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Anti hypertensive agent for hypertension in elderly (60 years and more)

A systematic review and meta-analysis of randomized clinical trials

2017 - 7 - 1

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This report should be referenced as follows:
TrialResults-center.org; Results of all major randomized clinical trials about Anti hypertensive agent for hypertension in elderly (60 years and more).

Contents

0.1 Synthesis of the meta-analysis results

In all 11 randomised controlled trials (RCTs) were included. These included 3 studies of **angiotensin-converting enzyme inhibitors** involving 14,902 patients, 2 studies of **beta-blockers** involving 5,498 patients, 5 studies of **calcium-channel blockers** involving 9,866 patients and 1 studie of **diuretics** involving 3,845 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 Angiotensin-converting enzyme inhibitors

Reports of 3 trials (including 14,902 patients) were identified .
Among these comparisons, one trial are about enalapril and two about various ACEI.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Enalapril

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

Table 1: *Results summary - Enalapril*

Benefit	Harmful	No evidence
	Enalapril versus diuretics	

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

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

Various ACEI

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

Table 2: *Results summary - Various ACEI*

Benefit	Harmful	No evidence
	Various ACEI versus calcium-channel blocker	
↓ heart failure RR=0.80* [0.65;0.98] k=1		→ cardiovascular events RR=0.94^{NS} [0.85;1.04] k=1 → cardiovascular death RR=1.06^{NS} [0.89;1.27] k=1 → stroke (fatal and non fatal) RR=1.03^{NS} [0.86;1.24] k=1 → coronary event RR=0.87^{NS} [0.73;1.05] k=1 → all cause death RR=1.05^{NS} [0.92;1.19] k=1

continued...

Benefit	Harmful	No evidence
	Various ACEI versus diuretic or beta-blocker	
↓ heart failure RR=0.63¶ [0.52;0.77] k=1		→ cardiovascular events RR=0.94^{NS} [0.71;1.24] k=1 → cardiovascular death RR=1.01^{NS} [0.72;1.42] k=1 → stroke (fatal and non fatal) RR=0.90^{NS} [0.74;1.09] k=1 → coronary event RR=0.90^{NS} [0.74;1.09] k=1 → all cause death RR=1.02^{NS} [0.77;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)

0.1.2 Beta-blockers

Reports of 1 trials (including 5,498 patients) were identified .
Among these comparisons, two trials are about atenolol.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with atenolol for all the endpoints with data in at least one trial are summarized table 3.

Table 3: *Results summary - Atenolol*

Benefit	Harmful	No evidence
	Atenolol versus placebo	
		→ myocardial infarction (fatal and non fatal) RR=1.01^{NS} [0.78;1.31] k=1 → stroke (fatal and non fatal) RR=0.84^{NS} [0.62;1.14] k=1 → all cause death RR=1.06^{NS} [0.90;1.27] k=1
	Atenolol versus hydrochlorothiazide+amiloride	
	↑ myocardial infarction (fatal and non fatal) RR=6.96¶ [4.90;9.90] k=1	→ stroke (fatal and non fatal) RR=1.22^{NS} [0.83;1.79] k=1 → all cause death RR=1.22^{NS} [0.99;1.51] 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-channel blockers

Reports of 5 trials (including 9,884 patients) were identified .

Among these comparisons, one trial are about felopidine or israpidine,one about lacidipine,one about nicardipine,one about nifedipine and one about nitrendipine.

No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Felopidine or israpidine

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

Table 4: *Results summary - Felopidine or israpidine*

Benefit	Harmful	No evidence
Felopidine or israpidine versus diuretic or beta-blocker		
		→ cardiovascular events RR=1.00^{NS} [0.90;1.10] k=1 → cardiovascular death RR=0.97^{NS} [0.81;1.16] k=1 → stroke (fatal and non fatal) RR=0.88^{NS} [0.74;1.05] k=1 → coronary event RR=1.12^{NS} [0.93;1.34] k=1 → heart failure RR=1.06^{NS} [0.87;1.29] k=1 → all cause death RR=0.99^{NS} [0.87;1.13] k=1

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

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

Lacidipine

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

Table 5: *Results summary - Lacidipine*

Benefit	Harmful	No evidence
Lacidipine versus chlorthalidone		

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

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

Nicardipine

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

Table 6: *Results summary - Nicardipine*

Benefit	Harmful	No evidence
Nicardipine versus trichlormethiazide		

continued...

Benefit	Harmful	No evidence
		→ cardiovascular events RR=0.69^{NS} [0.30;1.58] k=1 → cardiovascular death RR=3.98^{NS} [0.18;87.78] k=1 → stroke (fatal and non fatal) RR=0.75^{NS} [0.26;2.12] k=1 → coronary event RR=1.00^{NS} [0.14;7.00] k=1 → heart failure RR=0.17^{NS} [0.01;3.29] k=1 → all cause death RR=1.00^{NS} [0.14;7.00] k=1

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

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

Nifedipine

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

Table 7: *Results summary - Nifedipine*

Benefit	Harmful	No evidence
	Nifedipine versus atenolol+chlorthalidone	

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

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

Nitrendipine

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

Table 8: *Results summary - Nitrendipine*

Benefit	Harmful	No evidence
	Nitrendipine versus placebo	
↓ cardiovascular events RR=0.71¶ [0.57;0.87] k=1 ↓ stroke (fatal and non fatal) RR=0.59† [0.41;0.83] k=1		→ cardiovascular death RR=0.73^{NS} [0.53;1.03] k=1 → coronary event RR=0.75^{NS} [0.50;1.13] k=1 → heart failure RR=0.75^{NS} [0.50;1.13] k=1 → all cause death RR=0.86^{NS} [0.68;1.09] k=1

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

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

0.1.4 Diuretics

Only one trials including 3845 patients was found.
Among these comparisons, one trial are about indapamide.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with indapamide for all the endpoints with data in at least one trial are summarized table 9.

Table 9: *Results summary - Indapamide*

Benefit	Harmful	No evidence
	Indapamide versus placebo	

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

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

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 elderly (60 years and more). The following classes of treatment are considered:

1. angiotensin-converting enzyme inhibitors
2. beta-blockers
3. calcium-channel blockers
4. Diuretics

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 elderly (60 years and more).

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 cardiovascular events, Coronary event, Cardiovascular death, stroke (fatal and non fatal), Heart failure, 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 angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, Diuretics,
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

Angiotensin-converting enzyme inhibitors

2 Overview of angiotensin-converting enzyme inhibitors

2.1 Included trials

A total of 3 randomized comparisons which enrolled 14902 patients were identified. In all, 1 randomized comparison concerned enalapril and two various ACEI.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 23) for enalapril and in section 4 (page 29) for various ACEI.

The average study size was 4967 patients (range 4401 to 6083). The first study was published in 1999, and the last study was published in 2003.
All trials 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 18) 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 angiotensin-converting enzyme inhibitors provide the results listed in tables 2.2 to 2.3 (page 19) and in the following graphs.

2.2.1 Enalapril

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

2.2.2 Various ACEI

Various ACEI was superior to **calcium-channel blocker** in terms of heart failure (RR=0.80, 95% CI 0.65 to 0.98, p=0.0326, 1 trial). However, no significant difference was found on cardiovascular events (RR=0.94, 95% CI 0.85 to 1.04, p=0.2464, 1 trial), cardiovascular death (RR=1.06, 95% CI 0.89 to 1.27, p=0.5094, 1 trial), stroke (fatal and non fatal) (RR=1.03, 95% CI 0.86 to 1.24, p=0.7148, 1 trial), coronary event (RR=0.87, 95% CI 0.73 to 1.05, p=0.1513, 1 trial)and all cause death (RR=1.05, 95% CI 0.92 to 1.19, p=0.5070, 1 trial).

Various ACEI was superior to **diuretic or beta-blocker** in terms of heart failure (RR=0.63, 95% CI 0.52 to 0.77, p=0.0000, 1 trial). However, no significant difference was found on cardiovascular events (RR=0.94, 95% CI 0.71 to 1.24, p=0.6617, 1 trial), cardiovascular death (RR=1.01, 95% CI 0.72 to 1.42, p=0.9542, 1 trial), stroke (fatal and non fatal) (RR=0.90, 95% CI 0.74 to 1.09, p=0.2921, 1 trial), coronary event (RR=0.90, 95% CI 0.74 to 1.09, p=0.2921, 1 trial)and all cause death (RR=1.02, 95% CI 0.77 to 1.35, p=0.8886, 1 trial).

