Anti hypertensive agent for hypertension in diabetic patients

A systematic review and meta-analysis of randomized clinical trials

2017 - 7 - 1

This report should be referenced as follows:
TrialResults-center.org; Results of all major randomized clinical trials about Anti hypertensive agent for hypertension in diabetic patients .

Contents

0.1 Synthesis of the meta-analysis results

In all 34 randomised controlled trials (RCTs) were included. These included 7 studies of **ACE inhibitor** involving 13,928 patients, 13 studies of **angiotensin receptor blocker** (1 unpublished) involving 35,291 patients, 9 studies of **calcium blockers** involving 14,995 patients, 1 studie of **direct renin inhibitor** involving 599 patients, 1 studie of **diuretics** involving 583 patients, 1 studie of **intensive treatment** involving 4,734 patients, 0 studie of **other BP lowering drugs** involving NaN patients and 2 studies of **treatment blood pressure target** involving 950 patients. Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).

0.1.1 ACE inhibitor

Reports of 5 trials (including 13,928 patients) were identified .
Among these comparisons, 3 trials are about ACE inhibitor,two about captopril,one about captopril or atenolol and one about lisinopril.
During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

ACE inhibitor

Results obtained with ACE inhibitor for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - ACE inhibitor*

Benefit	Harmful	No evidence
	ACE inhibitor versus placebo	
	ACE inhibitor versus CCB	
	ACE inhibitor versus diuretic or beta-blocker	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Captopril

Results obtained with captopril for all the endpoints with data in at least one trial are summarized table 2.

Table 2: *Results summary - Captopril*

Benefit	Harmful	No evidence
	Captopril versus atenolol	
		→ myocardial infarction (fatal and non fatal) RR=1.19^{NS} [0.83;1.69] k=1 → stroke (fatal and non fatal) RR=1.38^{NS} [0.74;2.57] k=1 → all cause death RR=1.14^{NS} [0.83;1.55] k=1
	Captopril versus diuretic and/or beta-blockers	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Captopril or atenolol

Results obtained with captopril or atenolol for all the endpoints with data in at least one trial are summarized table 3.

Table 3: *Results summary - Captopril or atenolol*

Benefit	Harmful	No evidence
	Captopril or atenolol versus control	
↓ stroke (fatal and non fatal) RR=0.58* [0.37;0.90] k=1		→ myocardial infarction (fatal and non fatal) RR=0.80^{NS} [0.60;1.05] k=1 → all cause death RR=0.83^{NS} [0.65;1.06] k=1

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Lisinopril

Results obtained with lisinopril for all the endpoints with data in at least one trial are summarized table 4.

Table 4: *Results summary - Lisinopril*

Benefit	Harmful	No evidence
	Lisinopril versus chlorthalidone	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

0.1.2 Angiotensin receptor blocker

Reports of 9 trials (including 35,291 patients) were identified (including 1 unpublished).
Among these comparisons, 6 trials are about irbesartan,3 about losartan,one about telmisartan and 3 about valsartan.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Irbesartan

Results obtained with irbesartan for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Irbesartan*

Benefit	Harmful	No evidence
	Irbesartan versus placebo	
		→ coronary event RR=0.91^{NS} [0.72;1.15] k=1
	Irbesartan versus amlodipine	
↑ myocardial infarction (fatal and non fatal) RR=1.60* [1.00;2.54] k=1	↓ heart failure RR=0.63† [0.47;0.86] k=1	→ cardiovascular events RR=1.03^{NS} [0.81;1.31] k=1 → cardiovascular death RR=1.38^{NS} [0.92;2.06] k=1 → stroke (fatal and non fatal) RR=1.83^{NS} [0.99;3.39] k=1 → all cause death RR=1.03^{NS} [0.78;1.35] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Losartan

Results obtained with losartan for all the endpoints with data in at least one trial are summarized table 6.

Table 6: *Results summary - Losartan*

Benefit	Harmful	No evidence
	Losartan versus placebo	
	Losartan versus atenolol	
↓ cardiovascular events RR=0.86† [0.77;0.96] k=1		→ cardiovascular death RR=0.87^{NS} [0.72;1.04] k=1 → coronary event RR=1.05^{NS} [0.86;1.28] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Telmisartan

Results obtained with telmisartan for all the endpoints with data in at least one trial are summarized table 7.

Table 7: *Results summary - Telmisartan*

Benefit	Harmful	No evidence
	Telmisartan versus enalapril	

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

Valsartan

Results obtained with valsartan for all the endpoints with data in at least one trial are summarized table 8.

Table 8: *Results summary - Valsartan*

Benefit	Harmful	No evidence
	Valsartan versus amlodipine	
↑ myocardial infarction (fatal and non fatal) RR=1.17* [1.01;1.36] k=1 ↓ diabetes onset RR=0.81¶ [0.74;0.89] k=1		→ cardiovascular events RR=1.02^{NS} [0.93;1.12] k=1 → cardiovascular death RR=0.99^{NS} [0.85;1.16] k=1 → stroke (fatal and non fatal) RR=1.14^{NS} [0.97;1.33] k=1 → coronary event RR=1.02^{NS} [0.93;1.12] k=1 → heart failure RR=0.88^{NS} [0.76;1.01] k=1 → all cause death RR=1.02^{NS} [0.93;1.12] k=1

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.3 Calcium blockers

Reports of 9 trials (including 14,995 patients) were identified .
Among these comparisons, 3 trials are about amlodipine,one about benazepril + amlodipine,one about calcium-channel blocker,one about diltiazem,one about nifedipine,one about nisoldipine and one about nitrendipine.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Amlodipine

Results obtained with amlodipine for all the endpoints with data in at least one trial are summarized table 9.

Table 9: *Results summary - Amlodipine*

Benefit	Harmful	No evidence
	Amlodipine versus placebo	
	Amlodipine versus chlorthalidone	
	Amlodipine versus fosinopril	
	↑ cardiovascular events RR=1.91* [1.03;3.52] k=1	→ myocardial infarction (fatal and non fatal) RR=1.29^{NS} [0.58;2.86] k=1 → stroke (fatal and non fatal) RR=2.47^{NS} [0.79;7.75] k=1 → all cause death RR=1.24^{NS} [0.34;4.54] k=1

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Benazepril + amlodipine

Results obtained with benazepril + amlodipine for all the endpoints with data in at least one trial are summarized table 10.

Table 10: *Results summary - Benazepril + amlodipine*

Benefit	Harmful	No evidence
	Benazepril + amlodipine versus benazepril + hydrochlorothiazide	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Calcium-channel blocker

Results obtained with calcium-channel blocker for all the endpoints with data in at least one trial are summarized table 11.

Table 11: *Results summary - Calcium-channel blocker*

Benefit	Harmful	No evidence
	Calcium-channel blocker versus diuretic or beta-blocker	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Diltiazem

Results obtained with diltiazem for all the endpoints with data in at least one trial are summarized table 12.

Table 12: *Results summary - Diltiazem*

Benefit	Harmful	No evidence
	Diltiazem versus diuretic or beta-blocker	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Nifedipine

Results obtained with nifedipine for all the endpoints with data in at least one trial are summarized table 13.

Table 13: *Results summary - Nifedipine*

Benefit	Harmful	No evidence
	Nifedipine versus coamilozide	

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Nisoldipine

Results obtained with nisoldipine for all the endpoints with data in at least one trial are summarized table 14.

Table 14: *Results summary - Nisoldipine*

Benefit	Harmful	No evidence
	Nisoldipine versus enalapril	
↑ myocardial infarction (fatal and non fatal) RR=5.00¶ [1.95;12.84] k=1	↑ cardiovascular events RR=5.00¶ [1.95;12.84] k=1	→ cardiovascular death RR=2.00^{NS} [0.69;5.76] k=1 → stroke (fatal and non fatal) RR=1.57^{NS} [0.62;3.98] k=1 → all cause death RR=1.31^{NS} [0.65;2.63] k=1

* $p < 0.05$; † $p < 0.01$; ¶ $p < 0.001$ RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test $p < 0.05$)

Nitrendipine

Results obtained with nitrendipine for all the endpoints with data in at least one trial are summarized table 15.

Table 15: *Results summary - Nitrendipine*

Benefit	Harmful	No evidence
	Nitrendipine versus placebo	

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.4 Direct renin inhibitor

Only one trials including 599 patients was found.
Among these comparisons, one trial are about aliskiren.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with aliskiren for all the endpoints with data in at least one trial are summarized table 16.

Table 16: *Results summary - Aliskiren*

Benefit	Harmful	No evidence
	Aliskiren versus placebo	

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.5 Diuretics

Only one trials including 583 patients was found.
Among these comparisons, one trial are about chlorthalidone.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with chlorthalidone for all the endpoints with data in at least one trial are summarized table 17.

Table 17: *Results summary - Chlorthalidone*

Benefit	Harmful	No evidence
	Chlorthalidone versus placebo	

continued...

Benefit	Harmful	No evidence

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.6 Intensive treatment

Only one trials including 4734 patients was found.
Among these comparisons, one trial are about intensive.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with intensive for all the endpoints with data in at least one trial are summarized table 18.

Table 18: *Results summary - Intensive*

Benefit	Harmful	No evidence
Intensive versus usual		

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

0.1.7 Other BP lowering drugs

Reports of 0 trials (including patients) were identified . .
During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

0.1.8 Treatment blood pressure target

Reports of 2 trials (including 950 patients) were identified .
Among these comparisons, two trials are about more intensive blood pressure lowering strategie.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with more intensive blood pressure lowering strategie for all the endpoints with data in at least one trial are summarized table 19.

Table 19: *Results summary - More intensive blood pressure lowering strategie*

Benefit	Harmful	No evidence
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie		

* p <0.05; † p <0.01; ¶ p <0.001 RR: relative risk

H: heterogeneity with fixed effect model detected (heterogeneity test p <0.05)

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of anti hypertensive agent for the treatment of hypertension in diabetic patients . The following classes of treatment are considered:

1. ACE inhibitor
2. angiotensin receptor blocker
3. calcium blockers
4. direct renin inhibitor
5. diuretics
6. intensive treatment
7. other BP lowering drugs
8. Treatment blood pressure target

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of anti hypertensive agent for the treatment of hypertension in diabetic patients .

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2017 - 7 - 1:

- MEDLINE,
- EMBASE,
- Cochrane Database of Systematic Reviews (CDSR),
- Cochrane Central Register of Controlled Trials (CCTR),
- Health Technology Assessment (HTA) database,
- ISI Web of Science Proceedings (Index to Scientific and Technical Proceedings),
- ISI Web of Science Science Citation Index Expanded,

Each database was searched as far back as possible, with no language restrictions.
Search strategies of relevant clinical keywords were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.
In addition, the reference lists of relevant articles were handsearched.
Attempts to identify further studies were made by consulting health technology assessment and guideline producing agencies, and research and trials registers via the Internet.
Titles and, when available, abstracts of all studies identified in the searches were assessed by a single researcher for relevance to the review. In cases of doubt, the full article was obtained.

1.2.2 Search restrictions

No language, study/publication or date restrictions were applied to the main searches.

1.3 Inclusion criteria

Participants only those studies were included in which the participants had been diagnosed as having established hypertension.

Interventions studies in which anti hypertensive agent was used.
Studies using other interventions in addition to anti hypertensive agent therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of anti hypertensive agent.

Methodology randomised controlled trials (RCTs). Trials were accepted as RCTs if the allocation of subjects to treatment groups was described by the authors as either randomised or double-blind.

1.4 Exclusion criteria

Studies considered methodologically unsound. The list of excluded studies with reason of their exclusion are given in a separate section for each treatment categories considered.

1.5 Meta-analysis strategy

Studies that met the reviews entry criteria were eligible for inclusion in the meta-analyses provided that they reported outcomes in terms of the number of subjects suffering clinical outcomes, as only this would allow calculation of the relative risk of subjects in the intervention group developing each outcome, compared with subjects in the control group.
Studies that only presented results in the form of relative risks, relative hazards or odds ratios, without the underlying numbers were also include in the meta-analyses.
Binary outcomes were analysed using the fixed-effect model. For continuous outcomes, weighted mean differences (WMDs) were analysed, using a fixed-effect model.
Heterogeneity was tested by the chi-2 test and the I2 statistic was obtained to describe the proportion of the variability.
Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.
Meta-analyses were conducted for data on Death related to diabetes, myocardial infarction (fatal and non fatal), stroke (fatal and non fatal), All cause death, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part I to **??**, listed by therapeutic class. The therapeutic classes included ACE inhibitor, angiotensin receptor blocker, calcium blockers, direct renin inhibitor, diuretics, intensive treatment, other BP lowering drugs, Treatment blood pressure target,
In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

Part I

ACE inhibitor

2 Overview of ACE inhibitor

2.1 Included trials

A total of 7 randomized comparisons which enrolled 13928 patients were identified. In all, 3 randomized comparisons concerned ACE inhibitor , two captopril , one captopril or atenolol and one lisinopril.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 26) for ACE inhibitor, in section 4 (page 36) for captopril, in section 5 (page 46) for captopril or atenolol and in section 6 (page 54) for lisinopril.

The average study size was 1989 patients (range 466 to 6929). The first study was published in 1998, and the last study was published in 2002.
A total of 2 trials were double blind and 5 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 2.1 (page 21) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about ACE inhibitor provide the results listed in tables 2.2 to 2.5 (page 23) and in the following graphs.

2.2.1 ACE inhibitor

Data were insufficient to compare **ACE inhibitor** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **ACE inhibitor** to **CCB**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **ACE inhibitor** to **diuretic or beta-blocker**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

2.2.2 Captopril

No significant difference was found between **captopril** and **atenolol** in terms of myocardial infarction (fatal and non fatal) (RR=1.19, 95% CI 0.83 to 1.69, p=0.3445, 1 trial), stroke (fatal and non fatal) (RR=1.38, 95% CI 0.74 to 2.57, p=0.3110, 1 trial)and all cause death (RR=1.14, 95% CI 0.83 to 1.55, p=0.4144, 1 trial).

Data were insufficient to compare **captopril** to **diuretic and/or beta-blockers**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

2.2.3 Captopril or atenolol

Captopril or atenolol was superior to **control** in terms of stroke (fatal and non fatal) (RR=0.58, 95% CI 0.37 to 0.90, p=0.0151, 1 trial). However, no significant difference was found on myocardial infarction (fatal and non fatal) (RR=0.80, 95% CI 0.60 to 1.05, p=0.1099, 1 trial)and all cause death (RR=0.83, 95% CI 0.65 to 1.06, p=0.1378, 1 trial).

2.2.4 Lisinopril

Data were insufficient to compare **lisinopril** to **chlorthalidone**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 2.1: *Main study characteristics - ACE inhibitor*

Trial	Patients	Treatments	Trial design and method
ACE inhibitor			
ACE inhibitor versus placebo			
HOPE (diabetic subgroup), 2000 [1, 2] n = 1808 vs. 1759	patients with diabetes (sub group), aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction	ramipril 10 mg once per day orally **versus** placebo	double-blind factorial plan Primary endpoint: CV events multicentre, North, South america, Europe subgroup: yes
ACE inhibitor versus CCB			
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000 [3, 4] n = 235 vs. 231	diabetic (subgroup) elderly patients aged 70-84 years	ACE inhibitor **versus** calcium antagonists	open with blind assessment Primary endpoint: cardiovascular mortality 312 centres, Sweden subgroup: yes
ACE inhibitor versus diuretic or beta-blocker			
STOP-2 ACEI (diabetic subgroup), 2000 [5, 6, 7] n = 235 vs. 253	diabetic (subgroup) elderly patients aged 70-84 years with hypertension	ACE inhibitor **versus** conventional treatment (diuretic or beta-blocker)	open with blind assessment parallel groups Primary endpoint: cardiovascular mortality 312 centres, Sweden subgroup: yes
Captopril			
Captopril versus atenolol			
UKPDS 39, 1998 [1, 2] n = 400 vs. 358	hypertensive patients with type 2 diabetes	captopril 25 mg/d aiming at a BP $<$150/85 **versus** atenolol 50mg/d aiming at a BP $<$150/85	open parallel groups Primary endpoint: not unique (3) 20 centres, UK subgroup: no

continued...

Trial	Patients	Treatments	Trial design and method
Captopril versus diuretic and/or beta-blockers			
CAPP (diabetic subgroup), 1999 [3, 4, 5] n = 309 vs. 263	patients aged 25-66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions; subgroup of diabetic patients	captopril initial dose of 50 mg daily given in one or two doses **versus** thiazide diuretic or beta-blocker	open with blinded assessment parallel groups Primary endpoint: CV events 536 centres, Sweden, Finland subgroup: yes
Captopril or atenolol			
Captopril or atenolol versus control			
UKPDS 38, 1998 [1, 2] n = 758 vs. 390	hypertensive patients with type 2 diabetes	tight control of blood pressure aiming at a BP <150/85 (with the use of captopril or atenolol as main treatment, other treatment were added if the control criteria were not met) **versus** less tight control aiming at a blood pressure of <180/105 (avoiding treatment with ACE inhibitors or beta-blockers)	open parallel groups Primary endpoint: not unique (3) 20 centres, UK subgroup: no
Lisinopril			
Lisinopril versus chlorthalidone			
ALLHAT (lisi vs chlor, diabetic subgroup), 2002 [1, 2] n = 2431 vs. 4498	diabetic (subgroup) participants aged 55 years or older with hypertension	lisinopril 10 to 40 mg/d **versus** chlorthalidone 12.5 to 25 mg/d	double-blind parallel groups Primary endpoint: fatal CHD or nonfatal MI subgroup: yes

Table 2.2: *Summary of all results for ACE inhibitor*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ACE inhibitor versus placebo						
No data were presented in the trial identified						
ACE inhibitor versus CCB						
No data were presented in the trial identified						
ACE inhibitor versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.3: *Summary of all results for captopril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
captopril versus atenolol						
myocardial infarction (fatal and non fatal)	RR=1.19	0.83;1.69	0.3445	1.0000 (0.00)	1	758
stroke (fatal and non fatal)	RR=1.38	0.74;2.57	0.3110	1.0000 (0.00)	1	758
all cause death	RR=1.14	0.83;1.55	0.4144	1.0000 (0.00)	1	758
captopril versus diuretic and/or beta-blockers						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.4: *Summary of all results for captopril or atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
captopril or atenolol versus control						
myocardial infarction (fatal and non fatal)	RR=0.80	0.60;1.05	0.1099	1.0000 (0.00)	1	1148
stroke (fatal and non fatal)	RR=0.58	0.37;0.90	0.0151	1.0000 (0.00)	1	1148
all cause death	RR=0.83	0.65;1.06	0.1378	1.0000 (1.00)	1	1148

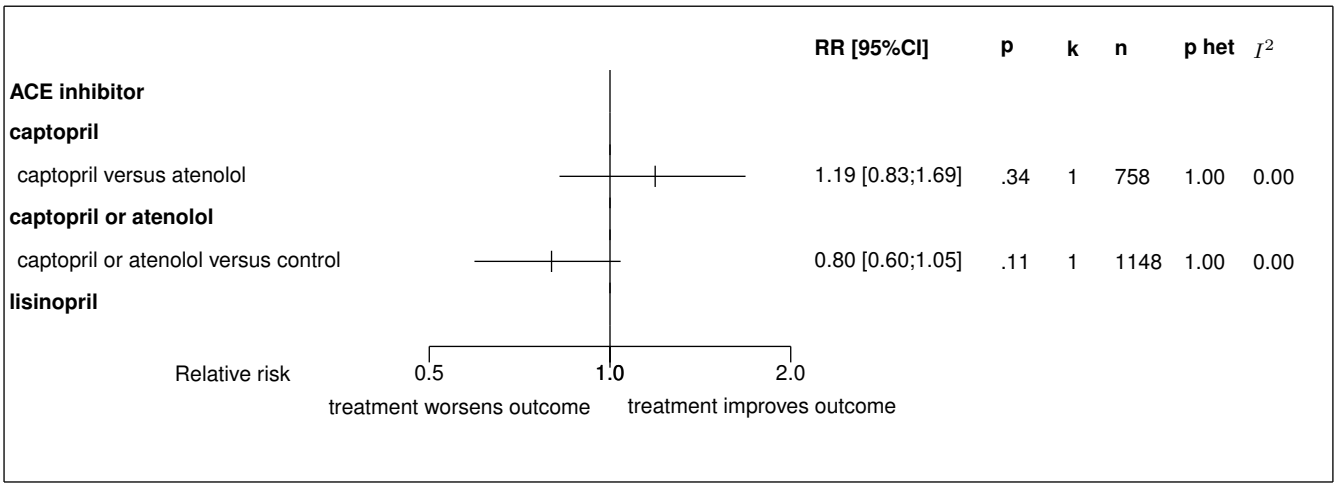
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.5: *Summary of all results for lisinopril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
lisinopril versus chlorthalidone						
No data were presented in the trial identified						

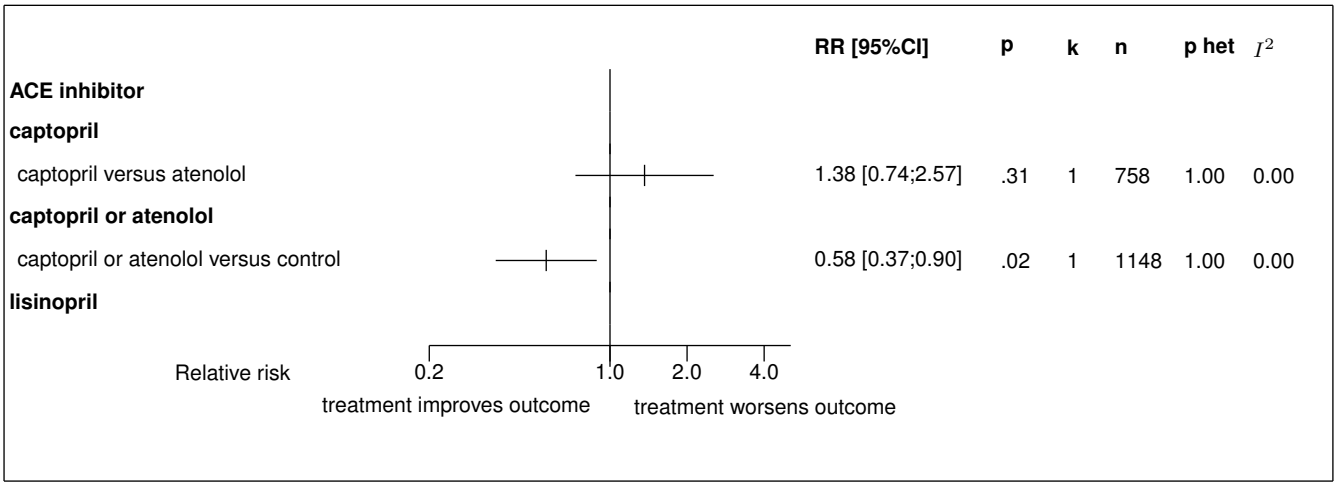
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for myocardial infarction (fatal and non fatal)*



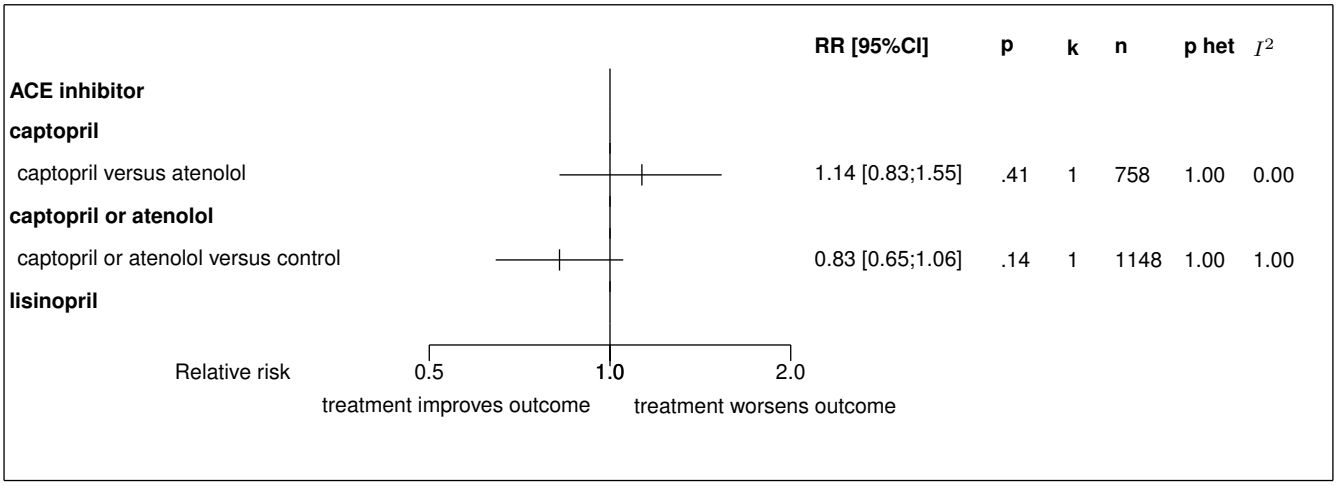
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 2.2: *Forest's plot for stroke (fatal and non fatal)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 2.3: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

3 Detailed results for ACE inhibitor

3.1 Available trials

A total of 3 RCTs which randomized 4521 patients were identified: it compared ACE inhibitor with placebo , it compared ACE inhibitor with CCB and it compared ACE inhibitor with diuretic or beta-blocker.
The average study size was 1507 patients (range 466 to 3567). The first study was published in 2000, and the last study was published in 2000.
A total of 1 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 3.1 (page 26), 3.2 (page 27), 3.5 (page 29), and 3.3 (page 27) summarized the main characteristics of the trials including in this systematic review of randomized trials of ACE inhibitor.

Table 3.1: *Treatment description - ACE inhibitor - ACE inhibitor*

Trial	Studied treatment	Control treatment
ACE inhibitor versus placebo		
HOPE (diabetic subgroup) (2000) [1, 2] [a]	ramipril 10 mg once per day orally	placebo
ACE inhibitor versus CCB		
STOP-2 (ACEI vs CCB) (diabetic subgroup) (2000) [3, 4]	ACE inhibitor enalapril 10 mg or lisinopril 10 mg daily. if the target blood pressure (<160/95 mm Hg) had not been reached at the 2-month visit or later, patients were given hydrochlorothiazide 125250 mg	calcium antagonists felodipine 25 mg or isradipine 25 mgdaily. if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later patients were given anyof the b-blockers in the doses listed
ACE inhibitor versus diuretic or beta-blocker		
STOP-2 ACEI (diabetic subgroup) (2000) [5, 6, 7]	ACE inhibitor enalapril 10 mg or lisinopril 10 mg daily. if the target blood pressure (<160/95 mm Hg) had not been reached at the 2-month visit or later, patients were given hydrochlorothiazide 125250 mg	conventional treatment (diuretic or beta-blocker) atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, orfixed-ratio hydrochlorothiazide 25 mg plus amiloride 25 mgdaily. Patients on beta-blockers were givenhydrochlorothiazide 25 mg plus amiloride 25 mg as additionaltreatment if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later. Patients who had started on diuretic treatment were given anyof the b-blockers in the doses listed

a) factorial design of ramipril and vitamin E

Table 3.2: *Descriptions of participants - ACE inhibitor - ACE inhibitor*

Trial	Patients
ACE inhibitor versus placebo	
HOPE (diabetic subgroup) (2000) [1, 2] [a]	Patients with diabetes (sub group), aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction
ACE inhibitor versus CCB	
STOP-2 (ACEI vs CCB) (diabetic subgroup) (2000) [3, 4] [a]	Diabetic (subgroup) elderly patients aged 70-84 years **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included **Exclusion criteria:**
ACE inhibitor versus diuretic or beta-blocker	
STOP-2 ACEI (diabetic subgroup) (2000) [5, 6, 7] [a]	Diabetic (subgroup) elderly patients aged 70-84 years with hypertension **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included **Exclusion criteria:**

a) of all 9541 patients in the HOPE trial, 3654 had diabetesa) Of all 6614 patients included in the trial, 719 had diabetesa) Of all 6614 patients included in the trial, 719 had diabetes

Table 3.3: *Design and methodological quality of trials - ACE inhibitor - ACE inhibitor*

Trial	Design	Duration	Centre	Primary endpoint
ACE inhibitor versus placebo				
HOPE (diabetic subgroup), 2000 [1, 2] n=3567	Factorial plan double-blind exploratory trial	4.5 years	North, South america, Europe multicentre	CV events
ACE inhibitor versus CCB				
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000 [3, 4] n=466	open with blind assessment exploratory trial	5.03y inclusion period: sep 1992 - dec 1994	Sweden 312 centres	cardiovascular mortality
ACE inhibitor versus diuretic or beta-blocker				
STOP-2 ACEI (diabetic subgroup), 2000 [5, 6, 7] n=488	Parallel groups open with blind assessment exploratory trial	5.03y inclusion period: sep 1992 - dec 1994	Sweden 312 centres	cardiovascular mortality

Table 3.4: *Trial characteristics - ACE inhibitor - ACE inhibitor(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
ACE inhibitor versus placebo								
HOPE (diabetic subgroup), 2000 [1, 2]	-1.39%	-0.83%	-1	-1.37				65.4 y
ACE inhibitor versus CCB								
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000 [3, 4]	#N/A	#N/A						75.8 y
ACE inhibitor versus diuretic or beta-blocker								
STOP-2 ACEI (diabetic subgroup), 2000 [5, 6, 7]	-2.88%	-3.16%						75.8 y

continued...

Table 3.5: *Trial characteristics - ACE inhibitor - ACE inhibitor*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
ACE inhibitor versus placebo								
HOPE (diabetic subgroup), 2000 [1, 2]	37%			142/80 mmHg		56%		CAD
ACE inhibitor versus CCB								
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000 [3, 4]	60%		7.6%	195/96 mmHg		100%		hypertension
ACE inhibitor versus diuretic or beta-blocker								
STOP-2 ACEI (diabetic subgroup), 2000 [5, 6, 7]	60%		7.6%	195/96 mmHg		100%		hypertension

3.2 Meta-analysis results

The results are detailed in table 3.6 (page 30). This table is followed by the Forest's plot corresponding to each endpoint.

