UP: 98% - ITT: Yes Other important methodological remarks - 6 w placebo run-in Sponsor: Daiichi Sankyo.
			Composite outcome of doubling of SCr, ESRD (SCr >442.01 µmol/l [5 mg/dl]), chronic dialysis, transplantation and all-cause death (= primary outcome)	Olm=41.1% Pla= 45.4% HR: 0.97 (95% CI 0.75 to 1.24) NS	
			Doubling of SCR	37.6 vs 42.3% HR= 1.09 (0.78-1.49) NS	
			All-cause mortality	6.7 vs 7.0% HR= 0.99 (0.53-1.86) NS	

	88.40–221.00 µmol/l in women and 106.08–221.00 µmol/l in men <u>Exclusion</u> - type 1 diabetes - recent CV event or revascularization - heart failure III-IV - rapidly progressive renal disease - severe orthostatic hypotension - serum potassium level ≤3.5 mmol/l or ≥5.5 mmol/l.		ESRD	0 in both groups	
			Safety		
			Adverse events	Olm= 26% Pla=23% NT	
			Hyperkalemia	Olm= 9% Pla= 5% NT	

Table 297

<u>Clinical evidence profile: Beta blocker (BB) versus placebo</u>

Ref	Comparison	Results		
AHRQ-CER37 MA(105)	N=2 (post hoc analyses) n=2173	**BB** Event rate	**placebo** Event rate	**RR (95% CI)**
Mortality				
Cohen-Solal 2009(201), Ghali 2009(202)		Total (N=2)		
		BB= 134/1083 (12.4%)	Pla= 197/1090 (18.1%)	**RR=0.69 (0.53-0.91) SS in favour of BB I^2:45%**
Cardiovascular mortality				

Cohen-Solal 2009	Total (N=1)		
	BB= 49/348	Pla= 67/356	RR=0.75 (0.53-1.05) NS
Heart failure hospitalisation			
Ghali 2009	BB= 90/735 (12.2%)	Pla= 147/734 (20%)	**RR= 0.61 (0.48-0.78) SS in favour of BB**
CV events: MI (any)			
	NR		
CV events: stroke (any)			
	NR		
Doubling of sCr			
	NR		
End-stage renal disease			
	NR		
Progression from micro-to macroalbuminuria			
	NR		
Blood pressure			
	NR		
Any adverse events			
Cohen-Solal 2009	Total (N=1; n=886)		
	BB= 23/440 (5.2%)	Pla= 11/446 (2.5%)	NT

Table 298

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Cohen-Solal 2009(201)	Inclusion criteria: - age ≥70 years	n=704 (this is subgroup with GFR ≤55.5 ml/min/1.73m2 from larger	Nebivolol, 1.25-10 mg/d vs	- Allocation Concealment: Adequate

SENIORS Country Europe (11 countries) Followup period: 21 months	- clinical history of chronic heart failure with at least one of the following: a)hospital admission in past 12 months with discharge diagnosis of CHF or b) LVEF ≤35% in past 6 months <u>Exclusion criteria:</u> - heart failure due primarily to uncorrected valvular heart disease - significant hepatic or renal dysfunction - recent cerebrovascular accident	study of 2,135 patients) Age (yr): 77.4 Gender (Male %): 59.2 Race/Ethnicity (%): NR BP (mm Hg): 134/78 Serum creatinine (umol/L): 137.8 (=1.56 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m2): 43.5 Diabetes (%): 29.4	Placebo	- Blinding: double blind - Intention to Treat Analysis (ITT): no - Withdrawals/Dropouts adequately described: unclear - Study withdrawals: NR Other methodological remarks: **post hoc analysis** Funding Source: Private Industry
Ghal, 2009(202) MERIT-HF Country U.S., Sweden Norway, multisite Followup period: 1 year	<u>Inclusion criteria:</u> - aged 40-80 y - supine resting heart rate ≥68/min. - symptomatic heart failure NYHA II-IV - receiving optimum standard therapy - stable clinical condition - leftventricular ejection fraction of 0.40 or lower. - Patients with ejection fraction 0.36 to 0.40 included only if their maximum walking distance was 450 m or less in a 6 min walk test. <u>Exclusion criteria:</u> - recent acute myocardial infarction or unstable angina - heart failure secondary to systemic	n=1469 (this is subgroup with GFR ≤60 ml/min/1.73m2 from larger MERIT study of 3,991 patients) Age (yr): 68.1 Gender (Male %): 68.3 Race/Ethnicity (%): NR BP (mm Hg): 130/77 Serum creatinine (umol/L): 134.1 (=1.52 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m2): 47.7 Diabetes (%): 29.3	Metoprolol CR/XL, 12.5 mg daily for NYHA III-IV pts and 25.0 mg daily for NYHA II pts, to a targeted 200 mg daily over 8 weeks vs Placebo	Allocation Concealment: Adequate - Blinding: double blind Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: unclear - Study withdrawals: NR - Other methodological remarks: **post hoc analysis** Funding Source: NA

	disease or alcohol abuse - atrioventricular block - use of calcium antagonists or amiodarone			

Table 299

Clinical evidence profile: CCB versus placebo

Ref	Comparison	Results		
AHRQ-CER37 MA(105)	N=2 Lewis (IDNT) 2001, Crepaldi 1998	**CCB** Mean (SD) or event rate	**placebo** Mean (SD) or event rate	**RR (95% CI)**
Mortality				
Lewis (IDNT) 2001(166), Crepaldi 1998(188)		Diabetic nephropathy (N=2)		
		CCB= 84/608 (13.8%)	Pla= 93/618 (15.0%)	RR=0.90 (0.69-1.19) NS I^2:0%
Cardiovascular mortality				
Lewis (IDNT) 2001, Crepaldi 1998		Diabetic nephropathy (N=2)		
		CCB= 38/608 (6.3%)	Pla= 46/618 (7.4%)	RR=0.83 (0.55-1.25) NS I^2:0%
CV events: MI (any)				
Lewis (IDNT) 2001, Crepaldi 1998		Total = Diabetic nephropathy (N=2)		
		CCB= 27/608 (4.4%)	Pla= 47/618 (7.6%)	**RR=0.58 (0.37-0.92)** **SS in favour of CCB** **I^2:0%**
CV events: stroke (any)				
Lewis (IDNT) 2001		Diabetic nephropathy (N=1)		
		CCB= 15/567	Pla= 26/569	RR=0.58 (0.31-

	(2.6%)	(4.6%)	1.08) NS
Doubling of sCr			
Lewis (IDNT) 2001	Diabetic nephropathy (N=1)		
	CCB= 144/567 (25.4%)	Pla= 135/569 (23.7%)	RR=1.07 (0.87-1.31) NS
End-stage renal disease			
Lewis (IDNT) 2001	Diabetic nephropathy (N=1)		
	CCB= 104/567 (18.3%)	Pla= 101/569 (17.8%)	RR=1.03 (0.81-1.32) NS
Progression from micro-to macroalbuminuria			
Crepaldi 1998	Total (N=1)		
	CCB= 2/26 (7.7%)	Pla= 7/34 (20.6%)	RR=0.37 (0.08-1.65) NS
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
	NR		
Renal adverse events leading to study withdrawal			
	NR		

Table 300

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Lewis 2001(166) IDNT	Inclusion Criteria - ages 30-70 - type 2 DM	N=1.136 Age (yr): 58.7	amlodipine (titrated from 2.5 to 10 mg/day) vs	- Allocation Concealment: Adequate - Blinding: Double blind

International Multi-site Followup period: 2.5 years (mean)	- hypertension - proteinuria (urinary protein excretion >900 mg/24h) - serum creatinine between 1.0 and 3.0 mg/dL (women) and 1.2-3.0 mg/dL (men) <u>Exclusion criteria</u>: none stated	Gender (Male %): 67 Race/Ethnicity (%): 71.0% white, BP (mm Hg): 158/87 Serum creatinine (mg/dL): 1.7 Creatinine clearance (mL/min): NR Albuminuria (gday): 1.9 Proteinuria (g/day): 2.9 Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m2): NR Diabetes (%): 100	placebo Antihypertensives other than ACEIs, ARBs, and CCBs used as needed;	- Intention to Treat Analysis (ITT): Yes - Withdrawals/Dropouts adequately described: Yes - Study withdrawals: 0.5% Funding Source: Industry
Crepaldi 1998(188) Italy Multi-site Followup period: 3 years	<u>Inclusion criteria</u> - ages 18 to 65 years; - onset of insulin-dependent diabetes mellitus before age 35; insulin treatment within 3 years of diagnosis; - standing SBP from 115 to 140 mm Hg (without antihypertensives) - median albumin excretion rate between 20 and 200 µg/min - GFR ≥80 ml/min/1.73m2 <u>Exclusion criteria:</u> - impaired renal function; serum creatinine >10% above upper limit of normal laboratory - history of any nondiabetic renal disease - clinically significant liver or hematological disease - arrhythmias, unstable angina, or	N= 90 (baseline data reported for 60 patients who were not excluded during run-in phase) Age (yr): 36.6 Gender (Male %): 70 Race/Ethnicity (%): NR BP (mm Hg): NR Albumin (g/dl): 4.4 Serum creatinine (µmol/L): 85.8 (=0.97 mg/dL) Creatinine clearance (mL/min): 107.8 Albuminuria (µg/min): 80.2 Albumin/Creatinine ratio (mg/mmol): NR GFR (ml/min/1.73m2): 111.8 Diabetes (%): 100	10 mg nifedipine vs placebo Antihypertensives other than ACEIs, ARBs, and CCBs used as needed;	- Allocation Concealment: Unclear - Blinding: Double blind - Intention to Treat Analysis (ITT): No - Withdrawals/Dropouts adequately described: Yes - Study withdrawals (%): 32.2 Funding Source: None reported

	history of myocardial infarction - autonomic neuropathy - systematic malignancy			

Table 301

4.3.5.1.1.2 Summary and conclusions

ACE (ACEI) inhibitors versus placebo			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	11536 (16 studies) 6m - 5y	RR= 0.94 (0.80-1.12) NS Diabetic (N=11) RR= 0.91 (0.70-1.18) NS Non diabetic RR= 1.01 (0.72-1.43)	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Cardiovascular mortality	7533 (3 studies)	RR=1.03 (0.86-1.23) NS Diabetic (N=1) RR= 1.07 (0.85-1.35) NS Non diabetic RR= 0.97 (0.74-1.29) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
Myocardial infarction (any)	5100 (3 studies)	Diabetic (N=3) RR=0.79 (0.57-1.09) NS Non diabetic NR	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Stroke (any)	7719 (4 studies)	RR= 0.80 (0.52-1.23) NS Diabetic (N=1) RR= 1.03 (0.80-1.32) NS Non diabetic (N=3) RR= 0.51 (0.13-2.09) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for posthoc analysis Consistency: -1 Directness: OK Imprecision: OK
Doubling of serum creatinine	7392 (7 studies)	**RR= 0.60 (0.40-0.89)** **SS in favour of ACEI** Diabetic RR= 0.69 (0.44-1.09) Non diabetic RR= 0.31 (0.07-1.35)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
ESRD	7490 (7 studies)	**RR=0.65 (0.49-0.88)** **SS in favour of ACEI** Diabetic (N=4) RR= 0.73 (0.48-1.10) Non diabetic (N=3) **RR= 0.59 (0.39-0.89)**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Progression from micro- to macroalbuminuria	1682 (7 studies)	**RR=0.48 (0.27-0.85)** **SS in favour of ACEI**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for posthoc analysis Consistency: OK Directness: OK Imprecision: OK
Any or serious adverse events leading to study withdrawal	7336 (14 studies)	**RR=1.12 (1.02-1.23)** **SS more frequent with ACEI**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: -1 Directness: OK Imprecision: OK
Cough	7361 (10 studies)	**RR=2.33 (1.49-3.63)** **SS more frequent with ACEI**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia	2758 (8 studies)	RR=1.08 (0.53-2.23)	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Table 302

In this meta-analysis, ACE inhibitors (ACEIs) were compared to placebo in patients with CKD (mostly early stage disease). The majority of the trials was performed in diabetic patients with albuminuria. Included patients could be normotensive or hypertensive.

Treatment with ACEI does not significantly reduce risk of all-cause mortality in patients with or without diabetes, compared to placebo.
GRADE: HIGH quality of evidence

Treatment with ACEI does not significantly reduce risk of all-cause mortality in patients with or without diabetes, compared to placebo.
GRADE: MODERATE quality of evidence

Patients with diabetic CKD randomized to ACEIs did not have a significantly reduced risk of myocardial infarction compared with those assigned placebo. There are no date on patients with non-diabetic CKD.
GRADE: HIGH quality of evidence

Patients with CKD, diabetic and non-diabetic, randomized to ACEIs did not have a significantly reduced risk of stroke compared with those assigned placebo.
GRADE: LOW quality of evidence

CKD patients overall assigned ACEI treatment had a significantly reduced risk for doubling of baseline serum creatinine, compared with placebo. In subgroup analysis according to diabetic status, this effect was not statistically significant.
GRADE: MODERATE quality of evidence

In CKD patients overall, ACEIs significantly reduced the risk of ESRD, compared with placebo. This effect was significant in patients without diabetes but not in the subgroup with diabetic CKD.
GRADE: HIGH quality of evidence

CKD patients overall assigned ACEI treatment had a significantly reduced risk for progression from microalbuminuria to macroalbuminuria, compared with placebo.
GRADE: MODERATE quality of evidence

Patients allocated to an ACEI were significantly more likely to withdraw from treatment due to any or a serious adverse event than patients assigned placebo.
GRADE: MODERATE quality of evidence

Cough was significantly more likely in patients treated with ACEIs, compared to placebo.
GRADE: HIGH quality of evidence

Hyperkalemia was not significantly increased with use of an ACEI, compared to placebo.
GRADE: HIGH quality of evidence

Angiotensin II receptor antagonists (ARB) versus placebo			
Bibliography: meta-analysis AHRQ CER 37(105), Imai 2011(200)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5242+577 (4+1 studies) 1-4.5 y	RR= 1.04 (0.92-1.18) NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Cardiovascular mortality	1991 (1 study)	RR=1.03 (0.80-1.31) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 for post hoc analysis only available study Consistency: NA Directness: OK Imprecision: OK
Myocardial infarction (any)	1513 (1 study)	RR= 0.75 (0.53-1.06) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1
Doubling of sCr	4652+577 (3+1 studies)	**RR=0.78 (0.68-0.90) SS in favour of ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
ESRD	4652 (3 studies)	**RR=0.77 (0.66-0.90) SS in favour of ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Progression from	1104	**RR=0.42 (0.33-0.52)**	⊕⊕⊕⊕ **HIGH**

micro-to macroalbuminuria	(2 studies)	**SS in favour of ARB**	Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia necessitating discontinuation of study medication	4652 (3 studies)	**RR=2.38 (1.57-3.61)** **SS more frequent with ARB**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Table 303

In this meta-analysis and an additional RCT, angiotensin II receptor blockers (ARB) were compared to placebo in patients with diabetic CKD and albuminuria. The majority of patients were hypertensive at baseline.