Table 2.1: *Main study characteristics - angiotensin-converting enzyme inhibitors*

Trial	Patients	Treatments	Trial design and method
Enalapril			
Enalapril versus diuretics			
ANBP2, 2003 [1] n = 3044 vs. 3039	subjects with hypertension 65 to 84 years	enalapril **versus** hydrochlorothiazide	open parallel groups Primary endpoint: all cardiovascular events or death from any cause 1594 centres, Australia
Various ACEI			
Various ACEI versus calcium-channel blocker			
STOP-2 (vs felodipine or isradipine), 1999 [1] n = 2205 vs. 2196	patients aged 70-84 years with hypertension (blood pressure >or = 180 mm Hg systolic, >or = 105 mm Hg diastolic, or both)	enalapril or lisinopril , enalapril 10 mg or lisinopril 10 mg daily **versus** felodipine 2.5 mg or isradipine 2-5 mg daily	open parallel groups 312 centres, Sweden
Various ACEI versus diuretic or beta-blocker			
STOP 2 (vs conventional drugs), 1999 [2] n = 2205 vs. 2213	patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).	enalapril 10 mg or lisinopril10 mg daily **versus** conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 25 mg daily)	open parallel groups Primary endpoint: fatal stroke, fatal MI, other cardiovascular death 312 centres, Sweden

Table 2.2: *Summary of all results for enalapril*

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

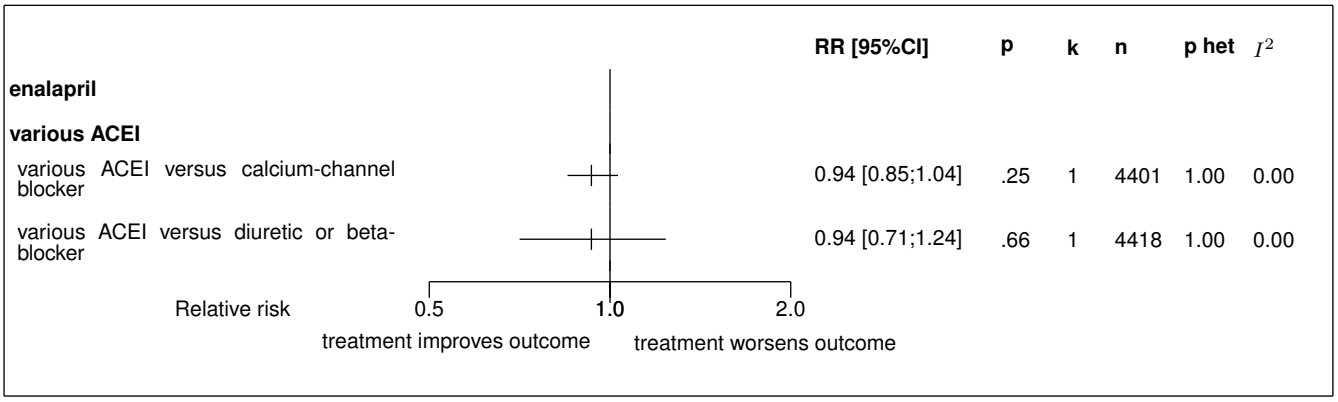
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.3: *Summary of all results for various ACEI*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
various ACEI versus calcium-channel blocker						
cardiovascular events	RR=0.94	0.85;1.04	0.2464	1.0000 (0.00)	1	4401
cardiovascular death	RR=1.06	0.89;1.27	0.5094	1.0000 (0.00)	1	4401
stroke (fatal and non fatal)	RR=1.03	0.86;1.24	0.7148	1.0000 (0.00)	1	4401
coronary event	RR=0.87	0.73;1.05	0.1513	1.0000 (0.00)	1	4401
heart failure	RR=0.80	0.65;0.98	0.0326	1.0000 (0.00)	1	4401
all cause death	RR=1.05	0.92;1.19	0.5070	1.0000 (0.00)	1	4401
various ACEI versus diuretic or beta-blocker						
cardiovascular events	RR=0.94	0.71;1.24	0.6617	1.0000 (0.00)	1	4418
cardiovascular death	RR=1.01	0.72;1.42	0.9542	1.0000 (0.00)	1	4418
stroke (fatal and non fatal)	RR=0.90	0.74;1.09	0.2921	1.0000 (0.00)	1	4418
coronary event	RR=0.90	0.74;1.09	0.2921	1.0000 (0.00)	1	4418
heart failure	RR=0.63	0.52;0.77	0.0000	1.0000 (0.00)	1	4418
all cause death	RR=1.02	0.77;1.35	0.8886	1.0000 (0.00)	1	4418

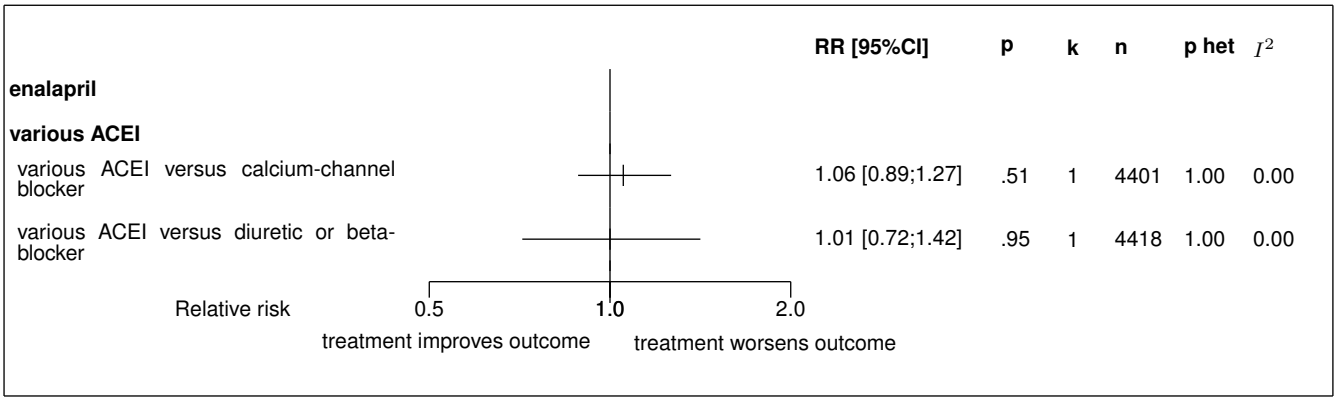
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for cardiovascular events*



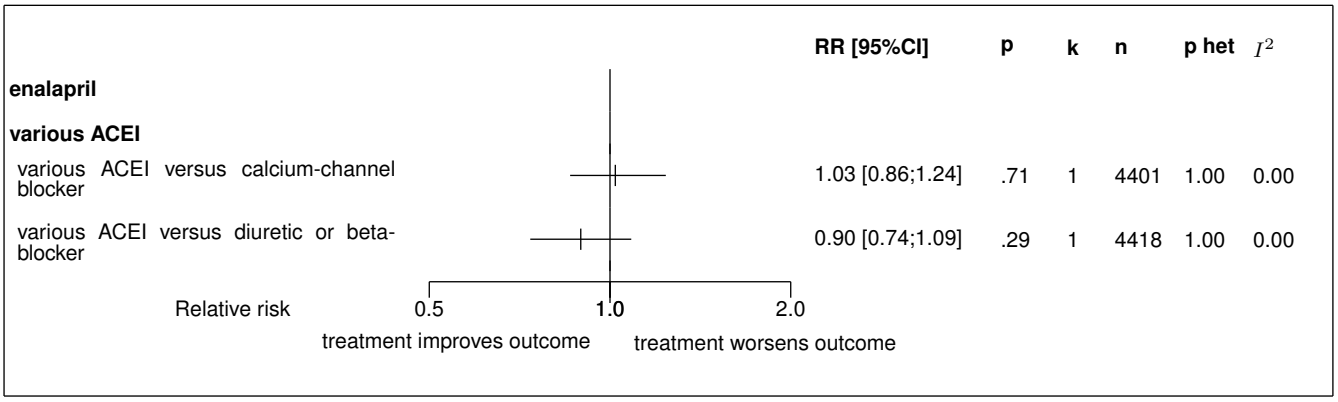
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.2: *Forest's plot for cardiovascular death*



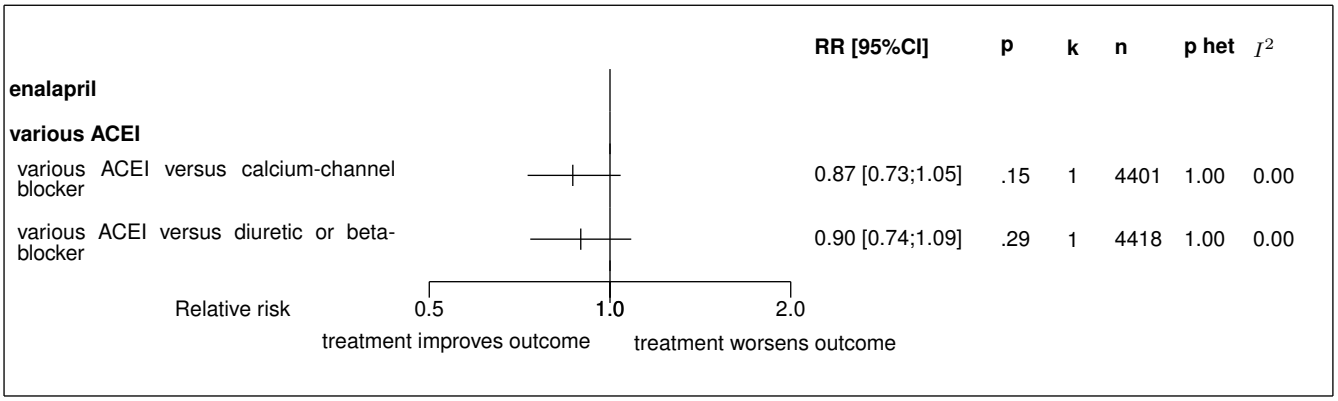
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for stroke (fatal and non fatal)*