ACE inhibitor versus placebo

No data were presented in the 1 trial identified

ACE inhibitor versus CCB

No data were presented in the 1 trial identified

ACE inhibitor versus diuretic or beta-blocker

No data were presented in the 1 trial identified

Table 3.6: *Results details - ACE inhibitor - ACE inhibitor*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ACE inhibitor versus placebo						
No data were presented in the trial identified						
ACE inhibitor versus CCB						
No data were presented in the trial identified						
ACE inhibitor versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] . Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9. [PMID=10675071]

[2] Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53. [PMID=10639539]

[3] Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000 Nov;18:1671-5. [PMID=11081782]

[4] Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6. [PMID=10577635]

[5] Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000;18:1671-5. [PMID=11081782]

[6] Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6. [PMID=10577635]

[7] Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1:113-9. [PMID=1366259]

3.3 Individual trial summaries

Table 3.7: *HOPE (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3567 (1808 vs. 1759) **Follow-up duration:** 4.5 years **Study design:** Randomized controlled trial Factorial plan Double-blind Exploratory trial North, South america, Europe, multicentre	Patients with diabetes (sub group), aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction **note:** of all 9541 patients in the HOPE trial, 3654 had diabetes	**Studied treatment:** ramipril 10 mg once per day orally **Control treatment:** placebo **note:** factorial design of ramipril and vitamin E	

References

. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253-9 [PMID=10675071]
Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53 [PMID=10639539]

Table 3.8: *STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=466 (235 vs. 231) **Follow-up duration:** 5.03y **Study design:** Randomized controlled trial Open with blind assessment Exploratory trial Sweden, 312 centres **Inclusion period:** sep 1992 - dec 1994	Diabetic (subgroup) elderly patients aged 70-84 years **note:** Of all 6614 patients included in the trial, 719 had diabetes **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included	**Studied treatment:** ACE inhibitor enalapril 10 mg or lisinopril 10 mg daily. if the target blood pressure (<160/95 mm Hg) had not been reached at the 2-month visit or later, patients were given hydrochlorothiazide 125250 mg **Control treatment:** calcium antagonists felodipine 25 mg or isradipine 25 mgdaily. if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later patients were given anyof the b-blockers in the doses listed	

References

Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000 Nov;18:1671-5 [PMID=11081782]
Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6 [PMID=10577635]

Table 3.9: *STOP-2 ACEI (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=488 (235 vs. 253) **Follow-up duration:** 5.03y **Study design:** Randomized controlled trial Parallel groups Open with blind assessment Exploratory trial Sweden, 312 centres **Inclusion period:** sep 1992 - dec 1994	Diabetic (subgroup) elderly patients aged 70-84 years with hypertension **note:** Of all 6614 patients included in the trial, 719 had diabetes **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included	**Studied treatment:** ACE inhibitor enalapril 10 mg or lisinopril 10 mg daily. if the target blood pressure (<160/95 mm Hg) had not been reached at the 2-month visit or later, patients were given hydrochlorothiazide 125250 mg **Control treatment:** conventional treatment (diuretic or beta-blocker) atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, orfixed-ratio hydrochlorothiazide 25 mg plus amiloride 25 mgdaily. Patients on beta-blockers were givenhydrochlorothiazide 25 mg plus amiloride 25 mg as additionaltreatment if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later. Patients who had started on diuretic treatment were given anyof the b-blockers in the doses listed	

References

Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000;18:1671-5 [PMID=11081782]
Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6 [PMID=10577635]
Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1:113-9 [PMID=1366259]

4 Detailed results for captopril

4.1 Available trials

A total of 2 RCTs which randomized 1330 patients were identified: it compared captopril with atenolol and it compared captopril with diuretic and/or beta-blockers.
The average study size was 665 patients (range 572 to 758). The first study was published in 1998, and the last study was published in 1999.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Death related to diabetes data was reported in 1 trials; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on all cause death.
Following tables 4.1 (page 36), 4.2 (page 36), 4.5 (page 39), and 4.3 (page 37) summarized the main characteristics of the trials including in this systematic review of randomized trials of captopril.

Table 4.1: *Treatment description - ACE inhibitor - captopril*

Trial	Studied treatment	Control treatment
Captopril versus atenolol		
UKPDS 39 (1998) [1, 2]	captopril 25 mg/d aiming at a BP <150/85	atenolol 50mg/d aiming at a BP <150/85
	Concomittant treatment: furosemide, slow release nifedipine, methyldopa, prazosin	
Captopril versus diuretic and/or beta-blockers		
CAPP (diabetic subgroup) (1999) [3, 4, 5]	Captopril initial dose of 50 mg daily given in one or two doses	thiazide diuretic or beta-blocker initial dose ofatenolol and metoprolol of 50100 mg once daily. Hydrochlorothiazide was given as 25 mg once daily, andbendrofluazide as 25 mg once daily

Table 4.2: *Descriptions of participants - ACE inhibitor - captopril*

Trial	Patients
Captopril versus atenolol	

continued...

Trial	Patients	
UKPDS 39 (1998) [1, 2]	Hypertensive patients with type 2 diabetes	
	Inclusion criteria: fasting plasmaglucose concentration >6 mmol/l on two mornings; hypertension, defined in 727 untreated patients as a systolic bloodpressure >160 mm Hg and/or a diastolic blood pressure >90 mm Hg or in 421 patients receivingantihypertensive treatment as a systolic pressure of >150 mm Hg and/or a diastolic pressure >85 mm Hg	**Exclusion criteria:** clinical requirement for strict blood pressure control(previous stroke, accelerated hypertension, cardiac failure, or renal failure) or blockade (myocardial infarction in the previous year or current angina); severevascular disease (more than one major vascularepisode); a severe concurrent illness or contraindications to blockers (asthma, intermittent claudication,foot ulcers, or amputations); pregnancy;
Captopril versus diuretic and/or beta-blockers		
CAPP (diabetic subgroup) (1999) [3, 4, 5]	Patients aged 25-66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions; subgroup of diabetic patients	

Table 4.3: *Design and methodological quality of trials - ACE inhibitor - captopril*

Trial	Design	Duration	Centre	Primary endpoint
Captopril versus atenolol				
UKPDS 39, 1998 [1, 2] n=758	Parallel groups open exploratory trial	ND inclusion period: NA	UK 20 centres	not unique (3)
Captopril versus diuretic and/or beta-blockers				
CAPP (diabetic subgroup), 1999 [3, 4, 5] n=572	Parallel groups open with blinded assessment exploratory trial	6.1 year	Sweden, Finland 536 centres	CV events

Table 4.4: *Trial characteristics - ACE inhibitor - captopril(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Captopril versus atenolol								
UKPDS 39, 1998 [1, 2]	#N/A	#N/A						56 y
Captopril versus diuretic and/or beta-blockers								
CAPP (diabetic subgroup), 1999 [3, 4, 5]	#N/A	#N/A	+1.0 mmHg	+2mmHg				55.3y

continued...

Table 4.5: *Trial characteristics - ACE inhibitor - captopril*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Captopril versus atenolol								
UKPDS 39, 1998 [1, 2]	46%	NA	7.0%	159/93	2.6 y (median)			hypertension
Captopril versus diuretic and/or beta-blockers								
CAPP (diabetic subgroup), 1999 [3, 4, 5]	38.1%			163.5 / 97.2 mmHg		100%		hypertension

4.2 Meta-analysis results

The results are detailed in table 4.6 (page 40). This table is followed by the Forest's plot corresponding to each endpoint.

Captopril versus atenolol

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.19 (95% CI 0.83 to 1.69, p=0.3445).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 1.38 (95% CI 0.74 to 2.57, p=0.3110).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.14 (95% CI 0.83 to 1.55, p=0.4144).

Captopril versus diuretic and/or beta-blockers

No data were presented in the 1 trial identified

Table 4.6: *Results details - ACE inhibitor - captopril*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
captopril versus atenolol						
myocardial infarction (fatal and non fatal)	RR=1.19	[0.83;1.69]	0.3445	1.0000 (I^2=0.00)	1	758
stroke (fatal and non fatal)	RR=1.38	[0.74;2.57]	0.3110	1.0000 (I^2=0.00)	1	758
all cause death	RR=1.14	[0.83;1.55]	0.4144	1.0000 (I^2=0.00)	1	758
captopril versus diuretic and/or beta-blockers						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 4.1: *Forest's plot for myocardial infarction (fatal and non fatal)*

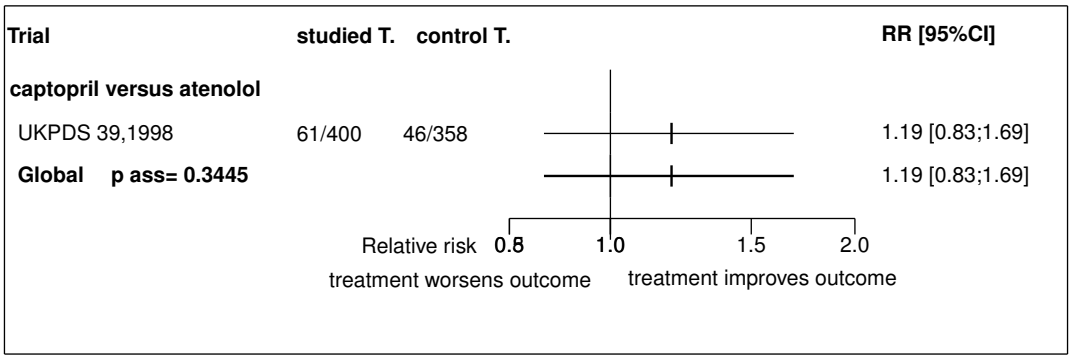


Figure 4.2: *Forest's plot for stroke (fatal and non fatal)*

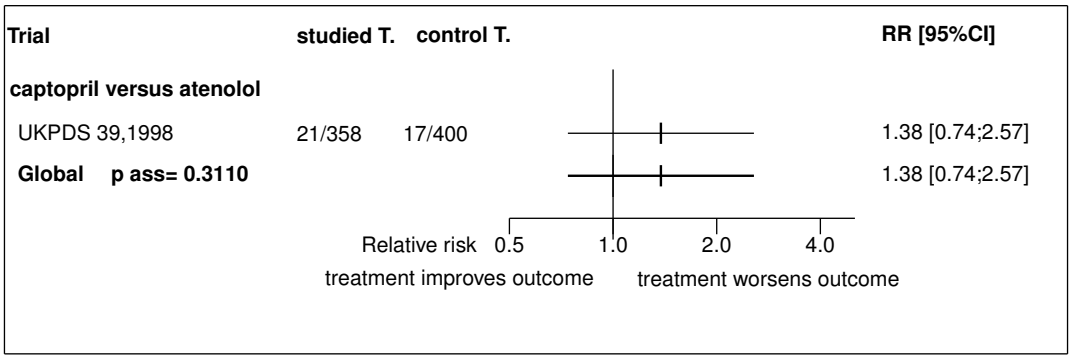
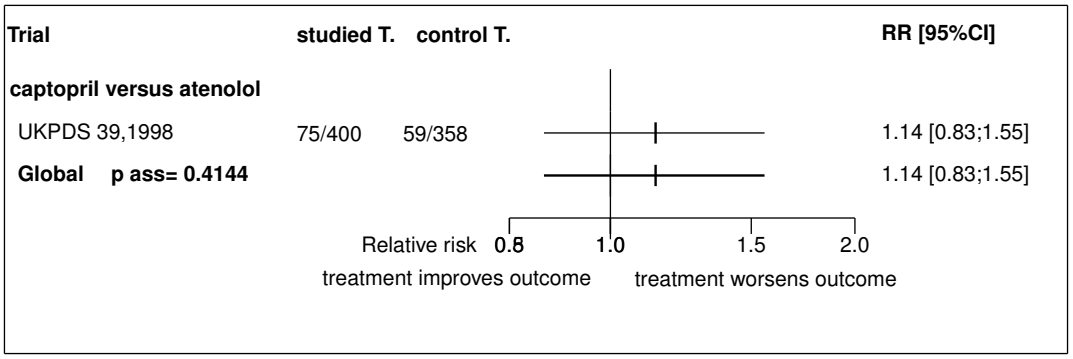


Figure 4.3: *Forest's plot for all cause death*



References

[1] . Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13. [PMID=9732337]

[2] . Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317:713-20. [PMID=9732338]

[3] Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6. [PMID=10030325]

[4] Niklason A, Hedner T, Niskanen L, Lanke J. Development of diabetes is retarded by ACE inhibition in hypertensive patients–a subanalysis of the Captopril Prevention Project (CAPPP). J Hypertens 2004;22:645-52. [PMID=15076172]

[5] Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-

based treatment regimen: a subanalysis of the Captopril Prevention Project. Diabetes Care 2001;24:2091-6. [PMID=11723089]

4.3 Individual trial summaries

Table 4.7: *UKPDS 39, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=758 (400 vs. 358) **Follow-up duration:** ND **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial UK, 20 centres **Inclusion period:** NA	Hypertensive patients with type 2 diabetes **Inclusion criteria:** fasting plasmaglucose concentration >6 mmol/l on two mornings; hypertension, defined in 727 untreated patients as a systolic bloodpressure >160 mm Hg and/or a diastolic blood pressure >90 mm Hg or in 421 patients receivingantihypertensive treatment as a systolic pressure of >150 mm Hg and/or a diastolic pressure >85 mm Hg **Exclusion criteria:** clinical requirement for strict blood pressure control(previous stroke, accelerated hypertension, cardiac failure, or renal failure) or blockade (myocardial infarction in the previous year or current angina); severevascular disease (more than one major vascularepisode); a severe concurrent illness or contraindications to blockers (asthma, intermittent claudication,foot ulcers, or amputations); pregnancy;	**Studied treatment:** captopril 25 mg/d aiming at a BP <150/85 **Control treatment:** atenolol 50mg/d aiming at a BP <150/85 **Concomittant treat.:**furosemide, slow release nifedipine, methyldopa, prazosin	Myocardial infarction (fatal and non fatal) RR=1.19 [0.83;1.69] Stroke (fatal and non fatal) RR=1.38 [0.74;2.57] All cause death RR=1.14 [0.83;1.55]

References

. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13 [PMID=9732337]

. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317:713-20 [PMID=9732338]

Table 4.8: *CAPP (diabetic subgroup), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=572 (309 vs. 263) **Follow-up duration:** 6.1 year **Study design:** Randomized controlled trial Parallel groups Open with blinded assessment Exploratory trial Sweden, Finland, 536 centres	Patients aged 25-66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions; subgroup of diabetic patients	**Studied treatment:** Captopril initial dose of 50 mg daily given in one or two doses **Control treatment:** thiazide diuretic or beta-blocker initial dose ofatenolol and metoprolol of 50100 mg once daily. Hydrochlorothiazide was given as 25 mg once daily, andbendrofluazide as 25 mg once daily	

References

Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6 [PMID=10030325]
Niklason A, Hedner T, Niskanen L, Lanke J. Development of diabetes is retarded by ACE inhibition in hypertensive patients–a subanalysis of the Captopril Prevention Project (CAPPP). J Hypertens 2004;22:645-52 [PMID=15076172]
Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. Diabetes Care 2001;24:2091-6 [PMID=11723089]

5 Detailed results for captopril or atenolol

5.1 Available trials

Only one trial which randomized 1148 patients was identified: it compared captopril or atenolol with control.
This trial included 1148 patients and was published in 1998.
This trial was open-label in design.
It was reported in English language.
Death related to diabetes data was reported in 1 trials; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on stroke (fatal and non fatal); and 1 trials reported data on all cause death.
Following tables 5.1 (page 46), 5.2 (page 46), 5.5 (page 49), and 5.3 (page 47) summarized the main characteristics of the trial including in this systematic review of randomized trials of captopril or atenolol.

Table 5.1: *Treatment description - ACE inhibitor - captopril or atenolol*

Trial	Studied treatment	Control treatment
Captopril or atenolol versus control		
UKPDS 38 (1998) [1, 2]	tight control of blood pressure aiming at a BP <150/85 (with the use of captopril or atenolol as main treatment, other treatment were added if the control criteria were not met)	less tight control aiming at a blood pressure of <180/105 (avoiding treatment with ACE inhibitors or beta-blockers)

Table 5.2: *Descriptions of participants - ACE inhibitor - captopril or atenolol*

Trial	Patients	
Captopril or atenolol versus control		
UKPDS 38 (1998) [1, 2]	Hypertensive patients with type 2 diabetes **Inclusion criteria:** fasting plasmaglucose concentration >6 mmol/l on two mornings; hypertension, defined in 727 untreated patients as a systolic bloodpressure >160 mm Hg and/or a diastolic blood pressure >90 mm Hg or in 421 patients receivingantihypertensive treatment as a systolic pressure of >150 mm Hg and/or a diastolic pressure >85 mm Hg	**Exclusion criteria:** clinical requirement for strict blood pressure control(previous stroke, accelerated hypertension, cardiac failure, or renal failure) or blockade (myocardial infarction in the previous year or current angina); severevascular disease (more than one major vascularepisode); a severe concurrent illness or contraindications to blockers (asthma, intermittent claudication,foot ulcers, or amputations); pregnancy;

Table 5.3: *Design and methodological quality of trials - ACE inhibitor - captopril or atenolol*

Trial	Design	Duration	Centre	Primary end-point
Captopril or atenolol versus control				
UKPDS 38, 1998 [1, 2] n=1148	Parallel groups open exploratory trial	8.4y (median) inclusion period: NA	UK 20 centres	not unique (3)

Table 5.4: *Trial characteristics - ACE inhibitor - captopril or atenolol(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Captopril or atenolol versus control								
UKPDS 38, 1998 [1, 2]	#N/A	#N/A						56.5y

continued...

Table 5.5: *Trial characteristics - ACE inhibitor - captopril or atenolol*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Captopril or atenolol versus control								
UKPDS 38, 1998 [1, 2]	44%	NA	6.9%	159/94	2.6 y (median)			hypertension

5.2 Meta-analysis results

The results are detailed in table 5.6 (page 50). This table is followed by the Forest's plot corresponding to each endpoint.

Captopril or atenolol versus control

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.80 (95% CI 0.60 to 1.05, p=0.1099).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of captopril or atenolol in stroke (fatal and non fatal), with a RR of 0.58 (95% CI 0.37 to 0.90, p=0.0151).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.83 (95% CI 0.65 to 1.06, p=0.1378).

Table 5.6: *Results details - ACE inhibitor - captopril or atenolol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
captopril or atenolol versus control						
myocardial infarction (fatal and non fatal)	RR=0.80	[0.60;1.05]	0.1099	1.0000 (I^2=0.00)	1	1148
stroke (fatal and non fatal)	RR=0.58	[0.37;0.90]	0.0151	1.0000 (I^2=0.00)	1	1148
all cause death	RR=0.83	[0.65;1.06]	0.1378	1.0000 (I^2=1.00)	1	1148

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 5.1: *Forest's plot for myocardial infarction (fatal and non fatal)*

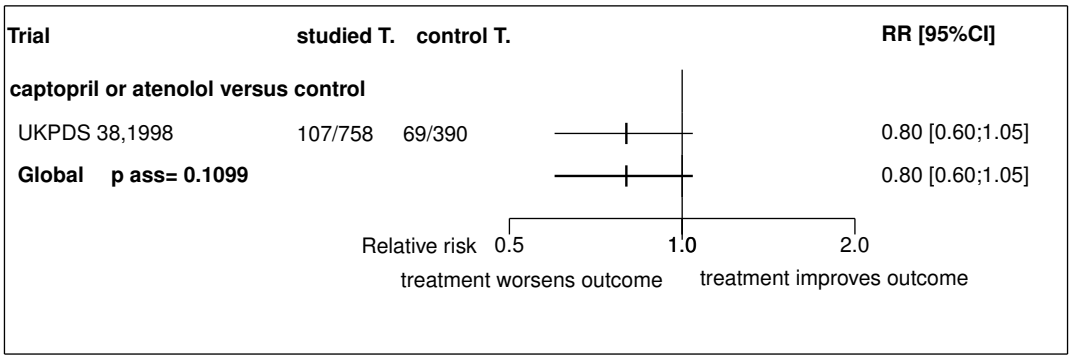


Figure 5.2: *Forest's plot for stroke (fatal and non fatal)*

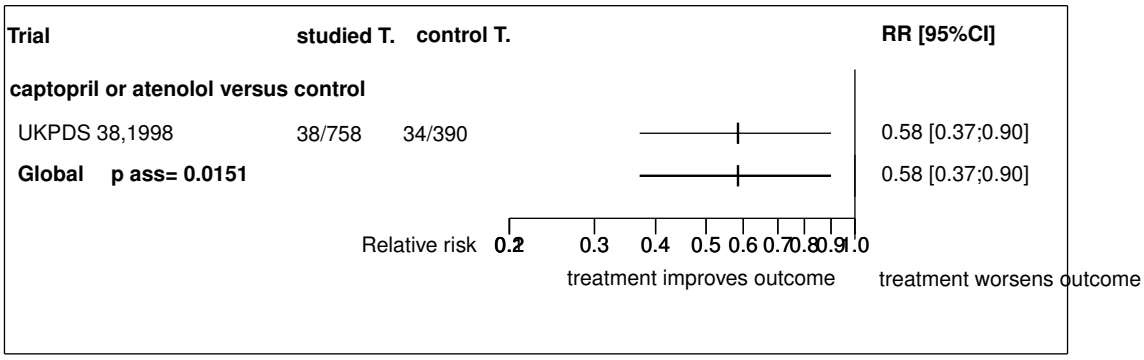
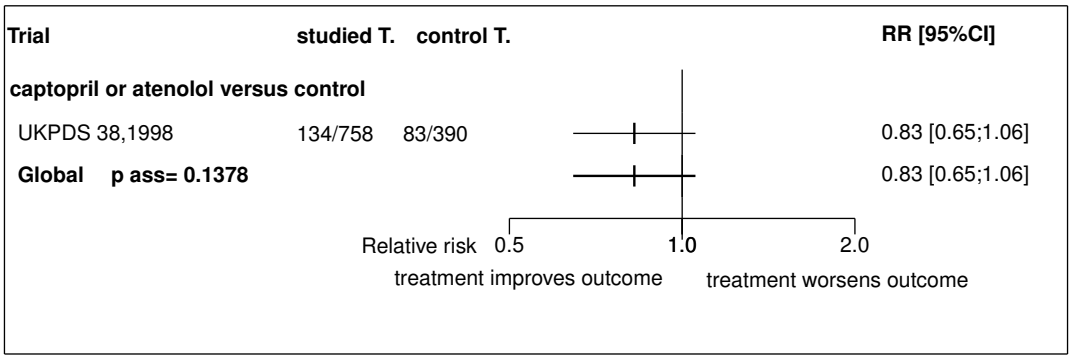


Figure 5.3: *Forest's plot for all cause death*



References

[1] . Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317:713-20. [PMID=9732338]

[2] . Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13. [PMID=9732337]

5.3 Individual trial summaries

Table 5.7: *UKPDS 38, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1148 (758 vs. 390) **Follow-up duration:** 8.4y (median) **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial UK, 20 centres **Inclusion period:** NA	Hypertensive patients with type 2 diabetes **Inclusion criteria:** fasting plasmaglucose concentration >6 mmol/l on two mornings; hypertension, defined in 727 untreated patients as a systolic bloodpressure >160 mm Hg and/or a diastolic blood pressure >90 mm Hg or in 421 patients receivingantihypertensive treatment as a systolic pressure of >150 mm Hg and/or a diastolic pressure >85 mm Hg **Exclusion criteria:** clinical requirement for strict blood pressure control(previous stroke, accelerated hypertension, cardiac failure, or renal failure) or blockade (myocardial infarction in the previous year or current angina); severevascular disease (more than one major vascularepisode); a severe concurrent illness or contraindications to blockers (asthma, intermittent claudication,foot ulcers, or amputations); pregnancy;	**Studied treatment:** tight control of blood pressure aiming at a BP <150/85 (with the use of captopril or atenolol as main treatment, other treatment were added if the control criteria were not met) **Control treatment:** less tight control aiming at a blood pressure of <180/105 (avoiding treatment with ACE inhibitors or beta-blockers)	Myocardial infarction (fatal and non fatal) RR=0.80 [0.60;1.05] Stroke (fatal and non fatal) RR=0.58 [0.37;0.90] All cause death RR=0.83 [0.65;1.06]

References

. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317:713-20 [PMID=9732338]

. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703-13 [PMID=9732337]

6 Detailed results for lisinopril

6.1 Available trials

Only one trial which randomized 6929 patients was identified: it compared lisinopril with chlorthalidone.
This trial included 6929 patients and was published in 2002.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 6.1 (page 54), 6.2 (page 54), 6.5 (page 57), and 6.3 (page 54) summarized the main characteristics of the trial including in this systematic review of randomized trials of lisinopril.

Table 6.1: *Treatment description - ACE inhibitor - lisinopril*

Trial	Studied treatment	Control treatment
Lisinopril versus chlorthalidone		
ALLHAT (lisi vs chlor, diabetic subgroup) (2002) [1, 2]	lisinopril 10 to 40 mg/d	chlorthalidone 12.5 to 25 mg/d

Table 6.2: *Descriptions of participants - ACE inhibitor - lisinopril*

Trial	Patients
Lisinopril versus chlorthalidone	
ALLHAT (lisi vs chlor, diabetic subgroup) (2002) [1, 2]	Diabetic (subgroup) participants aged 55 years or older with hypertension

Table 6.3: *Design and methodological quality of trials - ACE inhibitor - lisinopril*

Trial	Design	Duration	Centre	Primary endpoint
Lisinopril versus chlorthalidone				

continued...

Trial	Design	Duration	Centre	Primary endpoint
ALLHAT (lisi vs chlor, diabetic subgroup), 2002 [1, 2] n=6929	Parallel groups double-blind exploratory trial	4.9 y		fatal CHD or non-fatal MI

Table 6.4: *Trial characteristics - ACE inhibitor - lisinopril(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Lisinopril versus chlorthalidone								
ALLHAT (lisi vs chlor, diabetic subgroup), 2002 [1, 2]	1.03%	1.22%	-0.2	-2.9				

continued...

Table 6.5: *Trial characteristics - ACE inhibitor - lisinopril*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Lisinopril versus chlorthalidone								
ALLHAT (lisi vs chlor, diabetic subgroup), 2002 [1, 2]								hypertension

6.2 Meta-analysis results

The results are detailed in table 6.6 (page 58). This table is followed by the Forest's plot corresponding to each endpoint.

Lisinopril versus chlorthalidone

No data were presented in the 1 trial identified

Table 6.6: *Results details - ACE inhibitor - lisinopril*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
lisinopril versus chlorthalidone						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] . Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97. [PMID=12479763]

[2] Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401-9. [PMID=15983290]

6.3 Individual trial summaries

Table 6.7: *ALLHAT (lisi vs chlor, diabetic subgroup), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=6929 (2431 vs. 4498) **Follow-up duration:** 4.9 y **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Diabetic (subgroup) participants aged 55 years or older with hypertension	**Studied treatment:** lisinopril 10 to 40 mg/d **Control treatment:** chlorthalidone 12.5 to 25 mg/d	

References

. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97 [PMID=12479763]
Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401-9 [PMID=15983290]

7 Global meta-analysis: all ACE inhibitor

7.1 Global meta-analysis: all ACE inhibitor versus atenolol

Table 7.1: *All ACE inhibitorversus atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=1.19	0.83;1.69	0.3445	1.0000 (0.00)	1	758
stroke (fatal and non fatal)	RR=1.38	0.74;2.57	0.3110	1.0000 (0.00)	1	758
all cause death	RR=1.14	0.83;1.55	0.4144	1.0000 (0.00)	1	758

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.2 Global meta-analysis: all ACE inhibitor versus CCB

Table 7.2: *All ACE inhibitorversus CCB*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.3 Global meta-analysis: all ACE inhibitor versus chlorthalidone

Table 7.3: *All ACE inhibitorversus chlorthalidone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.4 Global meta-analysis: all ACE inhibitor versus control

Table 7.4: *All ACE inhibitorversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=0.80	0.60;1.05	0.1099	1.0000 (0.00)	1	1148
stroke (fatal and non fatal)	RR=0.58	0.37;0.90	0.0151	1.0000 (0.00)	1	1148
all cause death	RR=0.83	0.65;1.06	0.1378	1.0000 (1.00)	1	1148

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.5 Global meta-analysis: all ACE inhibitor versus diuretic and/or beta-blockers

Table 7.5: *All ACE inhibitorversus diuretic and/or beta-blockers*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.6 Global meta-analysis: all ACE inhibitor versus diuretic or beta-blocker

Table 7.6: *All ACE inhibitorversus diuretic or beta-blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

7.7 Global meta-analysis: all ACE inhibitor versus placebo

Table 7.7: *All ACE inhibitorversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

8 Ongoing studies of ACE inhibitor

No ongoing trial was identified.

9 Excluded studies for ACE inhibitor

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 9.1.

Table 9.1: *Excluded studies of ACE inhibitor*

Study	Exclusion reason
UKPDS 38 10 years (2008) [1]	too much attrition

References

[1] Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes. N Engl J Med 2008;:. [PMID=18784091]

Part II

Angiotensin receptor blocker

10 Overview of angiotensin receptor blocker

10.1 Included trials

A total of 13 randomized comparisons which enrolled 35291 patients were identified. In all, 6 randomized comparisons concerned irbesartan , 3 losartan , one telmisartan and 3 valsartan. The detailed descriptions of trials and meta-analysis results is given in section 11 (page 78) for irbesartan, in section 12 (page 94) for losartan, in section 13 (page 106) for telmisartan and in section 14 (page 111) for valsartan.

The average study size was 2714 patients (range 250 to 15245). The first study was published in 2001, and the last study was published in 2011.
A total of 11 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We found one unpublished trial.
The table 10.1 (page 69) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

10.2 Summary of meta-analysis results

The meta-analysis of the available trials about angiotensin receptor blocker provide the results listed in tables 10.2 to 10.5 (page 72) and in the following graphs.