Treatment with ARB does not significantly reduce risk of all-cause mortality compared with placebo.
GRADE: HIGH quality of evidence

Treatment with ARB does not significantly reduce risk of cardiovascular mortality compared with placebo.
GRADE: LOW quality of evidence

Treatment with ARB does not significantly reduce risk of myocardial infarction compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with ARB significantly reduces risk of doubling of sCr and risk of progression from micro- to macro-albuminuria.
GRADE: HIGH quality of evidence

Treatment with ARB significantly reduces risk of ESRD.
GRADE: HIGH quality of evidence

Hyperkalemia necessitating discontinuation of study medication was more frequent in patients treated with ARB, compared to placebo.
GRADE: HIGH quality of evidence

There are no data on the following outcomes: stroke and other adverse events than hyperkalemia.

Beta blockers versus placebo			
Bibliography: AHRQ Fink CER 37(105)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2173 (2 studies) 1-2 years	**RR=0.69 (0.53-0.91)** **SS in favour of BB**	⊕⊖⊖ ⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: OK

			Directness: -1 for only heart failure patients included Imprecision: OK
Cardiovascular mortality	704 (1 study)	RR=0.75 (0.53-1.05) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: NA Directness: -1 for only heart failure patients included Imprecision: OK
Heart failure hospitalization	1469 (1 study)	**RR= 0.61 (0.48-0.78)** **SS in favour of BB**	⨁⊖⊖ ⊖ **VERY LOW** Study quality: -2 for only post hoc analyses Consistency: NA Directness: -1 for only heart failure patients included Imprecision: OK

Table 304

This meta-analysis includes two post hoc analyses of patients with CKD, selected from bigger trials with heart failure patients. Patients on optimal medical therapy for heart failure were randomized to beta blocker or placebo.

There was a significant reduction in the risk of all-cause mortality in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

There was a significant reduction in the risk of cardiovascular mortality in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

There was a significant reduction in the risk of hospitalization for heart failure in patients treated with beta blockers compared to patients treated with placebo.
GRADE: VERY LOW quality of evidence

No data for the following outcomes: AMI, stroke, renal outcomes, blood pressure, adverse events.

Calcium channel blockers (CCB) versus placebo			
Bibliography: AHRQ Fink CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
All-cause mortality	1226 (2 studies) 2.5-3 years	RR=0.90 (0.69-1.19) NS	⨁⨁⨁⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cardiovascular mortality	1226 (2 studies)	RR=0.83 (0.55-1.25) NS	⨁⨁⨁⊖ **MODERATE** Study quality: OK Consistency: OK

			Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (any)	1226 (2 studies)	**RR=0.58 (0.37-0.92)** **SS in favour of CCB**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke (any)	1136 (1 study)	RR=0.58 (0.31-1.08) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Doubling of sCr	1136 (1 study)	RR=1.07 (0.87-1.31) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
End-stage renal disease	1136 (1 study)	RR=1.03 (0.81-1.32) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	60 (1 study)	RR=0.37 (0.08-1.65) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data

Table 305

This meta-analysis included 2 trials in patients with diabetes and CKD. Patients in the largest trial (n=1136) had type 2 diabetes and were hypertensive; patients in the smallest trial (n=60)had type 1 diabetes and were normotensive.

Treatment with CCB does not significantly reduce the risk of all-cause and cardiovascular mortality compared with placebo.
GRADE: MODERATE quality of evidence

Patients treated with CCB had a significantly lower risk of myocardial infarction compared to those treated with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of stroke compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of doubling of sCR and the risk of ESRD compared with placebo.
GRADE: MODERATE quality of evidence

Treatment with CCB does not significantly reduce the risk of progression from micro-to macroalbuminuria compared with placebo.
GRADE: VERY LOW quality of evidence

No data are available for the following outcomes: blood pressure, total, serious or renal adverse events.

4.3.5.1.2 ACE-inhibitor versus angiotensin receptor blocker

4.3.5.1.2.1 Clinical evidence profile

Intervention: ACE inhibitoren (ACEI) versus ARB (sartanen)

Clinical evidence profile: ACEI versus ARB

Ref	Comparison	Results		
AHRQ-CER37(105) MA	ACEI vs ARB N=6 , n=4799	**ACEI** Event rate	**ARB** Event rate	**RR (95% CI)**
Mortality				
Barnett 2004(203), Lacourcière 2000(204), Menne 2008(205), Muirhead 1999(186)		Total (N=4 ; n=534)		
		ACEI= 7/257 (2.7%)	ARB= 5/277 (1.8%)	RR=1.04 (0.37-2.95) NS I^2: 0%
Cardiovascular mortality				
Barnett 2004(203), Lacourcière 2000(204), Menne 2008(205), Muirhead 1999(186)		Total (N=4; n=534)		
		ACEI= 3/257 (1.2%)	ARB= 3/277 (1.1%)	RR= 0.88 (0.19-4.13) NS I^2: 0%
CV events: stroke (non-fatal and fatal)				
Lacourcière 2000(204)		Total (N=1; n=103)		
		ACEI= 0/51	ARB= 0/52	NR
CV events: MI (non-fatal)				
Barnett 2004(203), Lacourcière 2000(204)		Total (N= 2; n=353)		
		ACEI= 6/181 (3.3%)	ARB= 9/172 (5.2%)	RR= 0.62 (0.23-1.68) NS I^2: not applicable
Doubling of sCr				
		NR		

End-stage renal disease			
	NR		
Progression from micro-to macroalbuminuria			
Sengul 2006(206)	Total (N=1; n=219)		
	ACEI= 0/110	ARB= 0/109	
Blood pressure			
	NR		
Any study withdrawal			
Barnett 2004(203), Lacourcière 2000(204), Menne 2008(205), Muirhead 1999(186), Sengul 2006(206)	Total (N= 5; n=753)		
	ACEI= 74/366 (20.2%)	ARB= 70/387 (18.1%)	RR=1.07 (0.80-1.42) NS I^2: 0%
Study withdrawal due to AE			
Barnett 2004(203), Lacourcière 2000(204), Menne 2008(205), Muirhead 1999(186)	Total (N=4 ; n=534)		
	ACEI= 37/257 (14.4%)	ARB= 27/277 (9.7%)	RR= 1.35 (0.86-2.13) NS I^2: 0%
Cough			
Lacourcière 2000(204), Menne 2008(205), Muirhead 1999(186)	Total (N= 3; n=284)		
	ACEI= 15/127 (11.8%)	ARB= 4/157 (2.5%)	**RR= 4.10 (1.47-11.48) SS more frequent with ACEI** **I^2: 0%**
Hyperkalemia			
Menne 2008(205)	Total (N=1; n=90)		
	ACEI= 1/47 (2.1%)	ARB= 1/43 (2.3%)	NT

Table 306

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Menne, 2008(205) VALERIA Germany and Hungary Follow up period: 2.5 years	Inclusion criteria - microalbuminuria - aged 18 to 75 years - essential hypertension Exclusion criteria: - primary kidney Disease - renal impairment - serum potassium values >5.5mmol/L; - heart failure, significant arrhythmias or bradycardia - type I DM, uncontrolled type II DM with HbA1c >8.0%; - history of MI; recent PTCA or stroke percutaneous - unstable angina pectoris; renal transplantation; - severe hepatic disease - malignant concomitant diseases - systemic inflammatory diseases	N= 90 Age (yr): 58 Race/ethnicity (%): NR Gender (male%): 69 BP: 153/91 mmHg Urinary protein excretion (g/24 h): NR Urine albumin creatinine ratio (mg/min): 9.4 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 112 Diabetes (%): 74	Lisinopril 40 mg/d (n=47) versus Valsartan 320 mg/d (n=43)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 86% Funding: Industry
Sengul, 2006(206) Turkey Followup period: 1 year	Inclusion criteria - Type 2 diabetes - microalbuminuria - aged 40 to 65 years - previously diagnosed hypertension despite receiving ACE inhibitor monotherapy for ≥6 month	N= 219 Age (yr): 57 Race/ethnicity (%): NR Gender (male%): 37 BP: 151/89 mmHg Urinary protein excretion (g/24 h): 260	Lisinopril 20 mg/d (n=110) versus Telmisartan 80 mg/d (n=109)	- Allocation concealment: unclear - Blinding: open-label - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 88%

	Exclusion criteria - type 1 DM; BMI ≥40 - any non-diabetic cause of secondary HTN (including bilateral renal artery stenosis) - chronic liver disease - overt carcinoma - any recent cardiovascular event - serum creatinine ≥ 150 mmol/L - serum potassium ≥ 5.5 mmol/L	Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 97 Diabetes (%): 100		Other methodological remarks: no Funding: none stated
Barnett, 2004(203) DETAIL Europe Followup period: 5 years	Inclusion criteria - urinary albumin excretion rate 11-999 µg per minute, - aged 35 to 80 years - type 2 diabetes - mild-to-moderate hypertension - normal renal morphology - serum creatinine <1.6 mg/dL - GFR >70 ml/min/1.73m2. Exclusion criteria - any condition (other than cardiovascular disease) that could restrict long-term survival	N= 250 Age (yr): 61 Race/ethnicity (%): white 98 Gender (male%): 73 BP: 152/86 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): median 46 to 60 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): 93 Creatinine clearance (mg/min): NR Diabetes (%): 100	Enalapril 20 mg/d (n=130) versus Telmisartan 80 mg/d (n=120)	- Allocation concealment: adequate - Blinding: double - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 67% Funding: industry
Lacourcière, 2000(204) Canada Followup period: 1 year	Inclusion criteria - early nephropathy characterized by a UAE rate 20 to 350 µg/min without evidence of urinary tract infection - type 2 diabetes - mild to moderate hypertension	N= 103 Age (yr): 59 Race/ethnicity (%): white 96; asian: 3; black: 1 Gender (male%): 81 BP: 160/96 mmHg Urinary protein excretion (g/24 h):	Enalapril 5 mg/d (n=51) versus Losartan 50 mg/d (n=52)	- Allocation concealment: unclear - Blinding: double blind - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 89%

	Exclusion criteria - renovascular disease; - history of malignant hypertension; - recent CVA, TIA or AMI - arrhythmias; unstable angina; history of heart failure - serum creatinine ≥ 200 mmol/L; - serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L	NR Urinary AER (µg/min): 69 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 96 Creatinine clearance (mg/min): NR Diabetes (%): 100		Funding: Industry
Muirhead, 1999(186) Kunz review Canada Followup period: 1 year	Inclusion criteria - incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m² - aged ≥ 18 years - type 2 DM Exclusion criteria - "brittle" diabetes (increased risk of hypoglycemia) or patients with a history of non compliance with medical regimens.	N= 91 Age (yr): 56 Race/ethnicity (%): white: 90; black: 1; asian: 4 Gender (male%): 67 BP: 136/83 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): 54 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 91 Creatinine clearance (mg/min): NR Diabetes (%): 100	Captopril 75 mg/d (n=29) Versus Valsartsan 80 mg/d (n=31) versus Valsartsan 160 mg/d (n=31)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 87% Funding: Industry

Table 307

4.3.5.1.2.2 Summary and conclusions

ACE inhibitors (ACEI) versus angiotensin receptor II antagonists (ARB)			
Bibliography: AHRQ-CER37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	534 (4 studies) 1-5 years (mean 2.5 y)	RR=1.04 (0.37-2.95)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cardiovascular mortality	534 (4 studies)	RR= 0.88 (0.19-4.13)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke (any)	103 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Myocardial infarction (non fatal)	353 (2 studies)	RR= 0.62 (0.23-1.68)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	219 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Any study withdrawal	753 (5 studies)	RR=1.07 (0.80-1.42)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Study withdrawal due to AE	534 (4 studies)	RR= 1.35 (0.86-2.13)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data
Cough	284 (3 studies)	**RR= 4.10 (1.47-11.48)** **SS more frequent with ACE-I**	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 for sparse data

Table 308

In this meta-analysis, ACE-I were compared to ARB in patients with early stages of CKD. The majority of included patients had diabetes and albuminuria. Nearly all patients were hypertensive at baseline. Overall, trials were small and of low methodological quality.

Between patients assigned to ACE-I versus those assigned to ARB, there is no significant difference in risk for total mortality, cardiovascular mortality, myocardial infarction or stroke.
GRADE: LOW quality of evidence

Between patients assigned to ACE-I versus those assigned to ARB, there is no significant difference in risk of progression from micro- to macro-albuminuria.
GRADE: LOW quality of evidence

There was no significant difference between ACE-I and ARB for total study withdrawal or withdrawal due to adverse events.
GRADE: LOW quality of evidence

Cough was more frequent in patients treated with ACE-I compared with ARB.
GRADE: LOW quality of evidence

No data are available for the following outcomes: doubling of sCr and end-stage renal disease.