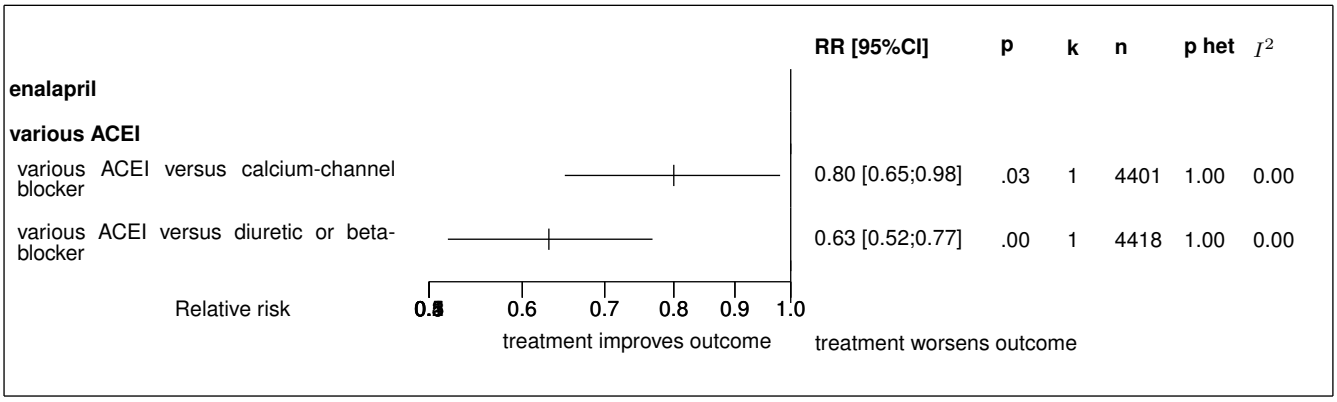
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for coronary event*



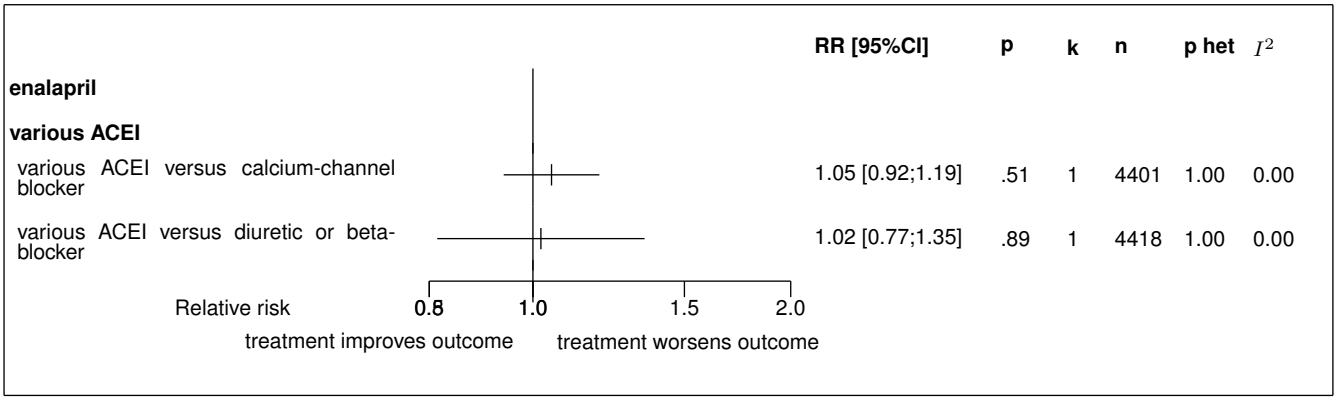
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *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; ᶠ: random effect model used

Figure 2.6: *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; ᶠ: random effect model used

3 Detailed results for enalapril

3.1 Available trials

Only one trial which randomized 6083 patients was identified: it compared enalapril with diuretics.
This trial included 6083 patients and was published in 2003.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 3.1 (page 23), 3.2 (page 23), 3.4 (page 25), and 3.3 (page 23) summarized the main characteristics of the trial including in this systematic review of randomized trials of enalapril.

Table 3.1: *Treatment description - angiotensin-converting enzyme inhibitors - enalapril*

Trial	Studied treatment	Control treatment
Enalapril versus diuretics		
ANBP2 (2003) [1] [a]	enalapril choice of the specific agent and dose was made bythe family practitioner	hydrochlorothiazide

a) The ACE inhibitorenalapril and the diuretic hydrochlorothiazidewere recommended as initial therapy; however, thechoice of the specific agent and dose was made bythe family practitioner

Table 3.2: *Descriptions of participants - angiotensin-converting enzyme inhibitors - enalapril*

Trial	Patients	
Enalapril versus diuretics		
ANBP2 (2003) [1]	Subjects with hypertension 65 to 84 years	
	Inclusion criteria: SBPat least160 mm Hg or an average sitting diastolic blood pressureof at least 90 mm Hg (if the systolic blood pressure-was at least 140 mm Hg); absence of recent cardiovascularevents	**Exclusion criteria:** contraindication to an ACE inhibitor or diuretic, aplasma creatinine concentration of more than 2.5mg per deciliter (221 mol per liter), malignant hypertension,or dementia

Table 3.3: *Design and methodological quality of trials - angiotensin-converting enzyme inhibitors - enalapril*

Trial	Design	Duration	Centre	Primary endpoint
Enalapril versus diuretics				

continued...

Trial	Design	Duration	Centre	Primary endpoint
ANBP2, 2003 [1] n=6083	Parallel groups open confirmatory trial at risk of bias	4.1 y inclusion period: apr 1995 - jun 1998	Australia 1594 centres	all cardiovascular events or death from any cause

Table 3.4: *Trial characteristics - angiotensin-converting enzyme inhibitors - enalapril*

Trial
Enalapril versus diuretics
ANBP2, 2003 [1]

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 26). This table is followed by the Forest's plot corresponding to each endpoint.

Enalapril versus diuretics

No data were presented in the 1 trial identified

Table 3.5: *Results details - angiotensin-converting enzyme inhibitors - enalapril*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
enalapril versus diuretics						
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] Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583-92. [PMID=12584366]

3.3 Individual trial summaries

Table 3.6: *ANBP2, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=6083 (3044 vs. 3039) **Follow-up duration:** 4.1 y **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias Australia, 1594 centres **Inclusion period:** apr 1995 - jun 1998	Subjects with hypertension 65 to 84 years **Inclusion criteria:** SBPat least160 mm Hg or an average sitting diastolic blood pressureof at least 90 mm Hg (if the systolic blood pressurewas at least 140 mm Hg); absence of recent cardiovascularevents **Exclusion criteria:** contraindication to an ACE inhibitor or diuretic, aplasma creatinine concentration of more than 2.5mg per deciliter (221 mol per liter), malignant hypertension,or dementia	**Studied treatment:** enalapril choice of the specific agent and dose was made bythe family practitioner **Control treatment:** hydrochlorothiazide **note:** The ACE inhibitorenalapril and the diuretic hydrochlorothiazidewere recommended as initial therapy; however, thechoice of the specific agent and dose was made bythe family practitioner	

Reference

Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583-92 [PMID=12584366]

4 Detailed results for various ACEI

4.1 Available trials

A total of 2 RCTs which randomized 8819 patients were identified: it compared various ACEI with calcium-channel blocker and it compared various ACEI with diuretic or beta-blocker.
The average study size was 4409 patients (range 4401 to 4418). The first study was published in 1999, 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.
Cardiovascular death data was reported in 2 trials; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on cardiovascular events; 2 trials reported data on coronary event; 1 trials reported data on heart failure; and 1 trials reported data on all cause death.
Following tables 4.1 (page 29), 4.2 (page 29), 4.4 (page 31), and 4.3 (page 30) summarized the main characteristics of the trials including in this systematic review of randomized trials of various ACEI.

Table 4.1: *Treatment description - angiotensin-converting enzyme inhibitors - various ACEI*

Trial	Studied treatment	Control treatment
Various ACEI versus calcium-channel blocker		
STOP-2 (vs felodipine or isradipine) (1999) [1]	Enalapril or lisinopril , enalapril 10 mg or lisinopril 10 mg daily	felodipine 2.5 mg or isradipine 2-5 mg daily
Various ACEI versus diuretic or beta-blocker		
STOP 2 (vs conventional drugs) (1999) [2]	enalapril 10 mg or lisinopril10 mg daily	conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 25 mg daily)

Table 4.2: *Descriptions of participants - angiotensin-converting enzyme inhibitors - various ACEI*

Trial	Patients
Various ACEI versus calcium-channel blocker	
STOP-2 (vs felodipine or isradipine) (1999) [1]	Patients aged 70-84 years with hypertension (blood pressure >or = 180 mm Hg systolic, >or = 105 mm Hg diastolic, or both)
Various ACEI versus diuretic or beta-blocker	

continued...

Trial	Patients
STOP 2 (vs conventional drugs) (1999) [2]	Patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).