10.2.1 Irbesartan

No significant difference was found between **irbesartan** and **placebo** in terms of coronary event (RR=0.91, 95% CI 0.72 to 1.15, p=0.4211, 1 trial).

Irbesartan was superior to **amlodipine** in terms of myocardial infarction (fatal and non fatal) (RR=1.60, 95% CI 1.00 to 2.54, p=0.0488, 1 trial). But irbesartan increased the risk of heart failure (RR=0.63, 95% CI 0.47 to 0.86, p=0.0030, 1 trial). However, no significant difference was found on cardiovascular events (RR=1.03, 95% CI 0.81 to 1.31, p=0.8095, 1 trial), cardiovascular death (RR=1.38, 95% CI 0.92 to 2.06, p=0.1225, 1 trial), stroke (fatal and non fatal) (RR=1.83, 95% CI 0.99 to 3.39, p=0.0551, 1 trial)and all cause death (RR=1.03, 95% CI 0.78 to 1.35, p=0.8536, 1 trial).

10.2.2 Losartan

Data were insufficient to compare **losartan** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Losartan was superior to **atenolol** in terms of cardiovascular events (RR=0.86, 95% CI 0.77 to 0.96, p=0.0084, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.87, 95% CI 0.72 to 1.04, p=0.1318, 1 trial)and coronary event (RR=1.05, 95% CI 0.86 to 1.28, p=0.6292, 1 trial).

10.2.3 Telmisartan

Data were insufficient to compare **telmisartan** to **enalapril**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

10.2.4 Valsartan

Valsartan was superior to **amlodipine** in terms of myocardial infarction (fatal and non fatal) (RR=1.17, 95% CI 1.01 to 1.36, p=0.0359, 1 trial). However, no significant difference was found on cardiovascular events (RR=1.02, 95% CI 0.93 to 1.12, p=0.6832, 1 trial), cardiovascular death (RR=0.99, 95% CI 0.85 to 1.16, p=0.9303, 1 trial), stroke (fatal and non fatal) (RR=1.14, 95% CI 0.97 to 1.33, p=0.1062, 1 trial), coronary event (RR=1.02, 95% CI 0.93 to 1.12, p=0.6832, 1 trial), heart failure (RR=0.88, 95% CI 0.76 to 1.01, p=0.0696, 1 trial)and all cause death (RR=1.02, 95% CI 0.93 to 1.12, p=0.6540, 1 trial).

Table 10.1: *Main study characteristics - angiotensin receptor blocker*

Trial	Patients	Treatments	Trial design and method
Irbesartan			
Irbesartan versus placebo			
IDNT (vs placebo), 2001 [1, 2] n = 579 vs. 569	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300mg/d (target 135/85) **versus** placebo	double-blind parallel groups Primary endpoint: doubling of the base-line serum creatinine concentration, end-stage renal disease, or death 210 centres, worldwide
IRMA 2, 2001 [3] n = 404 vs. 207	hypertensive patients with type 2 diabetes and microalbuminuria	irbesartan 150 mg daily or 300 mg daily **versus** placebo	double-blind parallel groups Primary endpoint: onset of diabetic nephropathy multinational
IDNT irbesartan, 2001 [4] n = 579 vs. 569	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300 mg daily **versus** placebo	double blind parallel groups Primary endpoint: renal death 210 centres, Worldwide subgroup: no
IPDM 150mg, 2001 [5] n = 195 vs. 201	hypertensive patients with type 2 diabetes and microalbuminuria	irbesartan 150 mg daily **versus** placebo	double-blind parallel groups Primary endpoint: diabetic nephropathy 96 centres, Worldwide subgroup: no
Irbesartan versus amlodipine			
IDNT (vs amlodipine), 2001 [6] n = 579 vs. 567	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300mg/d (with a target of 135/85) **versus** amlodipine 10mg/d (with a target of 135/85)	double-blind parallel groups Primary endpoint: doubling of creatinine or endstage renal disease or death 210 centres, worldwide

continued...

Trial	Patients	Treatments	Trial design and method
IDNT (irbesartan vs amlodipine), 2001 [7] n = 579 vs. 567	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300 mg daily **versus** amlodipine 10 mg daily	double blind parallel groups Primary endpoint: renal death 210 centres, Worldwide subgroup: no
Losartan			
Losartan versus placebo			
RENAAL, 2001 [1] n = 751 vs. 762	patients with type 2 diabetes and nephropathy	losartan 50 to 100 mg once daily **versus** placebo	double-blind parallel groups Primary endpoint: doubling of the creatinine, end-stage renal disease, death 250 centres, America, Europe, Asia subgroup: no
Losartan versus atenolol			
LIFE, 2002 [2] n = 4605 vs. 4588	patients aged 5580 years, with previously treated or untreated hypertension (sitting blood pressure 160200/95115 mm Hg) and ECG signs of LVH.	losartan **versus** atenolol	double blind parallel groups Primary endpoint: cardiovascular mortality, stroke, and myocardial infarction 945 centres, USA, Europe
LIFE (diabetic subgroup), 2002 [3, 4] n = 586 vs. 609	patients with diabetes (subgroup) , hypertension, and signs of left-ventricular hypertrophy on electrocardiograms	losartan 50mg daily at step 1 **versus** atenolol 50mg daily at step 1	double-blind parallel groups Primary endpoint: CV events 945 centres, USA, UK, Nordic countries subgroup: yes
Telmisartan			
Telmisartan versus enalapril			
DETAIL, 2004 [1] n = 120 vs. 130	subjects with type 2 diabetes and early nephropathy	telmisartan 80 mg daily **versus** enalapril 20 mg daily	double-blind parallel groups Primary endpoint: glomerular filtration rate
Valsartan			

continued...

Trial	Patients	Treatments	Trial design and method
Valsartan versus amlodipine			
NAGOYA HEART, n= 1150	patients with hypertension with type 2 diabetes or impaired glucose tolerance	blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg **versus** blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg	open parallel groups Primary endpoint: CV events 46 centres, Japan
VALUE, 2004 [1] n = 7649 vs. 7596	patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events	valsartan based regimen **versus** amlodipine based regimen	double blind parallel groups Primary endpoint: cardiac event multicentre, 31 countries
NAGOYA HEART, 2011 [2] n = 575 vs. 575	patients with hypertension with type 2 diabetes or impaired glucose tolerance	blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg **versus** blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg	open parallel groups Primary endpoint: CV events 46 centres, Japan subgroup: no

Table 10.2: *Summary of all results for irbesartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
irbesartan versus placebo						
coronary event	RR=0.91	0.72;1.15	0.4211	1.0000 (0.00)	1	1148
irbesartan versus amlodipine						
cardiovascular events	RR=1.03	0.81;1.31	0.8095	1.0000 (0.00)	1	1146
cardiovascular death	RR=1.38	0.92;2.06	0.1225	1.0000 (0.00)	1	1146
myocardial infarction (fatal and non fatal)	RR=1.60	1.00;2.54	0.0488	1.0000 (0.00)	1	1146
stroke (fatal and non fatal)	RR=1.83	0.99;3.39	0.0551	1.0000 (0.00)	1	1146
heart failure	RR=0.63	0.47;0.86	0.0030	1.0000 (0.00)	1	1146
all cause death	RR=1.03	0.78;1.35	0.8536	1.0000 (0.00)	1	1146

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 10.3: *Summary of all results for losartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
losartan versus placebo						
No data were presented in the trial identified						
losartan versus atenolol						
cardiovascular events	RR=0.86	0.77;0.96	0.0084	1.0000 (0.00)	1	9193
cardiovascular death	RR=0.87	0.72;1.04	0.1318	1.0000 (0.00)	1	9193
coronary event	RR=1.05	0.86;1.28	0.6292	1.0000 (0.00)	1	9193

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 10.4: *Summary of all results for telmisartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
telmisartan versus enalapril						
No data were presented in the trial identified						

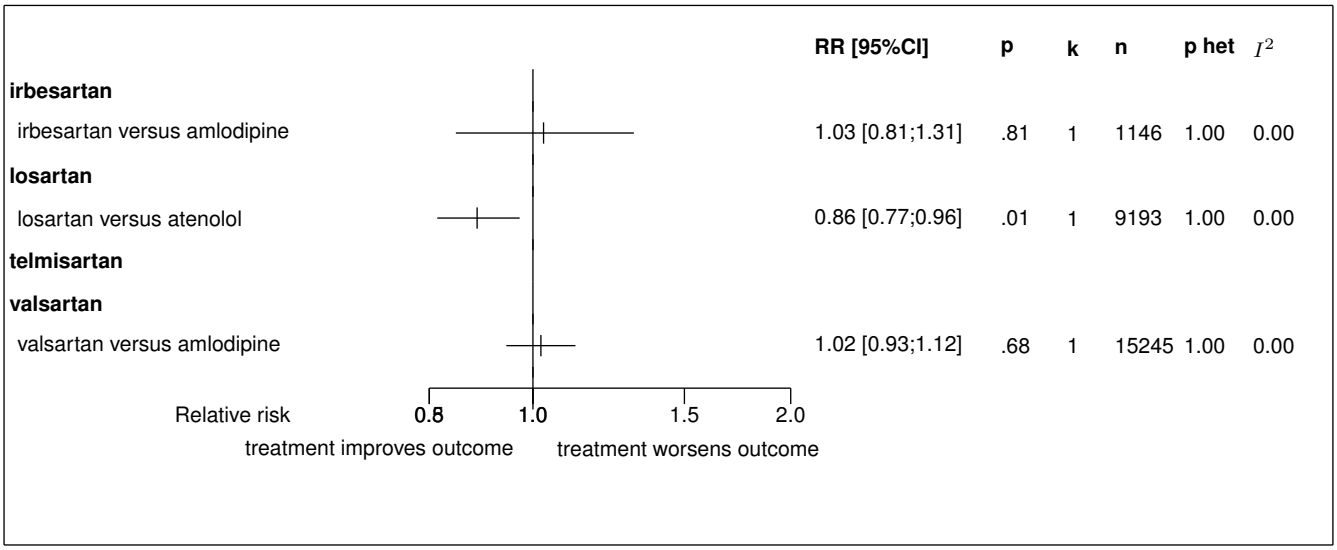
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 10.5: *Summary of all results for valsartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
valsartan versus amlodipine						
cardiovascular events	RR=1.02	0.93;1.12	0.6832	1.0000 (0.00)	1	15245
cardiovascular death	RR=0.99	0.85;1.16	0.9303	1.0000 (0.00)	1	15245
myocardial infarction (fatal and non fatal)	RR=1.17	1.01;1.36	0.0359	1.0000 (0.00)	1	15245
stroke (fatal and non fatal)	RR=1.14	0.97;1.33	0.1062	1.0000 (1.00)	1	15245
coronary event	RR=1.02	0.93;1.12	0.6832	1.0000 (0.00)	1	15245
heart failure	RR=0.88	0.76;1.01	0.0696	1.0000 (0.00)	1	15245
diabetes onset	RR=0.81	0.74;0.89	0.0000	1.0000 (0.00)	1	15245
all cause death	RR=1.02	0.93;1.12	0.6540	1.0000 (0.00)	1	15245

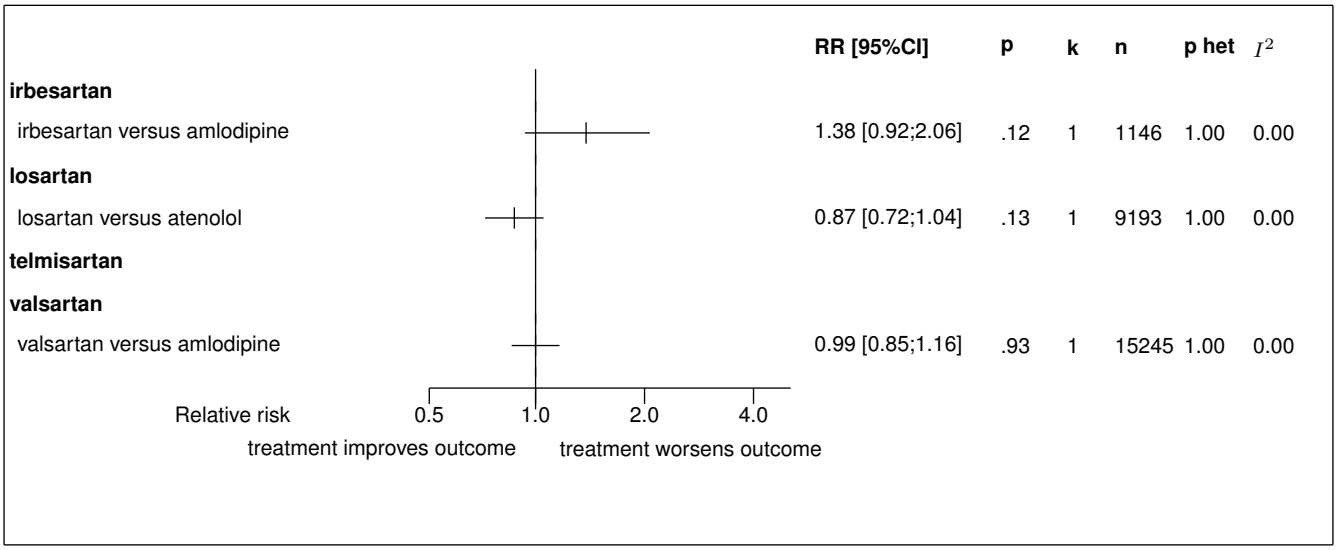
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 10.1: *Forest's plot for cardiovascular events*



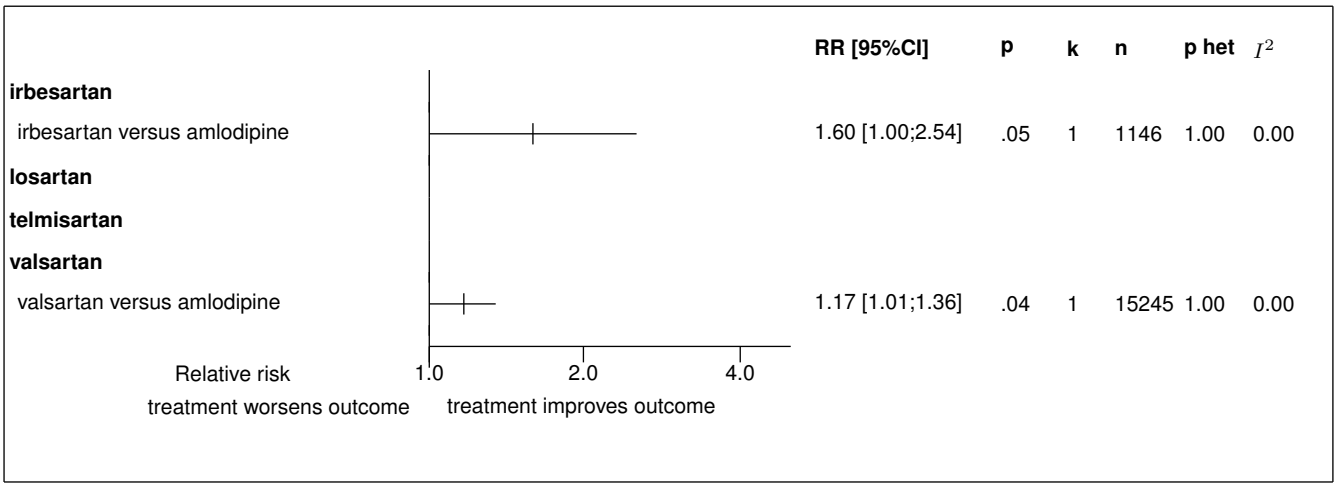
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 10.2: *Forest's plot for cardiovascular death*



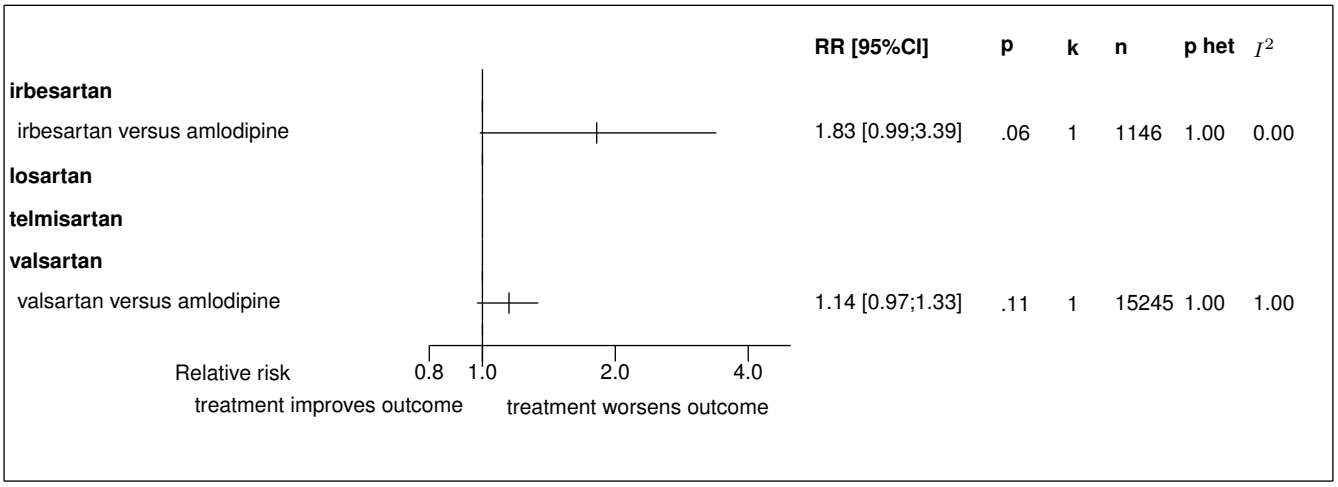
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ᶠ: random effect model used

Figure 10.3: *Forest's plot for myocardial infarction (fatal and non fatal)*



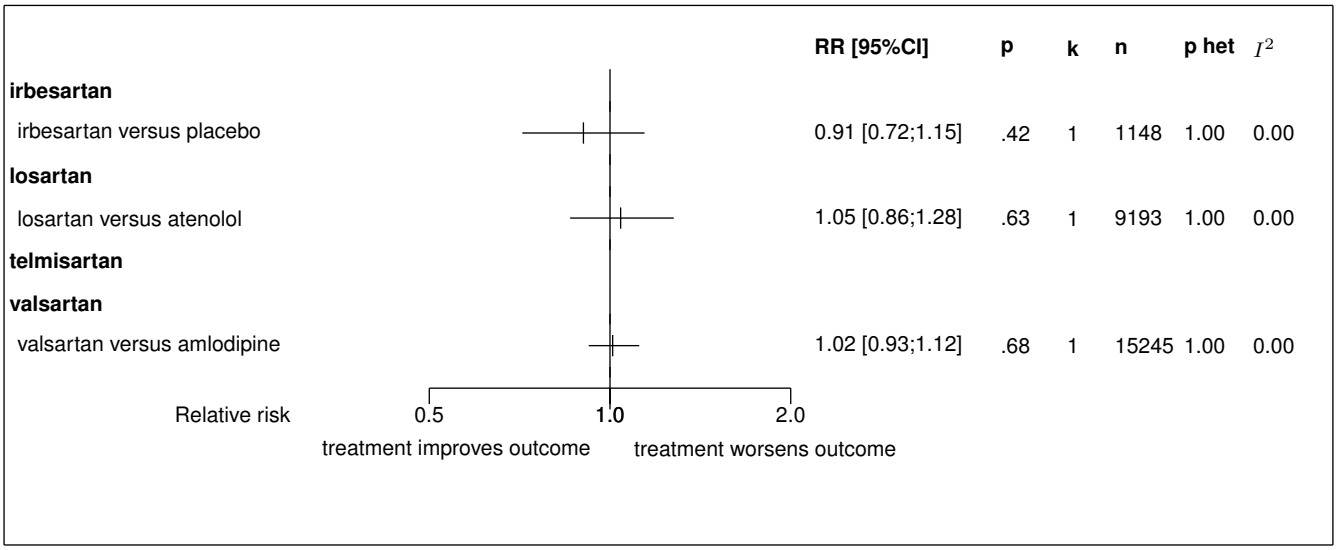
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ᶠ: random effect model used

Figure 10.4: *Forest's plot for stroke (fatal and non fatal)*



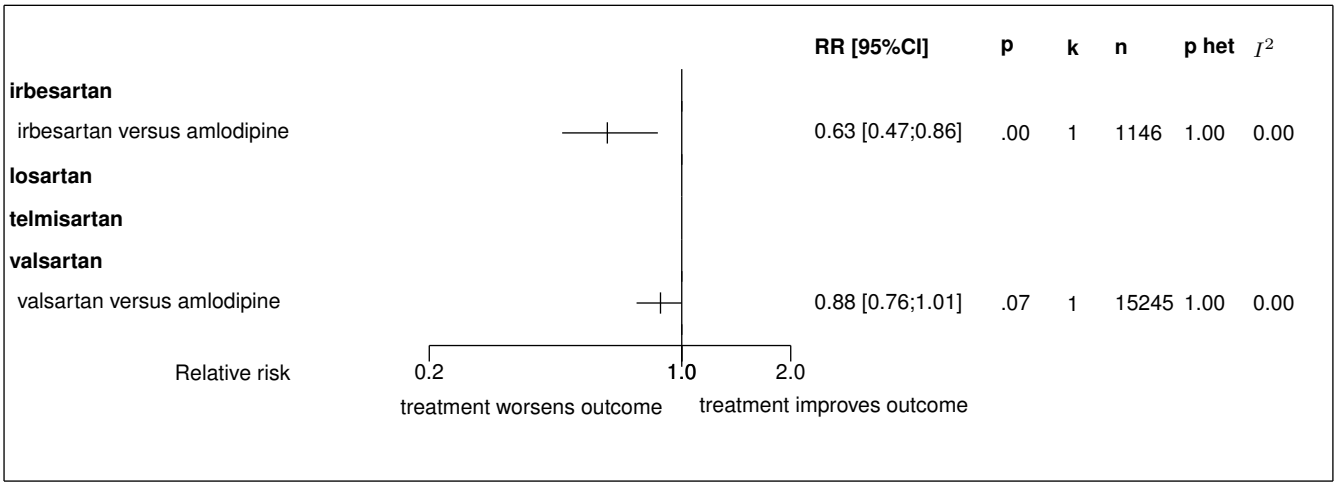
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 10.5: *Forest's plot for coronary event*



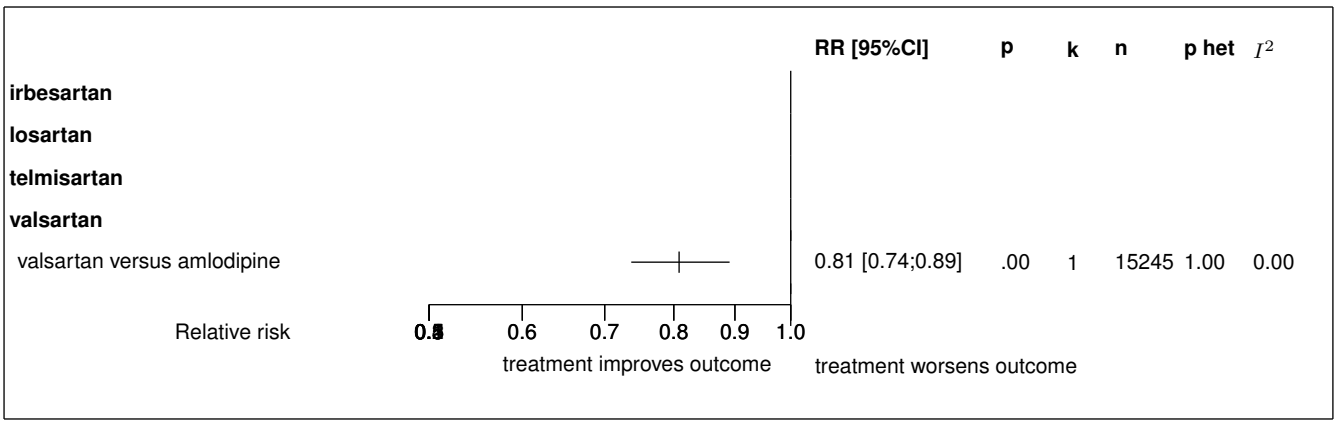
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 10.6: *Forest's plot for heart failure*



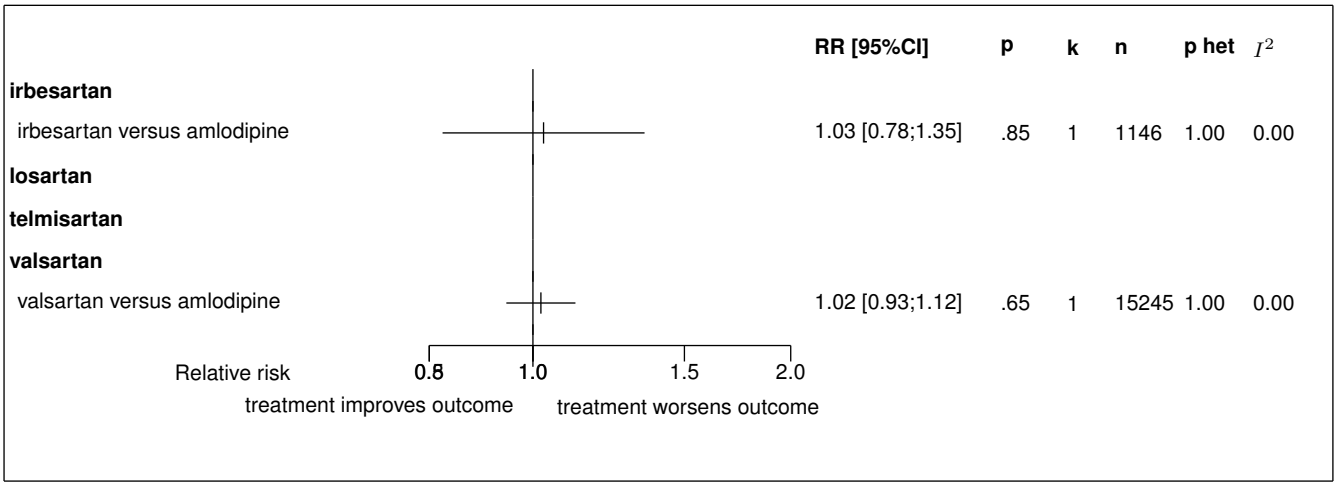
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 10.7: *Forest's plot for diabetes onset*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 10.8: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

11 Detailed results for irbesartan

11.1 Available trials

A total of 6 RCTs which randomized 5595 patients were identified: 4 trials compared irbesartan with placebo and 2 trials compared irbesartan with amlodipine.
The average study size was 932 patients (range 396 to 1148). The first study was published in 2001, and the last study was published in 2001.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Heart failure data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on myocardial infarction (fatal and non fatal); and 1 trials reported data on cardiovascular death.
Following tables 11.1 (page 78), 11.2 (page 79), 11.4 (page 82), and 11.3 (page 80) summarized the main characteristics of the trials including in this systematic review of randomized trials of irbesartan.

Table 11.1: *Treatment description - angiotensin receptor blocker - irbesartan*

Trial	Studied treatment	Control treatment
Irbesartan versus placebo		
IDNT (vs placebo) (2001) [1, 2]	Irbesartan 300mg/d (target 135/85) target blood pressure: 135/85 mm Hg or less	placebo
IRMA 2 (2001) [3]	irbesartan 150 mg daily or 300 mg daily	placebo
IDNT irbesartan (2001) [4]	Irbesartan 300 mg daily	placebo
IPDM 150mg (2001) [5] [d]	irbesartan 150 mg daily	placebo
Irbesartan versus amlodipine		
IDNT (vs amlodipine) (2001) [6]	Irbesartan 300mg/d (with a target of 135/85) target blood pressure: 135/85 mm Hg or less	amlodipine 10mg/d (with a target of 135/85)
IDNT (irbesartan vs amlodipine) (2001) [7]	Irbesartan 300 mg daily	amlodipine 10 mg daily

d) 3 arms trial: irbesartan 150 and 300 mg daily, placebo

Table 11.2: *Descriptions of participants - angiotensin receptor blocker - irbesartan*

Trial	Patients	
Irbesartan versus placebo		
IDNT (vs placebo) (2001) [1, 2]	Hypertensive patients with nephropathy due to type 2 diabetes	
IRMA 2 (2001) [3]	Hypertensive patients with type 2 diabetes and microalbuminuria	
IDNT irbesartan (2001) [4]	Hypertensive patients with nephropathy due to type 2 diabetes	
	Inclusion criteria: age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Exclusion criteria:**
IPDM 150mg (2001) [5]	Hypertensive patients with type 2 diabetes and microalbuminuria	
	Inclusion criteria: hypertension (at least two of three consecutive measurementsobtained one week apart during the run-in period of a mean systolicblood pressure of more than 135 mm Hg or a mean diastolicblood pressure of more than 85 mm Hg, or both); age between 30 and 70 years; persistent microalbuminuria (definedas an albumin excretion rate of 20 to 200 g per minute intwo of three consecutive, sterile, overnight urine samples) and a serumcreatinine concentration of no more than 1.5 mg per deciliter(133 mol per liter) for men and no more than 1.1 mg per deciliter(97 mol per liter) for women	**Exclusion criteria:** nondiabetic kidneydisease; cancer; life-threatening disease with death expected to occurwithin two years; indication for angiotensin-convertingenzyme (ACE) inhibitors or angiotensin-IIreceptor antagonists
Irbesartan versus amlodipine		
IDNT (vs amlodipine) (2001) [6]	Hypertensive patients with nephropathy due to type 2 diabetes	
IDNT (irbesartan vs amlodipine) (2001) [7]	Hypertensive patients with nephropathy due to type 2 diabetes	
	Inclusion criteria: age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Exclusion criteria:**

continued...