4.3.5.1.3 ACE-inhibitor versus beta blocker

4.3.5.1.3.1 Clinical evidence profile

Clinical evidence profile: ACEI versus BB

Ref	Comparison	Results		
AHRQ-CER37(105) MA	ACEI vs BB	**ACEI** Event rate	**BB** Event rate	**RR (95% CI)**
Mortality				
Hannedouche 1994(207), Norris 2006 (AASK)(208), van Essen 1997(209)		Total (N=3; n = 1080)		
		ACEI= 37/540 (6.9%)	BB= 52/540 (9.6%)	RR= 0.71 (0.48-1.07) NS I^2: 0%
Cardiovascular mortality				
Norris 2006(208), van Essen 1997		Total (N=1; n=980)		
		ACEI= 14/488 (2.9%)	BB= 13/492 (2.6%)	RR= 1.08 (0.51-2.28) NS I^2: 0%
CV events: MI (any)				
		NR		
CV events: stroke (any)				
Norris 2006(208)		Total (N=1; n=877)		
		ACEI= 23/436 (5.3%)	BB= 23/441 (5.2%)	RR= 1.01 (0.58-1.78) NS
Doubling of sCr				
		NR		
End-stage renal disease				
Hannedouche 1994(207), Norris 2006(208), van Essen 1997(209)		Total (N=3; n = 1080)		
		ACEI= 77/540	BB= 92/540	RR= 0.81 (0.50-

	(14.3%)	(17.0%)	1.33) NS I^2: 40%
Progression from micro-to macroalbuminuria			
	NR		
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
Hannedouche 1994(207), van Essen 1997(209), Wright 2002(109)	Total (N3=; n=1080)		
	ACEI= 2.2%	BB= 1.5%	P=0.39 (NS)
Renal adverse events leading to study withdrawal			
	NR		
Cough			
Wright 2002(109)	Total (N= 1; n=877)		
	ACEI= 54.9% per patient year	BB= 41.5% per patient year	NT
Hyperkalemia			
Van Essen 1997(209), Wright 2002(109)	Total (N=2; n=980)		
	ACEI= 2.9%	BB= 0.0%	NT

Table 309

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Wright 2002(109) Norris 2006(208) AASK USA	Inclusion criteria - African Americans with hypertension - aged 18 to 70 years - GFR between 20 and 65 mL/min/1.73 m^2 - no other identified causes of renal insufficiency.	N= 877 (minus amlodipine arm of 1094 randomized) Age (yr): 55 Race/ethnicity (%): NR Gender (male%): 61.5 BP: 150.5/95.5 mmHg	Ramipril 2.5-10.0 mg/d (n=436) versus Metoprolol 50-200 mg/d (n=441)	- Allocation concealment: adequate - Blinding: adequate - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 100%

Followup period: 4 years	Exclusion criteria - diastolic BP <95 mm Hg - diabetes - urinary protein to creatinine ratio >2.5 - malignant or secondary hypertension - evidence of non-BP-related causes of chronic kidney disease - serious systemic disease	Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): 2.15 Estimated GFR (ml/min/1.73m²): 45.6 Creatinine clearance (mg/min): NR Diabetes (%): 0		Funding: Industry and others
Van Essen 1997(209) Followup period: median 3.9 years	Inclusion criteria - modest CKD defined as a creatinine clearance of 30-90 mL/min - aged 18 to 65 years old - no need for immunosuppressive agents or NSAIDS - no proven renal artery stenosis - Both patients with and without proteinuria could be included. Exclusion criteria NR	N= 103 Age (yr): 50 Race/ethnicity (%): NR Gender (male%): 64 BP: 152/90 mmHg Urinary protein excretion (g/24 h): median 3.3 Serum creatinine (mg/dL): 1.8 Estimated GFR (ml/min/1.73m²): 53 Creatinine clearance (ml/min/1.73m²): 55 Diabetes (%): 0	Enalapril 10 mg/d (n=52) versus Atenolol 50 mg/d (n=51)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 86% Funding: Industry
Hannedouche 1994(207) France Followup period: 3 years	Inclusion criteria - aged 18 to 70 years - chronic renal failure as defined by a serum creatinine concentration of 200-400 µmol/L Exclusion criteria -nephrotic syndrome - systemic diseases including diabetes, malignant hypertension,	N= 100 Age (yr): 51 Race/ethnicity (%): NR Gender (male%): 53 BP: 167/102 mmHg Urinary protein excretion (g/24 h): 2.2 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m²): NR	Enalapril 5-10 mg/d (n=52) versus Acebutolol 400 mg/d or Atenolol 100 mg/d (n=48)	- Allocation concealment: adequate - Blinding: open label - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 77%

	serious extrarenal disorders including malignancy, heart failure,	Creatinine clearance (mg/min): NR Diabetes (%): 0		Funding: Industry

Table 310

4.3.5.1.3.2 Summary and conclusions

ACE inhibitors versus beta blockers			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1080 (3 studies) 3-4 y	RR= 0.71 (0.48-1.07) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Cardiovascular mortality	980 (2 studies)	RR= 1.08 (0.51-2.28) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Stroke	877 (1 study)	RR= 1.01 (0.58-1.78) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
ESRD	1080 (3 studies)	RR= 0.81 (0.50-1.33) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data
Any or serious adverse events leading to study withdrawal	1080 (3 studies)	2.2 vs 1.5% P= 0.39 (NS)	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 (mainly data on African Americans) Imprecision: -1 for sparse data

Table 311

In this meta-analysis, ACEI were compared to beta blockers in patients with CKD without diabetes. The largest trial was performed in Afro-Americans with moderate CKD (stage 3). The majority of included patients were hypertensive at baseline.

When comparing ACEI with beta blockers, no significant differences were found for the incidence of all-cause or cardiovascular mortality.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the risk of stroke.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the risk of ESRD.
GRADE: LOW quality of evidence

When comparing ACEI with beta blockers, no significant differences were found for the total incidence of adverse events, nor for the occurrence of serious adverse events.
GRADE: LOW quality of evidence

There are no data available for the following outcomes: myocardial infarction, doubling of sCR, progression of micro- to macroalbuminuria, blood pressure, cough and hyperkalemia.

4.3.5.1.4 ACE-inhibitor versus calcium channel blocker

4.3.5.1.4.1 Clinical evidence profile

Clinical evidence profile: ACEI versus CCB

Ref	Comparison	Results		
AHRQ-CER37(105) MA	N = 6 ACEI vs CCB n = 4357	**ACEI** Event rate	**CCB** Event rate	**RR (95% CI)**
Mortality				
Crepaldi 1998(188), Fogari 2002(210), Marin 2001(211), Norris 2006 (AASK)(208), Zucchelli 1992(212, 213)		Total (N=5; n=1307)		
		ACEI= 42/774 (5.4%)	CCB= 33/533 (6.2%)	RR= 0.75 (0.48-1.16) NS I^2: 0%
Cardiovascular mortality				
Marin 2001(211), Norris 2006(208), Zucchelli 1992(212, 213)		Total (N=3; n=1011)		
		ACEI= 16/625 (2.6%)	CCB= 13/386 (3.4%)	RR= 0.75 (0.36-1.57) NS I^2: 0%
CV events: Any and fatal myocardial infarction				
Crepaldi 1998(188)		Total (N=1; n=58)		
		ACEI= 0/32	CCB= 0/26	Not determined
CV events: stroke (any)				
Marin 2001(211), Norris 2006(208), Rahman 2006(214)		Total (N=3; n=3943)		
		ACEI= 123/2098 (5.9%)	CCB= 111/1845 (6.0%)	RR= 1.00 (0.78-1.28) NS I^2: 0%
Doubling of sCr				

	NR		
End-stage renal disease			
Norris 2006(208), Rahman 2006(214), Zucchelli 1992(212, 213)	Total (N=3; n=3823)		
	ACEI= 124/2029 (6.1%)	CCB= 111/1794 (6.2%)	RR= 0.82 (0.57-1.19) NS I^2: 46%
Progression from micro-to macroalbuminuria			
Agodoa 2001(215), Rahman 2006(214)	N=2; n=3702		
	ACEI= 80/1969 (4.1%)	CCB= 48/1733 (2.8%)	NT
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
Fogari 2002(210), Wright 2002(109), Marin 2001(211), Crepaldi 1998(188), Zucchelli 1995(213)	Total (N=5)		
	ACEI= 3.2%	CCB= 4.7%	p=0.77 NS
Renal adverse events leading to study withdrawal			
Fogari 2002(210), Wright 2002(109), Crepaldi 1998	Total (N=3 ; n=504)		
	ACEI= 6/263 (2.3%)	CCB= 3/241 (1.2%)	NT
Cough			
Fogari 2002(210), Marin 2001(211), Zucchelli 1995(213)	Total (N=3 ; n=567)		
	7/291 (2.4%)	CCB= 0/276 (0.0%)	NT

Table 312

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Rahman 2006(214) ALLHAT	Inclusion criteria - aged 55 years or older	N= 3049 for patients with a baseline GFR <60 ml/min/ 1.73m²	Lisinopril up to 40 mg/d (n=1533)	- Allocation concealment: adequate

USA and CANADA Followup period: mean 4.9 years	- stage 1 or stage 2 hypertension - at least 1 additional risk factor for CHD events <u>Exclusion criteria</u> - heart failure and/or a known left ventricular ejection fraction <35% - serum creatinine level > 2 mg/dL	(of a total of 17118 randomized and minus the chlorthalidone arm) Subgroup analysis with diabetic patients: n=1007 Age (yr): 70 Race/ethnicity (%): white: 58; black 25; Hispanic: 13 Gender (male%): 48 BP: 147/83 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 50 Creatinine clearance (mg/min): NR Diabetes (%): 33	versus Amlodipine up to 10 mg/d (n=1516)	- Blinding: double - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: not reported for CKD subgroup - Follow-up: % study withdrawals : not reported for CKD subgroup Other methodological remarks: - 3 x 2 factorial design - **post hoc analysis** Funding: Industry and other
Fogari, 2002(210) Italy Followup period: 4 years	<u>Inclusion criteria</u> - microalbuminuria; - essential hypertension - type 2 DM - UAE ≥30 and ≤300 mg/24 h - serum creatinine <1.5 mg/dL. <u>Exclusion criteria</u> - history of previous CHD, stroke, heart failure - cancer; smoking - total cholesterol >240 mg/dL - use of diuretics or beta blockers.	N= 205 (minus the combination artm) Age (yr): 63 Race/ethnicity (%): NR Gender (male%): 58 BP: 160/97 mmHg Urinary protein excretion (g/24 h): NR Urinary AER (µg/min): 97 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): 90	Fosinopril 10-30 mg/d (n=102) versus Amlodipine up to 10 mg/d (n=103) *Combination arm*	- Allocation concealment: adequate - Blinding: open label - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 68% Other methodological remarks: no Funding: Industry and other

		Diabetes (%): 100		
Agodoa, 2001(215) Wright, 2002(109) Norris, 2006(208) AASK USA Followup period: mean 4 years (Norris 2006)	Inclusion criteria - African Americans with hypertension - aged 18 to 70 years - GFR between 20 and 65 mL/min/1.73 m2 - no other identified causes of renal insufficiency. Exclusion criteria - diastolic BP of <95 mm Hg - diabetes - urinary protein to creatinine ratio >2.5 - malignant or secondary hypertension - evidence of non–BP-related causes of chronic kidney disease - serious systemic disease	N= 653 (minus metoprolol arm of 1094 randomized) Age (yr): 54 Race/ethnicity (%): 100 African American Gender (male%): 61 BP: 151/96 mmHg Urinary protein excretion (g/24 h): 0.5 Serum creatinine (mg/dL): 2.21 for men and 1.76 for women Estimated GFR (ml/min/1.73m2): 46.3 Creatinine clearance (mg/min): NR Diabetes (%): 0	Ramipril 2.5-10 mg/d (n=436) Versus Amlodipine 5-10 mg/d (n=217)	- Allocation concealment: : adequate - Blinding: double blinded - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 100% - Other methodological remarks: 3 x 2 factorial design with lower and usual blood pressure goal arms The CCB treatment arm was stopped early . Funding: Industry and other
Marin, 2001(211) ESPIRAL Spain Followup period: Minimum 3 years	Inclusion criteria - aged 18 to 75 year - serum creatinine values between 1.5 and 5 mg/dl - hypertension - proven progression of chronic renal failure in the previous 2 years (increase by more than 25% or > 0.5 mg/dl in serum creatinine). Exclusion criteria - diabetes	N= 241 Age (yr): 56 Race/ethnicity (%): NR Gender (male%): 59 BP: 156/96 mmHg Urinary protein excretion (g/24 h): 1.7 Serum creatinine (mg/dL): 2.8 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance	Fosinopril 10-30 mg/d (n=129) versus Nifedepine 30-60 mg/d (n=112)	- Allocation concealment: unclear - Blinding: open label - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 66% Funding: none stated

	-recent history of cardiovascular disease	(ml/min/1.73m²): 36 Diabetes (%): 0		
Crepaldi, 1998(188) (Sarafidis review) Italy Followup period: 3 years	Inclusion criteria - age 18 to 70 years -onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis - median AER value between 20 and 200 µg/min - GFR ≥80 ml/min/1.73m2 - systolic BP ≥115 and ≤145 mmHg (without HTN therapy) and diastolic BP ≥75 and ≤90 mmHg. Exclusion criteria - impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min - nondiabetic renal disease; - liver or hematological disease - arrhythmias; unstable angina; recent AMI - systemic Malignancy - hyperkalemia	N= 88 (58 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Race/ethnicity (%): NR Gender (male%): 69 BP: 128/83 mmHg Urinary protein excretion (g/24 h): NR Albumin excretion rate (µg/min): 61.2 Serum creatinine (mg/dL): 0.96 Estimated GFR (ml/min/1.73m²): 120 Creatinine clearance (ml/min/1.73m²): 109 Diabetes (%): 100	Lisinoprol 2.5-20 mg/d (n=48) versus Nifedepine 10-20 mg/d (n=41)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: no - Withdrawals/dropouts adequately described: yes - Follow-up: 63% Funding: none stated
Zucchelli 1992(212)/1995(213) Italy	Inclusion criteria - aged 18 to 70 y - established chronic renal failure (serum creatinine ranging between	N= 121 Age (yr): 55 Race/ethnicity (%): NR	Captopril 25-100 mg/d (n=60) versus	- Allocation concealment: unclear - Blinding: none stated - Intention to treat (ITT)

Followup period: 3 years	1.8 to 5 mg/dL); - hypertension - good general health Exclusion criteria: - diabetes - potentially reversible renal disease - systemic diseases - severe cardiac or hepatic dysfunction - peripheral edema; - proteinuria >5 g/24 h.	Gender (male%): 58 BP: 165/100 mmHg Urinary protein excretion (g/24 h): 1.8 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 0	Nifedepine 20-40 mg/d (n=61)	analysis: yes - Withdrawals/dropouts adequately described: yes - Follow-up: 74% - Other methodological remarks: no Funding: none stated

Table 313

4.3.5.1.4.2 Summary and conclusions

ACE inhibitors versus calcium channel blockers			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1307 (5 studies) 3-5 y	RR= 0.75 (0.48-1.16)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: -1 for mostly African Americans Imprecision: OK
Cardiovascular mortality	1011 (3 studies)	RR= 0.75 (0.36-1.57)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: -1 for mostly African Americans Imprecision: OK
Myocardial infarction (any)	58 (1 study)	0 in both groups	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data
Stroke (any)	3943 (3 studies)	RR= 1.00 (0.78-1.28)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for post hoc analysis Consistency: OK Directness: OK Imprecision: OK
ESRD	3823 (3 studies)	RR= 0.82 (0.57-1.19)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 for post hoc analysis Consistency: OK Directness: OK Imprecision: OK
Any or serious adverse events leading to study withdrawal	1307 (5 studies)	3.2 vs 4.7% (NS)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK

Table 314

In this meta-analysis ACE-I were compared to channel blockers in patients with CKD, mostly non-diabetic. The largest included study is a post hoc analysis performed in the subset of 3,049 individuals with GFR <60 ml/min/ 1.73m2 from the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Another large trial in this analysis included only African Americans. All patients had hypertension at baseline

When comparing ACEI with calcium channel blockers, no significant differences were found for the incidence of total and cardiovascular mortality and for the risk of myocardial infarction.
GRADE: LOW quality of evidence

When comparing ACEI with calcium channel blockers, no significant differences were found for the risk of stroke.
GRADE: MODERATE quality of evidence
When comparing ACEI with calcium channel blockers, no significant differences were found for the risk ESRD.
GRADE: MODERATE quality of evidence

No significant differences were found between ACEI and calcium channel blockers for the total incidence of adverse events and the occurrence of serious adverse events.
GRADE: MODERATE quality of evidence

There are no data available for the following outcomes: doubling of sCr, progression from micro- to macroalbuminuria, blood pressure, cough and hyperkalemia.