Table 4.3: *Design and methodological quality of trials - angiotensin-converting enzyme inhibitors - various ACEI*

Trial	Design	Duration	Centre	Primary endpoint
Various ACEI versus calcium-channel blocker				
STOP-2 (vs felodipine or isradipine), 1999 [1] n=4401	Parallel groups Open	50 y inclusion period: Sep 1992 - dec 1994	Sweden 312 centres	
Various ACEI versus diuretic or beta-blocker				
STOP 2 (vs conventional drugs), 1999 [2] n=4418	Parallel groups Open	5.0 y inclusion period: sept 1991 - dec 1994	Sweden 312 centres	fatal stroke, fatal MI, other cardiovascular death

Table 4.4: *Trial characteristics - angiotensin-converting enzyme inhibitors - various ACEI*

Trial
Various ACEI versus calcium-channel blocker
STOP-2 (vs felodipine or isradipine), 1999 [1]
Various ACEI versus diuretic or beta-blocker
STOP 2 (vs conventional drugs), 1999 [2]

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 33). This table is followed by the Forest's plot corresponding to each endpoint.

Various ACEI versus calcium-channel blocker

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between various ACEI and calcium-channel blocker, with a RR of 0.94 (95%CI 0.85 to 1.04, p=0.2464) in favour of various ACEI. In other words, cardiovascular events was slightly lower in the various ACEI group , but this was not statistically significant.
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 1.06 (95% CI 0.89 to 1.27, p=0.5094).
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 1.03 (95% CI 0.86 to 1.24, p=0.7148).
The single study 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 0.87 (95% CI 0.73 to 1.05, p=0.1513).
The single study eligible for this comparison provided data on **heart failure**. The analysis detected a statistically significant difference in favor of various ACEI in heart failure, with a RR of 0.80 (95% CI 0.65 to 0.98, p=0.0326).
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 1.05 (95% CI 0.92 to 1.19, p=0.5070).

Various ACEI versus diuretic or beta-blocker

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between various ACEI and diuretic or beta-blocker, with a RR of 0.94 (95%CI 0.71 to 1.24, p=0.6617) in favour of various ACEI. In other words, cardiovascular events was slightly lower in the various ACEI group , but this was not statistically significant.
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 1.01 (95% CI 0.72 to 1.42, p=0.9542).
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 0.90 (95% CI 0.74 to 1.09, p=0.2921).
The single study 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 0.90 (95% CI 0.74 to 1.09, p=0.2921).
The single study eligible for this comparison provided data on **heart failure**. The analysis detected a statistically significant difference in favor of various ACEI in heart failure, with a RR of 0.63 (95% CI 0.52 to 0.77, p=0.0000).
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 1.02 (95% CI 0.77 to 1.35, p=0.8886).

Table 4.5: *Results details - angiotensin-converting enzyme inhibitors - various ACEI*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
various ACEI versus calcium-channel blocker						
cardiovascular events	RR=0.94	[0.85;1.04]	0.2464	1.0000 (I^2=0.00)	1	4401
cardiovascular death	RR=1.06	[0.89;1.27]	0.5094	1.0000 (I^2=0.00)	1	4401
stroke (fatal and non fatal)	RR=1.03	[0.86;1.24]	0.7148	1.0000 (I^2=0.00)	1	4401
coronary event	RR=0.87	[0.73;1.05]	0.1513	1.0000 (I^2=0.00)	1	4401
heart failure	RR=0.80	[0.65;0.98]	0.0326	1.0000 (I^2=0.00)	1	4401
all cause death	RR=1.05	[0.92;1.19]	0.5070	1.0000 (I^2=0.00)	1	4401
various ACEI versus diuretic or beta-blocker						
cardiovascular events	RR=0.94	[0.71;1.24]	0.6617	1.0000 (I^2=0.00)	1	4418
cardiovascular death	RR=1.01	[0.72;1.42]	0.9542	1.0000 (I^2=0.00)	1	4418
stroke (fatal and non fatal)	RR=0.90	[0.74;1.09]	0.2921	1.0000 (I^2=0.00)	1	4418
coronary event	RR=0.90	[0.74;1.09]	0.2921	1.0000 (I^2=0.00)	1	4418
heart failure	RR=0.63	[0.52;0.77]	0.0000	1.0000 (I^2=0.00)	1	4418
all cause death	RR=1.02	[0.77;1.35]	0.8886	1.0000 (I^2=0.00)	1	4418