Trial	Patients

Table 11.3: *Design and methodological quality of trials - angiotensin receptor blocker - irbesartan*

Trial	Design	Duration	Centre	Primary endpoint
Irbesartan versus placebo				
IDNT (vs placebo), 2001 [1, 2] n=1148	Parallel groups double-blind confirmatory trial at low risk of bias	2.6 y inclusion period: mar 1996 - feb 1999	worldwide 210 centres	doubling of the base-line serum creatinine concentration, end-stage renal disease, or death
IRMA 2, 2001 [3] n=611	Parallel groups double-blind confirmatory trial at low risk of bias	2 years	multinational	onset of diabetic nephropathy
IDNT irbesartan, 2001 [4] n=1148	Parallel groups double blind confirmatory trial at low risk of bias	2.6 years inclusion period: mar 1996 - Feb 1999	Worldwide 210 centres	renal death
IPDM 150mg, 2001 [5] n=396	Parallel groups double-blind exploratory trial	2 years	Worldwide 96 centres	diabetic nephropathy
Irbesartan versus amlodipine				
IDNT (vs amlodipine), 2001 [6] n=1146	Parallel groups double-blind confirmatory trial at low risk of bias	26y inclusion period: mar 1996 - feb 1999	worldwide 210 centres	doubling of creatinine or endstage renal disease or death
IDNT (irbesartan vs amlodipine), 2001 [7] n=1146	Parallel groups double blind confirmatory trial at low risk of bias	2.6 years inclusion period: mar 1996 - Feb 1999	Worldwide 210 centres	renal death

Table 11.4: *Trial characteristics - angiotensin receptor blocker - irbesartan*

Trial	target blood pressure
Irbesartan versus placebo	
IDNT (vs placebo), 2001 [1, 2]	
IRMA 2, 2001 [3]	
IDNT irbesartan, 2001 [4] #N/A 59 y	#N/A
IPDM 150mg, 2001 [5] #N/A -1 58.3 y	#N/A 0
Irbesartan versus amlodipine	
IDNT (vs amlodipine), 2001 [6]	
IDNT (irbesartan vs amlodipine), 2001 [7]	#N/A

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 83). This table is followed by the Forest's plot corresponding to each endpoint.

Irbesartan versus placebo

Only one of the 4 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 0.91 (95% CI 0.72 to 1.15, p=0.4211).

Irbesartan versus amlodipine

Only one of the 2 studies eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between irbesartan and amlodipine, with a RR of 1.03 (95%CI 0.81 to 1.31, p=0.8095) in favour of amlodipine. In other words, cardiovascular events was slightly lower in the amlodipine group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 1.38 (95% CI 0.92 to 2.06, p=0.1225).
Only one of the 2 studies eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of irbesartan in myocardial infarction (fatal and non fatal), with a RR of 1.60 (95% CI 1.00 to 2.54, p=0.0488).
Only one of the 2 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 1.83 (95% CI 0.99 to 3.39, p=0.0551).
Only one of the 2 studies eligible for this comparison provided data on **heart failure**. The analysis detected a statistically significant difference in favor of irbesartan in heart failure, with a RR of 0.63 (95% CI 0.47 to 0.86, p=0.0030).
Only one of the 2 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.03 (95% CI 0.78 to 1.35, p=0.8536).

Table 11.5: *Results details - angiotensin receptor blocker - irbesartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
irbesartan versus placebo						
coronary event	RR=0.91	[0.72;1.15]	0.4211	1.0000 (I^2=0.00)	1	1148
irbesartan versus amlodipine						
cardiovascular events	RR=1.03	[0.81;1.31]	0.8095	1.0000 (I^2=0.00)	1	1146
cardiovascular death	RR=1.38	[0.92;2.06]	0.1225	1.0000 (I^2=0.00)	1	1146
myocardial infarction (fatal and non fatal)	RR=1.60	[1.00;2.54]	0.0488	1.0000 (I^2=0.00)	1	1146
stroke (fatal and non fatal)	RR=1.83	[0.99;3.39]	0.0551	1.0000 (I^2=0.00)	1	1146
heart failure	RR=0.63	[0.47;0.86]	0.0030	1.0000 (I^2=0.00)	1	1146

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=1.03	[0.78;1.35]	0.8536	1.0000 (I^2=0.00)	1	1146

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 11.1: *Forest's plot for cardiovascular events*

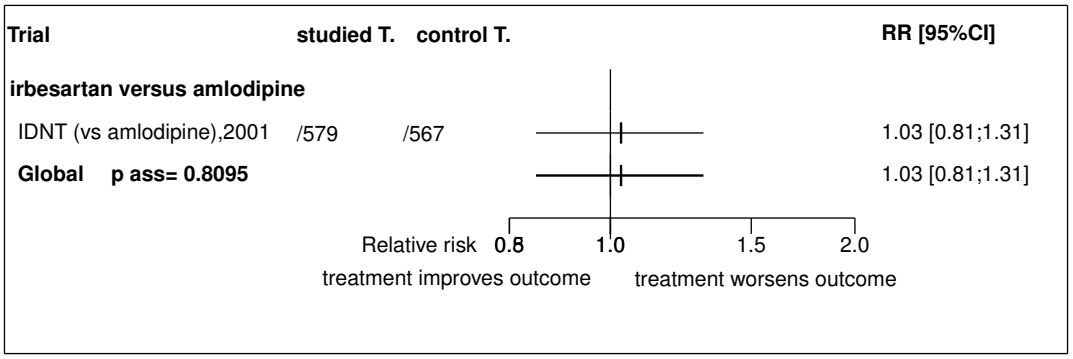


Figure 11.2: *Forest's plot for cardiovascular death*

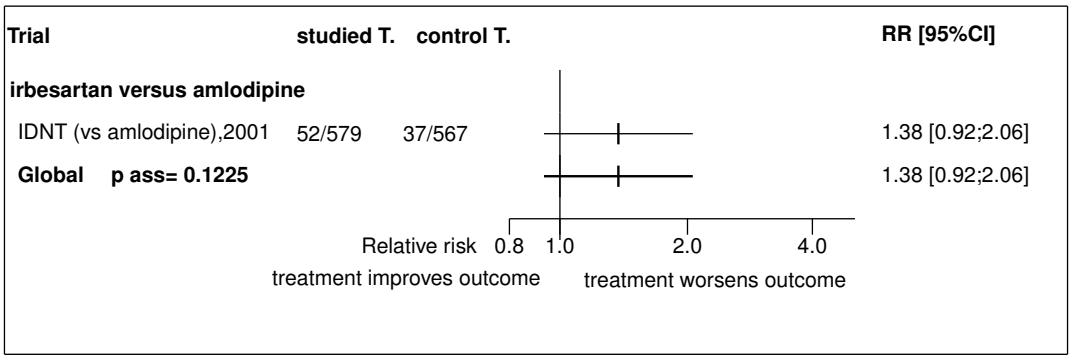


Figure 11.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

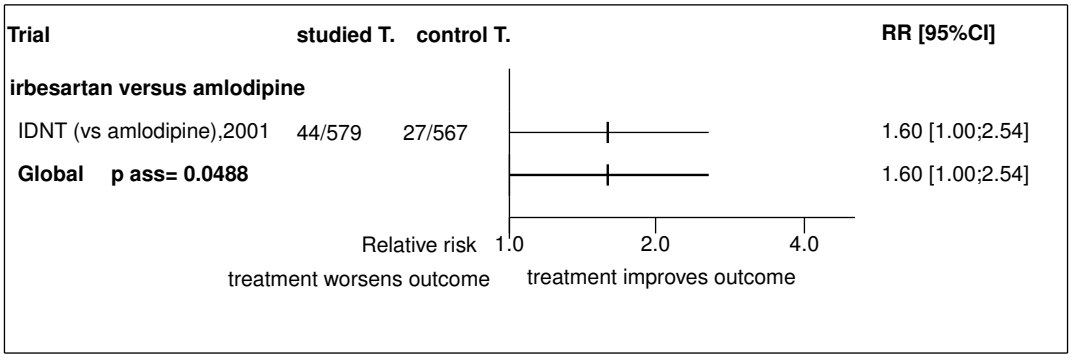


Figure 11.4: *Forest's plot for stroke (fatal and non fatal)*

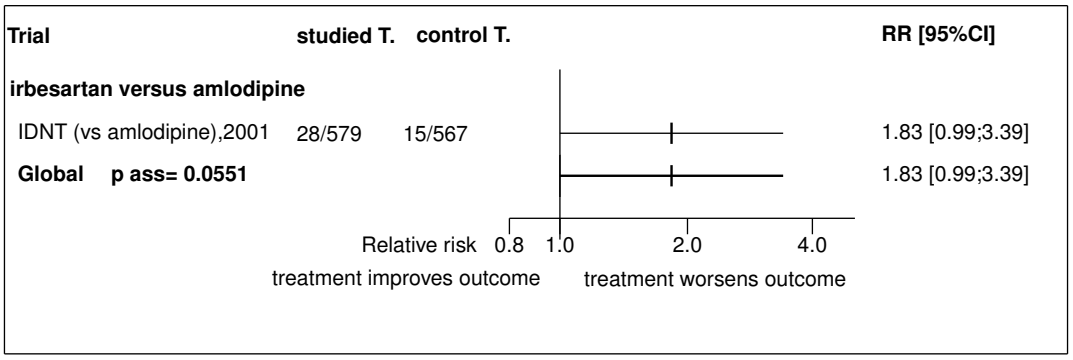


Figure 11.5: *Forest's plot for coronary event*

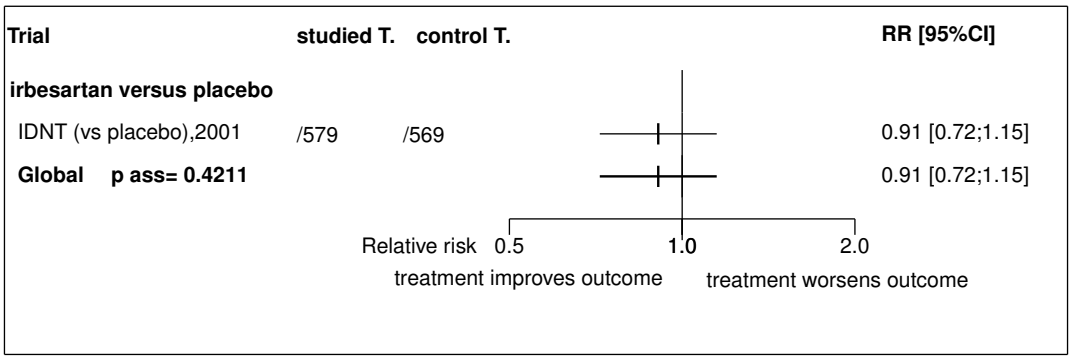


Figure 11.6: *Forest's plot for heart failure*

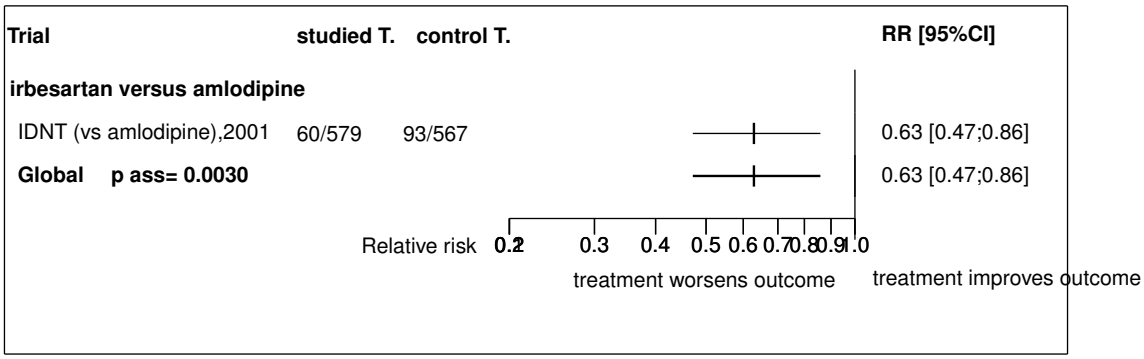
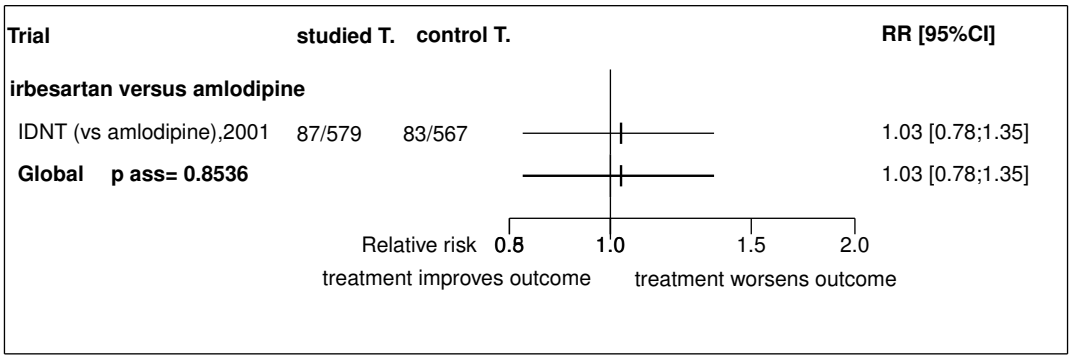


Figure 11.7: *Forest's plot for all cause death*



References

[1] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

[2] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

[3] Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8. [PMID=11565519]

[4] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

[5] Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8. [PMID=11565519]

[6] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

[7] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

11.3 Individual trial summaries

Table 11.6: *IDNT (vs placebo), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1148 (579 vs. 569) **Follow-up duration:** 2.6 y **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias worldwide, 210 centres **Inclusion period:** mar 1996 - feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes	**Studied treatment:** Irbesartan 300mg/d (target 135/85) target blood pressure: 135/85 mm Hg or less **Control treatment:** placebo	

References

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]
Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]

Table 11.7: *IRMA 2, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=611 (404 vs. 207) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias multinational	Hypertensive patients with type 2 diabetes and microalbuminuria	**Studied treatment:** irbesartan 150 mg daily or 300 mg daily **Control treatment:** placebo	

Reference

Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8 [PMID=11565519]

Table 11.8: *IDNT irbesartan, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1148 (579 vs. 569) **Follow-up duration:** 2.6 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Worldwide, 210 centres **Inclusion period:** mar 1996 - Feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes **Inclusion criteria:** age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Studied treatment:** Irbesartan 300 mg daily **Control treatment:** placebo	

Reference

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]

Table 11.9: *IPDM 150mg, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=396 (195 vs. 201) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial Worldwide, 96 centres	Hypertensive patients with type 2 diabetes and microalbuminuria **Inclusion criteria:** hypertension (at least two of three consecutive measurementsobtained one week apart during the run-in period of a mean systolicblood pressure of more than 135 mm Hg or a mean diastolicblood pressure of more than 85 mm Hg, or both); age between 30 and 70 years; persistent microalbuminuria (definedas an albumin excretion rate of 20 to 200 g per minute intwo of three consecutive, sterile, overnight urine samples) and a serumcreatinine concentration of no more than 1.5 mg per deciliter(133 mol per liter) for men and no more than 1.1 mg per deciliter(97 mol per liter) for women **Exclusion criteria:** nondiabetic kidneydisease; cancer; life-threatening disease with death expected to occurwithin two years; indication for angiotensin-convertingenzyme (ACE) inhibitors or angiotensin-IIreceptor antagonists	**Studied treatment:** irbesartan 150 mg daily **Control treatment:** placebo **note:** 3 arms trial: irbesartan 150 and 300 mg daily, placebo	

Reference

Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8 [PMID=11565519]

Table 11.10: *IDNT (vs amlodipine), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1146 (579 vs. 567) **Follow-up duration:** 26y **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias worldwide, 210 centres **Inclusion period:** mar 1996 - feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes	**Studied treatment:** Irbesartan 300mg/d (with a target of 135/85) target blood pressure: 135/85 mm Hg or less **Control treatment:** amlodipine 10mg/d (with a target of 135/85)	Cardiovascular death RR=1.38 [0.92;2.06] Myocardial infarction (fatal and non fatal) RR=1.60 [1.00;2.54] Stroke (fatal and non fatal) RR=1.83 [0.99;3.39] Heart failure RR=0.63 [0.47;0.86] All cause death RR=1.03 [0.78;1.35]

Reference

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]

Table 11.11: *IDNT (irbesartan vs amlodipine), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1146 (579 vs. 567) **Follow-up duration:** 2.6 years **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias Worldwide, 210 centres **Inclusion period:** mar 1996 - Feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes **Inclusion criteria:** age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Studied treatment:** Irbesartan 300 mg daily **Control treatment:** amlodipine 10 mg daily	

Reference

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]

12 Detailed results for losartan

12.1 Available trials

A total of 3 RCTs which randomized 11901 patients were identified: it compared losartan with placebo and 2 trials compared losartan with atenolol.
The average study size was 3967 patients (range 1195 to 9193). The first study was published in 2001, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Cardiovascular events data was reported in 1 trials; 1 trials reported data on cardiovascular death; and 1 trials reported data on coronary event.
Following tables 12.1 (page 94), 12.2 (page 94), 12.5 (page 98), and 12.3 (page 95) summarized the main characteristics of the trials including in this systematic review of randomized trials of losartan.

Table 12.1: *Treatment description - angiotensin receptor blocker - losartan*

Trial	Studied treatment	Control treatment
Losartan versus placebo		
RENAAL (2001) [1]	losartan 50 to 100 mg once daily	placebo
	Concomittant treatment: in addition to conventional antihypertensive treatment(calcium-channel antagonists, diuretics, alpha-blockers,beta-blockers, and centrally acting agents)	
Losartan versus atenolol		
LIFE (2002) [2]	losartan	atenolol
LIFE (diabetic subgroup) (2002) [3, 4]	losartan 50mg daily at step 1	atenolol 50mg daily at step 1

Table 12.2: *Descriptions of participants - angiotensin receptor blocker - losartan*

Trial	Patients
Losartan versus placebo	

continued...

Trial	Patients	
RENAAL (2001) [1]	Patients with type 2 diabetes and nephropathy	
	Inclusion criteria: age between 31 to 70 years; ratio of urinary albumin (measured in milligrams per liter) to urinary creatinine (measured in grams per liter) from a first morning specimen of at least 300 (or a rate of urinary protein excretion of at least 0.5 g per day) and serum creatinine values between 1.3 and 3.0 mg per deciliter (115 and 265 mol per liter), with a lower limit of 1.5 mg per deciliter (133 mol per liter) for male patients weighing more than 60 kg	**Exclusion criteria:** type 1 diabetes or non-diabetic renal disease; myocardial infarction; coronary- artery bypass grafting within the previous month; cerebrovascular accident; percutaneous transluminal coronary angioplasty within the previous six months; transient ischemic attack within the previous year; history of heart failure
Losartan versus atenolol		
LIFE (2002) [2]	Patients aged 5580 years, with previously treated or untreated hypertension (sitting blood pressure 160200/95115 mm Hg) and ECG signs of LVH.	
	Inclusion criteria:	**Exclusion criteria:** secondary hypertension;myocardial infarction or stroke within the previous6 months; angina pectoris requiring treatment with-blockers or calcium-antagonists; heart failure or leftventricular ejection fraction of 40% or less; or a disorderthat, in the treating physicians opinion, requiredtreatment with losartan or another angiotensinII type1-receptor antagonist, atenolol or another -blocker,hydrochlorothiazide, or angiotensin-converting-enzymeinhibitors
LIFE (diabetic subgroup) (2002) [3, 4] [b]	Patients with diabetes (subgroup) , hypertension, and signs of left-ventricular hypertrophy on electrocardiograms	
	Inclusion criteria:	**Exclusion criteria:** secondary hypertension; myocardial infarction or stroke within the previous 6 months; angina pectoris requiring treatment with beta-blockers or calcium-antagonists; heart failure or left ventricular ejection fraction of 40% or less; or a disorder that, in the treating physicians opinion, required treatment with losartan or another angiotensinII type 1-receptor antagonist, atenolol or another beta-blocker, hydrochlorothiazide,or angiotensin-converting-enzyme inhibitors

b) of all 9193 patients included in the trial, 1195 had diabetes

Table 12.3: *Design and methodological quality of trials - angiotensin receptor blocker - losartan*

Trial	Design	Duration	Centre	Primary endpoint
Losartan versus placebo				
RENAAL, 2001 [1] n=1513	Parallel groups double-blind confirmatory trial at low risk of bias	3.4 y	America, Europe, Asia 250 centres	doubling of the creatinine, end-stage renal disease, death
Losartan versus atenolol				

continued...

Trial	Design	Duration	Centre	Primary end-point
LIFE, 2002 [2] n=9193	Parallel groups Double blind confirmatory trial at low risk of bias	4.8 y (mean) inclusion period: Jun 1995 May 1997	USA, Europe 945 centres	Cardiovascular mortality, stroke, and myocardial infarction
LIFE (diabetic subgroup), 2002 [3, 4] n=1195	Parallel groups double-blind exploratory trial	4.7 years inclusion period: jun 1995 - may 1997	USA, UK, Nordic countries 945 centres	CV events

Table 12.4: *Trial characteristics - angiotensin receptor blocker - losartan(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Losartan versus placebo								
RENAAL, 2001 [1]	#N/A	#N/A						60 y
Losartan versus atenolol								
LIFE, 2002 [2]								
LIFE (diabetic subgroup), 2002 [3, 4]	#N/A	#N/A	0	-2				67 y

continued...

Table 12.5: *Trial characteristics - angiotensin receptor blocker - losartan*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Losartan versus placebo								
RENAAL, 2001 [1]	36.8%		8.5%	152/82		93%		nephropathy
Losartan versus atenolol								
LIFE, 2002 [2]								
LIFE (diabetic subgroup), 2002 [3, 4]	53%			177/96 mmHg		100%		hypertension

12.2 Meta-analysis results

The results are detailed in table 12.6 (page 99). This table is followed by the Forest's plot corresponding to each endpoint.

Losartan versus placebo

No data were presented in the 1 trial identified

Losartan versus atenolol

Only one of the 2 studies eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of losartan in cardiovascular events, with a RR of 0.86 (95% CI 0.77 to 0.96, p=0.0084).
Only one of the 2 studies eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 0.87 (95% CI 0.72 to 1.04, p=0.1318).
Only one of the 2 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 1.05 (95% CI 0.86 to 1.28, p=0.6292).

Table 12.6: *Results details - angiotensin receptor blocker - losartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
losartan versus placebo						
No data were presented in the trial identified						
losartan versus atenolol						
cardiovascular events	RR=0.86	[0.77;0.96]	0.0084	1.0000 (I^2=0.00)	1	9193
cardiovascular death	RR=0.87	[0.72;1.04]	0.1318	1.0000 (I^2=0.00)	1	9193
coronary event	RR=1.05	[0.86;1.28]	0.6292	1.0000 (I^2=0.00)	1	9193

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 12.1: *Forest's plot for cardiovascular events*

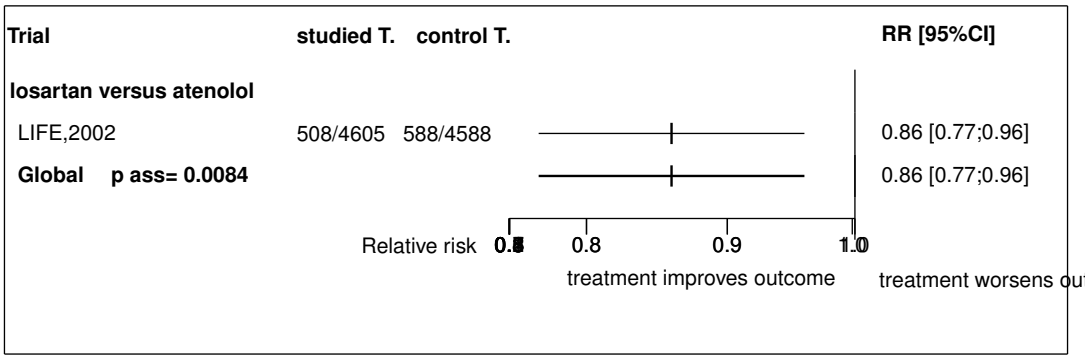


Figure 12.2: *Forest's plot for cardiovascular death*

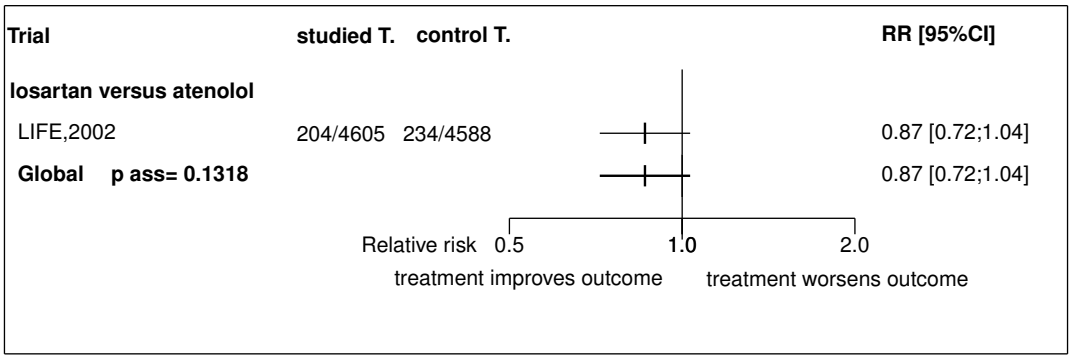
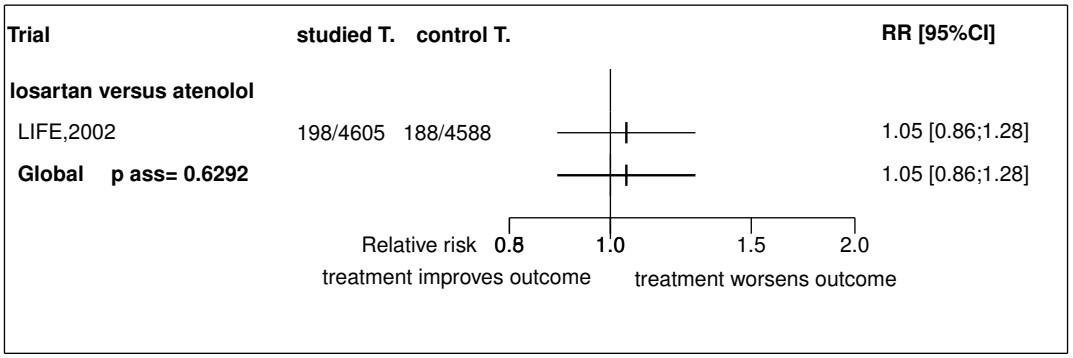


Figure 12.3: *Forest's plot for coronary event*



References

[1] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9. [PMID=11565518]

[2] Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002 Mar 23;359:995-1003. [PMID=11937178]

[3] Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:1004-10. [PMID=11937179]

[4] Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003. [PMID=11937178]

12.3 Individual trial summaries

Table 12.7: *RENAAL, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1513 (751 vs. 762) **Follow-up duration:** 3.4 y **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias America, Europe, Asia, 250 centres	Patients with type 2 diabetes and nephropathy **Inclusion criteria:** age between 31 to 70 years; ratio of urinary albumin (measured in milligrams per liter) to urinary creatinine (measured in grams per liter) from a first morning specimen of at least 300 (or a rate of urinary protein excretion of at least 0.5 g per day) and serum creatinine values between 1.3 and 3.0 mg per deciliter (115 and 265 mol per liter), with a lower limit of 1.5 mg per deciliter (133 mol per liter) for male patients weighing more than 60 kg **Exclusion criteria:** type 1 diabetes or nondiabetic renal disease; myocardial infarction; coronary- artery bypass grafting within the previous month; cerebrovascular accident; percutaneous transluminal coronary angioplasty within the previous six months; transient ischemic attack within the previous year; history of heart failure	**Studied treatment:** losartan 50 to 100 mg once daily **Control treatment:** placebo **Concomittant treat.:**in addition to conventional antihypertensive treatment(calcium-channel antagonists, diuretics, alpha-blockers,beta-blockers, and centrally acting agents)	

Reference

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9 [PMID=11565518]

Table 12.8: *LIFE, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=9193 (4605 vs. 4588) **Follow-up duration:** 4.8 y (mean) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias USA, Europe, 945 centres **Inclusion period:** Jun 1995 May 1997	Patients aged 5580 years, with previously treated or untreated hypertension (sitting blood pressure 160200/95115 mm Hg) and ECG signs of LVH. **Exclusion criteria:** secondary hypertension;myocardial infarction or stroke within the previous6 months; angina pectoris requiring treatment with-blockers or calcium-antagonists; heart failure or leftventricular ejection fraction of 40% or less; or a disorderthat, in the treating physicians opinion, requiredtreatment with losartan or another angiotensinII type1-receptor antagonist, atenolol or another -blocker,hydrochlorothiazide, or angiotensin-converting-enzymeinhibitors	**Studied treatment:** losartan **Control treatment:** atenolol	Cardiovascular events RR=0.86 [0.77;0.96] (Cardiovascular mortality, stroke, MI) Cardiovascular death RR=0.87 [0.72;1.04] Coronary event RR=1.05 [0.86;1.28] (MI fatal and non fatal)

Reference

Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002 Mar 23;359:995-1003 [PMID=11937178]

Table 12.9: *LIFE (diabetic subgroup), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1195 (586 vs. 609) **Follow-up duration:** 4.7 years **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial USA, UK, Nordic countries, 945 centres **Inclusion period:** jun 1995 - may 1997	Patients with diabetes (subgroup) , hypertension, and signs of left-ventricular hypertrophy on electrocardiograms **note:** of all 9193 patients included in the trial, 1195 had diabetes **Exclusion criteria:** secondary hypertension; myocardial infarction or stroke within the previous 6 months; angina pectoris requiring treatment with beta-blockers or calcium-antagonists; heart failure or left ventricular ejection fraction of 40% or less; or a disorder that, in the treating physicians opinion, required treatment with losartan or another angiotensinII type 1-receptor antagonist, atenolol or another beta-blocker, hydrochlorothiazide,or angiotensin-converting-enzyme inhibitors	**Studied treatment:** losartan 50mg daily at step 1 **Control treatment:** atenolol 50mg daily at step 1	

References

Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:1004-10 [PMID=11937179]
Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003 [PMID=11937178]

13 Detailed results for telmisartan

13.1 Available trials

Only one trial which randomized 250 patients was identified: it compared telmisartan with enalapril.
This trial included 250 patients and was published in 2004.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 13.1 (page 106), 13.2 (page 106), 13.4 (page 107), and 13.3 (page 106) summarized the main characteristics of the trial including in this systematic review of randomized trials of telmisartan.