4.3.5.1.5 ACE-inhibitor versus diuretic

4.3.5.1.5.1 Clinical evidence profile

Clinical evidence profile: ACEI versus diuretics

Ref	Comparison	Results		
AHRQ-CER37(105) MA	N=2 ACEI versus diuretics n=4716	**ACEI** Event rate	**Diuretics** Event rate	**RR (95% CI)**
All-cause mortality= cardiovascular mortality				
Marre 2004(216) Remark: all deaths were cardiovascular deaths		Total (N=1; n=570)		
		ACE= 1/286 (0.3%)	Diur= 2/284 (0.7%)	RR= 0.50 (0.05-5.44) NS
CV events: MI (fatal)				
Marre 2004(216)		Total (N=1; n=570)		
		ACE= 0/286	Diur= 1/284 (0.3%)	NT
CV events: stroke (any)				
Rahman 2006(214)		Total (N=1; n=4146)		
		ACE= 99/1533 (6.5%)	Diur= 157/2613 (6.0%)	RR= 1.07 (0.84-1.37) NS
		Diabetes patients (N=1; n=1382)		
		ACE= 33/501 (6.6%)	Diur= 63/881 (7.2%)	NT
Doubling of sCr				
		NR		
End-stage renal disease				

Rahman 2006(214)	Total (N=1; n =4146)		
	ACE= 70/1533 (4.6%)	Diur= 124/2613 (4.7%)	RR= 0.96 (0.72-1.28) NS
	Diabetes patients (N=1; n=1382)		
	ACE= 41/501 (8.2%)	Diur= 68/881 (7.7%)	NT
Progression from micro- to macroalbuminuria			
Marre 2004(216)	Total (N=1; n=570)		
	ACE= 18/286 (6.3%)	Diur= 26/283 (9.2%)	RR= 0.69 (0.38-1.22) NS
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
Marre 2004(216)	Total (N=1; n=570)		
	ACE= 15/286 (5.2%)	Diur= 14/286 (4.9%)	NS
Cough			
	NR		
Hyperkalemia			
	NR		

Table 315

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Rahman 2006(214)	Inclusion criteria -aged 55 years or older - stage 1 or stage 2	N= 4146 for patients with a baseline GFR <60 ml/min/ 1.73m² (of a total of 17118 randomized and minus the	Lisinopril up to 40 mg/d (n=1533)	- Allocation concealment: adequate - Blinding: double

ALLHAT USA and Canada Followup period: mean 4.9 years	Hypertension - at least 1 additional risk factor for CHD <u>Exclusion criteria</u> - history of symptomatic heart failure and/or a known left ventricular ejection fraction <35% - serum creatinine level > 2 mg/dL	amlodipine arm) Subgroup analysis for diabetes patients: 1382 Age (yr): 71 Race/ethnicity (%): white: 57, black: 26, Hispanic: 12 Gender (male%): 49 BP: 147/83 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): 50 Creatinine clearance (mg/min): NR Diabetes (%): 33	versus Chlorthalidone up to 25 mg/d (n=2613)	- Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: Not reported for CKD subgroup - Follow-up: NR for this subgroup Other methodological remarks: - 3 x 2 factorial design **- Post hoc analysis** performed within subset of participants with CKD from the ALLHAT trial Funding: Industry and others
Marre 2004(216) NESTOR France Followup period: 1 year	<u>Inclusion criteria</u> - aged between 35 and 80 years - type 2 DM - persistent micro-albuminuria - essential hypertension <u>Exclusion criteria</u> - severe hypertension - ventricular rhythm disorders - plasma creatinine >150 µmol/l - kalaemia < 3.5 mmol/l > 5.5 mmol/l - uric acid > 536 µmol/l	N= 570 Age (yr): 60 Race/ethnicity (%): white: 86, black: 4, Asian: 2 Gender (male%): 65 BP: 161/94 mmHg Urinary protein excretion (g/24 h): NR Albumin excretion rate (µg/min): 58 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (ml/min/1.73m²): 92 Diabetes (%): 100	Enalapril 10 mg/d (n=286) versus Indapamide 1.5 mg/d (n=284)	- Allocation concealment: unclear - Blinding: double - Intention to treat (ITT) analysis: 'modified' ITT - Withdrawals/dropouts adequately described: yes - Follow-up: 89% Funding: Industry

Table 316

4.3.5.1.5.2 Summary and conclusions

ACE inhibitors versus diuretics			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cardiovascular mortality= all cause mortality	570 (1 study) 1 y	RR= 0.50 (0.05-5.44)	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data, -1 for wide CI
Myocardial infarction (fatal)	570 (1 study)	NT (0 vs 0.3%)	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: OK Imprecision: -1 for sparse data, -1 for wide CI
Stroke (any)	4146 (1 study) 5 y	RR= 1.07 (0.84-1.37)	⨁⨁⊖⊖ **LOW** Study quality: -2 for posthoc analysis of only available trial Consistency: NA Directness: OK Imprecision: OK
ESRD	4146 (1 study)	RR= 0.96 (0.72-1.28)	⨁⨁⊖⊖ **LOW** Study quality: -2 for posthoc analysis of only available trial Consistency: NA Directness: OK Imprecision: OK
Progression from micro- to macroalbuminuria	570 (1 study)	RR= 0.69 (0.38-1.22)	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 allocation concealment unclear, -1 for wide CI Consistency: NA Directness: OK Imprecision: -1 for limited data
Any or serious adverse events leading to study withdrawal	570 (1 study)	NT (5.2% vs 4.9%)	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 allocation concealment unclear, -1 for wide CI Consistency: NA Directness: OK Imprecision: -1 for limited data

Table 317

In this meta-analysis ACE-I were compared to diuretics in patients with CKD. The largest trial is a post hoc analysis of the ALLHAT trial; diabetic and non-diabetic patients were included in this analysis. The other trial included patients with diabetic CKD. All patients had hypertension at baseline.

When comparing ACE-I with diuretics, no significant differences were found for the incidence of all-cause and cardiovascular mortality.
GRADE: VERY LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of myocardial infarction.
GRADE: VERY LOW quality of evidence
When comparing ACE-I with diuretics, no significant differences were found for the risk of stroke.
GRADE: LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of ESRD.
GRADE: LOW quality of evidence

When comparing ACE-I with diuretics, no significant differences were found for the risk of progression from micro- to macroalbuminuria.
GRADE: VERY LOW quality of evidence

No significant differences were found between ACEI and diuretics for the total incidence of adverse events and the occurrence of serious adverse events.
GRADE: VERY LOW quality of evidence

There are no data for the following outcomes: myocardial infarction,doubling of sCr, blood pressure, cough and hyperkalemia.

4.3.5.1.6 Angiotensin receptor blocker versus calcium channel blocker

4.3.5.1.6.1 Clinical evidence profile

Intervention: Sartans (ARB) versus calcium channel blockers (CCB)

Clinical evidence profile: ARB versus CCB

Ref	Comparison	Results		
AHRQ-CER37(105)	ARB vs CCB	**ARB** Event rate	**CCB** Event rate	**RR (95% CI)**
Mortality				
Lewis 2001(166), Ogawa 2007(217)		Total (N=2; n=1204)		
		ARB= 87/619 (14.1%)	CCB= 83/585 (14.2%)	RR= 1.03 (0.79-1.35) NS I^2: not applicable
Cardiovascular mortality				
		NR		
CV events: MI (any)				
		NR		
CV events: stroke (any)				
Saruta 2009(218)		Total (N=1; n=2720)		
		ARB= 44/1376 (3.2%)	CCB= 40/1344 (3.0%)	RR= 1.07 (0.70-1.64) NS
Doubling of sCr				
Lewis 2001(166)		Total (N=1; n=1146)		
		ARB= 98/579 (17.0%)	CCB= 144/567 (25.4%)	**RR= 0.67 (0.53-0.84)** **SS**

End-stage renal disease			
Lewis 2001(166)	Total (N=1; n=1146)		
	ARB= 82/579 (14.2%)	CCB= 104/567 (18.3%)	RR= 0.77 (0.59-1.01) NS
Progression from micro-to macroalbuminuria			
Ogawa 2007(217)	Total (N=1; n=58)		
	ARB= 4/40 (10.0%)	CCB= 5/18 (27.8%)	RR= 0.36 (0.11-1.18) NS
Blood pressure			
	NR		
Any or serious adverse events leading to study withdrawal			
Ogawa 2007(217)	Total (N=1; n=58)		
	ARB= 0/40	CCB= 0/18	NA
Renal adverse events leading to study withdrawal			
	NR		
Hyperkalemia			
Lewis 2001(166)	Total (N=1; n=1146)		
	ARB= 11/579 (1.9%)	CCB= 3/567 (0.5%)	**SS** **P < 0.05**

Table 318

Characteristics of included studies in the above mentioned meta-analysis, from the evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Saruta 2009(218) CASE-J	Inclusion criteria - SBP >180mmHg or DBP >110mmHg - type II diabetes, history of stroke or TIA	N= 2720 (subset with GFR <60ml/min/1.73m² from among larger study cohort of 4728)	Candesartan 4 to 12mg daily titrated to target BP (n=1376)	- Allocation concealment: not defined - Blinding: Assessor -Intention to treat (ITT)

Japan Followup period: 36 months	- leftventricular hypertrophy - angina pectoris or a history of myocardial infarction - proteinuria or a serum creatinine >1.3mg/dL -arteriosclerotic peripheral artery obstruction. <u>Exclusion criteria</u> - SBP ≥200 mmHg or DBP ≥120 mmHg - Type I DM, - recent AMI or CVA - CHF NYHA II-IV - atrial fibrillation or atrial flutter, - serum creatinine ≥3 mg/dL - malignancy <5 years before enrollment	Age (yr): 65 Race/ethnicity (%): NR Gender (male%): 51.8 BP: 163/91 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 42.4	versus Amlodipine 2.5 to 10mg daily titrated to target BP (n=1344) Doses titrated to goal BP <130/85 for ages <60 years <140/90 for ages 60-69 <150/90 for ages 70-79 <160/90 for ages >80	analysis: Yes - Withdrawals/dropouts adequately described: inadequate - Follow-up: % study withdrawals: NR - sungroup analysis, unclear if predefinied Funding: Industry and government
Ogawa 2007(217) Japan Followup period: median 56 weeks	<u>Inclusion criteria</u> - type 2 DM - untreated moderate hypertension (130/80 – 200/110 mmHg) - microalbuminuria - HbA1c<8% - serum creatinine < 1.2 mg/dl <u>Exclusion criteria</u> - other renal diseases - severe cerebral or cardiovascular diseases or liver dysfunction - active retinopathy.	N= 58 Age (yr): 6.7 Race/ethnicity (%): NR Gender (male%): 46.6 BP: 152/90 mmHg Urinary protein excretion (g/24 h): NR Serum creatinine (mg/dL): 0.74 Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 100	Candesartan 4 - 8mg/d (n=40) Versus Nifedipine 20 - 40mg/d (n=18) .	- Allocation concealment: not defined - Blinding: Patient only - Intention to treat (ITT) analysis: Unclear - Withdrawals/dropouts adequately described: Yes - Follow-up: % study withdrawals: 3.4% Funding: NR
Lewis 2001(166) IDNT	<u>Inclusion criteria</u> - Age 30 - 70 yrs, - type 2 DM	N= 1146 Age (yr): 59	Irbesartan 300 mg daily (n=579) versus	- Allocation concealment: yes - Blinding: Patients,

USA Followup period: 2.6 years	- hypertension - proteinuria - serum creatinine 1.0 -3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men <u>Exclusion criteria</u> Not stated	Race/ethnicity (%): white: 72.1, Hispanic: 5.0, Black: 13.0, Asian: 5.1, Other: 4.7 Gender (male%): 64.3 BP: 160/87 mmHg Urinary protein excretion (g/24 h): 2.9 (median) Estimated GFR (ml/min/1.73m²): NR Creatinine clearance (mg/min): NR Diabetes (%): 100	Amlodipine 10mg daily (n=567) Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85.	investigators, assessors - Intention to treat (ITT) analysis: yes - Withdrawals/dropouts adequately described: Adequate - Follow-up: % study withdrawals: 0.6 Funding: Industry

Table 319

4.3.5.1.6.2 Summary and conclusions

Angiotensin II receptor antagonists (ARB) versus calcium channel blockers (CCB)			
Bibliography: meta-analysis AHRQ CER 37(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1204 (2 studies) 1.8 to 3.2 y	RR= 1.03 (0.79-1.35) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 for sparse data
Stroke	2720 (1 study)	RR= 1.07 (0.70-1.64) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only subgroup Consistency: NA Directness: -1 only Japanese Imprecision:
Doubling of sCr	1146 (1 study)	**RR= 0.67 (0.53-0.84)** **SS in favour of ARB**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
ESRD	1146 (1 study)	RR= 0.77 (0.59-1.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data
Progression from micro-to macroalbuminuria	58 (1 study)	RR= 0.36 (0.11-1.18) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: NA Directness: -1 only Japanese Imprecision: -1 for sparse date
Hyperkalemia	1146 (1 study)	**1.9 vs 0.5%** **SS more frequent with ARB (p<0.05)**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 for sparse data

Table 320

In this meta-analysis, angiotensin II receptor blockers (ARB) were compared to calcium channel blockers (CCB) in patients with diabetic CKD, albuminuria and hypertension.

When comparing ARB with CCB, no significant difference was found for the incidence of total mortality.
GRADE: MODERATE quality of evidence

When comparing ARB with CCB, no significant difference was found for the risk of stroke.
GRADE: LOW quality of evidence

Patients treated with ARB were significantly less likely to develop a doubling of their baseline sCr than patients treated with CCB.
GRADE: MODERATE quality of evidence

The risk of developing hyperkalemia is higher with ARB, compared with CCB
GRADE: MODERATE quality of evidence

No data are available for the following outcomes: cardiovascular mortality, myocardial infarction, blood pressure, total incidence of adverse events.