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 cardiovascular events*

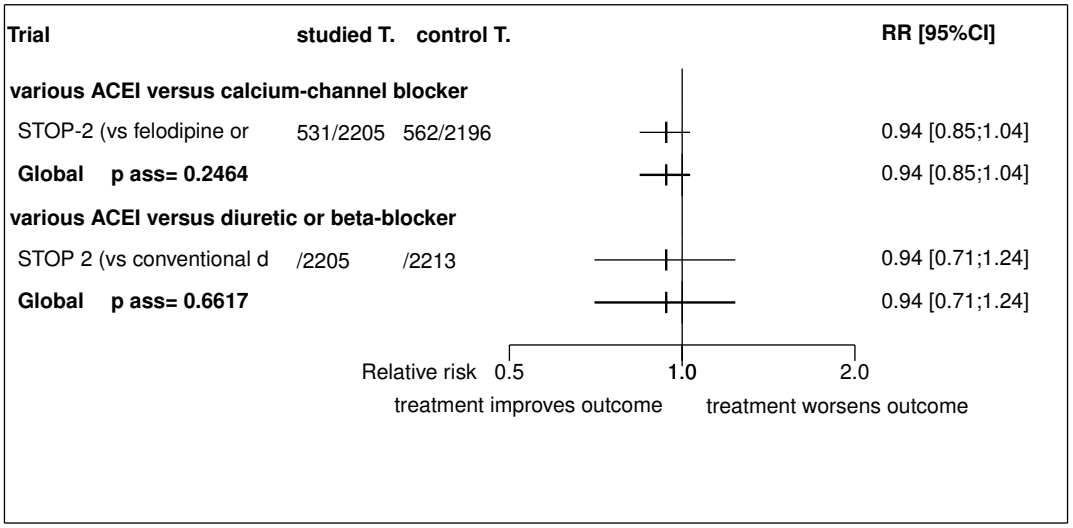


Figure 4.2: *Forest's plot for cardiovascular death*

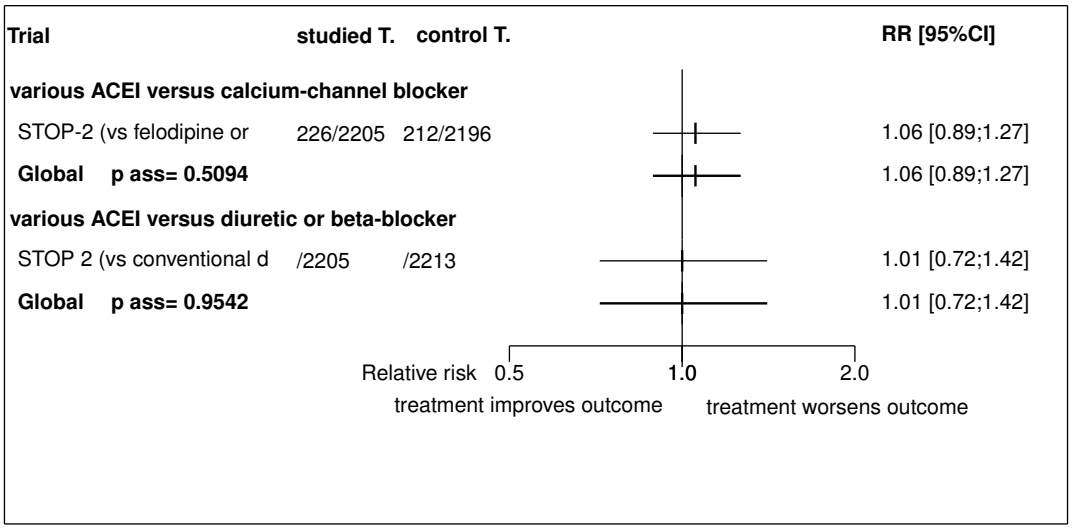


Figure 4.3: *Forest's plot for stroke (fatal and non fatal)*

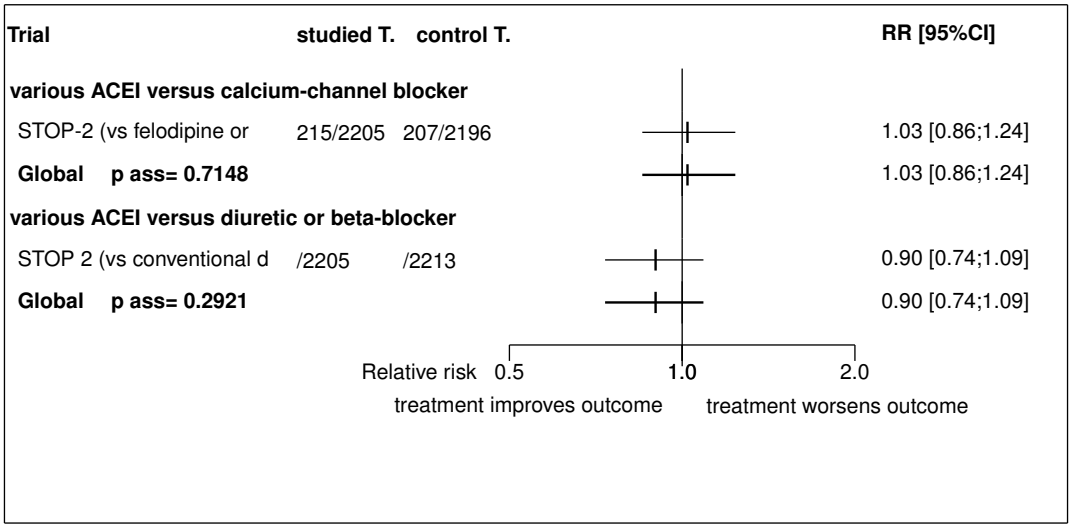


Figure 4.4: *Forest's plot for coronary event*

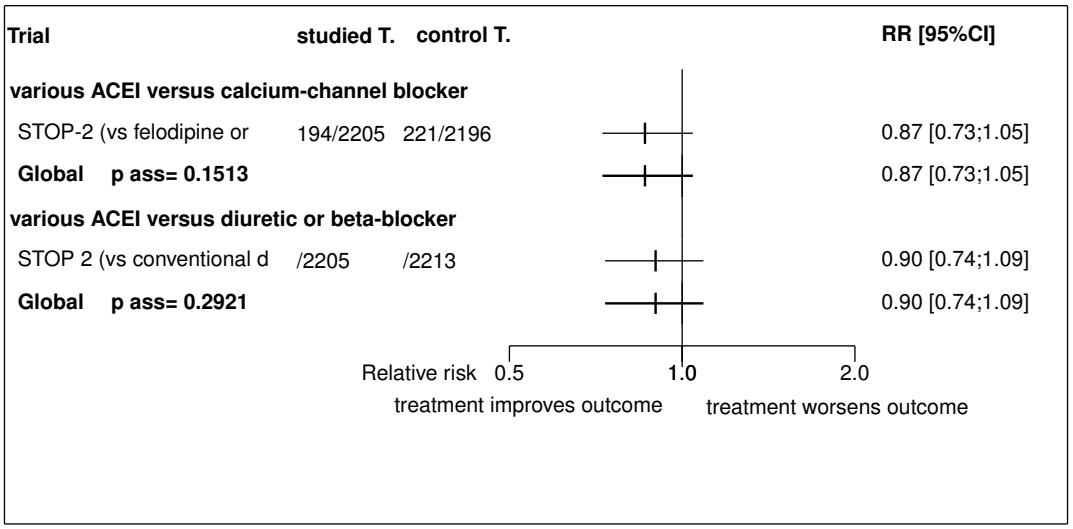


Figure 4.5: *Forest's plot for heart failure*

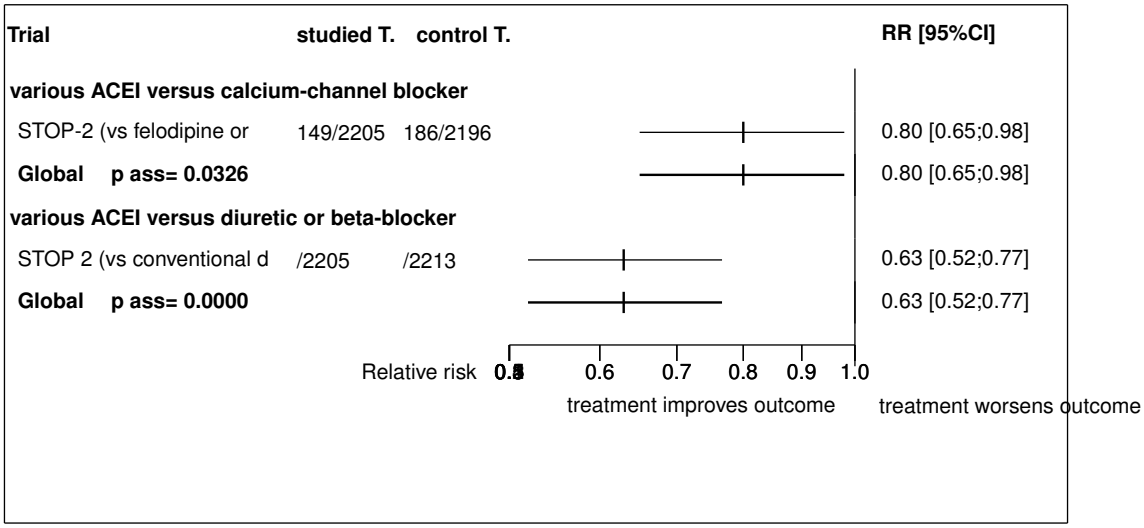
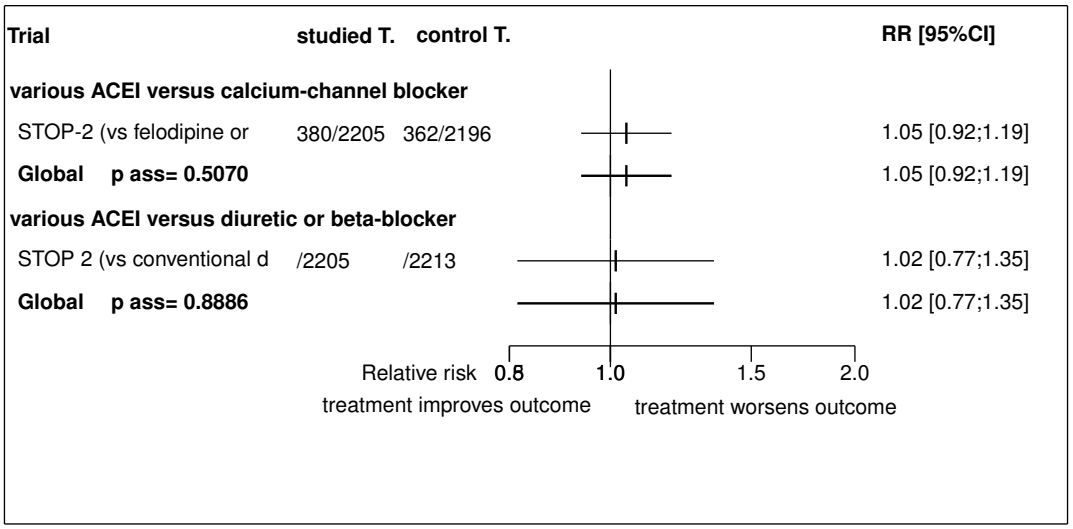


Figure 4.6: *Forest's plot for all cause death*



References

[1] Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten 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 Nov 20;354:1751-6. [PMID=10577635]

[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 Nov 20;354:1751-6. [PMID=10577635]

4.3 Individual trial summaries

Table 4.6: *STOP-2 (vs felodipine or isradipine), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4401 (2205 vs. 2196) **Follow-up duration:** 50 y **Study design:** Randomized controlled trial Parallel groups Open Sweden, 312 centres **Inclusion period:** Sep 1992 - dec 1994	Patients aged 70-84 years with hypertension (blood pressure >or = 180 mm Hg systolic, >or = 105 mm Hg diastolic, or both)	**Studied treatment:** Enalapril or lisinopril , enalapril 10 mg or lisinopril 10 mg daily **Control treatment:** felodipine 2.5 mg or isradipine 2-5 mg daily	Cardiovascular events RR=0.94 [0.85;1.04] Cardiovascular death RR=1.06 [0.89;1.27] Stroke (fatal and non fatal) RR=1.03 [0.86;1.24] Coronary event RR=0.87 [0.73;1.05] Heart failure RR=0.80 [0.65;0.98] All cause death RR=1.05 [0.92;1.19]

Reference

Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten 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 Nov 20;354:1751-6 [PMID=10577635]

Table 4.7: *STOP 2 (vs conventional drugs), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4418 (2205 vs. 2213) **Follow-up duration:** 5.0 y **Study design:** Randomized controlled trial Parallel groups Open Sweden, 312 centres **Inclusion period:** sept 1991 - dec 1994	Patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).	**Studied treatment:** enalapril 10 mg or lisinopril10 mg daily **Control treatment:** conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 25 mg daily)	

Reference

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 Nov 20;354:1751-6 [PMID=10577635]

5 Global meta-analysis: all angiotensin-converting enzyme inhibitors

5.1 Global meta-analysis: all angiotensin-converting enzyme inhibitors versus calcium-channel blocker

Table 5.1: *All angiotensin-converting enzyme inhibitorsversus calcium-channel blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.94	0.85;1.04	0.2464	1.0000 (0.00)	1	4401
cardiovascular death	RR=1.06	0.89;1.27	0.5094	1.0000 (0.00)	1	4401
stroke (fatal and non fatal)	RR=1.03	0.86;1.24	0.7148	1.0000 (0.00)	1	4401
coronary event	RR=0.87	0.73;1.05	0.1513	1.0000 (0.00)	1	4401
heart failure	RR=0.80	0.65;0.98	0.0326	1.0000 (0.00)	1	4401
all cause death	RR=1.05	0.92;1.19	0.5070	1.0000 (0.00)	1	4401

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

5.2 Global meta-analysis: all angiotensin-converting enzyme inhibitors versus diuretic or beta-blocker

Table 5.2: *All angiotensin-converting enzyme inhibitorsversus diuretic or beta-blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.94	0.71;1.24	0.6617	1.0000 (0.00)	1	4418
cardiovascular death	RR=1.01	0.72;1.42	0.9542	1.0000 (0.00)	1	4418
stroke (fatal and non fatal)	RR=0.90	0.74;1.09	0.2921	1.0000 (0.00)	1	4418
coronary event	RR=0.90	0.74;1.09	0.2921	1.0000 (0.00)	1	4418
heart failure	RR=0.63	0.52;0.77	0.0000	1.0000 (0.00)	1	4418
all cause death	RR=1.02	0.77;1.35	0.8886	1.0000 (0.00)	1	4418

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

5.3 Global meta-analysis: all angiotensin-converting enzyme inhibitors versus diuretics

Table 5.3: *All angiotensin-converting enzyme inhibitorsversus diuretics*

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

6 Ongoing studies of angiotensin-converting enzyme inhibitors

No ongoing trial was identified.