Table 13.1: *Treatment description - angiotensin receptor blocker - telmisartan*

Trial	Studied treatment	Control treatment
Telmisartan versus enalapril		
DETAIL (2004) [1]	telmisartan 80 mg daily	enalapril 20 mg daily

Table 13.2: *Descriptions of participants - angiotensin receptor blocker - telmisartan*

Trial	Patients
Telmisartan versus enalapril	
DETAIL (2004) [1]	Subjects with type 2 diabetes and early nephropathy

Table 13.3: *Design and methodological quality of trials - angiotensin receptor blocker - telmisartan*

Trial	Design	Duration	Centre	Primary endpoint
Telmisartan versus enalapril				
DETAIL, 2004 [1] n=250	Parallel groups double-blind exploratory trial	5 year		glomerular filtration rate

Table 13.4: *Trial characteristics - angiotensin receptor blocker - telmisartan*

Trial	target blood pressure
Telmisartan versus enalapril	
DETAIL, 2004 [1]	

13.2 Meta-analysis results

The results are detailed in table 13.5 (page 108). This table is followed by the Forest's plot corresponding to each endpoint.

Telmisartan versus enalapril

No data were presented in the 1 trial identified

Table 13.5: *Results details - angiotensin receptor blocker - telmisartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
telmisartan versus enalapril						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952-61. [PMID=15516696]

13.3 Individual trial summaries

Table 13.6: *DETAIL, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=250 (120 vs. 130) **Follow-up duration:** 5 year **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Subjects with type 2 diabetes and early nephropathy	**Studied treatment:** telmisartan 80 mg daily **Control treatment:** enalapril 20 mg daily	

Reference

Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952-61 [PMID=15516696]

14 Detailed results for valsartan

14.1 Available trials

A total of 3 RCTs which randomized 17545 patients were identified: all compared valsartan with amlodipine.
The average study size was 5848 patients (range 1150 to 15245). The first study was published in 2004, and the last study was published in 2011.
A total of 1 trials were double blind and 2 were open-label in design. All included studies were reported in English language. We found one unpublished trial.
Cardiovascular events data was reported in 1 trials; 1 trials reported data on all cause death; 1 trials reported data on heart failure; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on coronary event; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on cardiovascular death; and 1 trials reported data on diabetes onset.
Following tables 14.1 (page 111), 14.2 (page 111), 14.4 (page 113), and 14.3 (page 112) summarized the main characteristics of the trials including in this systematic review of randomized trials of valsartan.

Table 14.1: *Treatment description - angiotensin receptor blocker - valsartan*

Trial	Studied treatment	Control treatment
Valsartan versus amlodipine		
NAGOYA HEART ()	blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg	blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg
VALUE (2004) [1]	valsartan based regimen	amlodipine based regimen
NAGOYA HEART (2011) [2]	blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg	blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg
	Concomittant treatment: excluding ACEIs/other ARBs, and CCBs	

Table 14.2: *Descriptions of participants - angiotensin receptor blocker - valsartan*

Trial	Patients
Valsartan versus amlodipine	
NAGOYA HEART ()	Patients with hypertension with type 2 diabetes or impaired glucose tolerance

continued...

Trial	Patients	
VALUE (2004) [1]	Patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events	
	Inclusion criteria: men or women of any racial background, 50 years of age and older, and presence of cardiovascular risk factors or disease according to an algorithm based on age and sex.The qualifying risk factors weremale sex, age older than 50 years,verified diabetes mellitus, currentsmoking, high total cholesterol, leftventricular hypertrophy by electrocardiogram,proteinuria on dipstickand raised serum creatinine between150 and 265 micromol/L. Thequalifying diseases were verified coronary-disease, cerebrovascular diseaseor peripheral arterial occlusive disease,or left ventricular hypertrophy withstrain pattern.	**Exclusion criteria:** renal artery stenosis, pregnancy, acute myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with blockers for both coronary artery disease and hypertension
NAGOYA HEART (2011) [2]	Patients with hypertension with type 2 diabetes or impaired glucose tolerance	
	Inclusion criteria:	**Exclusion criteria:** prior cardiovascular diseases within 6 mo; Taking CCBs continuously for angina pectoris; Left ventricular ejection fraction (LVEF) $<$40%; Advanced atrioventricular block; Secondary or severe hypertension (200/110 mmHg); Serum creatinine 221 mol/L (2.5 mg/dL); Pregnant women; Estimated prognosis within 3 years

Table 14.3: *Design and methodological quality of trials - angiotensin receptor blocker - valsartan*

Trial	Design	Duration	Centre	Primary endpoint
Valsartan versus amlodipine				
NAGOYA HEART, n=1150	Parallel groups open confirmatory trial at risk of bias		Japan 46 centres	CV events
VALUE, 2004 [1] n=15245	Parallel groups Double blind confirmatory trial at low risk of bias	4.2 y (mean) inclusion period: Sep 1997 - nov 1999	31 countries multicentre	cardiac event
NAGOYA HEART, 2011 [2] n=1150	Parallel groups open confirmatory trial at risk of bias	3.2 y median inclusion period: oct 2004 -	Japan 46 centres	CV events

Table 14.4: *Trial characteristics - angiotensin receptor blocker - valsartan*

Trial	target blood pressure
Valsartan versus amlodipine	
NAGOYA HEART,	
VALUE, 2004 [1]	
NAGOYA HEART, 2011 [2]	#N/A
#N/A	
63 y	

14.2 Meta-analysis results

The results are detailed in table 14.5 (page 114). This table is followed by the Forest's plot corresponding to each endpoint.

Valsartan versus amlodipine

Only one of the 3 studies eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between valsartan and amlodipine, with a RR of 1.02 (95%CI 0.93 to 1.12, p=0.6832) in favour of amlodipine. In other words, cardiovascular events was slightly lower in the amlodipine group , but this was not statistically significant.
Only one of the 3 studies eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 0.99 (95% CI 0.85 to 1.16, p=0.9303).
Only one of the 3 studies eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of valsartan in myocardial infarction (fatal and non fatal), with a RR of 1.17 (95% CI 1.01 to 1.36, p=0.0359).
Only one of the 3 studies eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 1.14 (95% CI 0.97 to 1.33, p=0.1062).
Only one of the 3 studies eligible for this comparison provided data on **coronary event**. No statistically significant difference between the groups was found in coronary event, with a RR of 1.02 (95% CI 0.93 to 1.12, p=0.6832).
Only one of the 3 studies eligible for this comparison provided data on **heart failure**. No statistically significant difference between the groups was found in heart failure, with a RR of 0.88 (95% CI 0.76 to 1.01, p=0.0696).
Only one of the 3 studies eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.02 (95% CI 0.93 to 1.12, p=0.6540).

Table 14.5: *Results details - angiotensin receptor blocker - valsartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
valsartan versus amlodipine						
cardiovascular events	RR=1.02	[0.93;1.12]	0.6832	1.0000 (I^2=0.00)	1	15245
cardiovascular death	RR=0.99	[0.85;1.16]	0.9303	1.0000 (I^2=0.00)	1	15245
myocardial infarction (fatal and non fatal)	RR=1.17	[1.01;1.36]	0.0359	1.0000 (I^2=0.00)	1	15245
stroke (fatal and non fatal)	RR=1.14	[0.97;1.33]	0.1062	1.0000 (I^2=1.00)	1	15245
coronary event	RR=1.02	[0.93;1.12]	0.6832	1.0000 (I^2=0.00)	1	15245
heart failure	RR=0.88	[0.76;1.01]	0.0696	1.0000 (I^2=0.00)	1	15245
diabetes onset	RR=0.81	[0.74;0.89]	0.0000	1.0000 (I^2=0.00)	1	15245
all cause death	RR=1.02	[0.93;1.12]	0.6540	1.0000 (I^2=0.00)	1	15245

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 14.1: *Forest's plot for cardiovascular events*

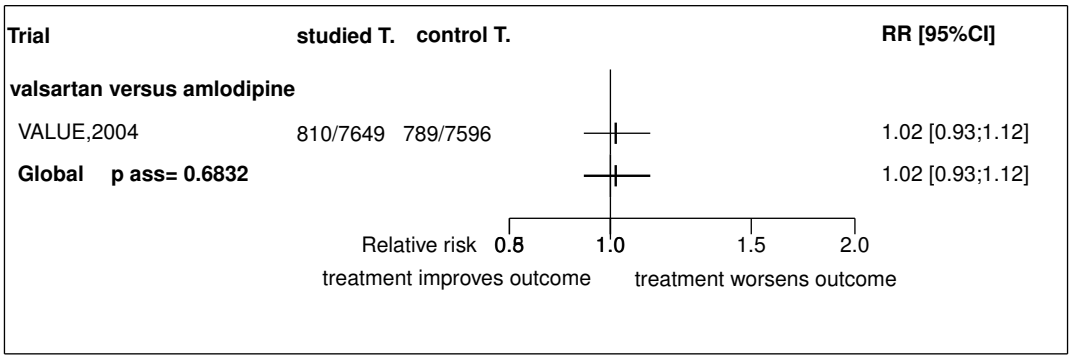


Figure 14.2: *Forest's plot for cardiovascular death*

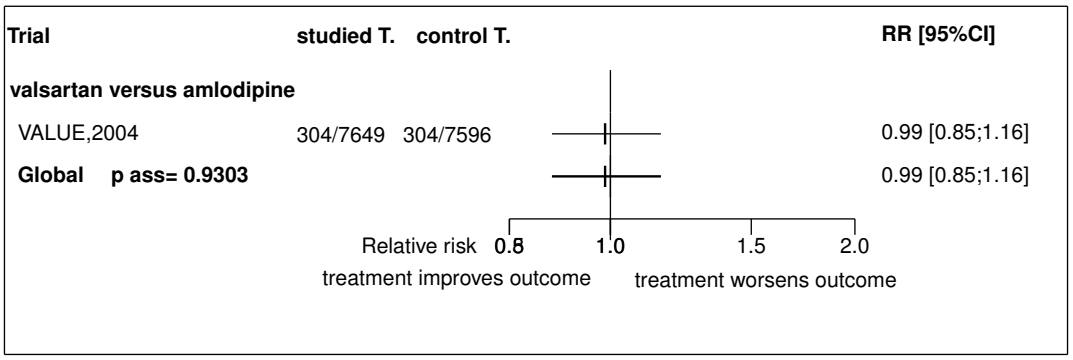


Figure 14.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

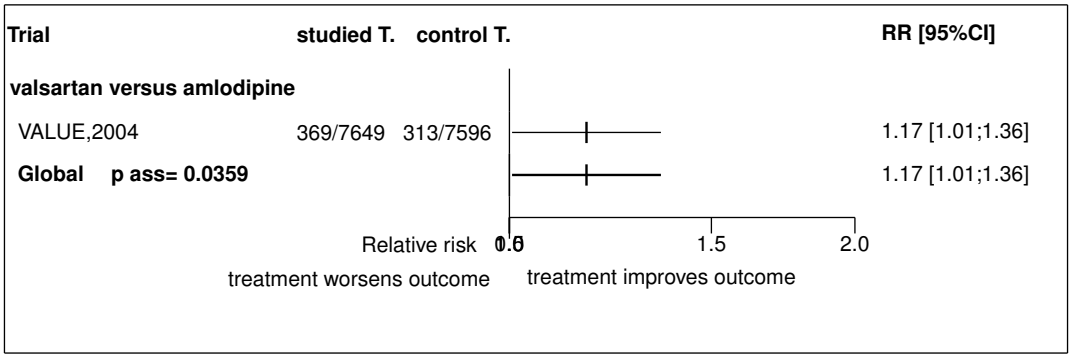


Figure 14.4: *Forest's plot for stroke (fatal and non fatal)*

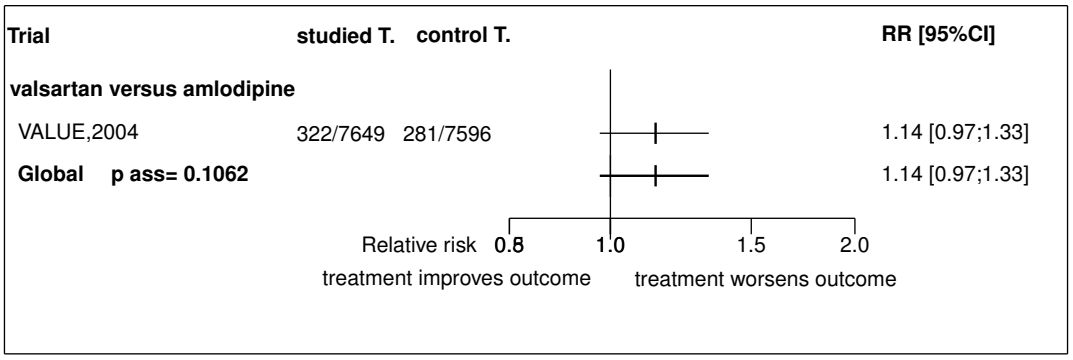


Figure 14.5: *Forest's plot for coronary event*

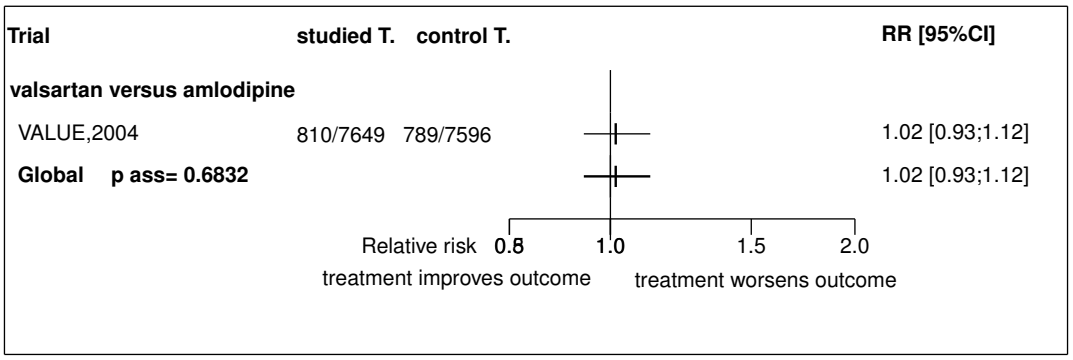


Figure 14.6: *Forest's plot for heart failure*

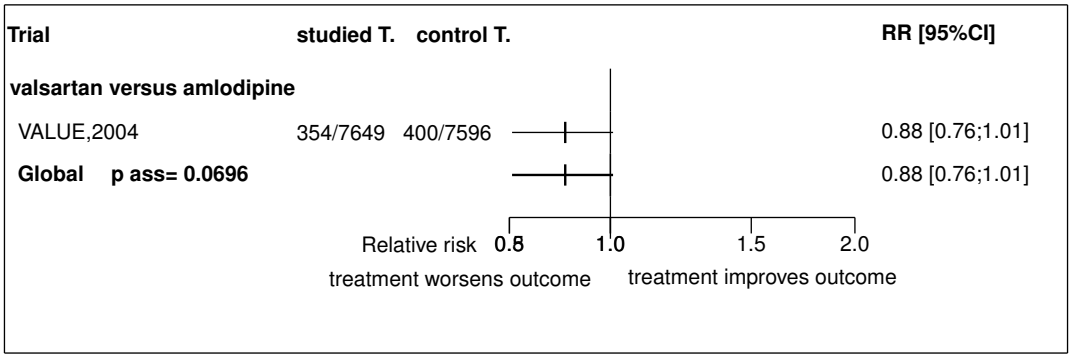


Figure 14.7: *Forest's plot for diabetes onset*

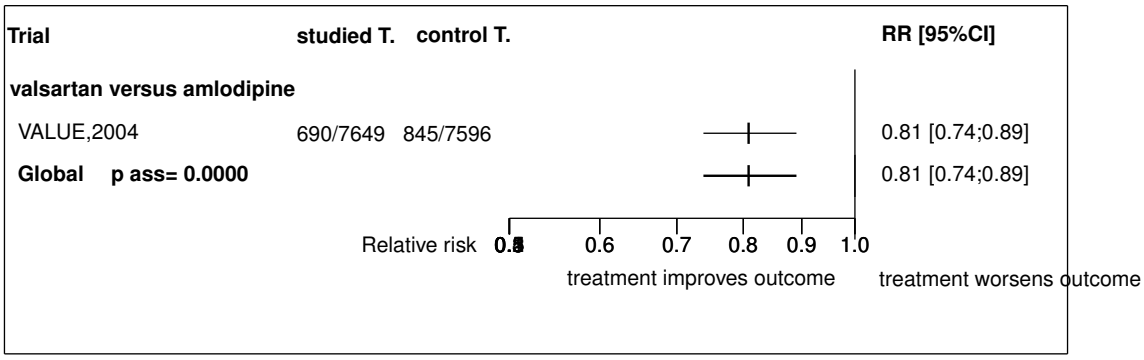
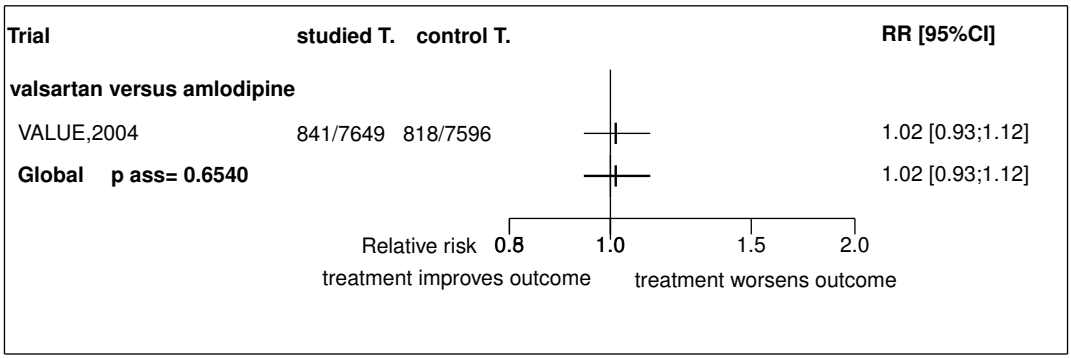


Figure 14.8: *Forest's plot for all cause death*



References

[1] Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004 Jun 19;363:2022-31. [PMID=15207952]

[2] Matsushita K, Muramatsu T, Kondo T, Maeda K, Shintani S, Murohara T. Rationale and design of the NAGOYA HEART Study: comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance. J Cardiol 2010;56:111-7. [PMID=20409690]

14.3 Individual trial summaries

Table 14.6: *NAGOYA HEART, - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (1150 vs. 0) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Japan, 46 centres	Patients with hypertension with type 2 diabetes or impaired glucose tolerance	**Studied treatment:** blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg **Control treatment:** blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg	
Reference			

Table 14.7: *VALUE, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=15245 (7649 vs. 7596) **Follow-up duration:** 4.2 y (mean) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 31 countries, multicentre **Inclusion period:** Sep 1997 - nov 1999	Patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events **Inclusion criteria:** men or women of any racial background, 50 years of age and older, and presence of cardiovascular risk factors or disease according to an algorithm based on age and sex.The qualifying risk factors weremale sex, age older than 50 years,verified diabetes mellitus, currentsmoking, high total cholesterol, leftventricular hypertrophy by electrocardiogram,proteinuria on dipstickand raised serum creatinine between150 and 265 micromol/L. Thequalifying diseases were verified coronarydisease, cerebrovascular diseaseor peripheral arterial occlusive disease,or left ventricular hypertrophy withstrain patter **Exclusion criteria:** renal artery stenosis, pregnancy, acute myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with blockers for both coronary artery disease and hypertension	**Studied treatment:** valsartan based regimen **Control treatment:** amlodipine based regimen	Cardiovascular events RR=1.02 [0.93;1.12] Cardiovascular death RR=0.99 [0.85;1.16] (cardiac mortality) Myocardial infarction (fatal and non fatal) RR=1.17 [1.01;1.36] Stroke (fatal and non fatal) RR=1.14 [0.97;1.33] Coronary event RR=1.02 [0.93;1.12] Heart failure RR=0.88 [0.76;1.01] Diabetes onset RR=0.81 [0.74;0.89] All cause death RR=1.02 [0.93;1.12]

Reference

Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004 Jun 19;363:2022-31 [PMID=15207952]

Table 14.8: *NAGOYA HEART, 2011 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1150 (575 vs. 575) **Follow-up duration:** 3.2 y median **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Japan, 46 centres **Inclusion period:** oct 2004 -	Patients with hypertension with type 2 diabetes or impaired glucose tolerance **Exclusion criteria:** Prior cardiovascular diseases within 6 mo; Taking CCBs continuously for angina pectoris; Left ventricular ejection fraction (LVEF) <40%; Advanced atrioventricular block; Secondary or severe hypertension (200/110 mmHg); Serum creatinine 221 mol/L (2.5 mg/dL); Pregnant women; Estimated prognosis within 3 years	**Studied treatment:** blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg **Control treatment:** blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg **Concomittant treat.:**excluding ACEIs/other ARBs, and CCBs	

Reference

Matsushita K, Muramatsu T, Kondo T, Maeda K, Shintani S, Murohara T. Rationale and design of the NAGOYA HEART Study: comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance. J Cardiol 2010;56:111-7 [PMID=20409690]

15 Global meta-analysis: all angiotensin receptor blocker

15.1 Global meta-analysis: all angiotensin receptor blocker versus amlodipine

Table 15.1: *All angiotensin receptor blockerversus amlodipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.02	0.94;1.11	0.6401	0.9379 (0.00)	2	16391
cardiovascular death	RR=1.11	0.82;1.49	0.5127	0.1408 (0.54)	2	16391
myocardial infarction (fatal and non fatal)	RR=1.26	0.97;1.63	0.0794	0.2132 (0.35)	2	16391
stroke (fatal and non fatal)	RR=1.31	0.86;2.00	0.2135	0.1441 (0.53)	2	16391
coronary event	RR=1.02	0.93;1.12	0.6832	1.0000 (0.00)	1	15245
heart failure	RR=0.77	0.56;1.05	0.1023	0.0526 (0.73)	2	16391
all cause death	RR=1.02	0.94;1.11	0.6289	0.9714 (0.00)	2	16391

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

15.2 Global meta-analysis: all angiotensin receptor blocker versus atenolol

Table 15.2: *All angiotensin receptor blockerversus atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.86	0.77;0.96	0.0084	1.0000 (0.00)	1	9193
cardiovascular death	RR=0.87	0.72;1.04	0.1318	1.0000 (0.00)	1	9193
coronary event	RR=1.05	0.86;1.28	0.6292	1.0000 (0.00)	1	9193

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

15.3 Global meta-analysis: all angiotensin receptor blocker versus enalapril

Table 15.3: *All angiotensin receptor blockerversus enalapril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

15.4 Global meta-analysis: all angiotensin receptor blocker versus placebo

Table 15.4: *All angiotensin receptor blockerversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
coronary event	RR=0.91	0.72;1.15	0.4211	1.0000 (0.00)	1	1148

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

16 Ongoing studies of angiotensin receptor blocker

No ongoing trial was identified.

17 Excluded studies for angiotensin receptor blocker

No trial was excluded.

References

Part III

Calcium blockers

18 Overview of calcium blockers

18.1 Included trials

A total of 9 randomized comparisons which enrolled 14995 patients were identified. In all, 3 randomized comparisons concerned amlodipine , one benazepril + amlodipine , one calcium-channel blocker , one diltiazem , one nifedipine , one nisoldipine and one nitrendipine.
The detailed descriptions of trials and meta-analysis results is given in section 19 (page 137) for amlodipine, in section 20 (page 150) for benazepril + amlodipine, in section 21 (page 158) for calcium-channel blocker, in section 22 (page 165) for diltiazem, in section 23 (page 172) for nifedipine, in section 24 (page 179) for nisoldipine and in section 25 (page 188) for nitrendipine.

The average study size was 1666 patients (range 380 to 7162). The first study was published in 1997, and the last study was published in 2010.
A total of 6 trials were double blind and 3 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 18.1 (page 129) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

18.2 Summary of meta-analysis results

The meta-analysis of the available trials about calcium blockers provide the results listed in tables 18.2 to 18.8 (page 132) and in the following graphs.

18.2.1 Amlodipine

Data were insufficient to compare **amlodipine** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Data were insufficient to compare **amlodipine** to **chlorthalidone**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Amlodipine was inferior to **fosinopril** in terms of cardiovascular events (RR=1.91, 95% CI 1.03 to 3.52, p=0.0389, 1 trial). No significant difference was found on myocardial infarction (fatal and non fatal) (RR=1.29, 95% CI 0.58 to 2.86, p=0.5370, 1 trial), stroke (fatal and non fatal) (RR=2.47, 95% CI 0.79 to 7.75, p=0.1200, 1 trial)and all cause death (RR=1.24, 95% CI 0.34 to 4.54, p=0.7484, 1 trial).

18.2.2 Benazepril + amlodipine

Data were insufficient to compare **benazepril + amlodipine** to **benazepril + hydrochlorothiazide**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

18.2.3 Calcium-channel blocker

Data were insufficient to compare **calcium-channel blocker** to **diuretic or beta-blocker**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

18.2.4 Diltiazem

Data were insufficient to compare **diltiazem** to **diuretic or beta-blocker**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

18.2.5 Nifedipine

Data were insufficient to compare **nifedipine** to **coamilozide**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

18.2.6 Nisoldipine

Nisoldipine was superior to **enalapril** in terms of myocardial infarction (fatal and non fatal) (RR=5.00, 95% CI 1.95 to 12.84, p=0.0000, 1 trial). But nisoldipine increased the risk of cardiovascular events (RR=5.00, 95% CI 1.95 to 12.84, p=0.0000, 1 trial). However, no significant difference was found on cardiovascular death (RR=2.00, 95% CI 0.69 to 5.76, p=0.1992, 1 trial), stroke (fatal and non fatal) (RR=1.57, 95% CI 0.62 to 3.98, p=0.3409, 1 trial)and all cause death (RR=1.31, 95% CI 0.65 to 2.63, p=0.4520, 1 trial).

18.2.7 Nitrendipine

Data were insufficient to compare **nitrendipine** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 18.1: *Main study characteristics - calcium blockers*

Trial	Patients	Treatments	Trial design and method
Amlodipine			
Amlodipine versus placebo			
IDNT amlodipine, 2001 [1, 2, 3, 4] n = 567 vs. 569	hypertensive patients with nephropathy due to type 2 diabetes	amlodipine 10 mg daily **versus** placebo	double-blind parallel groups Primary endpoint: renal death 210 centres, Worldwide subgroup: no
Amlodipine versus chlorthalidone			
ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002 [5, 6, 7] n = 2664 vs. 4498	diabetic (subgroup) participants aged 55 years or older with hypertension	amlodipine **versus** chlorthalidone	double-blind parallel groups Primary endpoint: fatal CHD or nonfatal MI subgroup: yes
Amlodipine versus fosinopril			
FACET, 1997 [8, 9] n = 191 vs. 189	hypertensive patients with NIDDM	amlodipine (long acting) 10 mg daily **versus** fosinopril 20 mg daily	open parallel groups Primary endpoint: not defined single center, Italy subgroup: no
Benazepril + amlodipine			
Benazepril + amlodipine versus benazepril + hydrochlorothiazide			
ACCOMPLISH (diabetic subgroup), 2010 [1, 2] n = 1432 vs. 1410	patients with diabetes (subgroup) and hypertension at high risk of cardiovascular and related events	benazepril, combined with amlodipine **versus** benazepril, combined with hydrochlorothiazide	double-blind parallel groups Primary endpoint: cardiovascular morbidity and mortality 548 centres, US, Norway, Denmark, Finland subgroup: yes

continued...

Trial	Patients	Treatments	Trial design and method
Calcium-channel blocker			
Calcium-channel blocker versus diuretic or beta-blocker			
STOP-2 CCB (diabetic subgroup), 2000 [1, 2] n = 231 vs. 253	diabetic (subgroup) elderly patients aged 70-84 years	calcium-channel blocker **versus** diuretic or beta-blocker	open with blind assessment parallel groups Primary endpoint: renal death 312 centres, Sweden subgroup: yes
Diltiazem			
Diltiazem versus diuretic or beta-blocker			
NORDIL (diabetic subgroup), 2000 [1, 2, 3, 4] n = 351 vs. 376	diabetic patients (subgroup), aged 50-74 years who had diastolic blood pressure of 100 mm Hg or more	diltiazem 180360 mg diltiazem daily at step one **versus** thiazide diuretic or a beta-blocker at step one	open parallel groups Primary endpoint: CV events 1032 centres, Norway, Sweden subgroup: yes
Nifedipine			
Nifedipine versus coamilozide			
INSIGHT (diabetic subgroup), 2000 [1, 2] n = 649 vs. 653	diabetic (subgroup) patients aged 55-80 years with hypertension (blood pressure >= 150/95 mm Hg, or >= 160 mmHg systolic)	nifedipine GITS 30 mg daily **versus** co-amilozide hydrochlorothiazide 25 mg plus amiloride 2.5 mg	double-blind parallel groups Primary endpoint: CV events Europe, Israel subgroup: yes
Nisoldipine			
Nisoldipine versus enalapril			
ABCD hypertension, 1998 [1, 2] n = 235 vs. 235	patients with non-insulin-dependent diabetes and hypertension	nisoldipine (long acting) **versus** enalapril	double blind factorial plan Primary endpoint: 24-hour creatinine clearance single center, USA subgroup: no

continued...