4.3.5.1.7 Dual RAAS inhibition

4.3.5.1.7.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Parving 2012(219) ALTITUDE RCT Duration of follow-up: 33 months Trial was stopped prematurely	n= 8561 Mean age: 64y Previous CV event: 42% known CV diseases other than hypertension. Hypertension: 95% Diabetes: 82% Hypercholesterolemia: NR Smoking: 13% CKD: 98% Proteinuria: 84% <u>Inclusion</u> - type 2 diabetes - evidence of	Aliskiren 300 mg/d Vs Placebo As an adjunct to ACE-I or sartan	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: % in safety analysis % in efficacy analysis FOLLOW-UP: 97% ITT: yes Other important methodological remarks - trial was stopped prematurely Sponsor: Novartis
			Time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum creatinine level. = primary outcome	Aliskiren= 18.3% Pla= 17.1% HR= 1.08 (0.98-1.20) NS	
			Total mortality	Aliskiren= 8.8% Placebo= 8.4% HR= 1.06 (0.92-1.23) NS	
			Cardiovascular mortality	Aliskiren= 5.8% Placebo= 5.0% HR= 1.16 (0.96-1.39) NS	
			ESRD mortality	Aliskiren= 2.8% Placebo= 2.6% HR= 1.08 (0.84-1.40) NS	

	microalbuminuria, macroalbuminuria, or cardiovascular disease <u>Exclusion</u> -Serum potassium >5.0 mmol/L - Congestive heart failure III-IV - renal transplant - CV event in prior 3m		Doubling of sCr	Ali= 4.9% Pla= 5.1% HR= 0.97 (0.80-1.17) NS	
			Safety		
			Discontinuation due to adverse events	Aliskiren= 13.2% Placebo= 10.2% **P<0.001 in favour of placebo**	
			Hyperkalemia	Aliskiren= 39.1% Placebo= 29.0% **P<0.001 in favour of placebo**	
			Hypotension	Aliskiren= 12.1% Placebo= 8.3% **P<0.001 in favour of placebo**	

Table 321

Study details	n/Population	Comparison	Outcomes		Methodological
Fried 2013(220) VA NEPHRON-D RCT	n= 1448 Mean age: Previous CV event: % Hypertension: % Diabetes: % Cholesterol: mean	Losartan 100 mg/d (all patients) and Lisinopril 10-40 mg/d (= ass.)	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : yes FOLLOW-UP: NR ITT: NR Other important methodological
			Change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m2 if the initial estimated GFR was ≥60 ml per minute per 1.73 m2 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m2), end-stage renal disease	Ass= 18.2% Mono= 21.0% HR= 0.88 (0.70-1.12) NS	

	total 158 mg/dl Smoking: NR	vs	(ESRD), or death (= primary outcome)		remarks - Trial was stopped prematurely owing to safety concerns. - Initial run-in with losartan Sponsor: Veterans Affairs Office
Duration of follow-up: 2.2y Trial was stopped prematurely owing to safety concerns.	<u>Inclusion</u> - veterans with type 2 diabetes - eGFR 30.0-89.9 mL/min/1.73 m^2 <u>Exclusion</u> - non-diabetic kidney disease - serum potassium >5.5 mmol/L	placebo (= mono)	First occurrence of a decline in the estimated GFR or ESRD (= secondary renal end point)	Ass= 10.6% Mono= 14.0% HR= 0.78 (0.58-1.05) NS	
			ESRD	Ass= 3.7% Mono= 5.9% HR= 0.66 (0.41-1.07) NS	
			Total mortality	Ass= 8.7% Mono= 8.3% HR= 1.04 (0.73-1.49) NS	
			Safety		
			Hyperkalemia	Ass= 9.9% Mono= 4.4% HR= 2.8 (1.8-4.3) **P<0.001, SS more frequent with association**	
			Acute kidney injury	Ass= 18.0% Mono= 11.0% HR= 1.7 (1.3-2.2) **P<0.001, SS more frequent with association**	
			Serious adverse events	NR	

Table 322

4.3.5.1.7.2 Summary and conclusions

Dual inhibition of the renin-angiotensin system (RAS)

Dual ACEI-ARB therapy arose around 2000 from the concept that monotherapy resulted in incomplete blockade of the renin-angiotensin system. Several studies demonstrated that patients with the greatest reduction in proteinuria had the lowest rates of progression to end-stage renal disease and supported the idea that reducing proteinuria should be a target of treatment. Despite improvement in proteinuria, overwhelming evidence now demonstrates significant harm with dual therapy without any benefit in mortality or kidney function(221).

Most trials assessing the efficacy and safety of dual inhibition of the RAS are very small and of short duration. Here we discuss only the 2 major RCTs.

Dual versus single inhibition of the RAS			
Bibliography: Parving 2012(219), Fried 2013(220)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	10.009 (2 studies) 2-3 y	NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
ESRD	10.009 (2 studies) 2-3 y	NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Hyperkalemia	10.009 (2 studies) 2-3 y	**SS more frequent with dual therapy**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Acute kidney injury	1448 (1 study)	HR= 1.7 (1.3-2.2) **SS more frequent with dual therapy**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1

Table 323

Two large trials assessed the efficacy and safety of dual RAS inhibition compared to the use of a single RAS-inhibiting agent. The largest trial compared aliskiren versus placebo, in patients already treated with an ACE or an ARB. The second trial compared the association of losartan and lisinopril to losartan alone. Both trials were stopped prematurely due to safety concerns.

Dual inhibition of the RAS is not significantly superior to the use of a single agent for the prevention of mortality or progression to ESRD.
GRADE: HIGH quality of evidence

Dual inhibition of the RAS is associated with a higher risk for hyperkalemia compared to the use of a single agent.
GRADE: HIGH quality of evidence

Dual inhibition of the RAS is associated with a higher risk for acute kidney injury compared to the use of a single agent.
GRADE: MODERATE quality of evidence

In May 2014 the European Medicines Agency advised against the use of dual inhibition of the renin-angiotensin system in patients with CKD.

- Where combination of these medicines (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination.
- The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

4.3.5.2 Results from a recent network meta-analysis

4.3.5.2.1 Summary and conclusions

Palmer 2015 was a network meta-analysis that compared all pharmacological agents to lower blood pressure in adults with diabetes and kidney disease. The primary outcomes were all-cause mortality and end-stage kidney disease.

This meta-analysis was not included in our search for it was not in line with several of the quality criteria we had. Studies with <100 patients were included in the meta-analysis, studies with follow up of <1 year as well. Population selected had both CKD and diabetes and all ages were present (ranging from 18+ to elderly patients).

None of the medication comparison had a statistically significant difference in the effect on mortality.

4.3.6 Coronary artery disease

4.3.6.1 ACE-inhibitor versus placebo (+/- existing medication) in stable coronary disease

4.3.6.1.1 Clinical evidence profile

Ref + design	n	Population	Duration	Comparison	Methodology
Yui, JMIC-B 2004(147)	1650	- hypertensive patients with coronary heart disease (75% stenosis on coronary angiography) - Japanese - mean age: 64 - 23% diabetic patients	3 years	2 arms: nifedipine retard (a long-acting nifedipine formulation that is given at a dose of 20–40 mg/day in Japan) ACE inhibitor (enalapril 5–10 mg/day, imidapril 5–10 mg/day, or lisinopril 10–20 mg/day as recommended in Japan) concomitant treatment with a β-blocker or α-blocker was permitted if the BP reduction did not meet the target of <150/90mmHg	ALLOC. CONC.: unclear RANDOM.: states randomized, unclear BLINDING: patients: open; assessors: blinded (independent endpoint assessment committee) (PROBE design) Rated “Fair” by JNC-8

Table 324

4.3.6.1.2 Summary and conclusions

The EUROPA study 2003(222) was a double blind RCT that compared an ACE-inhibitor (perindopril) with placebo in 12218 patients with previous coronary artery disease, with a mean follow-up of 4.2 years.

The primary outcome was a composite of cardiovascular death, myocardial infarction, or cardiac arrest.

There was a statistically significant decrease of risk of developing this primary outcome with the ACE-inhibitor, compared to placebo.

A subgroup analysis in the participants with hypertension showed a borderline non-significant result for this outcome.

The HOPE study 2000(128), also discussed p 366, was a double blind RCT that compared an ACE-inhibitor (ramipril) with placebo in 9297 patients at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure, with a mean follow-up of 5 years.

The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

There was a statistically significant decrease of risk of developing this primary outcome with an ACE-inhibitor, compared to placebo.

A subgroup analysis in the participants with hypertension also showed a statistically significant result for this outcome.

Calcium channel blocker versus ACE-inhibitor in hypertension patients with coronary artery disease			
Bibliography: JMIC-B 2004(147)			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Mortality	1650 (1 study) 3 years	0.76 (0.35, 1.63) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Cardiac events	1650 (1 study) 3 years	1.05 (0.81, 1.37) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; 95%CI crosses

			both no effect and appreciable harm or benefit
Myocardial infarction	1650 (1 study) 3 years	1.31 (0.63, 2.74) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Cerebrovascular events	1650 (1 study) 3 years	1.00 (0.50, 2.02) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Heart failure requiring hospitalization	1650 (1 study) 3 years	1.25 (0.52, 2.98) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Worsening of renal function	1650 (1 study) 3 years	2.70 (0.54, 13.49) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Withdrawals because of adverse effects	1650 (1 study) 3 years	**CCB: 5.0%** **ACE-I: 8.8%** **P=0.002** **In favour of CCB**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; no CI
Dry cough	1650 (1 study) 3 years	**CCB: 0%** **ACE-I: 7.3%** **P<0.01** **In favour of CCB**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; no CI
Hypotension	1650 (1 study) 3 years	**CCB: 1.0%** **ACE-I: 0.2%** **P<0.01** **In favour of ACE-I**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; no CI
Edema	1650 (1 study) 3 years	**CCB: 0.8%** **ACE-I: 0%** **P<0.01** **In favour of ACE-I**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; no CI
Facial erythema, hot flushes	1650 (1 study) 3 years	**CCB: 0.7%** **ACE-I: 0%** **P<0.05** **In favour of ACE-I**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japanese Imprecision: -1; no CI

Table 325

This open-label RCT in 1650 Japanese hypertension patients under 75 years of age, who also had coronary artery disease, compared treatment with a calcium channel blocker (nifedipine retard) to treatment with an ACE-inhibitor. The median follow-up in this study was 3 years.

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker, compared to treatment with an ACE-inhibitor, does not result in a statistically significant difference in **cardiac events**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker, compared to treatment with an ACE-inhibitor, does not result in a statistically significant difference in **mortality**, **myocardial infarction**, **cerebrovascular events**, **heart failure requiring hospitalization**, or **worsening of renal function**.
GRADE: VERY LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker, compared to treatment with an ACE-inhibitor, significantly decreased the number of **withdrawals due to adverse effects**, and **dry cough**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker, compared to treatment with an ACE-inhibitor, significantly increased the rates of **hypotension**, **edema**, and **hot flushes**.
GRADE: LOW quality of evidence

4.3.6.2 Angiotensin receptor blocker versus placebo on top of concomitant therapy in high risk patients

4.3.6.2.1 Summary and conclusions

The TRANSCEND 2008 study(223), see also 4.3.5.1.1, was a single-blind RCT that compared an angiotensin-receptor blocker (telmisartan) with placebo, in 5926 ACE-inhibitor-intolerant patients with cardiovascular disease or diabetes with end-organ damage. Many of the patients were receiving concomitant therapy. There was a median follow-up of 4.7 years.

The primary outcome was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure.

There was no statistically significant difference of risk of developing this primary outcome with an angiotensin-receptor blocker, compared to placebo.

A subgroup analysis in the participants with hypertension did not show a statistically significant result on this outcome.

4.3.6.3 Calcium channel blocker versus beta blocker

4.3.6.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Pepine 2003 (INVEST)(145) Design: RCT OL,PG Duration of follow-up: Mean 2.7 years	n= 22576 Mean age: CCB: 66y BB: 66.1 y Previous MI: 32% Previous stroke: 51.4% Diabetes: 28.3% Smoking: 12.4% Age >70y: 33.3% <u>Inclusion</u> -Hypertension -Aged 50 years or older -documented coronary artery disease <u>Exclusion</u>	Calcium channel blocker (verapamil SR 240 mg/d) Vs Beta-blocker (atenolol 50 mg/d) *If needed to reach target:* *Step 2: CCB+ACE-I or BB+ D* *Step 3: higher doses* *Step 4:*	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes Remarks on blinding method: PROBE design FOLLOW-UP: Lost-to follow-up: 2.5 % Drop-out and Exclusions: 9% • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: yes/no
			All-cause mortality, non-fatal myocardial infarction, or non-fatal stroke (PO)	CCB: 1119/11267 BB: 1150/11309 RR=0.98 (95%CI 0.90 to 1.06) NS P=0.52	
			All-cause mortality	CCB: 873/11267 BB: 893/11309 RR= 0.98 (95%CI 0.90 to 1.07) NS P=0.72	
			Non-fatal myocardial infarction	CCB: 151/11267 BB: 153/11309 RR= 0.99 (95%CI 0.79 to 1.24) NS P=0.95	
			Non-fatal stroke	CCB: 131/11267 BB: 148/11309 RR= 0.89 (95%CI 0.70 to 1.12) NS P=0.33	
			Cardiovascular death	CCB: 431/11267	

	-heart failure - patients taking beta-blockers within 2 weeks of randomization or taking beta-blockers for an MI that occurred in the previous 12 months (to avoid withdrawal phenomena if randomized to CCB group)	*CCB+ACE-I+D* *Or* *BB+D+ACE-I*		BB: 431/11309 RR= 1.00 (95%CI 0.88 to 1.14) NS P= 0.94	(describe if yes) Sponsor: University of Florida and grants from BASF Pharma and Abbott Laboratories
			Safety		
			Angina	CCB: 2.32% BB: 2.02% P=0.13	
			Cancer	CCB: 1.70% BB: 1.64% P=0.73	
			Constipation	**CCB: 1.73%** **BB: 0.13%** **P<0.001** **SS in favour of BB**	
			Heart failure	CCB: 1.68% BB: 1.53% P=0.38	
			Symptomatic bradycardia	**CCB: 0.66%** **BB: 1.26%** **P<0.001** **SS in favour of CCB**	
			Wheezing	**CCB: 0.15%** **BB: 0.39%** **P <0.001** **SS in favour of CCB**	
			Subgroup analyses for PO		
			Age ≤70y vs ≥70y	≤70y CCB: 6.91%	

				BB: 6.50% RR=1.06 (0.94 to 1.20) ≥70y CCB: 16.13% BB: 17.34% RR= 0.93 (0.84 to 1.03)	
			Myocardial infarction at baseline	No CCB: 8.16% BB: 8.21% RR=0.99 (0.89 to 1.11) Yes CCB: 13.67% BB: 14.38% RR= 0.95 (0.85 to 1.07)	
			Left Ventricular hypertrophy	No CCB: 9.60% BB: 9.95 RR= 0.96 (0.88 to 1.06) Yes CCB: 11.15 BB: 10.93 RR= 1.02 (0.87 to 1.20)	
			Congestive heart failure	No CCB: 8.98 BB: 9.47 RR= 0.95 (0.87 to 1.03) Yes CCB: 26.33	

				BB: 21.82 RR= 1.21 (0.99 to 1.47)	
			Diabetes	No CCB: 8.10 BB: 8.67 RR=0.93 (0.84 to 1.04) Yes CCB: 14.61 BB: 13.93 RR= 1.05 (0.93 to 1.18)	

Table 326

4.3.6.3.2 Summary and conclusions

Calcium channel blocker versus beta-blocker in hypertension patients with coronary artery disease			
Bibliography: INVEST 2003(145)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	22576 (1 study) 2.7 years	RR= 0.98 (95%CI 0.90 to 1.07) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: ok
All-cause mortality, non-fatal myocardial infarction, or non-fatal stroke (composite)	22576 (1 study) 2.7 years	RR=0.98 (95%CI 0.90 to 1.06) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: ok
Non-fatal myocardial infarction	22576 (1 study) 2.7 years	RR= 0.99 (95%CI 0.79 to 1.24) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: ok
Non-fatal stroke	22576 (1 study) 2.7 years	RR= 0.89 (95%CI 0.70 to 1.12) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Cardiovascular death	22576 (1 study) 2.7 years	RR= 1.00 (95%CI 0.88 to 1.14) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: ok
Angina	22576 (1 study) 2.7 years	CCB: 2.32% BB: 2.02% P=0.13	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Cancer	22576 (1 study) 2.7 years	CCB: 1.70% BB: 1.64% P=0.73	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Constipation	22576 (1 study) 2.7 years	**CCB: 1.73%** **BB: 0.13%** **P<0.001** **SS in favour of BB**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Heart failure	22576 (1 study) 2.7 years	CCB: 1.68% BB: 1.53% P=0.38	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Symptomatic	22576	**CCB: 0.66%**	⊕⊕⊖⊖ **LOW**

bradycardia	(1 study) 2.7 years	**BB: 1.26%** **P<0.001** **SS in favour of CCB**	Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI
Wheezing	22576 (1 study) 2.7 years	**CCB: 0.15%** **BB: 0.39%** **P <0.001** **SS in favour of CCB**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: ok Imprecision: -1; no CI

Table 327

In this open-label RCT, 22576 hypertension patients older than 50, with documented coronary artery disease, were randomized to treatment with a calcium channel blocker (verapamil)-based strategy or a beta-blocker (atenolol)-based strategy. To achieve target blood pressure, an ACE-inhibitor or a thiazide diuretic could be added in either group. The mean follow-up was 2.7 years.