7 Excluded studies for angiotensin-converting enzyme inhibitors

No trial was excluded.

References

Part II

Beta-blockers

8 Overview of beta-blockers

8.1 Included trials

A total of 2 randomized comparisons which enrolled 5498 patients were identified. In all, 2 randomized comparisons concerned atenolol.
The detailed descriptions of trials and meta-analysis results is given in section 9 (page 49) for atenolol.

The average study size was 2749 patients (range 2183 to 3315). The first study was published in 1992, and the last study was published in 1992.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 8.1 (page 46) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

8.2 Summary of meta-analysis results

The meta-analysis of the available trials about beta-blockers provide the results listed in tables 8.2 to 8.2 (page 47) and in the following graphs.

8.2.1 Atenolol

No significant difference was found between **atenolol** and **placebo** in terms of myocardial infarction (fatal and non fatal) (RR=1.01, 95% CI 0.78 to 1.31, p=0.9375, 1 trial), stroke (fatal and non fatal) (RR=0.84, 95% CI 0.62 to 1.14, p=0.2575, 1 trial)and all cause death (RR=1.06, 95% CI 0.90 to 1.27, p=0.4782, 1 trial).

Atenolol was inferior to **hydrochlorothiazide+amiloride** in terms of myocardial infarction (fatal and non fatal) (RR=6.96, 95% CI 4.90 to 9.90, p=0.0000, 1 trial). No significant difference was found on stroke (fatal and non fatal) (RR=1.22, 95% CI 0.83 to 1.79, p=0.3078, 1 trial)and all cause death (RR=1.22, 95% CI 0.99 to 1.51, p=0.0623, 1 trial).

Table 8.1: *Main study characteristics - beta-blockers*

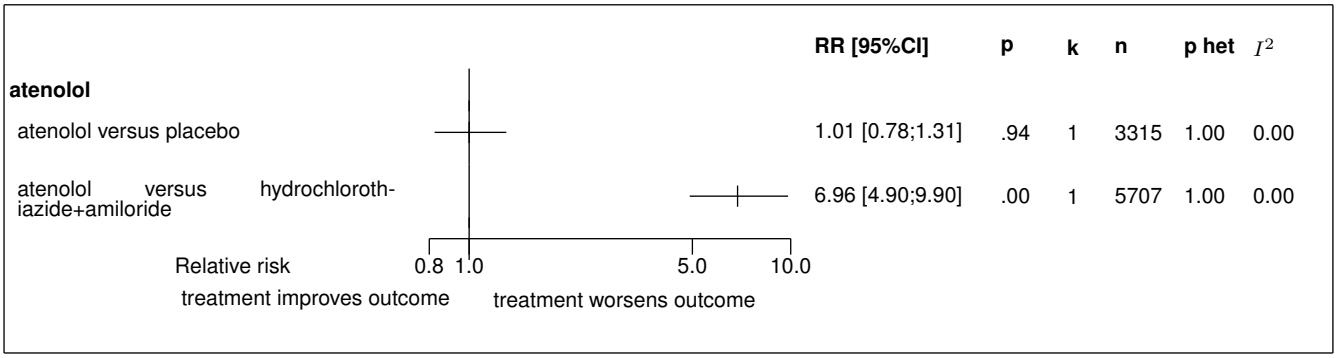
Trial	Patients	Treatments	Trial design and method
Atenolol			
Atenolol versus placebo			
MRC old (vs placebo), 1992 [1] n = 1102 vs. 2213	patients aged 65-74	atenolol **versus** placebo	double blind 226 centres, UK
Atenolol versus hydrochlorothiazide+amiloride			
MRC old (vs diuretics), 1992 [2] n = 1102 vs. 1081	hypertensive patients aged 65-74	atenolol **versus** hydrochlorothiazide/amiloride	double blind 226 centres, UK

Table 8.2: *Summary of all results for atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atenolol versus placebo						
myocardial infarction (fatal and non fatal)	RR=1.01	0.78;1.31	0.9375	1.0000 (0.00)	1	3315
stroke (fatal and non fatal)	RR=0.84	0.62;1.14	0.2575	1.0000 (0.00)	1	3315
all cause death	RR=1.06	0.90;1.27	0.4782	1.0000 (0.00)	1	3315
atenolol versus hydrochlorothiazide+amiloride						
myocardial infarction (fatal and non fatal)	RR=6.96	4.90;9.90	0.0000	1.0000 (0.00)	1	5707
stroke (fatal and non fatal)	RR=1.22	0.83;1.79	0.3078	1.0000 (0.00)	1	2183
all cause death	RR=1.22	0.99;1.51	0.0623	1.0000 (0.00)	1	2183

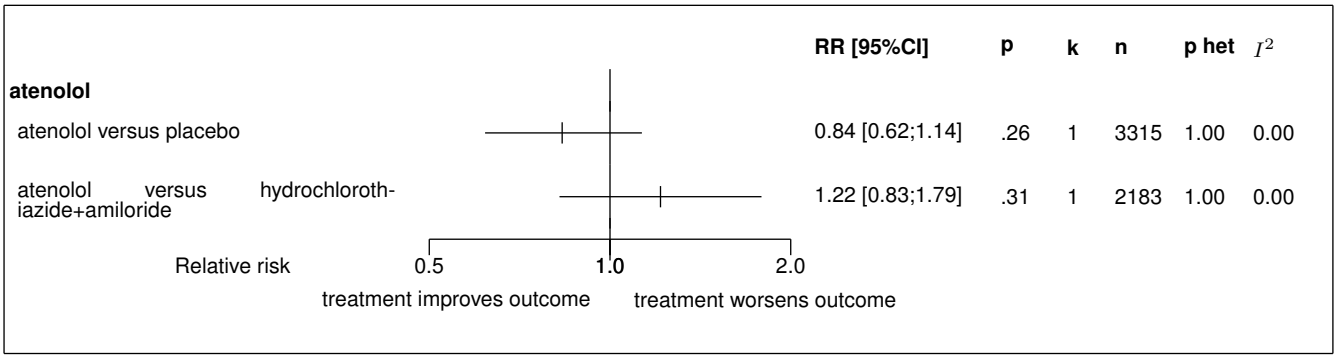
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 8.1: *Forest's plot for myocardial infarction (fatal and non fatal)*



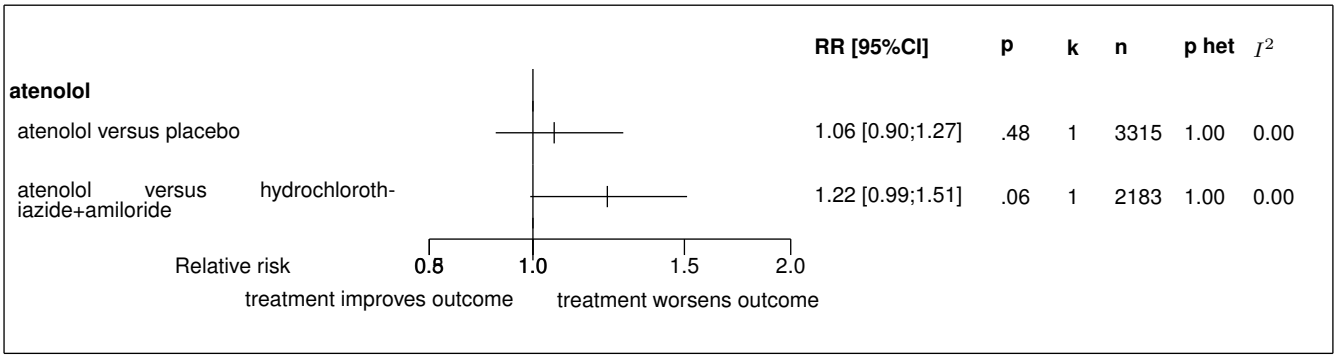
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 8.2: *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 8.3: *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

9 Details

9.1 Available trials

A total of 2 RCTs which randomized 5498 patients were identified: it compared atenolol with placebo and it compared atenolol with hydrochlorothiazide+amiloride.
The average study size was 2749 patients (range 2183 to 3315). The first study was published in 1992, and the last study was published in 1992.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Myocardial infarction (fatal and non fatal) data was reported in 2 trials; 2 trials reported data on stroke (fatal and non fatal); and 2 trials reported data on all cause death.
Following tables 9.1 (page 49), 9.2 (page 49), 9.4 (page 51), and 9.3 (page 50) summarized the main characteristics of the trials including in this systematic review of randomized trials of atenolol.