Trial	Patients	Treatments	Trial design and method
Nitrendipine			
Nitrendipine versus placebo			
Syst-Eur (diabetic subgroup), 1999 [1] n = 252 vs. 240	subgroup of diabetic patients, age, >=60 years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg	calcium-channel blocker **versus** placebo	double blind parallel groups Primary endpoint: persisting neurologic deficit subgroup: yes

Table 18.2: *Summary of all results for amlodipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
amlodipine versus placebo						
No data were presented in the trial identified						
amlodipine versus chlorthalidone						
No data were presented in the trial identified						
amlodipine versus fosinopril						
cardiovascular events	RR=1.91	1.03;3.52	0.0389	1.0000 (0.00)	1	380
myocardial infarction (fatal and non fatal)	RR=1.29	0.58;2.86	0.5370	1.0000 (0.00)	1	380
stroke (fatal and non fatal)	RR=2.47	0.79;7.75	0.1200	1.0000 (0.00)	1	380
all cause death	RR=1.24	0.34;4.54	0.7484	1.0000 (0.00)	1	380

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.3: *Summary of all results for benazepril + amlodipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
benazepril + amlodipine versus benazepril + hydrochlorothiazide						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.4: *Summary of all results for calcium-channel blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
calcium-channel blocker versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.5: *Summary of all results for diltiazem*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
diltiazem versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.6: *Summary of all results for nifedipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nifedipine versus coamilozide						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.7: *Summary of all results for nisoldipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nisoldipine versus enalapril						
cardiovascular events	RR=5.00	1.95;12.84	0.0000	1.0000 (0.00)	1	470
cardiovascular death	RR=2.00	0.69;5.76	0.1992	1.0000 (1.00)	1	470
myocardial infarction (fatal and non fatal)	RR=5.00	1.95;12.84	0.0000	1.0000 (0.00)	1	470
stroke (fatal and non fatal)	RR=1.57	0.62;3.98	0.3409	1.0000 (0.00)	1	470
all cause death	RR=1.31	0.65;2.63	0.4520	1.0000 (0.00)	1	470

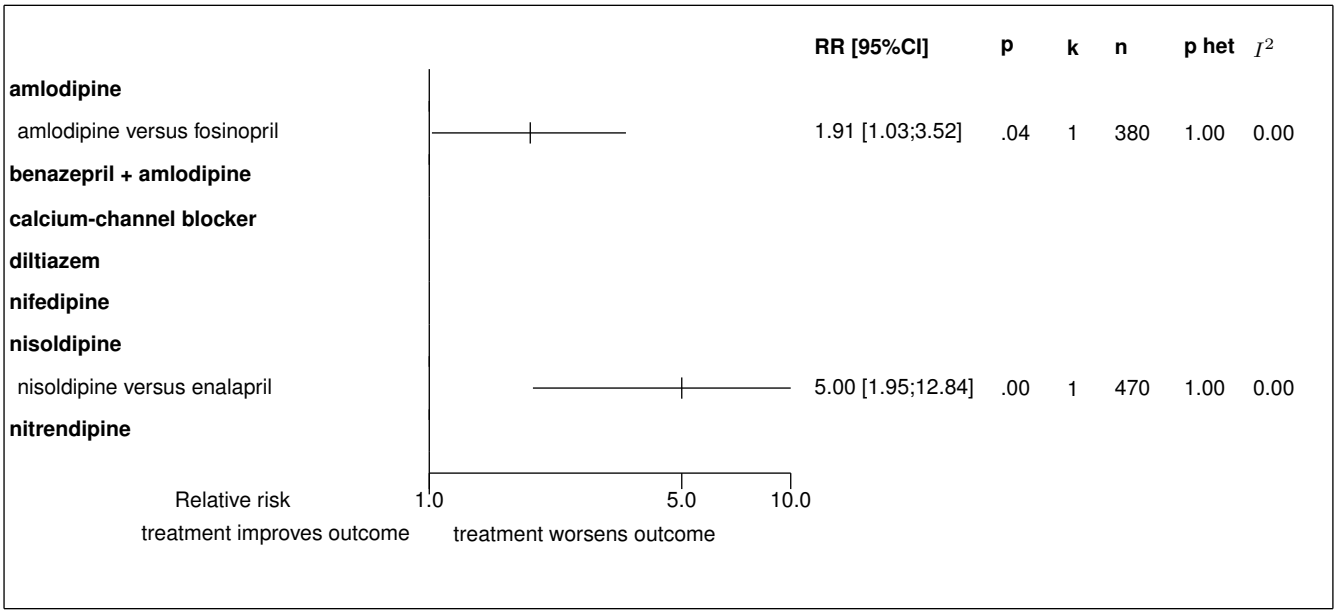
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 18.8: *Summary of all results for nitrendipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nitrendipine versus placebo						
No data were presented in the trial identified						

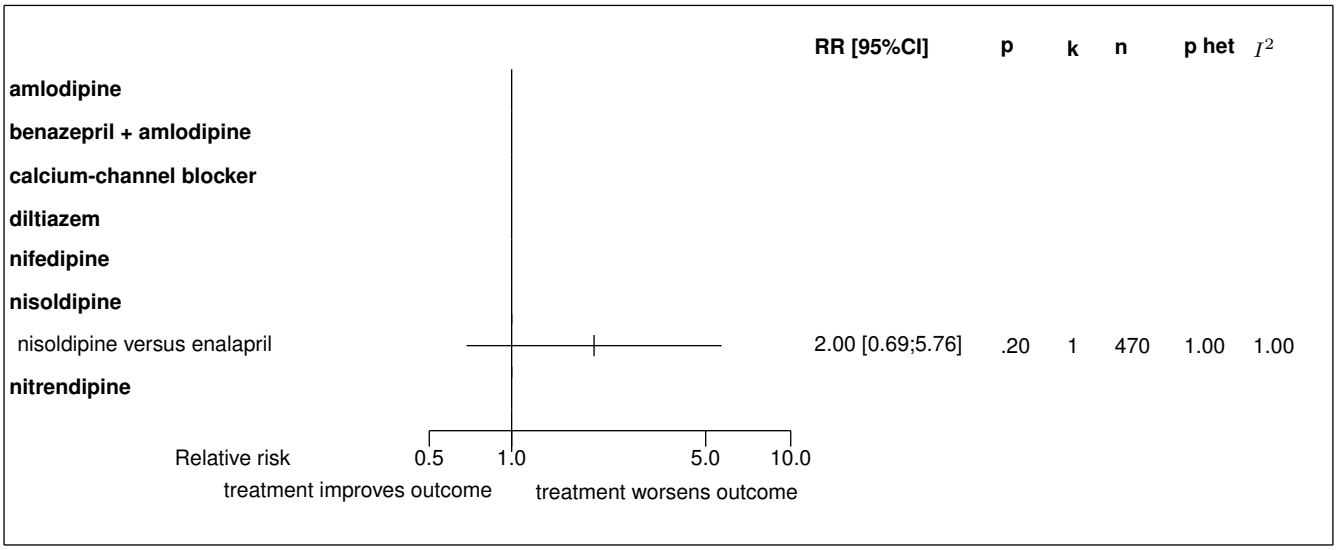
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 18.1: *Forest's plot for cardiovascular events*



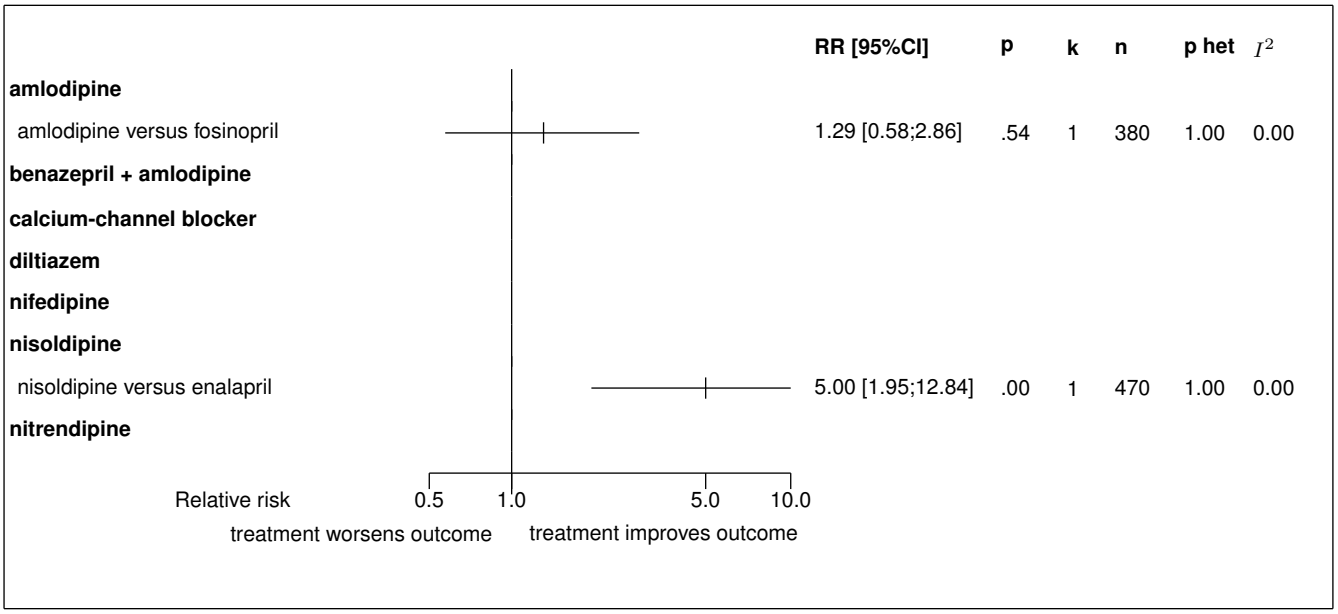
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 18.2: *Forest's plot for cardiovascular death*



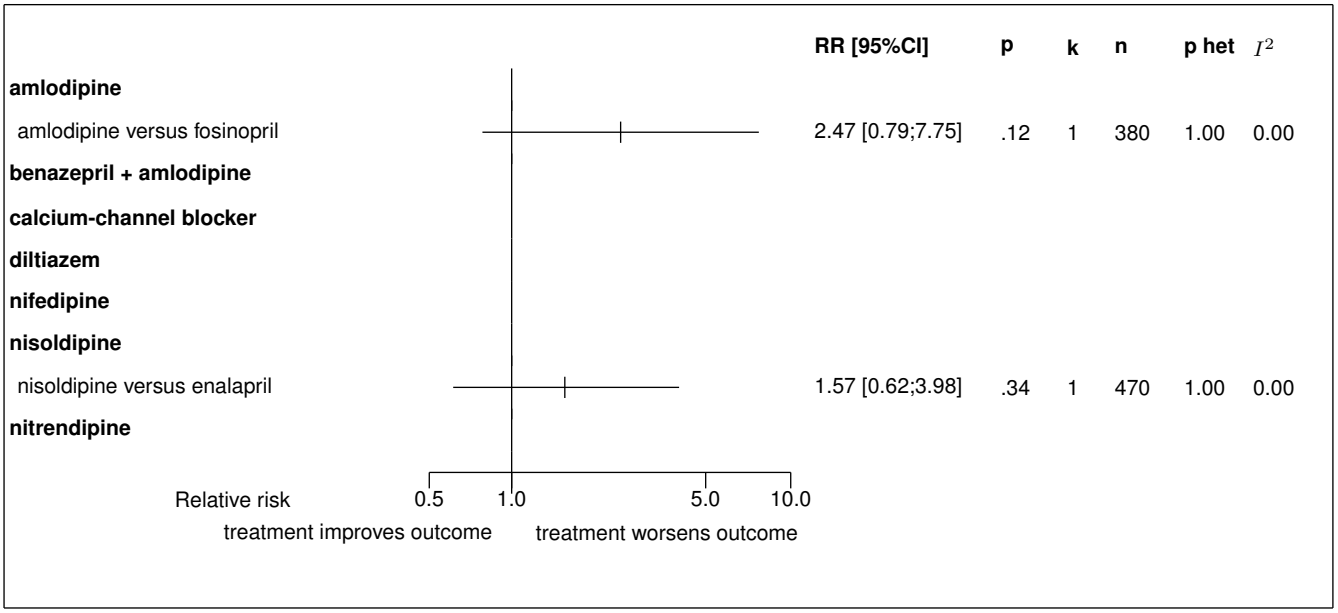
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 18.3: *Forest's plot for myocardial infarction (fatal and non fatal)*



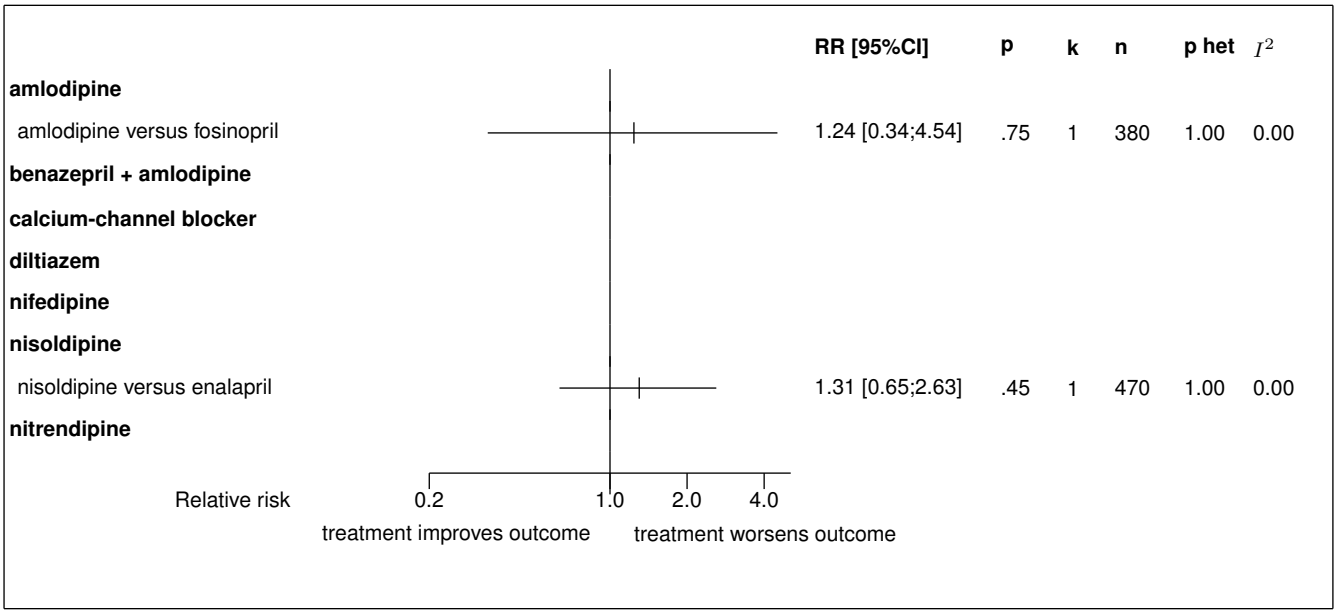
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 18.4: *Forest's plot for stroke (fatal and non fatal)*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ʳ: random effect model used

Figure 18.5: *Forest's plot for all cause death*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

19 Detailed results for amlodipine

19.1 Available trials

A total of 3 RCTs which randomized 8678 patients were identified: it compared amlodipine with placebo , it compared amlodipine with chlorthalidone and it compared amlodipine with fosinopril.
The average study size was 2892 patients (range 380 to 7162). The first study was published in 1997, and the last study was published in 2002.
A total of 2 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Stroke (fatal and non fatal) data was reported in 1 trials; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on cardiovascular events; and 1 trials reported data on all cause death.
Following tables 19.1 (page 137), 19.2 (page 137), 19.5 (page 141), and 19.3 (page 138) summarized the main characteristics of the trials including in this systematic review of randomized trials of amlodipine.

Table 19.1: *Treatment description - calcium blockers - amlodipine*

Trial	Studied treatment	Control treatment
Amlodipine versus placebo		
IDNT amlodipine (2001) [1, 2, 3, 4]	Amlodipine 10 mg daily	placebo
Amlodipine versus chlorthalidone		
ALLHAT (amlodipine vs chlor, diabetic subgroup) (2002) [5, 6, 7]	amlodipine	chlorthalidone
Amlodipine versus fosinopril		
FACET (1997) [8, 9] [a]	amlodipine (long acting) 10 mg daily	fosinopril 20 mg daily

a) if blood pressure was not controlled, the other study drug was added

Table 19.2: *Descriptions of participants - calcium blockers - amlodipine*

Trial	Patients
Amlodipine versus placebo	

continued...

Trial	Patients	
IDNT amlodipine (2001) [1, 2, 3, 4]	Hypertensive patients with nephropathy due to type 2 diabetes	
	Inclusion criteria: age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Exclusion criteria:**
Amlodipine versus chlorthalidone		
ALLHAT (amlodipine vs chlor, diabetic subgroup) (2002) [5, 6, 7]	Diabetic (subgroup) participants aged 55 years or older with hypertension	
Amlodipine versus fosinopril		
FACET (1997) [8, 9]	Hypertensive patients with NIDDM	
	Inclusion criteria: diagnosis of NIDDM and hypertension (systolic blood pre ssure of 140 mmHg or diastolic blood pressure of 90 mmHg)	**Exclusion criteria:** history of coronary heart disease or stroke, serum creatinine >1.5 mg/dl, albuminuria >40 g/min, and use of lipid-lowering drugs, aspirin, or antihypertensive agents other than beta-blockers or diuretics

Table 19.3: *Design and methodological quality of trials - calcium blockers - amlodipine*

Trial	Design	Duration	Centre	Primary end-point
Amlodipine versus placebo				
IDNT amlodipine, 2001 [1, 2, 3, 4] n=1136	Parallel groups double-blind confirmatory trial at low risk of bias	2.6 years inclusion period: mar 1996 - Feb 1999	Worldwide 210 centres	renal death
Amlodipine versus chlorthalidone				
ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002 [5, 6, 7] n=7162	Parallel groups double-blind exploratory trial	4.9 y		fatal CHD or non-fatal MI
Amlodipine versus fosinopril				

continued...

Trial	Design	Duration	Centre	Primary end-point
FACET, 1997 [8, 9] n=380	Parallel groups open confirmatory trial at risk of bias	3.5 y inclusion period: jan 1992 - dec 1992	Italy single center	not defined

Table 19.4: *Trial characteristics - calcium blockers - amlodipine(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Amlodipine versus placebo								
IDNT amlodipine, 2001 [1, 2, 3, 4]	-5.48%	-6.31%						59 y
Amlodipine versus chlorthalidone								
ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002 [5, 6, 7]	0.00%	-0.65%	-0.8	-1.3				
Amlodipine versus fosinopril								
FACET, 1997 [8, 9]	#N/A	#N/A	0	-4	0	-4		63 y

continued...

Table 19.5: *Trial characteristics - calcium blockers - amlodipine*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Amlodipine versus placebo								
IDNT amlodipine, 2001 [1, 2, 3, 4]	31%		8.2%	158/87		100%	type 2 DM + nephropathy	hypertension
Amlodipine versus chlorthalidone								
ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002 [5, 6, 7]								hypertension
Amlodipine versus fosinopril								
FACET, 1997 [8, 9]	40%		7.0 %	170/95	10.6 y	100%	type 2 DM + hypertension	diabetes patients

19.2 Meta-analysis results

The results are detailed in table 19.6 (page 142). This table is followed by the Forest's plot corresponding to each endpoint.

Amlodipine versus placebo

No data were presented in the 1 trial identified

Amlodipine versus chlorthalidone

No data were presented in the 1 trial identified

Amlodipine versus fosinopril

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of fosinopril in cardiovascular events, with a RR of 1.91 (95% CI 1.03 to 3.52, p=0.0389).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.29 (95% CI 0.58 to 2.86, p=0.5370).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 2.47 (95% CI 0.79 to 7.75, p=0.1200).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.24 (95% CI 0.34 to 4.54, p=0.7484).

Table 19.6: *Results details - calcium blockers - amlodipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
amlodipine versus placebo						
No data were presented in the trial identified						
amlodipine versus chlorthalidone						
No data were presented in the trial identified						
amlodipine versus fosinopril						
cardiovascular events	RR=1.91	[1.03;3.52]	0.0389	1.0000 (I^2=0.00)	1	380
myocardial infarction (fatal and non fatal)	RR=1.29	[0.58;2.86]	0.5370	1.0000 (I^2=0.00)	1	380
stroke (fatal and non fatal)	RR=2.47	[0.79;7.75]	0.1200	1.0000 (I^2=0.00)	1	380
all cause death	RR=1.24	[0.34;4.54]	0.7484	1.0000 (I^2=0.00)	1	380

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 19.1: *Forest's plot for cardiovascular events*

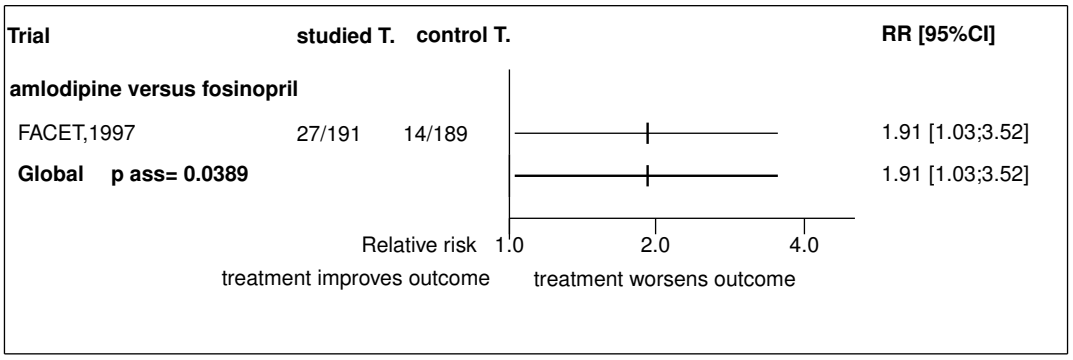


Figure 19.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

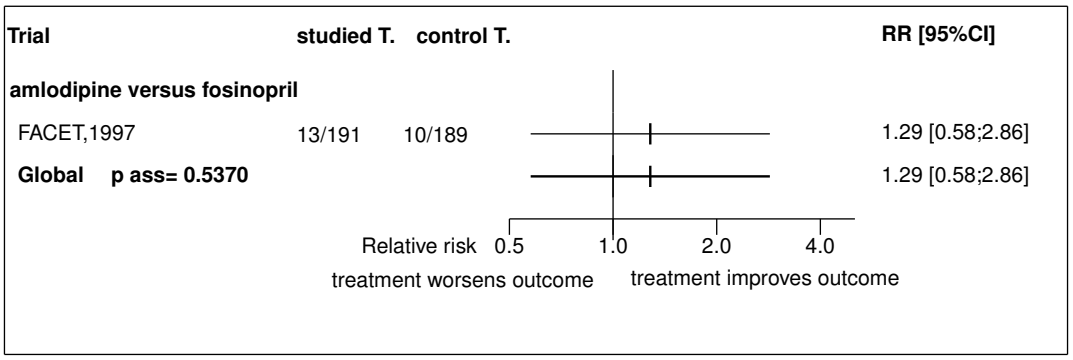


Figure 19.3: *Forest's plot for stroke (fatal and non fatal)*

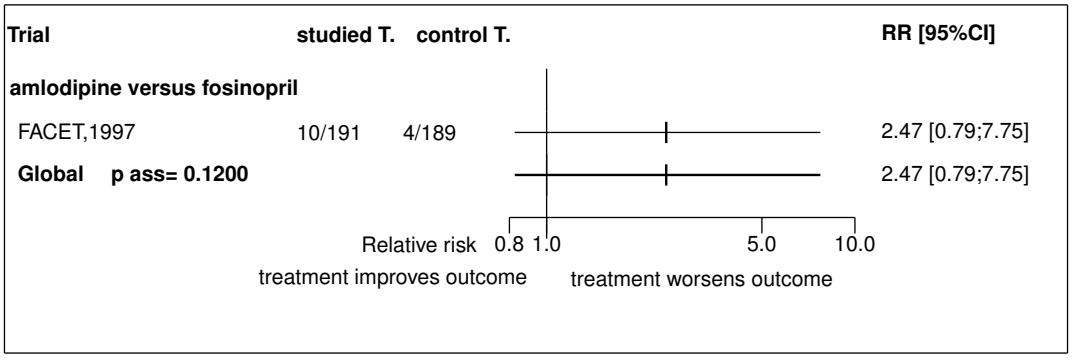
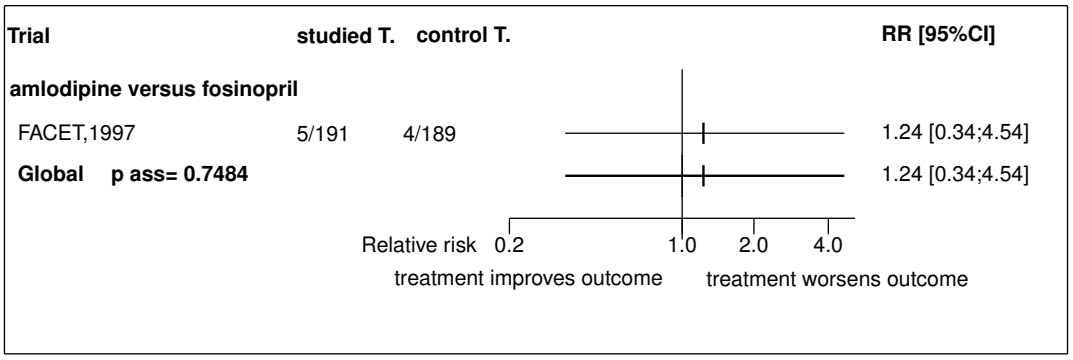


Figure 19.4: *Forest's plot for all cause death*



References

[1] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

[2] Hunsicker LG, Atkins RC, Lewis JB, Braden G, de Crespigny PJ, DeFerrari G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ. Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial. Kidney Int Suppl 2004;:S99-101. [PMID=15485429]

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[5] . Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97. [PMID=12479763]

[6] Berecek KH, Farag A, Bahtiyar G, Rothman J, McFarlane SI. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial: focus on the diabetic patient. Curr Hypertens Rep 2004;6:212-4. [PMID=15128474]

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[8] Tatti et al. . Circulation 1997; 96:I-764 (abstr). [PMID=0]

[9] Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998 Apr;21:597-603. [PMID=9571349]

19.3 Individual trial summaries

Table 19.7: *IDNT amlodipine, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1136 (567 vs. 569) **Follow-up duration:** 2.6 years **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias Worldwide, 210 centres **Inclusion period:** mar 1996 - Feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes **Inclusion criteria:** age between 30 and 70 years; documented diagnosis of type 2 diabetes mellitus, hypertension (systolic blood pressure of more than 135 mm Hg while sitting, diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol per liter) in men	**Studied treatment:** Amlodipine 10 mg daily **Control treatment:** placebo	

References

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60 [PMID=11565517]
Hunsicker LG, Atkins RC, Lewis JB, Braden G, de Crespigny PJ, DeFerrari G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ. Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial. Kidney Int Suppl 2004;:S99-101 [PMID=15485429]
POHL, MA, CORDONNIER, DJ, SPITALOWITZ, S, et al, FOR THE COLLABORATIVE STUDY GROUP. Impact of angiotensin receptor blockade with irbesartan on renal function at different systolic blood pressure (SBP) levels in type 2 diabetic nephropathy. J Am Soc Nephrol 2002 13: 650A,
Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, Esmatjes E, Gilbert RE, Hunsicker LG, de Faria JB, Mangili R, Moore J Jr, Reisin E, Ritz E, Schernthaner G, Spitalewitz S, Tindall H, Rodby RA, Lewis EJ. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005;16:3027-37 [PMID=16120823]

Table 19.8: *ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=7162 (2664 vs. 4498) **Follow-up duration:** 4.9 y **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Diabetic (subgroup) participants aged 55 years or older with hypertension	**Studied treatment:** amlodipine **Control treatment:** chlorthalidone	

References

. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97 [PMID=12479763]
Berecek KH, Farag A, Bahtiyar G, Rothman J, McFarlane SI. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial: focus on the diabetic patient. Curr Hypertens Rep 2004;6:212-4 [PMID=15128474]
Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401-9 [PMID=15983290]

Table 19.9: *FACET, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=380 (191 vs. 189) **Follow-up duration:** 3.5 y **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Italy, single center **Inclusion period:** jan 1992 - dec 1992	Hypertensive patients with NIDDM **Inclusion criteria:** diagnosis of NIDDM and hypertension (systolic blood pre ssure of 140 mmHg or diastolic blood pressure of 90 mmHg) **Exclusion criteria:** history of coronary heart disease or stroke, serum creatinine >1.5 mg/dl, albuminuria >40 g/min, and use of lipid-lowering drugs, aspirin, or antihypertensive agents other than beta-blockers or diuretics	**Studied treatment:** amlodipine (long acting) 10 mg daily **Control treatment:** fosinopril 20 mg daily **note:** if blood pressure was not controlled, the other study drug was added	Cardiovascular events RR=1.91 [1.03;3.52] (Any major vascular event) Myocardial infarction (fatal and non fatal) RR=1.29 [0.58;2.86] (Fatal or nonfatal acute myocardial infarction) Stroke (fatal and non fatal) RR=2.47 [0.79;7.75] (Fatal or nonfatal stroke) All cause death RR=1.24 [0.34;4.54] (All-cause mortality)

References

Tatti et al. . Circulation 1997; 96:I-764 (abstr) [PMID=0]

Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998 Apr;21:597-603 [PMID=9571349]

20 Detailed results for benazepril + amlodipine

20.1 Available trials

Only one trial which randomized 2842 patients was identified: it compared benazepril + amlodipine with benazepril + hydrochlorothiazide.
This trial included 2842 patients and was published in 2010.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 20.1 (page 150), 20.2 (page 150), 20.5 (page 153), and 20.3 (page 151) summarized the main characteristics of the trial including in this systematic review of randomized trials of benazepril + amlodipine.