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker based strategy, compared to a beta-blocker based strategy, did not result in a statistically significant difference in **mortality**, **non-fatal myocardial infarction**, **cardiovascular death**, or a **composite of mortality, non-fatal MI or non-fatal stroke**.
GRADE: MODERATE quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker based strategy, compared to a beta-blocker based strategy, did not result in a statistically significant difference in **non-fatal stroke** rate.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker based strategy, compared to a beta-blocker based strategy, significantly more patients had **constipation**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker based strategy, compared to a beta-blocker based strategy, significantly less patients had **symptomatic bradycardia** and **wheezing**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with a calcium channel blocker based strategy, compared to a beta-blocker based strategy, did not result in a statistically significant difference in patients with **angina**, **cancer**, or **heart failure**.
GRADE: LOW quality of evidence

A prespecified subgroup analysis of this RCT, in patients with previous myocardial infarction at baseline, did not show a statistically significant difference of the primary outcome (a composite of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke) when comparing a calcium channel blocker-based strategy to a beta-blocker-based strategy.
GRADE: LOW quality of evidence

4.3.6.4 Angiotensin receptor blocker versus other antihypertensive drugs

4.3.6.4.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Kasanuki 2009(224) Design: RCT Multicentre, OL, PG, Japan Duration of follow-up: median 4.2y maximal duration 5 years	n= 2049 CS: 1024 nA: 1025 Mean age: CS: 65±9 y <u>Previous myocardial infarction:</u> 38.0% <u>Cerebrovascular disease:</u> 10.0 % <u>Heart failure:</u> NYHA I: 79.4% NYHA II: 16.6% NYHA III: 2.0% NYHA IV: 2.0% <u>Diabetes</u>: 38.1%	Candesartan 4-12 mg/day Vs Non-ARB pharmacotherapy Doses of all antihypertensive drugs, including CS, were based on the guidelines of the Japanese Hypertension Society	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes <u>Remarks on blinding method:</u> Open-label. Event records were provided to the Endpoint Classification Committee (consisting of three experienced cardiologists who were not study investigators) and were then determined in a blinded fashion. An endpoint committee whose members were blinded to treatment group assignments adjudicated all potential endpoints.
			Occurrence of first major adverse cardiovascular event (a composite of cardiovascular death, non-fatal myocardial infarction, unstable angina, heart failure, stroke, and other cardiovascular events requiring hospitalization) (PO)	CS: 264 (25.8%) nA: 288 (28.1%) HR: 0.89 (95%CI 0.76 to 1.06) P=0.19 NS	
			Cardiovascular death	CS: 2.7% nA: 2.4% HR: 1.14 (95%CI 0.66 to 1.95) P=0.645 NS	
			Non-fatal myocardial infarction	CS: 2.8% nA: 2.5% HR: 1.12 (95%CI 0.66 to 1.88) P= 0.679 NS	
			Unstable angina pectoris	CS: 14.7% nA: 16.7% HR: 0.87(95%CI 0.70 to 1.08)	

	CrCl (mL/min): CS: 62.6±19.9 nA: 62.0±19.3 Smoking: 38.0% Inclusion Hospitalized patients with CAD and hypertension between 20 and 80 years old. Coronary angiography was performed for the diagnosis of CAD. Exclusion Secondary hypertension; acute myocardial infarction within the past week; cerebrovascular disorders within the past 3 months; severe aortic valve			P= 0.204 NS	FOLLOW-UP: Lost-to follow-up: 0.4% CS: 3 patients nA: 5 patients Drop-out and Exclusions: % • Described: no ITT: Yes ("all randomized patients were included in all analyses, regardless of protocol violations") SELECTIVE REPORTING: no Other important methodological remarks: For safety and ethical reasons, all patients underwent essential revascularization before randomization and continued to receive any prior antihypertensive agents until administration of the randomized medications, and
			Heart failure	CS: 3.9% nA: 4.3% HR: 0.91 (95%CI 0.59 to 1.40) P= 0.667 NS	
			Stroke	CS: 4.4% nA: 4.8% HR: 0.92 (95%CI 0.61 to 1.37) P=0.672 NS	
			New onset of diabetes (SO)	**CS: 1.1%** **nA: 2.9%** **HR: 0.37 (95%CI 0.16 to 0.89)** **P=0.027** **SS in favour of candesartan**	
			Subgroup analyses for PO		
			Age: <65y vs ≥65y	<65y CS: 20.4% nA: 21.6% HR: 0.93 (95%CI 0.70 to 1.23) ≥65y CS: 29.9% nA:33.2% HR: 0.88 (95%CI 0.71 to 1.08)	

	stenosis; obstructive hypertrophic cardiomyopathy; serum creatinine >2.0 mg/dL; potassium >5 mmol/L; female sex, of childbearing potential and not using contraception; history of serious or hypersensitivity reactions to other antihypertensive agents; acute liver disease or hepatic dysfunction (hepatic transaminases or bilirubin >1.5x the upper limit of normal); known malignant neoplasm; and current condition			P for interaction= 0.749 NS	before discharge were switched from the previous agents under close supervision with no run-in period. In the CS-based treatment arm, patients already receiving ARBs other than CS discontinued the previous agents and started receiving CS. Combined antihypertensive agents excluding ACE-Is were allowed in order to achieve the desired level of blood pressure. In the nA-based treatment arm, patients already receiving ARBs discontinued the previous agents and began receiving other classes of antihypertensive agents, including ACE-Is. Sponsor: Japan Research Promotion Society for Cardiovascular Diseases
			Acute coronary syndrome: no vs yes	No CS: 24.5% nA:26.7% HR: 0.90 (95%CI 0.72 to 1.11) Yes CS: 28.3% nA: 30.4% HR: 0.91 (95%CI 0.69 to 1.19) P for interaction= 0.962 NS	
			Ejection fraction: >35% vs ≤35%	>35% CS: 24.4% nA:36.7% HR: 0.90 (95%CI 0.74 to 1.08) ≤35% CS: 35.6% nA:42.6% HR: 0.78 (95%CI 0.43 to 1.40) P for interaction= 0.584 NS	
			CrCl: >60 vs <60 mL/min	>60 CS: 24.2% nA:23.1%	

	requiring ACE-Is or ARBs.			HR: 1.04 (95%CI 0.81 to 1.34) <60 CS: 27.3% nA:33.1% HR: 0.79 (95%CI 0.63 to 0.99) P for interaction=0.113 NS	
			Safety		
			Cough	**CS: 3.0%** **nA: 16.1%** **p=0.001**	
			Anaemia	**CS: 0.7%** **nA: 2.6%** **p=0.001**	
			Study drug discontinuation for adverse events	**CS: 12.2%** **nA: 5.7%** **p=0.001**	

Table 328

4.3.6.4.2 Summary and conclusions

Angiotensin receptor blocker versus other antihypertensive drugs in hypertension patients with coronary artery disease			
Bibliography: Kasanuki 2009(224)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Major cardiovascular event	2049 (1 study) 4.2 y	HR: 0.89 (95%CI 0.76 to 1.06) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: ok
Cardiovascular death	2049 (1 study) 4.2 y	HR: 1.14 (95%CI 0.66 to 1.95) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Non-fatal myocardial infarction	2049 (1 study) 4.2 y	HR: 1.12 (95%CI 0.66 to 1.88) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
Unstable angina pectoris	2049 (1 study) 4.2 y	HR: 0.87(95%CI 0.70 to 1.08) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit
Stroke	2049 (1 study) 4.2 y	HR: 0.92 (95%CI 0.61 to 1.37) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese: Imprecision: -2; 95%CI crosses both no effect and appreciable harm and appreciable benefit
New onset of diabetes	2049 (1 study) 4.2 y	**HR: 0.37 (95%CI 0.16 to 0.89)** **SS in favour of ARB**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision:-1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Discontinuation for adverse effects	2049 (1 study) 4.2 y	**ARB: 12.2%** **other: 5.7%** **p=0.001** **SS in favour of other drugs**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: -1; no CI
Cough	2049 (1 study)	**ARB: 3.0%** **other: 16.1%**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label Consistency: only one study

	4.2 y	**p=0.001** **SS in favour of ARB**	Directness: Japenese Imprecision: -1; no CI
Anaemia	2049 (1 study) 4.2 y	**ARB: 0.7%** **other: 2.6%** **p=0.001** **SS in favour of ARB**	⨁⨁⨀⨀ **LOW** Study quality: -1; open-label Consistency: only one study Directness: Japenese Imprecision: -1; no CI

Table 329

This open-label RCT in 2049 Japanese hypertension patients with coronary artery disease, compared an angiotensin receptor blocker (candesartan) to a non-ARB antihypertensive drug. Median follow-up in this study was 4.2 years.

In hypertension patients with coronary artery disease, treatment with an angiotensin receptor blocker, compared to a different antihypertensive drug, did not result in a statistically significant difference in the rate of **major cardiovascular events**.
GRADE: MODERATE quality of evidence

In hypertension patients with coronary artery disease, treatment with an angiotensin receptor blocker, compared to a different antihypertensive drug, did not result in a statistically significant difference in the rate of **unstable angina pectoris**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, treatment with an angiotensin receptor blocker, compared to a different antihypertensive drug, did not result in a statistically significant difference in **cardiovascular death**, **non-fatal myocardial infarction**, or **stroke**.
GRADE: VERY LOW quality of evidence

In hypertension patients with coronary artery disease, with an angiotensin receptor blocker, compared to a different antihypertensive drug, there were significantly lower rates of **new onset of diabetes**, **cough** and **anaemia**.
GRADE: LOW quality of evidence

In hypertension patients with coronary artery disease, with an angiotensin receptor blocker, compared to a different antihypertensive drug, there was a significantly higher rate of **discontinuation because of adverse effects**.
GRADE: LOW quality of evidence

A prespecified subgroup analysis of this RCT evaluated patients that had a previous acute coronary syndrome at baseline. In this subgroup, there was no statistically significant difference of an ARB compared to a non-ARB, for the primary outcome (**major cardiovascular events**).
GRADE: LOW quality of evidence

4.3.6.5 Angiotensin receptor blocker versus ACE-inhibitor

4.3.6.5.1 Summary and conclusions

The ONTARGET 2008 study(152), see also 4.3.4.3, was a double blind RCT that compared an ACE-inhibitor (ramipril) to an angiotensin receptor blocker (telmisartan), and to the combination of the two drugs, in 25620 patients with vascular disease or high-risk diabetes, with a median follow-up of 56 months.

The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

There was no statistically significant difference of risk of developing this primary outcome with an ACE-inhibitor, compared to an angiotensin receptor blocker, or compared to a combination therapy with both drugs.

As compared with the ACE-inhibitor group, the ARB group had significantly lower rates of cough and angio-edema, and a significantly higher rate of hypotensive symptoms.

As compared with the ACE-inhibitor group, the combination-therapy group had significantly higher rates of hypotensive symptoms, syncope, and renal dysfunction.

A subgroup analysis in the participants with hypertension did not show a statistically significant result for the primary outcome.

4.3.6.6 Angiotensin receptor blocker versus ACE-inhibitor versus both in myocardial infarction with heart failure

4.3.6.6.1 Summary and conclusions

The VALIANT 2003 study(225) was a double blind RCT that compared an angiotensin receptor blocker (valsartan) to an ACE-inhibitor (captopril), and to the combination of the two drugs, in 14703 patients with myocardial infarction complicated by left ventricular dysfunction, with a follow-up of 24.7 months.

The primary outcome was all-cause mortality.

There was no statistically significant difference of risk of developing this primary outcome with an angiotensin receptor blocker, compared to an ACE-inhibitor blocker, or compared to a combination therapy with both drugs.

Compared with the ACE-inhibitor group, the combination-therapy had significantly more drug-related adverse events. With monotherapy, hypotension and renal dysfunction were significantly more common in the angiotensin receptor blocker group, and cough, rash, and taste disturbance were significantly more common in the ACE-inhibitor group.

A subgroup analysis in the participants with hypertension did not show a statistically significant result for the primary outcome.

4.3.7 Heart failure

4.3.7.1 Summary and conclusions

We found little to no studies in a hypertensive population with heart failure. Guidelines recommend certain drugs (ACE-inhibitors, angiotensin receptor blockers, beta-blockers, diuretics,…) for the treatment of hypertension in heart failure; these recommendations are based on

- Studies in hypertensive populations without heart failure, that evaluate the outcome "incident heart failure" (e.g. studies in diuretics).

- Studies that evaluated these drugs in patients with heart failure, who did not necessarily have hypertension. Therefore, these are studies on drugs that improve the prognosis of heart failure (morbidity – mortality) (for example see 4.3.6.6.1).

Because this document is not an analysis on the treatment of heart failure, discussing these studies would lead us too far.

4.3.8 Previous stroke

4.3.8.1 Antihypertensive treatment versus placebo

4.3.8.1.1 Summary and conclusions

We found a systematic review (Feldstein 2014(226)) that searched RCT's that assessed antihypertensive treatment effects on recurrent stroke prevention. It included 7 RCT's that compared antihypertensive drug treatment to placebo, and 2 RCT's that compared different antihypertensive drugs head-to-head.

However, with the exception of one trial (MOSES(149)), which will be discussed in-depth later, none of the RCT's were conducted in a 100% hypertensive population.