Table 9.1: *Treatment description - beta-blockers - atenolol*

Trial	Studied treatment	Control treatment
Atenolol versus placebo		
MRC old (vs placebo) (1992) [1]	Atenolol	Placebo
Atenolol versus hydrochlorothiazide+amiloride		
MRC old (vs diuretics) (1992) [2]	Atenolol	Hydrochlorothiazide/amiloride

Table 9.2: *Descriptions of participants - beta-blockers - atenolol*

Trial	Patients
Atenolol versus placebo	
MRC old (vs placebo) (1992) [1]	Patients aged 65-74
Atenolol versus hydrochlorothiazide+amiloride	
MRC old (vs diuretics) (1992) [2]	Hypertensive patients aged 65-74

Table 9.3: *Design and methodological quality of trials - beta-blockers - atenolol*

Trial	Design	Duration	Centre	Primary end-point
Atenolol versus placebo				
MRC old (vs placebo), 1992 [1] n=3315	double blind	5.8y	UK 226 centres	
Atenolol versus hydrochlorothiazide+amiloride				
MRC old (vs diuretics), 1992 [2] n=2183	double blind	58y	UK 226 centres	

Table 9.4: *Trial characteristics - beta-blockers - atenolol*

Trial
Atenolol versus placebo
MRC old (vs placebo), 1992 [1]
Atenolol versus hydrochlorothiazide+amiloride
MRC old (vs diuretics), 1992 [2]

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 52). This table is followed by the Forest's plot corresponding to each endpoint.

Atenolol versus placebo

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 1.01 (95% CI 0.78 to 1.31, p=0.9375).
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 0.84 (95% CI 0.62 to 1.14, p=0.2575).
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 1.06 (95% CI 0.90 to 1.27, p=0.4782).

Atenolol versus hydrochlorothiazide+amiloride

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 hydrochlorothiazide+amiloride in myocardial infarction (fatal and non fatal), with a RR of 6.96 (95% CI 4.90 to 9.90, 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 1.22 (95% CI 0.83 to 1.79, p=0.3078).
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 1.22 (95% CI 0.99 to 1.51, p=0.0623).

Table 9.5: *Results details - beta-blockers - atenolol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atenolol versus placebo						
myocardial infarction (fatal and non fatal)	RR=1.01	[0.78;1.31]	0.9375	1.0000 (I^2=0.00)	1	3315
stroke (fatal and non fatal)	RR=0.84	[0.62;1.14]	0.2575	1.0000 (I^2=0.00)	1	3315
all cause death	RR=1.06	[0.90;1.27]	0.4782	1.0000 (I^2=0.00)	1	3315
atenolol versus hydrochlorothiazide+amiloride						
myocardial infarction (fatal and non fatal)	RR=6.96	[4.90;9.90]	0.0000	1.0000 (I^2=0.00)	1	5707
stroke (fatal and non fatal)	RR=1.22	[0.83;1.79]	0.3078	1.0000 (I^2=0.00)	1	2183
all cause death	RR=1.22	[0.99;1.51]	0.0623	1.0000 (I^2=0.00)	1	2183

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

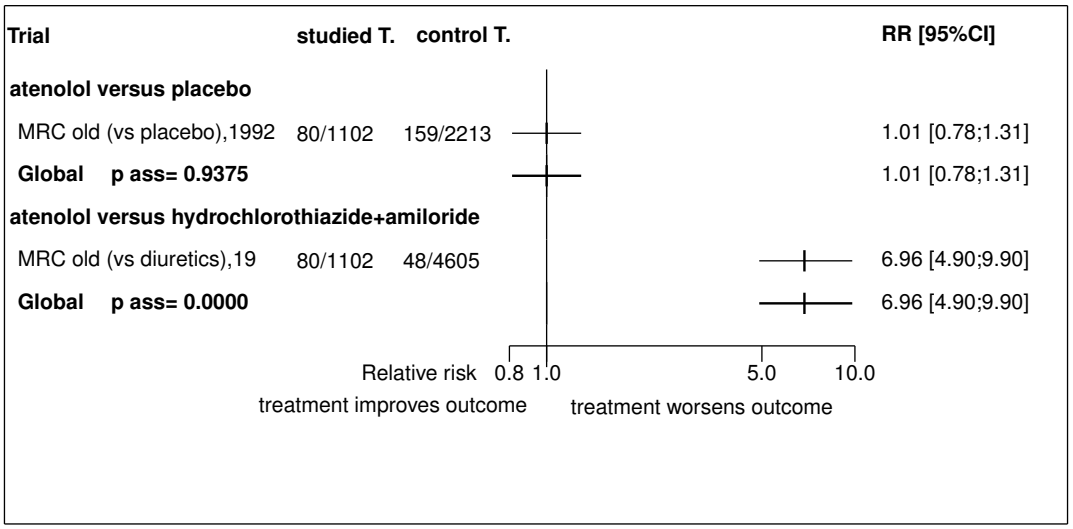


Figure 9.2: *Forest's plot for stroke (fatal and non fatal)*

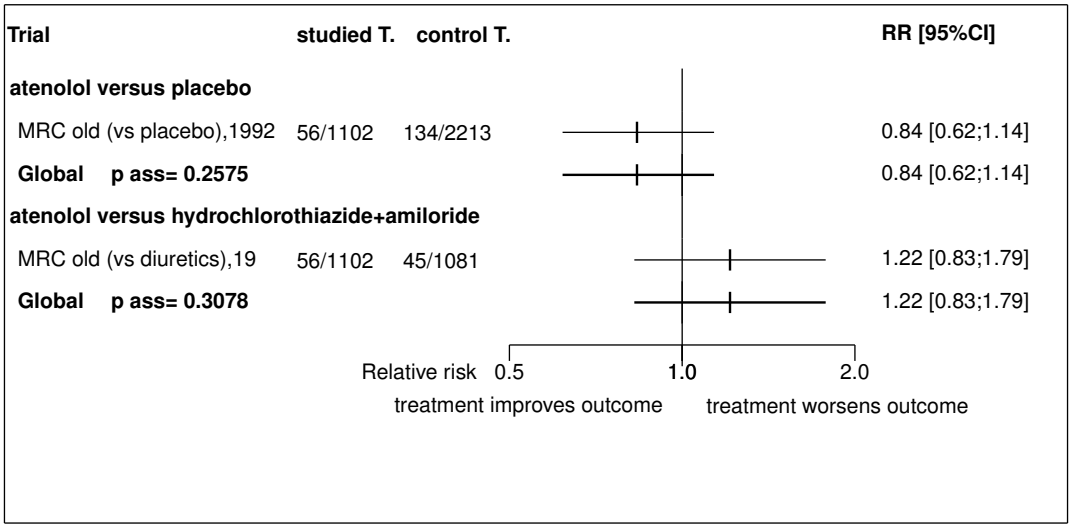
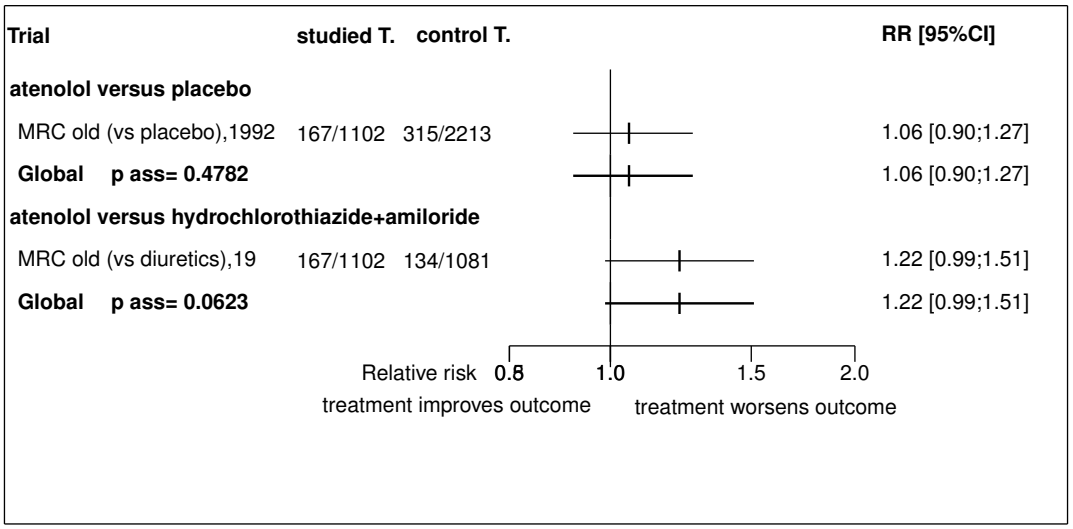