Table 20.1: *Treatment description - calcium blockers - benazepril + amlodipine*

Trial	Studied treatment	Control treatment
Benazepril + amlodipine versus benazepril + hydrochlorothiazide		
ACCOMPLISH (diabetic subgroup) (2010) [1, 2] [a]	benazepril, combined with amlodipine starting doses of benazepril 20 mg/day plus amlodipine 5 mg/day. amlodipine dose could be increased to 10 mg/day if required to achieve a target blood pressure goal of <140/90 mm Hg. For the diabetic patients a target blood pressure of <130/80 mmHg was recommended, but not mandated	benazepril, combined with hydrochlorothiazide starting doses of benazepril 20 mg/day plus hydrochlorothiazide 12.5 mg/day. hydrochlorothiazide dose could be increased to 25 mg/day if required to achieve a target blood pressure goal of <140/90 mm Hg. For the diabetic patients a target blood pressure of <130/80 mmHg was recommended, but not mandated

a) if needed investigators couldadd other antihypertensive agents as beta-blockers, clonidine,alpha-blockers, and spironolactone

Table 20.2: *Descriptions of participants - calcium blockers - benazepril + amlodipine*

Trial	Patients	
Benazepril + amlodipine versus benazepril + hydrochlorothiazide		
ACCOMPLISH (diabetic subgroup) (2010) [1, 2] [a]	Patients with diabetes (subgroup) and hypertension at high risk of cardiovascular and related events	
	Inclusion criteria: >=60 years of age; systolic BP >=160 mm Hg or currently on antihypertensive therapy; evidence of cardiovascular or renal disease or target organ damage; patients aged 55 to 59 years are eligible if they have evidence of two or more of the cardiovascular diseases or target organ damage	**Exclusion criteria:** current evidencefor angina pectoris; history ofsymptomatic heart failure or evidence of left ventricularejection fraction <40%; myocardial infarction, otheracute coronary syndromes, or coronary revascularizationswithin 1 month; stroke or other ischemic cerebrovascular episodes within 3 months; hypertension that is excessivelysevere, known to be refractory to treatment, orknown to have a secondary cause; concomitant illness, physical impairment, or mentalcondition that could interfere with the effective conductof the study

continued...

Trial	Patients

a) Of the all 11505 patients included in the trial, 6946 had diabetes (and 2842 high risk diabetes)

Table 20.3: *Design and methodological quality of trials - calcium blockers - benazepril + amlodipine*

Trial	Design	Duration	Centre	Primary endpoint
Benazepril + amlodipine versus benazepril + hydrochlorothiazide				
ACCOMPLISH (diabetic subgroup), 2010 [1, 2] n=2842	Parallel groups double-blind exploratory trial	36 months inclusion period: oct 2003 - may 2005	US, Norway, Denmark, Finland 548 centres	cardiovascular morbidity and mortality

Table 20.4: *Trial characteristics - calcium blockers - benazepril + amlodipine(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Benazepril + amlodipine versus benazepril + hydrochlorothiazide								
ACCOMPLISH (diabetic subgroup), 2010 [1, 2]	-2.86%	-5.76%	-1.1	-1.2				67.5 y

continued...

Table 20.5: *Trial characteristics - calcium blockers - benazepril + amlodipine*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Benazepril + amlodipine versus benazepril + hydrochlorothiazide								
ACCOMPLISH (diabetic subgroup), 2010 [1, 2]	43%		NA	145.2/79.3 mmHg		100%		hypertension

20.2 Meta-analysis results

The results are detailed in table 20.6 (page 154). This table is followed by the Forest's plot corresponding to each endpoint.

Benazepril + amlodipine versus benazepril + hydrochlorothiazide

No data were presented in the 1 trial identified

Table 20.6: *Results details - calcium blockers - benazepril + amlodipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
benazepril + amlodipine versus benazepril + hydrochlorothiazide						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, Velazquez EJ, Dahlöf B, Kelly RY, Hua TA, Hester A, Pitt B. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56:77-85. [PMID=20620720]

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20.3 Individual trial summaries

Table 20.7: *ACCOMPLISH (diabetic subgroup), 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2842 (1432 vs. 1410) **Follow-up duration:** 36 months **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial US, Norway, Denmark, Finland, 548 centres **Inclusion period:** oct 2003 - may 2005	Patients with diabetes (subgroup) and hypertension at high risk of cardiovascular and related events **note:** Of the all 11505 patients included in the trial, 6946 had diabetes (and 2842 high risk diabetes) **Inclusion criteria:** >=60 years of age; systolic BP >=160 mm Hg or currently on antihypertensive therapy; evidence of cardiovascular or renal disease or target organ damage; patients aged 55 to 59 years are eligible if they have evidence of two or more of the cardiovascular diseases or target organ damage **Exclusion criteria:** current evidencefor angina pectoris; history ofsymptomatic heart failure or evidence of left ventricularejection fraction <40%; myocardial infarction, otheracute coronary syndromes, or coronary revascularizationswithin 1 month; stroke or other ischemic cerebrovascular episodes within 3 months; hypertension that is excessivelysevere, known to be refractory to treatment, orknown to have a secondary cause; concomitant illness, physical impairment, or mentalcondition that could interfere with the effective conductof the study	**Studied treatment:** benazepril, combined with amlodipine starting doses of benazepril 20 mg/day plus amlodipine 5 mg/day. amlodipine dose could be increased to 10 mg/day if required to achieve a target blood pressure goal of <140/90 mm Hg. For the diabetic patients a target blood pressure of <130/80 mmHg was recommended, but not mandated **Control treatment:** benazepril, combined with hydrochlorothiazide starting doses of benazepril 20 mg/day plus hydrochlorothiazide 12.5 mg/day. hydrochlorothiazide dose could be increased to 25 mg/day if required to achieve a target blood pressure goal of <140/90 mm Hg. For the diabetic patients a target blood pressure of <130/80 mmHg was recommended, but not mandated **note:** if needed investigators couldadd other antihypertensive agents as beta-blockers, clonidine,alpha-blockers, and spironolactone	

continued...

trial details	Patients	Treatments	Outcomes

References

Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, Velazquez EJ, Dahlöf B, Kelly RY, Hua TA, Hester A, Pitt B. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56:77-85 [PMID=20620720]

Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417-28 [PMID=19052124]

21 Detailed results for calcium-channel blocker

21.1 Available trials

Only one trial which randomized 484 patients was identified: it compared calcium-channel blocker with diuretic or beta-blocker.
This trial included 484 patients and was published in 2000.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 21.1 (page 158), 21.2 (page 158), 21.5 (page 161), and 21.3 (page 159) summarized the main characteristics of the trial including in this systematic review of randomized trials of calcium-channel blocker.

Table 21.1: *Treatment description - calcium blockers - calcium-channel blocker*

Trial	Studied treatment	Control treatment
Calcium-channel blocker versus diuretic or beta-blocker		
STOP-2 CCB (diabetic subgroup) (2000) [1, 2]	Calcium-channel blocker felodipine 25 mg or isradipine 25 mgdaily. if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later patients were given anyof the b-blockers in the doses listed	diuretic or beta-blocker atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, orfixed-ratio hydrochlorothiazide 25 mg plus amiloride 25 mgdaily. Patients on beta-blockers were givenhydrochlorothiazide 25 mg plus amiloride 25 mg as additionaltreatment if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later. Patients who had started on diuretic treatment were given anyof the b-blockers in the doses listed

Table 21.2: *Descriptions of participants - calcium blockers - calcium-channel blocker*

Trial	Patients
Calcium-channel blocker versus diuretic or beta-blocker	
STOP-2 CCB (diabetic subgroup) (2000) [1, 2] [a]	Diabetic (subgroup) elderly patients aged 70-84 years **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included **Exclusion criteria:**

a) Of all 6614 patients included in the trial, 719 had diabetes

Table 21.3: *Design and methodological quality of trials - calcium blockers - calcium-channel blocker*

Trial	Design	Duration	Centre	Primary end-point
Calcium-channel blocker versus diuretic or beta-blocker				
STOP-2 CCB (diabetic subgroup), 2000 [1, 2] n=484	Parallel groups open with blind assessment exploratory trial	5.03y inclusion period: sep 1992 - dec 1994	Sweden 312 centres	renal death

Table 21.4: *Trial characteristics - calcium blockers - calcium-channel blocker(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Calcium-channel blocker versus diuretic or beta-blocker								
STOP-2 CCB (diabetic subgroup), 2000 [1, 2]	#N/A	#N/A						75.8 y

continued...

Table 21.5: *Trial characteristics - calcium blockers - calcium-channel blocker*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Calcium-channel blocker versus diuretic or beta-blocker								
STOP-2 CCB (diabetic subgroup), 2000 [1, 2]	60%		7.6%	195/96 mmHg		100%		hypertension

21.2 Meta-analysis results

The results are detailed in table 21.6 (page 162). This table is followed by the Forest's plot corresponding to each endpoint.

Calcium-channel blocker versus diuretic or beta-blocker

No data were presented in the 1 trial identified

Table 21.6: *Results details - calcium blockers - calcium-channel blocker*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
calcium-channel blocker versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000;18:1671-5. [PMID=11081782]

[2] Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6. [PMID=10577635]

21.3 Individual trial summaries

Table 21.7: *STOP-2 CCB (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=484 (231 vs. 253) **Follow-up duration:** 5.03y **Study design:** Randomized controlled trial Parallel groups Open with blind assessment Exploratory trial Sweden, 312 centres **Inclusion period:** sep 1992 - dec 1994	Diabetic (subgroup) elderly patients aged 70-84 years **note:** Of all 6614 patients included in the trial, 719 had diabetes **Inclusion criteria:** hypertension (blood pressure >=180 mm Hg systolic, >=105 mmHg diastolic, or both); aged 7084 years; isolated systolic hypertension could be included	**Studied treatment:** Calcium-channel blocker felodipine 25 mg or isradipine 25 mgdaily. if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later patients were given anyof the b-blockers in the doses listed **Control treatment:** diuretic or beta-blocker atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, orfixed-ratio hydrochlorothiazide 25 mg plus amiloride 25 mgdaily. Patients on beta-blockers were givenhydrochlorothiazide 25 mg plus amiloride 25 mg as additionaltreatment if the target blood pressure (<160/95 mm Hg) had notbeen reached at the 2-month visit or later. Patients who had started on diuretic treatment were given anyof the b-blockers in the doses listed	

References

Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000;18:1671-5 [PMID=11081782]
Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6 [PMID=10577635]

22 Detailed results for diltiazem

22.1 Available trials

Only one trial which randomized 727 patients was identified: it compared diltiazem with diuretic or beta-blocker.
This trial included 727 patients and was published in 2000.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 22.1 (page 165), 22.2 (page 165), 22.5 (page 168), and 22.3 (page 165) summarized the main characteristics of the trial including in this systematic review of randomized trials of diltiazem.

Table 22.1: *Treatment description - calcium blockers - diltiazem*

Trial	Studied treatment	Control treatment
Diltiazem versus diuretic or beta-blocker		
NORDIL (diabetic subgroup) (2000) [1, 2, 3, 4]	Diltiazem 180360 mg diltiazem daily at step one In step two, an angiotensin-converting-enzyme (ACE) inhibitor was added, and in step three, a diuretic or alpha-blocker was added to the ACE inhibitor. Any other antihypertensive compound could be added as step four.	thiazide diuretic or a beta-blocker at step one in step two, the two were combined. In step three an ACE inhibitor or alpha-blocker was added. In step four, any other antihypertensive compound could be added except a calcium antagonist

Table 22.2: *Descriptions of participants - calcium blockers - diltiazem*

Trial	Patients
Diltiazem versus diuretic or beta-blocker	
NORDIL (diabetic subgroup) (2000) [1, 2, 3, 4]	Diabetic patients (subgroup), aged 50-74 years who had diastolic blood pressure of 100 mm Hg or more

Table 22.3: *Design and methodological quality of trials - calcium blockers - diltiazem*

Trial	Design	Duration	Centre	Primary end-point
Diltiazem versus diuretic or beta-blocker				

continued...

Trial	Design	Duration	Centre	Primary endpoint
NORDIL (diabetic subgroup), 2000 [1, 2, 3, 4] n=727	Parallel groups open exploratory trial	4.5 y inclusion period: oct 1992 - oct 1999	Norway, Sweden 1032 centres	CV events

Table 22.4: *Trial characteristics - calcium blockers - diltiazem(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Diltiazem versus diuretic or beta-blocker								
NORDIL (diabetic subgroup), 2000 [1, 2, 3, 4]	#N/A	#N/A	NA	NA				

continued...

Table 22.5: *Trial characteristics - calcium blockers - diltiazem*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Diltiazem versus diuretic or beta-blocker								
NORDIL (diabetic subgroup), 2000 [1, 2, 3, 4]								hypertension

22.2 Meta-analysis results

The results are detailed in table 22.6 (page 169). This table is followed by the Forest's plot corresponding to each endpoint.

Diltiazem versus diuretic or beta-blocker

No data were presented in the 1 trial identified

Table 22.6: *Results details - calcium blockers - diltiazem*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
diltiazem versus diuretic or beta-blocker						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlöf B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359-65. [PMID=10972367]

[2] Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J, Lindholm LH, De Faire U, Dahlöf B, Karlberg BE. Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) Study. J Hypertens 2002 Jun;20:1231-7. [PMID=12023696]

[3] Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L. Comparison of home and office blood pressure in treated hypertensives in the Nordic Diltiazem (NORDIL) Study. Blood Press 2002;11:371-6. [PMID=12523681]

[4] Thijs L, Staessen JA, Wang J, Fagard R. Subgroup analysis of the NORDIL trial. J Hypertens 2002;20:1085-7. [PMID=12023676]

22.3 Individual trial summaries

Table 22.7: *NORDIL (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=727 (351 vs. 376) **Follow-up duration:** 4.5 y **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Norway, Sweden, 1032 centres **Inclusion period:** oct 1992 - oct 1999	Diabetic patients (subgroup), aged 50-74 years who had diastolic blood pressure of 100 mm Hg or more	**Studied treatment:** Diltiazem 180360 mg diltiazem daily at step one In step two, an angiotensin-converting-enzyme (ACE) inhibitor was added, and in step three, a diuretic or alpha-blocker was added to the ACE inhibitor. Any other antihypertensive compound could be added as step four. **Control treatment:** thiazide diuretic or a beta-blocker at step one in step two, the two were combined. In step three an ACE inhibitor or alpha-blocker was added. In step four, any other antihypertensive compound could be added except a calcium antagonist	

References

Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlöf B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359-65 [PMID=10972367]
Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J, Lindholm LH, De Faire U, Dahlöf B, Karlberg BE. Influence of age, sex and blood pressure on the principal end-points of the Nordic Diltiazem (NORDIL) Study. J Hypertens 2002 Jun;20:1231-7 [PMID=12023696]
Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L. Comparison of home and office blood pressure in treated hypertensives in the Nordic Diltiazem (NORDIL) Study. Blood Press 2002;11:371-6 [PMID=12523681]
Thijs L, Staessen JA, Wang J, Fagard R. Subgroup analysis of the NORDIL trial. J Hypertens 2002;20:1085-7 [PMID=12023676]

23 Detailed results for nifedipine

23.1 Available trials

Only one trial which randomized 1302 patients was identified: it compared nifedipine with coamilozide.
This trial included 1302 patients and was published in 2000.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 23.1 (page 172), 23.2 (page 172), 23.5 (page 175), and 23.3 (page 172) summarized the main characteristics of the trial including in this systematic review of randomized trials of nifedipine.

Table 23.1: *Treatment description - calcium blockers - nifedipine*

Trial	Studied treatment	Control treatment
Nifedipine versus coamilozide		
INSIGHT (diabetic subgroup) (2000) [1, 2]	Nifedipine GITS 30 mg daily	co-amilozide hydrochlorothiazide 25 mg plus amiloride 2.5 mg

Table 23.2: *Descriptions of participants - calcium blockers - nifedipine*

Trial	Patients
Nifedipine versus coamilozide	
INSIGHT (diabetic subgroup) (2000) [1, 2]	Diabetic (subgroup) patients aged 55-80 years with hypertension (blood pressure >= 150/95 mm Hg, or >= 160 mmHg systolic)

Table 23.3: *Design and methodological quality of trials - calcium blockers - nifedipine*

Trial	Design	Duration	Centre	Primary endpoint
Nifedipine versus coamilozide				

continued...

Trial	Design	Duration	Centre	Primary end-point
INSIGHT (diabetic subgroup), 2000 [1, 2] n=1302	Parallel groups double-blind exploratory trial	4 y	Europe, Israel	CV events

Table 23.4: *Trial characteristics - calcium blockers - nifedipine(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Nifedipine versus coamilozide								
INSIGHT (diabetic subgroup), 2000 [1, 2]	#N/A	#N/A	-2	-2				NA

continued...

Table 23.5: *Trial characteristics - calcium blockers - nifedipine*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Nifedipine versus coamilozide								
INSIGHT (diabetic subgroup), 2000 [1, 2]	52.1%							hypertension

23.2 Meta-analysis results

The results are detailed in table 23.6 (page 176). This table is followed by the Forest's plot corresponding to each endpoint.

Nifedipine versus coamilozide

No data were presented in the 1 trial identified

Table 23.6: *Results details - calcium blockers - nifedipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nifedipine versus coamilozide						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366-72. [PMID=10972368]

[2] Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G, Ruilope LM. Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003;41:431-6. [PMID=12623939]

23.3 Individual trial summaries

Table 23.7: *INSIGHT (diabetic subgroup), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1302 (649 vs. 653) **Follow-up duration:** 4 y **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial Europe, Israel	Diabetic (subgroup) patients aged 55-80 years with hypertension (blood pressure >= 150/95 mm Hg, or >= 160 mmHg systolic)	**Studied treatment:** Nifedipine GITS 30 mg daily **Control treatment:** co-amilozide hydrochlorothiazide 25 mg plus amiloride 2.5 mg	

References

Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366-72 [PMID=10972368]
Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G, Ruilope LM. Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003;41:431-6 [PMID=12623939]

24 Detailed results for nisoldipine

24.1 Available trials

Only one trial which randomized 470 patients was identified: it compared nisoldipine with enalapril.
This trial included 470 patients and was published in 1998.
This trial was double blind in design.
It was reported in English language.
Stroke (fatal and non fatal) data was reported in 1 trials; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on cardiovascular death; 1 trials reported data on cardiovascular events; and 1 trials reported data on all cause death.
Following tables 24.1 (page 179), 24.2 (page 179), 24.5 (page 182), and 24.3 (page 180) summarized the main characteristics of the trial including in this systematic review of randomized trials of nisoldipine.

Table 24.1: *Treatment description - calcium blockers - nisoldipine*

Trial	Studied treatment	Control treatment
Nisoldipine versus enalapril		
ABCD hypertension (1998) [1, 2]	nisoldipine (long acting) 10 mg per day, withincreases to 20, 40, and 60 mg per day **Concomittant treatment:** -	enalapril 5 mg perday, with increases to 10, 20, and 40 mg per day

Table 24.2: *Descriptions of participants - calcium blockers - nisoldipine*

Trial	Patients	
Nisoldipine versus enalapril		
ABCD hypertension (1998) [1, 2]	Patients with non-insulin-dependent diabetes and hypertension	
	Inclusion criteria: hypertensive patients with diabetes (NIDDM)ages: 40 to 74y; NIDDM according criteria of the WHO report of 1985; DBP >80 mmHg; no hypertensive drug at the time of randomization	**Exclusion criteria:** allergy to dihydropyridine calcium antagonist or ACE inhibitors; stroke or MI within the previous 6mo; CABG within 3mo; unstable angina pectoris within 6mo; heart failure stade III or IV, etc.

Table 24.3: *Design and methodological quality of trials - calcium blockers - nisoldipine*

Trial	Design	Duration	Centre	Primary endpoint
Nisoldipine versus enalapril				
ABCD hypertension, 1998 [1, 2] n=470	Factorial plan Double blind exploratory trial	5 y	USA single center	24-hour creatinine clearance

Table 24.4: *Trial characteristics - calcium blockers - nisoldipine(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Nisoldipine versus enalapril								
ABCD hypertension, 1998 [1, 2]	#N/A	#N/A	0 (graphic)	0 (graphic)				57 y

continued...

Table 24.5: *Trial characteristics - calcium blockers - nisoldipine*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Nisoldipine versus enalapril								
ABCD hypertension, 1998 [1, 2]	33%	12 y	11.6%	155/98	8.5 y	100%		hypertension

24.2 Meta-analysis results

The results are detailed in table 24.6 (page 183). This table is followed by the Forest's plot corresponding to each endpoint.

Nisoldipine versus enalapril

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of enalapril in cardiovascular events, with a RR of 5.00 (95% CI 1.95 to 12.84, p=0.0000).
The single study eligible for this comparison provided data on **cardiovascular death**. No statistically significant difference between the groups was found in cardiovascular death, with a RR of 2.00 (95% CI 0.69 to 5.76, p=0.1992).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of nisoldipine in myocardial infarction (fatal and non fatal), with a RR of 5.00 (95% CI 1.95 to 12.84, p=0.0000).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 1.57 (95% CI 0.62 to 3.98, p=0.3409).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.31 (95% CI 0.65 to 2.63, p=0.4520).

Table 24.6: *Results details - calcium blockers - nisoldipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nisoldipine versus enalapril						
cardiovascular events	RR=5.00	[1.95;12.84]	0.0000	1.0000 (I^2=0.00)	1	470
cardiovascular death	RR=2.00	[0.69;5.76]	0.1992	1.0000 (I^2=1.00)	1	470
myocardial infarction (fatal and non fatal)	RR=5.00	[1.95;12.84]	0.0000	1.0000 (I^2=0.00)	1	470
stroke (fatal and non fatal)	RR=1.57	[0.62;3.98]	0.3409	1.0000 (I^2=0.00)	1	470
all cause death	RR=1.31	[0.65;2.63]	0.4520	1.0000 (I^2=0.00)	1	470

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 24.1: *Forest's plot for cardiovascular events*

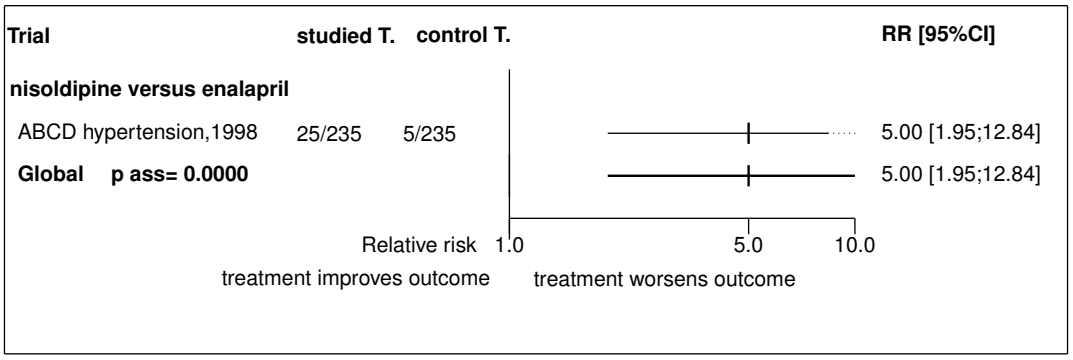


Figure 24.2: *Forest's plot for cardiovascular death*

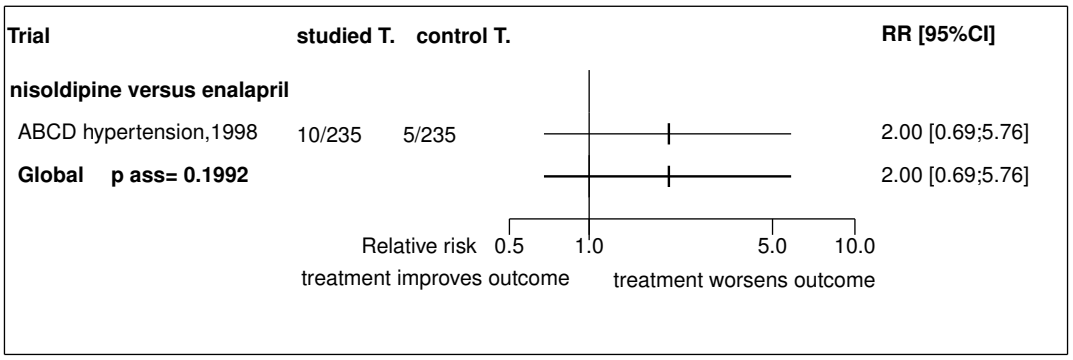


Figure 24.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

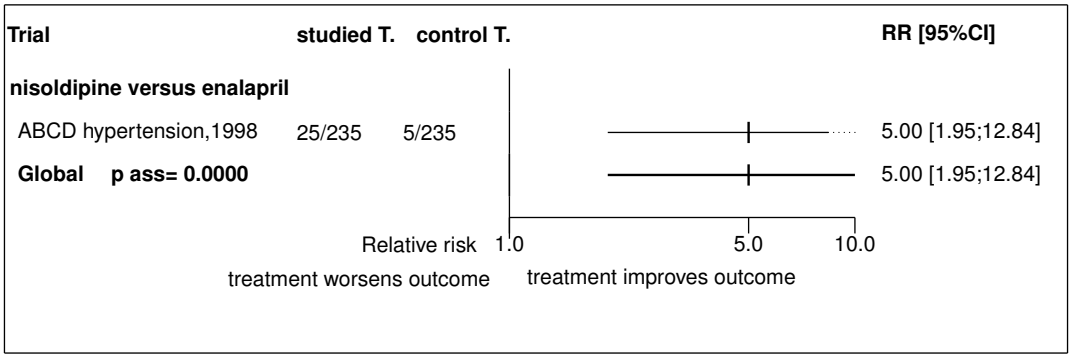


Figure 24.4: *Forest's plot for stroke (fatal and non fatal)*

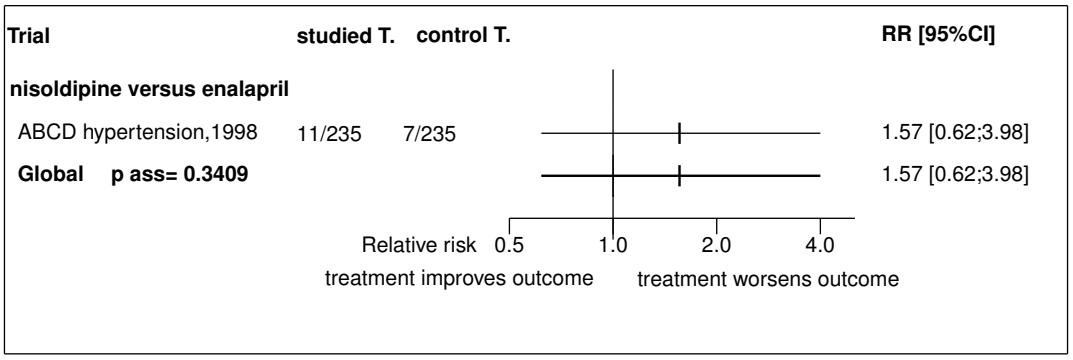
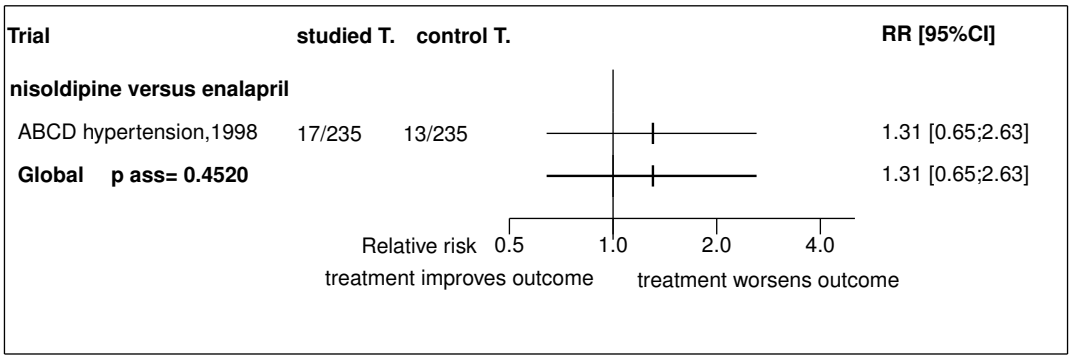


Figure 24.5: *Forest's plot for all cause death*



References

[1] Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52. [PMID=9486993]

[2] Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97. [PMID=11849464]

24.3 Individual trial summaries

Table 24.7: *ABCD hypertension, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=470 (235 vs. 235) **Follow-up duration:** 5 y **Study design:** Randomized controlled trial Factorial plan Double blind Exploratory trial USA, single center	Patients with non-insulin-dependent diabetes and hypertension **Inclusion criteria:** hypertensive patients with diabetes (NIDDM)ages: 40 to 74y; NIDDM according criteria of the WHO report of 1985; DBP >80 mmHg; no hypertensive drug at the time of randomization **Exclusion criteria:** allergy to dihydropyridine calcium antagonist or ACE inhibitors; stroke or MI within the previous 6mo; CABG within 3mo; unstable angina pectoris within 6mo; heart failure stade III or IV, etc.	**Studied treatment:** nisoldipine (long acting) 10 mg per day, withincreases to 20, 40, and 60 mg per day **Control treatment:** enalapril 5 mg perday, with increases to 10, 20, and 40 mg per day **Concomittant treat.:**-	Cardiovascular events RR=5.00 [1.95;12.84] Cardiovascular death RR=2.00 [0.69;5.76] Myocardial infarction (fatal and non fatal) RR=5.00 [1.95;12.84] Stroke (fatal and non fatal) RR=1.57 [0.62;3.98] All cause death RR=1.31 [0.65;2.63]

References

Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52 [PMID=9486993]

Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97 [PMID=11849464]

25 Detailed results for nitrendipine

25.1 Available trials

Only one trial which randomized 492 patients was identified: it compared nitrendipine with placebo.
This trial included 492 patients and was published in 1999.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 25.1 (page 188), 25.2 (page 188), 25.5 (page 191), and 25.3 (page 189) summarized the main characteristics of the trial including in this systematic review of randomized trials of nitrendipine.