Furthermore, not all of the trials were conducted in a population that consisted exclusively of post-stroke or TIA patients.

We will briefly discuss these trials below, with the exception of two trials, which we excluded because of a too low percentage of hypertensives (DUTCH TIA 1993(227); only 3.8% were hypertension patients) or because they assessed treatment of stroke in a subacute phase (TEST 1995(228); <3 weeks after stroke).

The PATS study(229), see also 4.3.1.2, was a double blind RCT that compared treatment with a thiazide diuretic (indapamide) to placebo in 5665 Chinese patients with a history of stroke or TIA, with a mean follow-up of 2 years. 84% of the participants were hypertensive.

The primary outcome was **recurrent fatal or non-fatal stroke**.

There was a statistically significant decrease of risk of developing this primary outcome with a thiazide diuretic, compared to placebo.

A subgroup analysis in the participants with hypertension, showed a similar statistically significant reduction of the primary outcome with a thiazide diuretic, compared to placebo.

The PROGRESS study(230), also briefly discussed in 4.1.1.3, 4.1.7.2, 4.2.8.3, was a double blind RCT that compared active treatment (a flexible regimen based on an ACE-inhibitor, with the possible addition of a thiazide diuretic) to placebo in 6105 patients with a history of stroke or TIA, with a follow-up of 4 years. 48% of the participants were hypertensive.

The primary outcome was **total stroke** (fatal or non-fatal).

There was a statistically significant decrease of risk of developing this primary outcome with active treatment, compared to placebo.

A subgroup analysis in the participants with hypertension showed a similar statistically significant reduction of the primary outcome in the active treatment group, compared to placebo.

The PRoFESS study(231) was a double blind RCT that compared an angiotensin receptor blocker (telmisartan) to placebo in 20332 patients who recently had an ischemic stroke, with a mean follow-up of 2.5 years. 66% of participants had a systolic blood pressure >135 mmHg.

The primary outcome was **recurrent stroke**.

There was no statistically significant difference of risk of developing this primary outcome with the angiotensin receptor blocker, compared to placebo.

There was a statistically significant increase of adverse effects leading to discontinuation of the study drug in the ARB group, including significantly increased rates of hypotensive symptoms, syncope, diarrhea, nausea, and atrial fibrillation, compared to the placebo group.

Subgroup analyses in the participants with different strata of systolic blood pressure values, showed a statistically significant decrease of the primary outcome in the subgroup with SBP >135 to 150 mmHg, but no statistically significant difference in the subgroup with SBP >150 mmHg with an ARB, compared to placebo.

The HOPE study 2000(128), also discussed in 4.3.1.5, was a double blind RCT that compared an ACE-inhibitor (ramipril) with placebo in 9297 patients at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure, with a mean follow-up of 5 years. Only 11% of the participants had a previous stroke or TIA. 47% of the participants were hypertensive.

The primary outcome was a **composite of myocardial infarction, stroke, or death from cardiovascular causes.**

There was a statistically significant decrease of risk of developing this primary outcome with an ACE-inhibitor, compared to placebo.

A subgroup analysis in the participants with hypertension also showed a statistically significant result for this outcome.

There was no subgroup analysis in participants with a history of stroke or TIA.

The TRANSCEND 2008 study(223), see also 4.3.5.1.1 and 4.3.6.2, was a single-blind RCT that compared an angiotensin-receptor blocker (telmisartan) with placebo, in 5926 ACE-inhibitor-intolerant patients with cardiovascular disease or diabetes with end-organ damage. Many of the patients were receiving concomitant therapy. There was a median follow-up of 4.7 years. Only 22% of the participants had a history of stroke or TIA. 76% of the participants were hypertensive.

The primary outcome was a **composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure**.

There was no statistically significant difference of risk of developing this primary outcome with an angiotensin-receptor blocker, compared to placebo.

A subgroup analysis in the participants with hypertension did not show a statistically significant result on this outcome.

There was no subgroup analysis in participants with a history of stroke or TIA.

4.3.8.2 Antihypertensive treatment versus other treatment

4.3.8.2.1 Summary and conclusions

The ONTARGET 2008 study(158), see also 4.3.4.3,was a double blind RCT that compared an ACE-inhibitor to an angiotensin receptor blocker, and to a combination of both drugs, in 25620 patients with vascular disease or high-risk diabetes without heart failure, with a follow-up of 56 months. 69% of the participants were hypertensives, and only 21% had had a previous stroke.

The primary outcome was a **composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure**.

There was no statistically significant difference of risk of developing this primary outcome with an ACE-inhibitor, compared to an angiotensin receptor blocker.

There was a statistically significant increase of total number of discontinuations, and of cough, with an ACE-inhibitor, compared to an angiotensin receptor blocker.

There was a statistically significant decrease of hypotensive symptoms with an ACE-inhibitor, compared to an angiotensin receptor blocker.

In the subgroup analyses by systolic blood pressure, the participants with hypertension did not show a statistically significant difference of risk for the primary outcome.

There was no subgroup analysis of participants with a history of stroke.

4.3.8.3 Angiotensin receptor blocker versus calcium channel blocker

4.3.8.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Schrader 2005(149) MOSES Design: Multicenter RCT, OL, PG, Germany, Austria Duration of follow-up: Mean 2.5y (SD 1.3)	n= 1405 ES: 710 ND: 695 Mean age: ES: 67.7±10.4 ND: 68.1±9.5 Myocardial infarction: 8.1% Coronary heart disease: 26.3% Stroke: 61.0% Intracerebral hemorrhage: 5.5% Diabetes: 36.8% Renal insufficiency: 5.3 %	Eprosartan (600 mg) Vs Nitrendipine (10 mg) *From week 3 of treatment (earlier if required for medical reasons) the dose could be increased or combination therapy could be initiated. Target blood pressures for long-term therapy were*	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes Remarks on blinding method: A blinded end point committee assessed all cerebrovascular and cardiovascular events. The data and safety monitoring board was blinded as well. FOLLOW-UP: Lost-to follow-up: 1.9 % Drop-out and Exclusions: 3.7% • Described: yes • Balanced across groups: yes ITT:
			Composite of all-cause mortality and the number of cardiovascular and cerebrovascular events, including all recurrent events (PO)	**ES: 206** **ND: 255** **IDR: 0.79 (95%CI 0.66 to 0.96)** **P: 0.014** **SS in favour of eprosartan**	
			Cerebrovascular events (SO)	**ES: 102** **ND: 134** **IDR: 0.75 (95%CI 0.58 to 0.97)** **P: 0.026** **SS in favour of eprosartan**	
			Ischemic strokes (SO)	ES: 31 ND: 39 NT	
			TIA (SO)	ES: 66 ND: 92 NT	
			Intracerebral hemorrhage (SO)	ES: 5 ND: 3 NT	
			Cardiovascular	ES: 77	

	Inclusion Treatment requiring hypertension and a history of cerebrovascular events (transient ischemic attack [TIA, focal neurological deficit attributable to ischemia resolving within 24 hours], ischemic stroke, cerebral hemorrhage), documented by either cranial computed tomography (CT) or magnetic resonance scan (within the past 24 months before inclusion) Exclusion Exclusion criteria included internal carotid artery occlusion or stenosis >70%, manifest heart	*sitting systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. It was intended to reach target blood pressure for two thirds of the patients within the first 3 months. It was recommended but not predefined to give diuretics as the first combination partner, followed by β-blockers and then α-blockers or centrally acting substances. Combination therapy with ACE inhibitors,*	events(SO)	ND: 101 IDR: 0.75 (95%CI 0.55 to 1.02) P: 0.061 NS	No; patients who withdrew consent prior to first intake of study-drug were excluded from ITT analysis. SELECTIVE REPORTING: yes (for some secondary endpoints no numbers are reported: "Total mortality was 109 patients without significant differences in the categories cardiovascular, cerebrovascular, and nonvascular death. The mean values before and at the end of the study showed no significant differences in the scores of MMSE, Barthel, and ranking.") Other important methodological remarks: A total of 1405 hypertensives with a history of cerebrovascular events were included. 53 Patients withdrew consent before first intake of study drug. 1352 remaining patients were available for intention-to treat analysis. Because the number of patients
			Acute coronary syndrome (SO)	ES: 39 ND: 48 NT	
			Heart failure (SO)	ES: 30 ND: 46 NT	
			Safety		
			Dizziness/hypotension	ES: 12.9% ND: 10.6% NT	
			Pneumonia	ES: 10.8% ND: 11.4% NT	
			Metabolic disorder	ES: 5.5% ND: 5.9% NT	

	failure (New York Heart Association grade III–IV), age >85 years at the time of the cerebrovascular event, patients treated with anticoagulants for a cardiac arrhythmia, high-grade aortic or mitral valve stenosis, or unstable angina pectoris.	*angiotensin II type 1 receptor antagonists, or calcium antagonists had to be avoided and should only be given when clinically necessary.*			per year was lower than expected, in an amendment to the protocol, it was decided to extend the observation period to receive the desired number of events. Sponsor: Financial support for the study was provided by Solvay Pharmaceuticals GmbH and Aventis Pharma Germany.

Table 330

4.3.8.3.2 Summary and conclusions

Angiotensin receptor blocker versus calcium antagonist in hypertension patients with previous stroke			
Bibliography: Schrader 2005 (MOSES)(149)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality, cardiovascular and cerebrovascular events (composite)	1405 (1 study) 2.5 years	**Incidence density ratio: 0.79 (95%CI 0.66 to 0.96) SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label; no ITT; selective reporting Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cerebrovascular events	1405 (1 study) 2.5 years	**Incidence density ratio: 0.75 (95%CI 0.58 to 0.97) SS**	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label; no ITT; selective reporting Consistency: only one study Directness: ok Imprecision: -1; 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
Cardiovascular events	1405 (1 study) 2.5 years	Incidence density ratio: 0.75 (95%CI 0.55 to 1.02) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; open-label; no ITT; selective reporting Consistency: only one study Directness: ok Imprecision: -1; 95%CI crosses both no effect and appreciable harm or benefit

Table 331

In this open-label RCT in 1405 hypertension patients with a previous cerebrovascular event (TIA or stroke), an angiotensin receptor blocker (eprosartan) was compared to a calcium channel blocker (nitrendipine). The follow-up in this trial was 2.5 years.

In hypertension patients with previous stroke, treatment with an angiotensin receptor blocker, compared to a calcium channel blocker, significantly decreases cerebrovascular events, and a composite of mortality, cardiovascular and cerebrovascular events.
GRADE: LOW quality of evidence

In hypertension patients with previous stroke, treatment with an angiotensin receptor blocker, compared to a calcium channel blocker, did not result in a statistically significant difference in cardiovascular event rate.
GRADE: LOW quality of evidence

5 Adverse effects

5.1 Potassium-wasting diuretics; Thiazides and related drugs

- Hypopotassemia: clinically important potassium loss is rare when using the low doses recommended for hypertension.
- Hyponatremia
- Magnesium deficiency.
- Hyperuricemia (sometimes with gout attacks).
- Photosensitivity (with hydrochlorothiazide) and thrombocytopenic purpura, rash (rare)
- Allergic vasculitis
- Acute allergic interstitial pneumonitis (rare, incidence unknown) (possible after first dose, sometimes after rechallenge)
- Increase of insulin resistance, increased glycemia; the long-term clinical relevance is unclear. A 44% increase in new-onset diabetes rate with diuretics, compared to ACE-inhibitors, was observed in a follow-up study to the ANBP2 trial[1].
- Hypertriglyceridemia, with increase of VLDL-cholesterol and decrease of HDL-cholesterol; it is unclear if these are long-term changes and whether they are clinically relevant.
- Dehydratation
- Dizziness at the start of treatment
- Dry mouth (and the formation of dental caries)
- Weakness, paresthesia, muscle cramps, especially in the lower limbs.
- Sexual disfunction (e.g. erectile dysfunction).
- Functional renal insufficiency
- Acute interstitial nephritis
- Cholestatic jaundice, pancreatitis (rare)
- Precipitation of hepatic encephalopathy in hepatic cirrhosis (rare)
- Fever (rare)
- Visual disturbances by dehydration of the lens tissue or by retinal edema.

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd29/6/5015)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *Folia farmacotherapeutica, april 2015 and august 2010*
- *1.Chowdhury E., Owen A., Ademi Z., et al.: Short- and long-term survival in treated elderly hypertensive patients with or without diabetes: findings from the Second Australian National Blood Pressure study. Am J Hypertens. 2014; 27; 199-206.*

5.2 Potassium-sparing diuretics

- Agranulocytosis (spironolactone, rare)
- Hyperpotassemia (also in low doses)
- Hyponatremia
- Hypersensivity rash and lupus-like syndrome (rare)
- Cutaneous vasculitis (spironolactone)
- Dehydratation

- Weakness, drowsiness, and confusion (spironolactone)
- Gastrointestinal intolerance (nausea and vomiting) (with spironolacton, triamterene)
- Neurologic symptoms
- Spironolactone, canrenoate and eplerenone: also gynaecomastia, amenorrhea, impotence, erectile- and ejaculation problems[1].
- Menstrual irregularities (in almost all women)
- Higher doses of spironolactone can cause infertility
- Breast pain and breast enlargement, changed vaginal lubrication and decreased libido.
- Breast cancer (some reported cases with spironolactone)
- Interstitial nephritis
- Triamterene: kidney stones.

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1. Folia Farmacotherapeutica, okt 2001*

5.3 β-blockers

- Sinus bradycardia (less pronounced in β-blockers with intrinsic sympathomimetic activity, atrioventricular block.
- Emergence or worsening of heart failure.
- Severe angina and myocardial infarction when abruptly discontinued, especially in patients with coronary heart disease.
- Syncope caused by severe blood pressure falls, more common in the elderly.
- Sotalol: important risk of torsades de pointes, especially when initating and increasing the dose, in bradycardia or hypopotassemia
- Exacerbation of psoriasis.
- β-blocker-induced gangrene (the symptoms generally disappear when discontinuing the medication, but there are also reported cases where amputation was necessary)
- Worsening of an anaphylactic reaction, and reduced effect of adrenalin when treating it.
- Elevation of VLDL-cholesterol and reduction of HDL-cholesterol by some β-blockers (the clinical relevance is unclear).
- Increased insulin resistance with increased glycemia and a limited weight gain (clinical relevance unclear) (less in β_1-selective drugs)
- More hypoglycemia in type I diabetics, but likely less pronounced with cardioselective β-blockers.
- β-blocker action can mask adrenalin-mediated symptoms of hypoglycemia in diabetes patients treated with insulin.
- Dysfunction of the carbohydrate metabolism with increased incidence of de novo-diabetes with β-blockers[1].
- Weight gain (1,2 kg, (range 0,4 – 3,5 kg), caused by the reduction of basal metabolic rate during the first months of treatment.
- Tremor (β-blockers met partial agonist activity)
- Tiredness and reduced exercise capacity. (Most common, up to more than 20%)
- Cold extremities, aggravation of vasospasms (Raynaud, in 0,5 tot 6% of patients), possibly less pronounced with β-blockers with a vasodilating action (one of the most common adverse effects; 5,8% of patients)

- Gastrointestinal trouble (nausea, dyspepsia, constipation or diarrhea, in 5 to 10% of patients). Dose reduction or changing drug class can cause improvement.
- Asthma attack in patients with a history of bronchospasm; less pronounced, but not absent, when using cardioselective β-blockers[2].
- Impotence, loss of libido
- Central phenomena (e.g. sleep disturbances, nightmares, depression), especially with lipophile β-blockers.
- Neuropathic adverse effects (visual and auditory hallucinations, illusions, sleep disturbances, vivid dreams, …) (causally related to long-term treatment with β-blockers)

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1. Folia Farmacotherapeutica, aug. 2007*
- *2. Folia Farmacotherapeutica, okt. 2008*

5.4 Calcium channel blockers

- Peripheral vasodilatation with headache, ankle edema, hot flashes, hypotension and reflex tachycardia (particularly with dihydropyridines) (in 1/3 of patients). There are indications that simultaneous administration of an ACE-inhibitor or an angiotensin receptor blocker lessens the occurence of ankle edema.
- Excessive reduction of heart contractility and frequency: particularly verapamil.
- Fatal and non fatal myocardial infarction (16 per 1000 with calcium channel blockers versus 10 per 1000 with β-blockers or thiazides; from a retrospectieve study, with the remark that this result was the effect of confounding factors)
- The possibility exists that abrupt discontinuation of calcium channel blocker can worsen angina, and can cause myocardial infarction (verapamil; diltiazem and nifedipine)
- Allergic reactions (skin eruptions, effects on liver and renal function) (verapamil, nifedipine and diltiazem)
- Dizziness
- Heart palpitations, muscle cramps
- Gingival hyperplasia (class effect)
- Obstipation (especially verapamil and diltiazem) (in 1/3 of patients)
- Elevated risk of gastrointestinal bleeding (prospective cohort study: RR=1,86 (95%CI 1,22 to 2,82, but unconfirmed by other studies)
- Gastro-oesophageal reflux
- Parkinson's disease (only few made a complete recovery after discontinuing treatment (class effect)
- Painful eyes (nifedipine)
- Cancer risk (retrospective study, RR = 1,72 (95%CI 1,27 to 2,34 and significant dose-response relationship, but unconfirmed by other studies)

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1. Folia Farmacotherapeutica, okt. 2001*

5.5 ACE-inhibitors

- Decline of hemoglobemia, possibly with anemia, particularly in chronic renal insufficiency.
- Hypotension after administration of the first dose of an ACE-inhibitor, especially in patients with pre-existing stimulation of the renin-angiotensin-aldosterone system (volume depletion by diuretics, heart failure, renal artery stenosis); this is more common in the treatment of heart failure than in the treatment of hypertension.
- Hyperpotassemia, rarely hyponatremia
- Rash
- Angioneurotic edema, which sometimes occurs months after treatment, and which is more frequent in black patients and in patients with a history of angioneurotic edema not due to the use of ACE-inhibitors (0,1%-0.5%).
- Pemphigus (rare, mainly with captopril). The time between initiation of the drug and the occurence of pemphigus is very variable (2 weeks to 2 years)[1].
- Elevated risk of hypoglycemia in combination with hypoglyciëmierende medication and insulin in diabetics (hospital admission because of hypoglycemia is increased by the use of ACE-inhibitors; from a case-control study) (OR = 2,4; 95%CI 1,1 to 5,3 with enalapril).
- Ankle edema
- Dizziness
- Headache
- Shortness of breath
- Heart palpitations
- Cough (sometimes after a couple of weeks of treatment).
- Deterioration of renal function (and sometimes acute renal insufficiency), particularly in patients with pre-existing kidney disease (e.g. bilateral renal artery stenosis or stenosis in a solitary kidney), or in patients with heart failure, pronounced volume depletion or dehydration (e.g. because of diarrhea or vomiting).
- Taste disorders, gastrointestinal disorders (e.g. diarrhea).
- Cholestatic hepatitis and hematological problems (e.g. neutropenia): rare.
- Acute pancreatitis

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1.Folia Farmacotherapeutica, jan. 2005.*

5.6 Angiotensin receptor blockers

- Decline of hemoglobemia, possibly with anemia, particularly in chronic renal insufficiency[1].
- Hypotension (after administration of the first dose and particularly in patients with volume depletion[1])
- Hyperpotassemia, rarely hyponatremia.
- Rash
- Angioedema
- Headache
- Dizziness
- Weakness and tiredness
- Cough (less frequent than with ACE-inhibitors)[1].

- Deterioration of renal function and acute renal failure (mainly in patients with renovascular disease, particularly bilateral renal artery stenosis)[1].
- Taste disorders, gastrointestinal disorders (e.g. diarrhea).
- Olmesartan: severe enteropathy (probably low incidence)[2].
- Elevated liver enzymes, cholestatic hepatitis and pancreatitis (mainly with losartan)

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1. Folia Farmacotherapeutica, aug. 2000*
- *2. Folia Farmacotherapeutica, feb. 2014*

5.7 Renin inhibitors

- Gastrointestinal disorders (e.g. diarrhea).
- Rash.
- Angioneurotic edema.
- Risk of hypotension, hyperpotassemia and renal insufficiency is comparable to that of ACE-inhibitors and angiontensin receptor blockers[1].
- Association with an ACE-inhibitor or an angiotensin receptor blocker is associated with a higher risk of cardiovascular and renal adverse effects[1].

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *1. Folia Farmacotherapeutica, jan. 2014*

5.8 Centrally acting antihypertensive drugs: moxonidine

- Contrary to clonidine, it does not cause sedation or diminishment of psychomotor performance or cognitive function.
- Dry mouth (and higher risk of dental caries[1]) in 10% of patients. Effect is dose-dependent and mild, occurring from initiation of treatment.
- Bradycardia.
- Moxonidine: increased mortality in patients with heart failure.

- *Belgisch Centrum voor Farmacotherapeutische Informatie(geconsulteerd dd 2013/10/08)*
- *Meyler's Side Effects of Drugs: the International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006, pages 1632-1639.*
- *1. Folia Farmacotherapeutica, april 2015*

6 APPENDIX: Search strategy

6.1 1. Medline search (using Pubmed)

- Using the references from NICE 2013, NICE 2011 and JNC-8 2011, we decided to start our systematic search from September 2012 (= end of search date NICE 2013) onwards:
- We searched for meta-analyses, systematic reviews, RCTs and observational studies (for threshold and target) from September 2012 up to 22 June 2015, using the following:

Threshold

((((("Hypertension"[Mesh] OR Hypertens*[tiab] OR elevated blood pressure[tiab] OR high blood pressure[tiab] OR increased blood pressure[tiab] OR high BP[tiab])) AND (((risk factors OR risk assessment OR threshold)) AND ("Antihypertensive Agents"[Mesh] OR Antihypertens*[tiab] OR anti hypertens*[tiab] OR blood pressure lowering[tiab] OR lowering blood pressure[tiab] OR BP lowering[tiab] OR lowering BP[tiab] OR blood pressure treatment[tiab] OR BP treatment[tiab] OR blood pressure control[tiab] OR BP control[tiab]))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB] OR observational[TIAB] OR cohort[TIAB] OR population-based[TIAB]))) AND ((mortality[tiab] OR death[tiab] OR cardiovascular[tiab] OR MI[tiab] OR myocardial infarct*[tiab] OR stroke[tiab] OR heart failure[tiab] OR coronary artery disease[tiab]))))) NOT ("Pregnancy"[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "Hypertension, Pulmonary"[Mesh] OR "Hypertension, Portal"[Mesh] OR "Intracranial Hypertension"[Mesh] OR "Ocular Hypertension"[Mesh] OR "Pregnancy"[tiab] OR pulmonary Hypertension[tiab] OR portal hypertension[tiab] OR Intracranial Hypertension[tiab] OR Ocular Hypertension[tiab])

Target

((((("Hypertension"[Mesh] OR Hypertens*[tiab] OR elevated blood pressure[tiab] OR high blood pressure[tiab] OR increased blood pressure[tiab] OR high BP[tiab])) AND (Target blood pressure[tiab] OR target BP[tiab] OR blood pressure target*[tiab] OR BP target*[tiab] OR blood pressure goal*[tiab] OR BP goal*[tiab] OR optimal blood pressure OR optimal BP OR optimum blood pressure OR optimum BP OR ((Intensive[tiab] OR strict*[tiab]) AND (Antihypertens*[tiab] OR anti hypertens*[tiab] OR blood pressure lowering[tiab] OR lowering blood pressure[tiab] OR BP lowering[tiab] OR lowering BP[tiab] OR blood pressure treatment[tiab] OR BP treatment[tiab] OR blood pressure control[tiab] OR BP control[tiab])))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB] OR observational[TIAB] OR cohort[TIAB] OR population-based[TIAB]))) AND ((mortality[tiab] OR death[tiab] OR cardiovascular[tiab] OR MI[tiab] OR myocardial infarct*[tiab] OR stroke[tiab] OR heart failure[tiab] OR coronary artery disease[tiab])))) NOT ("Pregnancy"[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "Hypertension, Pulmonary"[Mesh] OR "Hypertension, Portal"[Mesh] OR "Intracranial Hypertension"[Mesh] OR "Ocular Hypertension"[Mesh] OR "Pregnancy"[tiab] OR pulmonary Hypertension[tiab] OR portal hypertension[tiab] OR Intracranial Hypertension[tiab] OR Ocular Hypertension[tiab])

Antihypertensive treatment

Search **((((("Hypertension"[Mesh] OR Hypertens*[tiab] OR elevated blood pressure[tiab] OR high blood pressure[tiab] OR increased blood pressure[tiab] OR high BP[tiab])) AND (((("Antihypertensive Agents"[Mesh] OR Antihypertens*[tiab] OR anti hypertens*[tiab] OR blood pressure lowering[tiab] OR lowering blood pressure[tiab] OR BP lowering[tiab] OR lowering BP[tiab] OR blood pressure treatment[tiab] OR BP treatment[tiab] OR blood pressure control[tiab] OR BP control[tiab])) OR ((((("Angiotensin II Type 1 Receptor Blockers"[Mesh] OR "Angiotensin Receptor Antagonists"[Mesh] OR Angiotensin II receptor blocker*[tiab] OR ARB[tiab] OR sartan*[tiab] OR angiotensin receptor blocker*[tiab] OR Candesartan[tiab] OR Eprosartan[tiab] OR Irbesartan[tiab] OR Losartan[tiab] OR Olmesartan[tiab] OR Telmisartan[tiab] OR Valsartan[tiab])) OR ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR Angiotensin converting enzyme inhibitor*[tiab] OR ace inhibitor*[tiab] OR Benazepril[tiab] OR Captopril[tiab] OR Cilazapril[tiab] OR Enalapril[tiab] OR Fosinopril[tiab] OR Lisinopril[tiab] OR Perindopril[tiab] OR Quinapril[tiab] OR Ramipril[tiab] OR Zofenopril[tiab])) OR ("Calcium Channel Blockers"[Mesh] OR Calcium channel blocker*[tiab] OR dihydropyridines[tiab] OR Amlodipine[tiab] OR Barnidipine[tiab] OR Felodipine[tiab] OR Isradipine[tiab] OR Lacidipine[tiab] OR Lercanidipine[tiab] OR Nicardipine[tiab] OR Nifedipine[tiab] OR Nimodipine[tiab] OR Nisoldipine[tiab] OR Nitrendipine[tiab] OR Verapamil[tiab] OR Diltiazem[tiab])) OR ("Adrenergic beta-Antagonists"[Mesh] OR beta block*[tiab] OR betablock*[tiab] OR beta-block*[tiab] OR pindolol[tiab] OR acebutolol[tiab] OR celiprolol[tiab] OR atenolol[tiab] OR carvedilol[tiab] OR bisoprolol[tiab] OR metoprolol[tiab] OR nebivolol[tiab] OR propranolol[tiab] OR betaxolol[tiab] OR esmolol[tiab] OR labetalol[tiab])) OR ("Diuretics"[Mesh] OR Thiazide diuretic*[tiab] OR Chlorthalidon*[tiab] OR chlortalidon*[tiab] OR "Chlorthalidone"[Mesh] OR "Indapamide"[Mesh] OR indapamide[tiab] OR "Hydrochlorothiazide"[Mesh] OR hydrochlorothiazide[tiab] OR spironolactone [tiab] OR moxonidine[tiab] OR aliskiren[tiab]))))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB] OR observational[TIAB] OR cohort[TIAB] OR population-based[TIAB]))) AND ((mortality[tiab] OR death[tiab] OR cardiovascular[tiab] OR MI[tiab] OR myocardial infarct*[tiab] OR stroke[tiab] OR heart failure[tiab] OR coronary artery disease[tiab]))))) NOT ("Pregnancy"[Mesh] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "Hypertension, Pulmonary"[Mesh] OR "Hypertension, Portal"[Mesh] OR "Intracranial Hypertension"[Mesh] OR "Ocular Hypertension"[Mesh] OR "Pregnancy"[tiab] OR pulmonary Hypertension[tiab] OR portal hypertension[tiab] OR Intracranial Hypertension[tiab] OR Ocular Hypertension[tiab])**

Because not all subgroups of interest were researched by NICE and JNC-8, we had to consult a number of additional sources and/or perform additional searches.

- For people with hypertension and **coronary heart disease** or **heart failure**, we consulted the reference lists of the following (systematic) reviews:
    - Daskalopoulou SS, Rabi DM, Zarnke KB, et al. The 2015 canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2015;31:549-68, May. DOI: 10.1016/j.cjca.2015.02.016. (and previous editions up to 2006)

- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation 2015;131:e435-70, May 12. DOI: 10.1161/cir.0000000000000207.

- For people with hypertension and previous **stroke**
  - we consulted the literature search publication of the Consensus Conference on "The efficient pharmaceutical approach to prevention and treatment of cerebrovascular pathologies in primary health care", 10 mai 2012 (search date 15/10/2011)
  - we performed an additional search for 1 year (10/2011to 09/2012) to find missing publications

NICE did not do a search for observational studies for the following subgroups: Type 2 diabetes, coronary heart disease, heart failure, previous stroke and chronic kidney disease and possibly elderly patients. Because searching all the literature for cohort studies would be too time-consuming in relation to the benefit (by GRADE standards observational studies are considered to be low quality of evidence), we decided to limit ourselves to searching the last 10 years (2005 onwards), using the search phrase detailed above, combined with"cohort[tiab]" and "(elderly[tiab] OR aged[tiab] OR stroke[Mesh] OR myocardial ischemia [Mesh] OR heart failure[Mesh] OR type 2 diabetes mellitus [Mesh] OR chronic kidney disease[tiab])"

6.2 2. Cochrane database of systematic reviews

Searched with keyword 'hypertension'

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