Table 25.1: *Treatment description - calcium blockers - nitrendipine*

Trial	Studied treatment	Control treatment
Nitrendipine versus placebo		
Syst-Eur (diabetic subgroup) (1999) [1]	Calcium-channel blocker nitrendipine (10 to 40 mg per day) with the possible addition or substitution of enalapril (5 to 20 mg per day) or hydrochlorothiazide (12.5 to 25 mg per day) or both, titrated to reduce the systolic blood pressure by at least 20 mm Hg and to less than 150 mm Hg	placebo

Table 25.2: *Descriptions of participants - calcium blockers - nitrendipine*

Trial	Patients	
Nitrendipine versus placebo		
Syst-Eur (diabetic subgroup) (1999) [1] [a]	Subgroup of diabetic patients, age, >=60 years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg	
	Inclusion criteria: 60 years of age orolder; sitting systolic blood pressure ranging from 160 to 219 mm Hg systolic and diastolic blood pressure below 95 mm Hg with standing systolic pressure of 140 mm Hg orhigher	**Exclusion criteria:**

a) of all 4695 patients included in the study, 492 had diabetes

Table 25.3: *Design and methodological quality of trials - calcium blockers - nitrendipine*

Trial	Design	Duration	Centre	Primary endpoint
Nitrendipine versus placebo				
Syst-Eur (diabetic subgroup), 1999 [1] n=492	Parallel groups double blind exploratory trial	2 years		persisting neurologic deficit

Table 25.4: *Trial characteristics - calcium blockers - nitrendipine(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Nitrendipine versus placebo								
Syst-Eur (diabetic subgroup), 1999 [1]	#N/A	#N/A	-3.9	-8.6				NA

continued...

Table 25.5: *Trial characteristics - calcium blockers - nitrendipine*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Nitrendipine versus placebo								
Syst-Eur (diabetic subgroup), 1999 [1]	NA			175.3/84.5				hypertension

25.2 Meta-analysis results

The results are detailed in table 25.6 (page 192). This table is followed by the Forest's plot corresponding to each endpoint.

Nitrendipine versus placebo

No data were presented in the 1 trial identified

Table 25.6: *Results details - calcium blockers - nitrendipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nitrendipine versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Tuomilehto J, Rastenyte D, Birkenhger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999;340:677-84. [PMID=10053176]

25.3 Individual trial summaries

Table 25.7: *Syst-Eur (diabetic subgroup), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=492 (252 vs. 240) **Follow-up duration:** 2 years **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Subgroup of diabetic patients, age, >=60 years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg **note:** of all 4695 patients included in the study, 492 had diabetes **Inclusion criteria:** 60 years of age orolder; sitting systolic blood pressure ranging from 160 to 219 mm Hg systolic and diastolic blood pressure below 95 mm Hg with standing systolic pressure of 140 mm Hg orhigher	**Studied treatment:** Calcium-channel blocker nitrendipine (10 to 40 mg per day) with the possible addition or substitution of enalapril (5 to 20 mg per day) or hydrochlorothiazide (12.5 to 25 mg per day) or both, titrated to reduce the systolic blood pressure by at least 20 mm Hg and to less than 150 mm Hg **Control treatment:** placebo	

Reference

Tuomilehto J, Rastenyte D, Birkenhger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. N Engl J Med 1999;340:677-84 [PMID=10053176]

26 Global meta-analysis: all calcium blockers

26.1 Global meta-analysis: all calcium blockers versus benazepril + hydrochlorothiazide

Table 26.1: *All calcium blockersversus benazepril + hydrochlorothiazide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.2 Global meta-analysis: all calcium blockers versus chlorthalidone

Table 26.2: *All calcium blockersversus chlorthalidone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.3 Global meta-analysis: all calcium blockers versus coamilozide

Table 26.3: *All calcium blockersversus coamilozide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.4 Global meta-analysis: all calcium blockers versus diuretic or beta-blocker

Table 26.4: *All calcium blockersversus diuretic or beta-blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.5 Global meta-analysis: all calcium blockers versus enalapril

Table 26.5: *All calcium blockersversus enalapril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=5.00	1.95;12.84	0.0000	1.0000 (0.00)	1	470
cardiovascular death	RR=2.00	0.69;5.76	0.1992	1.0000 (1.00)	1	470
myocardial infarction (fatal and non fatal)	RR=5.00	1.95;12.84	0.0000	1.0000 (0.00)	1	470
stroke (fatal and non fatal)	RR=1.57	0.62;3.98	0.3409	1.0000 (0.00)	1	470
all cause death	RR=1.31	0.65;2.63	0.4520	1.0000 (0.00)	1	470

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.6 Global meta-analysis: all calcium blockers versus fosinopril

Table 26.6: *All calcium blockersversus fosinopril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.91	1.03;3.52	0.0389	1.0000 (0.00)	1	380
myocardial infarction (fatal and non fatal)	RR=1.29	0.58;2.86	0.5370	1.0000 (0.00)	1	380
stroke (fatal and non fatal)	RR=2.47	0.79;7.75	0.1200	1.0000 (0.00)	1	380
all cause death	RR=1.24	0.34;4.54	0.7484	1.0000 (0.00)	1	380

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

26.7 Global meta-analysis: all calcium blockers versus placebo

Table 26.7: *All calcium blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

27 Ongoing studies of calcium blockers

No ongoing trial was identified.

28 Excluded studies for calcium blockers

No trial was excluded.

References

Part IV

Direct renin inhibitor

29 Overview of direct renin inhibitor

29.1 Included trials

Only one trial which randomized 599 patients was identified. In all, 1 randomized comparison concerned aliskiren.
The detailed descriptions of trials and meta-analysis results is given in section 30 (page 204) for aliskiren.

This trial included 599 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
The table 29.1 (page 202) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

29.2 Summary of meta-analysis results

The meta-analysis of the available trials about direct renin inhibitor provide the results listed in tables 29.2 to 29.2 (page 203) and in the following graphs.

29.2.1 Aliskiren

Data were insufficient to compare **aliskiren** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 29.1: *Main study characteristics - direct renin inhibitor*

Trial	Patients	Treatments	Trial design and method
Aliskiren			
Aliskiren versus placebo			
AVOID, 2008 [1] n = 301 vs. 298	patients with hypertension and type 2 diabetes with nephropathy	aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months **versus** placebo	double blind parallel groups Primary endpoint: ratio of albumin to creatinine 150 centres, 15 countries

Table 29.2: *Summary of all results for aliskiren*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
aliskiren versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

30 Details

30.1 Available trials

Only one trial which randomized 599 patients was identified: it compared aliskiren with placebo.
This trial included 599 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 30.1 (page 204), 30.2 (page 204), 30.4 (page 206), and 30.3 (page 205) summarized the main characteristics of the trial including in this systematic review of randomized trials of aliskiren.

Table 30.1: *Treatment description - direct renin inhibitor - aliskiren*

Trial	Studied treatment	Control treatment
Aliskiren versus placebo		
AVOID (2008) [1]	aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months	placebo
	Concomittant treatment: maximal recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy	

Table 30.2: *Descriptions of participants - direct renin inhibitor - aliskiren*

Trial	Patients	
Aliskiren versus placebo		
AVOID (2008) [1]	Patients with hypertension and type 2 diabetes with nephropathy	
	Inclusion criteria: hypertension;18 to 85 years of age;type 2 diabetesand nephropathy defined by an early-morningurinary albumin-to-creatinine ratio of >300 mg/g or >200 mg/g in case oftherapy targeted at blockade of the reninangiotensinaldosterone system	**Exclusion criteria:** nondiabetic kidney disease; urinary albumin-to-creatinine ratio of moret han 3500 mg per gram; estimated glomerularfiltration rate of less than 30 ml per minuteper 1.73 m2; chronic urinary-tract infection; serum potassium level greater than 5.1 mmol per liter; severe hypertension, or major cardiovasculardisease within the previous 6 months

Table 30.3: *Design and methodological quality of trials - direct renin inhibitor - aliskiren*

Trial	Design	Duration	Centre	Primary end-point
Aliskiren versus placebo				
AVOID, 2008 [1] n=599	Parallel groups double blind exploratory trial	6 months	15 countries 150 centres	ratio of albumin to creatinine

Table 30.4: *Trial characteristics - direct renin inhibitor - aliskiren*

Trial
Aliskiren versus placebo
AVOID, 2008 [1]

30.2 Meta-analysis results

The results are detailed in table 30.5 (page 207). This table is followed by the Forest's plot corresponding to each endpoint.

Aliskiren versus placebo

No data were presented in the 1 trial identified

Table 30.5: *Results details - direct renin inhibitor - aliskiren*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
aliskiren versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433-46. [PMID=18525041]

30.3 Individual trial summaries

Table 30.6: *AVOID, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=599 (301 vs. 298) **Follow-up duration:** 6 months **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial 15 countries, 150 centres	Patients with hypertension and type 2 diabetes with nephropathy **Inclusion criteria:** hypertension;18 to 85 years of age;type 2 diabetesand nephropathy defined by an early-morningurinary albumin-to-creatinine ratio of >300 mg/g or >200 mg/g in case oftherapy targeted at blockade of the reninangiotensinaldosterone system **Exclusion criteria:** nondiabetic kidney disease; urinary albumin-to-creatinine ratio of moret han 3500 mg per gram; estimated glomerularfiltration rate of less than 30 ml per minuteper 1.73 m2; chronic urinary-tract infection; serum potassium level greater than 5.1 mmol per liter; severe hypertension, or major cardiovasculardisease within the previous 6 months	**Studied treatment:** aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months **Control treatment:** placebo **Concomittant treat.:**maximal recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy	

Reference

Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433-46 [PMID=18525041]

31 Global meta-analysis: all direct renin inhibitor

31.1 Global meta-analysis: all direct renin inhibitor versus placebo

Table 31.1: *All direct renin inhibitorversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

32 Ongoing studies of direct renin inhibitor

No ongoing trial was identified.

33 Excluded studies for direct renin inhibitor

No trial was excluded.

References

Part V

Diuretics

34 Overview of diuretics

34.1 Included trials

Only one trial which randomized 583 patients was identified. In all, 1 randomized comparison concerned chlorthalidone.
The detailed descriptions of trials and meta-analysis results is given in section 35 (page 216) for chlorthalidone.

This trial included 583 patients and was published in 1996.
This trial was double blind in design.
It was reported in English language.
The table 34.1 (page 214) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

34.2 Summary of meta-analysis results

The meta-analysis of the available trials about diuretics provide the results listed in tables 34.2 to 34.2 (page 215) and in the following graphs.

34.2.1 Chlorthalidone

Data were insufficient to compare **chlorthalidone** to **placebo**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 34.1: *Main study characteristics - diuretics*

Trial	Patients	Treatments	Trial design and method
Chlorthalidone			
Chlorthalidone versus placebo			
SHEP (diabetic subgroup), 1996 [1] n = 283 vs. 300	men and women aged 60 years and older , non-insulin-treated diabetic (sub group) patients with isolated systolic hypertension (systolic BP >= 160 mm Hg; diastolic BP, <90 mm Hg)	low dose of chlorthalidone (12.5-25.0 mg/d) with a step-up to atenolol (25.0-50.0 mg/d) or reserpine (0.05-0.10 mg/d) if needed **versus** placebo	double-blind parallel groups Primary endpoint: not defined subgroup: yes

Table 34.2: *Summary of all results for chlorthalidone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
chlorthalidone versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

35 Details

35.1 Available trials

Only one trial which randomized 583 patients was identified: it compared chlorthalidone with placebo.
This trial included 583 patients and was published in 1996.
This trial was double blind in design.
It was reported in English language.
data was reported in trials;
Following tables 35.1 (page 216), 35.2 (page 216), 35.5 (page 219), and 35.3 (page 216) summarized the main characteristics of the trial including in this systematic review of randomized trials of chlorthalidone.

Table 35.1: *Treatment description - diuretics - chlorthalidone*

Trial	Studied treatment	Control treatment
Chlorthalidone versus placebo		
SHEP (diabetic subgroup) (1996) [1]	low dose of chlorthalidone (12.5-25.0 mg/d) with a step-up to atenolol (25.0-50.0 mg/d) or reserpine (0.05-0.10 mg/d) if needed	placebo

Table 35.2: *Descriptions of participants - diuretics - chlorthalidone*

Trial	Patients
Chlorthalidone versus placebo	
SHEP (diabetic subgroup) (1996) [1]	Men and women aged 60 years and older , non-insulin-treated diabetic (sub group) patients with isolated systolic hypertension (systolic BP >= 160 mm Hg; diastolic BP, <90 mm Hg)

Table 35.3: *Design and methodological quality of trials - diuretics - chlorthalidone*

Trial	Design	Duration	Centre	Primary endpoint
Chlorthalidone versus placebo				
SHEP (diabetic subgroup), 1996 [1] n=583	Parallel groups double-blind exploratory trial	5 year		not defined

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 35.4: *Trial characteristics - diuretics - chlorthalidone(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Chlorthalidone versus placebo								
SHEP (diabetic subgroup), 1996 [1]	-2.05%	-1.82%	-2.2	-9.8				70.3

continued...

Table 35.5: *Trial characteristics - diuretics - chlorthalidone*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Chlorthalidone versus placebo								
SHEP (diabetic subgroup), 1996 [1]	49%			170.2 / 76.8 mmhg			hypertension	hypertension

35.2 Meta-analysis results

The results are detailed in table 35.6 (page 220). This table is followed by the Forest's plot corresponding to each endpoint.

Chlorthalidone versus placebo

No data were presented in the 1 trial identified

Table 35.6: *Results details - diuretics - chlorthalidone*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
chlorthalidone versus placebo						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996;276:1886-92. [PMID=8968014]

35.3 Individual trial summaries

Table 35.7: *SHEP (diabetic subgroup), 1996 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=583 (283 vs. 300) **Follow-up duration:** 5 year **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Men and women aged 60 years and older , non-insulin-treated diabetic (sub group) patients with isolated systolic hypertension (systolic BP >= 160 mm Hg; diastolic BP, <90 mm Hg)	**Studied treatment:** low dose of chlorthalidone (12.5-25.0 mg/d) with a step-up to atenolol (25.0-50.0 mg/d) or reserpine (0.05-0.10 mg/d) if needed **Control treatment:** placebo	

Reference

Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996;276:1886-92 [PMID=8968014]

36 Global meta-analysis: all diuretics

36.1 Global meta-analysis: all diuretics versus placebo

Table 36.1: *All diureticsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

37 Ongoing studies of diuretics

No ongoing trial was identified.

38 Excluded studies for diuretics

No trial was excluded.

References

Part VI

Intensive treatment

39 Overview of intensive treatment

39.1 Included trials

Only one trial which randomized 4734 patients was identified. In all, 1 randomized comparison concerned intensive.
The detailed descriptions of trials and meta-analysis results is given in section 40 (page 230) for intensive.

This trial included 4734 patients and was published in 2010.
This trial was open-label in design.
It was reported in English language.
The table 39.1 (page 228) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

39.2 Summary of meta-analysis results

The meta-analysis of the available trials about intensive treatment provide the results listed in tables 39.2 to 39.2 (page 229) and in the following graphs.

39.2.1 Intensive

Data were insufficient to compare **intensive** to **usual**. There was an eligible trial but it did not provided sufficient information about the endpoints considered by this meta-analysis.

Table 39.1: *Main study characteristics - intensive treatment*

Trial	Patients	Treatments	Trial design and method
Intensive			
Intensive versus usual			
ACCORD blood pressure, 2010 [1, 2, 3, 4, 5] n = 2363 vs. 2371	high-risk patients with type 2 diabetes, high HbA1c concentrations (>7.5%), and cardiovascular disease (or >=2 cardiovascular risk factors)	intensive blood-pressure control, targeting a systolic pressure of less than 120 mm Hg **versus** standard blood-pressure control	open factorial plan Primary endpoint: CV events 77 centres, United States, Canada subgroup: no

Table 39.2: *Summary of all results for intensive*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
intensive versus usual						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

40 Details

40.1 Available trials

Only one trial which randomized 4734 patients was identified: it compared intensive with usual.
This trial included 4734 patients and was published in 2010.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 40.1 (page 230), 40.2 (page 230), 40.5 (page 233), and 40.3 (page 231) summarized the main characteristics of the trial including in this systematic review of randomized trials of intensive.

Table 40.1: *Treatment description - intensive treatment - intensive*

Trial	Studied treatment	Control treatment
Intensive versus usual		
ACCORD blood pressure (2010) [1, 2, 3, 4, 5] [a]	intensive blood-pressure control, targeting a systolic pressure of less than 120 mm Hg target systolic BP goal of $<$120 mm Hg	standard blood-pressure control target systolic BP goal of $<$140 mm Hg

a) factorial design, patients were also randomized between intensive and standrd glycemic control

Table 40.2: *Descriptions of participants - intensive treatment - intensive*

Trial	Patients
Intensive versus usual	

continued...

Trial	Patients		
ACCORD blood pressure (2010) [1, 2, 3, 4, 5] [a]	High-risk patients with type 2 diabetes, high HbA1c concentrations (>7.5%), and cardiovascular disease (or >=2 cardiovascular risk factors)		
	Inclusion criteria: 1) Diagnosed with type 2 diabetes mellitus, as determined by the new American Diabetes Association guidelines, which include a fasting plasma glucose level greater than 126 mg/dl (7.0 mmol/l), or a 2-hour postload value in the oral glucose tolerance test of greater than 200 mg/dl, with confirmation by a retest; 2) For participants aged 40 years or older, history of CVD (heart attack, stroke, history of coronary revascularization, history of peripheral or carotid revascularization, or demonstrated angina); 3) For participants aged 55 years or older, a history of CVD is not required, but participant must be considered to be at high risk for experiencing a CVD event due to existing CVD, subclinical disease, or 2+ CVD risk factors; 4) HbA1c 7.5%-9% (if on more drugs) or 7.5%-11% (if on fewer drugs); patients with a systolic blood pressure between 130 and 180 mm Hg who were taking three 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	**Exclusion criteria:** body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per deciliter (132.6 mol per liter), and other serious illness.

a) Recruitment occurred during two noncontiguousperiods: 491 participants in the bloodpressuretrial were recruited from January 2001 throughearly June 2001 during a vanguard phase, andthe remaining 4242 participants were recruitedfrom January 2003 through October 2005 duringthe main trial phase.

Table 40.3: *Design and methodological quality of trials - intensive treatment - intensive*

Trial	Design	Duration	Centre	Primary endpoint
Intensive versus usual				
ACCORD blood pressure, 2010 [1, 2, 3, 4, 5] n=4734	Factorial plan open confirmatory trial at risk of bias	4.7 y inclusion period: mar 2003 - oct 2005	United States, Canada 77 centres	CV events

Table 40.4: *Trial characteristics - intensive treatment - intensive(continued...)*

Trial	DBP relative change (%)	SBP relative change (%)	treatment effect on DBP (mmHg)	treatment effect on SBP (mmHg)	change in DBP (mmHg)	change in SBP (mmHg)	donnes disponibles	Age
Intensive versus usual								
ACCORD blood pressure, 2010 [1, 2, 3, 4, 5]	-4.62%	-4.91%	-6.1	-14.2				62.2 y

continued...

Table 40.5: *Trial characteristics - intensive treatment - intensive*

Trial	Female (%)	Duration of hypertension	Glycosylated hemoglobin	BP (systolic/diastolic)	Duration of diabetes	hypertension (%)	primary population	study population
Intensive versus usual								
ACCORD blood pressure, 2010 [1, 2, 3, 4, 5]	47.7%		8.3%	139.2/76 mmHg	10 yr			diabetes patients

40.2 Meta-analysis results

The results are detailed in table 40.6 (page 234). This table is followed by the Forest's plot corresponding to each endpoint.

Intensive versus usual

No data were presented in the 1 trial identified

Table 40.6: *Results details - intensive treatment - intensive*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
intensive versus usual						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] . Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;:. [PMID=20587587]

[2] Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010 Jun 29;:. [PMID=20594588]

[3] Chew EY, Ambrosius WT, Howard LT, Greven CM, Johnson S, Danis RP, Davis MD, Genuth S, Domanski M. Rationale, design, and methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE). Am J Cardiol 2007;99:103i-111i. [PMID=17599420]

[4] Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59. [PMID=18539917]

[5] Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85. [PMID=20228401]

40.3 Individual trial summaries

Table 40.7: *ACCORD blood pressure, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4734 (2363 vs. 2371) **Follow-up duration:** 4.7 y **Study design:** Randomized controlled trial Factorial plan Open Confirmatory trial at risk of bias United States, Canada, 77 centres **Inclusion period:** mar 2003 - oct 2005	High-risk patients with type 2 diabetes, high HbA1c concentrations (>7.5%), and cardiovascular disease (or >=2 cardiovascular risk factors) **note:** Recruitment occurred during two noncontiguousperiods: 491 participants in the blood-pressuretrial were recruited from January 2001 throughearly June 2001 during a vanguard phase, andthe remaining 4242 participants were recruitedfrom January 2003 through October 2005 duringthe main trial phase. **Inclusion criteria:** 1) Diagnosed with type 2 diabetes mellitus, as determined by the new American Diabetes Association guidelines, which include a fasting plasma glucose level greater than 126 mg/dl (7.0 mmol/l), or a 2-hour postload value in the oral glucose tolerance test of greater than 200 mg/dl, with confirmation by a retest; 2) For participants aged 40 years or older, history of CVD (heart attack, stroke, history of coronary revascularization, history of peripheral or carotid revascularization, or demonstrated angina); 3) For participants aged 55 years or older, a history of CVD is not required, but partici **Exclusion criteria:** body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per deciliter (132.6 mol per liter), and other serious illness.	**Studied treatment:** intensive blood-pressure control, targeting a systolic pressure of less than 120 mm Hg target systolic BP goal of <120 mm Hg **Control treatment:** standard blood-pressure control target systolic BP goal of <140 mm Hg **note:** factorial design, patients were also randomized between intensive and standrd glycemic control	

continued...

trial details	Patients	Treatments	Outcomes

References

. Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;: [PMID=20587587]

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010 Jun 29;: [PMID=20594588]

Chew EY, Ambrosius WT, Howard LT, Greven CM, Johnson S, Danis RP, Davis MD, Genuth S, Domanski M. Rationale, design, and methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE). Am J Cardiol 2007;99:103i-111i [PMID=17599420]

Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59 [PMID=18539917]

Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85 [PMID=20228401]

41 Global meta-analysis: all intensive treatment

41.1 Global meta-analysis: all intensive treatment versus usual

Table 41.1: *All intensive treatmentversus usual*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

42 Ongoing studies of intensive treatment

No ongoing trial was identified.

43 Excluded studies for intensive treatment

No trial was excluded.

References

Part VII

Other BP lowering drugs

44 Overview of other BP lowering drugs

No completed trial meeting the eligibility criteria was available.

45 Ongoing studies of other BP lowering drugs

No ongoing trial was identified.

46 Excluded studies for other BP lowering drugs

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 46.1.

Table 46.1: *Excluded studies of other BP lowering drugs*

Study	Exclusion reason
MIDAS (diabetic sub group) (1997) [1]	explicative post hoc analysis of MIDAS

References

[1] Byington RP, Craven TE, Furberg CD, Pahor M. Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. Lancet 1997;350:1075-6. [PMID=10213554]

Part VIII

Treatment blood pressure target

47 Overview of treatment blood pressure target

47.1 Included trials

A total of 2 randomized comparisons which enrolled 950 patients were identified. In all, 2 randomized comparisons concerned more intensive blood pressure lowering strategie.
The detailed descriptions of trials and meta-analysis results is given in section 48 (page 248) for more intensive blood pressure lowering strategie.

The average study size was 475 patients (range 470 to 480). The first study was published in 2000, and the last study was published in 2002.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 47.1 (page 246) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

47.2 Summary of meta-analysis results

The meta-analysis of the available trials about treatment blood pressure target provide the results listed in tables 47.2 to 47.2 (page 247) and in the following graphs.

47.2.1 More intensive blood pressure lowering strategie

Data were insufficient to compare **more intensive blood pressure lowering strategie** to **less intensive blood pressure lowering strategie**. There were 2 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis.

Table 47.1: *Main study characteristics - Treatment blood pressure target*

Trial	Patients	Treatments	Trial design and method
More intensive blood pressure lowering strategie			
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie			
ABCD (H), 2000 [1] n = 237 vs. 233	diabetes patients with DBP >=90 mmHg	intensive treatment with a diastolic blood pressuregoal of 75 mmHg **versus** moderate treatment with a diastolic blood pressure goal of 80-89 mmHg target: DBP <75 achieved systolic blood: 132/138 achieved diastolic blood pressure: 78/86	open parallel groups
ABCD (N), 2002 [2] n = 237 vs. 243	diabetes patients with diastolicblood pressure between 80 and 89mmHg	intensive treatment (diastolic blood pressure decreaseof 10 mmHg below baseline DBP) **versus** moderate treatment (diastolic blood pressure goal of 80-89 mmHg) target: >-10 DBP achieved systolic blood: 128/137 achieved diastolic blood pressure: 75/81	open parallel groups

Table 47.2: *Summary of all results for more intensive blood pressure lowering strategie*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
more intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

48 Details

48.1 Available trials

A total of 2 RCTs which randomized 950 patients were identified: all compared more intensive blood pressure lowering strategie with less intensive blood pressure lowering strategie.
The average study size was 475 patients (range 470 to 480). The first study was published in 2000, and the last study was published in 2002.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
data was reported in trials;
Following tables 48.1 (page 248), 48.2 (page 248), 48.4 (page 250), and 48.3 (page 249) summarized the main characteristics of the trials including in this systematic review of randomized trials of more intensive blood pressure lowering strategie.

Table 48.1: *Treatment description - Treatment blood pressure target - more intensive blood pressure lowering strategie*

Trial	Studied treatment	Control treatment
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie		
ABCD (H) (2000) [1] [a]	intensive treatment with a diastolic blood pressuregoal of 75 mmHg	moderate treatment with a diastolic blood pressure goal of 80-89 mmHg
ABCD (N) (2002) [2] [b]	intensive treatment (diastolic blood pressure decreaseof 10 mmHg below baseline DBP)	moderate treatment (diastolic blood pressure goal of 80-89 mmHg)

a) factorial design: nisoldipine or enalapril as the initial antihypertensive b) patients randomized to intensive therapy received either nisoldipine or enalapril in a blindedmanner as the initial antihypertensive medication

Table 48.2: *Descriptions of participants - Treatment blood pressure target - more intensive blood pressure lowering strategie*

Trial	Patients	
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie		
ABCD (H) (2000) [1]	Diabetes patients with DBP >=90 mmHg **Inclusion criteria:**	**Exclusion criteria:** myocardial infarction or a cerebrovascular accident within the previous 6 months, had coronary artery bypasssurgery within the previous 3 months, had unstable angina pectoris within the previous 6 months, had congestiveheart failure NYHA class III or IV, demonstrated an absolute need for ACE inhibitors or CCB, and/or had a serumcreatinine level >3 mg/dl.
ABCD (N) (2002) [2]	Diabetes patients with diastolicblood pressure between 80 and 89mmHg	

continued...

Trial	Patients

Table 48.3: *Design and methodological quality of trials - Treatment blood pressure target - more intensive blood pressure lowering strategie*

Trial	Design	Duration	Centre	Primary end-point
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie				
ABCD (H), 2000 [1] n=470	Parallel groups open	5 year		
ABCD (N), 2002 [2] n=480	Parallel groups open			

Table 48.4: *Trial characteristics - Treatment blood pressure target - more intensive blood pressure lowering strategie*

Trial	target	Achieved systolic blood	Achieved diastolic blood pressure	Number of antihyper-tensive drugs
More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie				
ABCD (H), 2000 [1]	DBP <75	132/138	78/86	
ABCD (N), 2002 [2]	>-10 DBP	128/137	75/81	

48.2 Meta-analysis results

The results are detailed in table 48.5 (page 251). This table is followed by the Forest's plot corresponding to each endpoint.

More intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie

No data were presented in the 2 trials identified

Table 48.5: *Results details - Treatment blood pressure target - more intensive blood pressure lowering strategie*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
more intensive blood pressure lowering strategie versus less intensive blood pressure lowering strategie						
No data were presented in the trial identified						

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

References

[1] Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23 Suppl 2:B54-64. [PMID=10860192]

[2] Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97. [PMID=11849464]

48.3 Individual trial summaries

Table 48.6: *ABCD (H), 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=470 (237 vs. 233) **Follow-up duration:** 5 year **Study design:** Randomized controlled trial Parallel groups Open	Diabetes patients with DBP >=90 mmHg **Exclusion criteria:** myocardial infarction or a cerebrovascular accident within the previous 6 months, had coronary artery bypasssurgery within the previous 3 months, had unstable angina pectoris within the previous 6 months, had congestiveheart failure NYHA class III or IV, demonstrated an absolute need for ACE inhibitors or CCB, and/or had a serumcreatinine level >3 mg/dl.	**Studied treatment:** intensive treatment with a diastolic blood pressuregoal of 75 mmHg **Control treatment:** moderate treatment with a diastolic blood pressure goal of 80-89 mmHg **note:** factorial design: nisoldipine or enalapril as the initial antihypertensive	

Reference

Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23 Suppl 2:B54-64 [PMID=10860192]

Table 48.7: *ABCD (N), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=480 (237 vs. 243) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Open	Diabetes patients with diastolicblood pressure between 80 and 89mmHg	**Studied treatment:** intensive treatment (diastolic blood pressure decreaseof 10 mmHg below baseline DBP) **Control treatment:** moderate treatment (diastolic blood pressure goal of 80-89 mmHg) **note:** patients randomized to intensive therapy received either nisoldipine or enalapril in a blindedmanner as the initial antihypertensive medication	

Reference

Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97 [PMID=11849464]

49 Global meta-analysis: all Treatment blood pressure target

49.1 Global meta-analysis: all Treatment blood pressure target versus less intensive blood pressure lowering strategie

Table 49.1: *All Treatment blood pressure targetversus less intensive blood pressure lowering strategie*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

50 Ongoing studies of Treatment blood pressure target

No ongoing trial was identified.

51 Excluded studies for Treatment blood pressure target

No trial was excluded.

References