Figure 9.3: *Forest's plot for all cause death*



References

[1] . Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992 Feb 15;304:405-12. [PMID=1445513]

[2] . Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992;304:405-12. [PMID=1445513]

9.3 Individual trial summaries

Table 9.6: *MRC old (vs placebo), 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3315 (1102 vs. 2213) **Follow-up duration:** 5.8y **Study design:** Randomized controlled trial Double blind UK, 226 centres	Patients aged 65-74	**Studied treatment:** Atenolol **Control treatment:** Placebo	Myocardial infarction (fatal and non fatal) RR=1.01 [0.78;1.31] Stroke (fatal and non fatal) RR=0.84 [0.62;1.14] All cause death RR=1.06 [0.90;1.27]

Reference

. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992 Feb 15;304:405-12 [PMID=1445513]

Table 9.7: *MRC old (vs diuretics), 1992 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2183 (1102 vs. 1081) **Follow-up duration:** 58y **Study design:** Randomized controlled trial Double blind UK, 226 centres	Hypertensive patients aged 65-74	**Studied treatment:** Atenolol **Control treatment:** Hydrochlorothiazide/amiloride	Myocardial infarction (fatal and non fatal) RR=6.96 [4.90;9.90] Stroke (fatal and non fatal) RR=1.22 [0.83;1.79] All cause death RR=1.22 [0.99;1.51]

Reference

. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992;304:405-12 [PMID=1445513]

10 Global meta-analysis: all beta-blockers

10.1 Global meta-analysis: all beta-blockers versus hydrochlorothiazide+amiloride

Table 10.1: *All beta-blockersversus hydrochlorothiazide+amiloride*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=6.96	4.90;9.90	0.0000	1.0000 (0.00)	1	5707
stroke (fatal and non fatal)	RR=1.22	0.83;1.79	0.3078	1.0000 (0.00)	1	2183
all cause death	RR=1.22	0.99;1.51	0.0623	1.0000 (0.00)	1	2183

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

10.2 Global meta-analysis: all beta-blockers versus placebo

Table 10.2: *All beta-blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=1.01	0.78;1.31	0.9375	1.0000 (0.00)	1	3315
stroke (fatal and non fatal)	RR=0.84	0.62;1.14	0.2575	1.0000 (0.00)	1	3315
all cause death	RR=1.06	0.90;1.27	0.4782	1.0000 (0.00)	1	3315

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

11 Ongoing studies of beta-blockers

No ongoing trial was identified.

12 Excluded studies for beta-blockers

No trial was excluded.

References

Part III

Calcium-channel blockers

13 Overview of calcium-channel blockers

13.1 Included trials

A total of 5 randomized comparisons which enrolled 9884 patients were identified. In all, 1 randomized comparison concerned felopidine or israpidine , one lacidipine , one nicardipine , one nifedipine and one nitrendipine.
The detailed descriptions of trials and meta-analysis results is given in section 14 (page 72) for felopidine or israpidine, in section 15 (page 81) for lacidipine, in section 16 (page 86) for nicardipine, in section 17 (page 95) for nifedipine and in section 18 (page 100) for nitrendipine.

The average study size was 2471 patients (range 351 to 4695). The first study was published in 1994, and the last study was published in 2003.
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.
The table 13.1 (page 65) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

13.2 Summary of meta-analysis results

The meta-analysis of the available trials about calcium-channel blockers provide the results listed in tables 13.2 to 13.6 (page 67) and in the following graphs.

13.2.1 Felopidine or israpidine

No significant difference was found between **felopidine or israpidine** and **diuretic or beta-blocker** in terms of cardiovascular events (RR=1.00, 95% CI 0.90 to 1.10, p=0.9548, 1 trial), cardiovascular death (RR=0.97, 95% CI 0.81 to 1.16, p=0.7107, 1 trial), stroke (fatal and non fatal) (RR=0.88, 95% CI 0.74 to 1.05, p=0.1573, 1 trial), coronary event (RR=1.12, 95% CI 0.93 to 1.34, p=0.2259, 1 trial), heart failure (RR=1.06, 95% CI 0.87 to 1.29, p=0.5689, 1 trial)and all cause death (RR=0.99, 95% CI 0.87 to 1.13, p=0.8655, 1 trial).

13.2.2 Lacidipine

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

13.2.3 Nicardipine

No significant difference was found between **nicardipine** and **trichlormethiazide** in terms of cardiovascular events (RR=0.69, 95% CI 0.30 to 1.58, p=0.3784, 1 trial), cardiovascular death (RR=3.98, 95% CI 0.18 to 87.78, p=0.3813, 1 trial), stroke (fatal and non fatal) (RR=0.75, 95% CI 0.26 to 2.12, p=0.5822, 1 trial), coronary event (RR=1.00, 95% CI 0.14 to 7.00, p=0.9963, 1 trial), heart failure (RR=0.17, 95% CI 0.01 to 3.29, p=0.2386, 1 trial)and all cause death (RR=1.00, 95% CI 0.14 to 7.00, p=0.9963, 1 trial).

13.2.4 Nifedipine

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

13.2.5 Nitrendipine

Nitrendipine was superior to **placebo** in terms of cardiovascular events (RR=0.71, 95% CI 0.57 to 0.87, p=0.0000, 1 trial)and stroke (fatal and non fatal) (RR=0.59, 95% CI 0.41 to 0.83, p=0.0029, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.73, 95% CI 0.53 to 1.03, p=0.0697, 1 trial), coronary event (RR=0.75, 95% CI 0.50 to 1.13, p=0.1716, 1 trial), heart failure (RR=0.75, 95% CI 0.50 to 1.13, p=0.1716, 1 trial)and all cause death (RR=0.86, 95% CI 0.68 to 1.09, p=0.2116, 1 trial).

Table 13.1: *Main study characteristics - calcium-channel blockers*

Trial	Patients	Treatments	Trial design and method
Felopidine or israpidine			
Felopidine or israpidine versus diuretic or beta-blocker			
STOP 2 (vs diurectic or beta-blocker), 1999 [1] n = 2196 vs. 2213	patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).	felodipine 25 mg or isradipine 25 mg daily **versus** conventional antihypertensivedrugs (atenolol 50 mg, metoprolol 100 mg,pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride2.5 mg daily	open parallel groups Primary endpoint: fatal CV disease
Lacidipine			
Lacidipine versus chlorthalidone			
SHELL, 2003 [1] n = NA vs. NA	elderly patients with isolated systolic hypertension >or = 60 years	lacidipine 4 mg/d **versus** chlorthalidone 12.5 mg/d	Primary endpoint: cardiovascular and cerebrovascular events
Nicardipine			
Nicardipine versus trichlormethiazide			
NICS-EH, 1999 [1] n = 215 vs. 214	>=60 years of age with systolic blood pressure of 160 to 220 mm Hg and diastolic blood pressure <115 mm Hg	nicardipine SR 20mg twice daily **versus** trichlormethiazide 2mg once daily	double blind parallel groups Primary endpoint: CV events
Nifedipine			
Nifedipine versus atenolol+chlorthalidone			
Castel, 1994 [1] n = 146 vs. 205		nifedipine 20mg/d **versus** clonidine 0.15mg/d (n=61) or atenolol 100mg/d + chlorthalidone 25mg/d	
Nitrendipine			

continued...

Trial	Patients	Treatments	Trial design and method
Nitrendipine versus placebo			
SYST-EUR, 1997 [1] n = 2398 vs. 2297	HBP, >=60 years	nitrendipine 10-40 mg daily , nitrendipine 10-40 mg daily **versus** placebo	double aveugle parallel groups 198 centres, 23 countries across Europe

Table 13.2: *Summary of all results for felopidine or israpidine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
felopidine or israpidine versus diuretic or beta-blocker						
cardiovascular events	RR=1.00	0.90;1.10	0.9548	1.0000 (0.00)	1	4409
cardiovascular death	RR=0.97	0.81;1.16	0.7107	1.0000 (0.00)	1	4409
stroke (fatal and non fatal)	RR=0.88	0.74;1.05	0.1573	1.0000 (0.00)	1	4409
coronary event	RR=1.12	0.93;1.34	0.2259	1.0000 (0.00)	1	4409
heart failure	RR=1.06	0.87;1.29	0.5689	1.0000 (0.00)	1	4409
all cause death	RR=0.99	0.87;1.13	0.8655	1.0000 (0.00)	1	4409

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 13.3: *Summary of all results for lacidipine*

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

Table 13.4: *Summary of all results for nicardipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nicardipine versus trichlormethiazide						
cardiovascular events	RR=0.69	0.30;1.58	0.3784	1.0000 (0.00)	1	429
cardiovascular death	RR=3.98	0.18;87.78	0.3813	1.0000 (0.00)	1	429
stroke (fatal and non fatal)	RR=0.75	0.26;2.12	0.5822	1.0000 (0.00)	1	429
coronary event	RR=1.00	0.14;7.00	0.9963	1.0000 (0.00)	1	429
heart failure	RR=0.17	0.01;3.29	0.2386	1.0000 (0.00)	1	429
all cause death	RR=1.00	0.14;7.00	0.9963	1.0000 (0.00)	1	429

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 13.5: *Summary of all results for nifedipine*

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

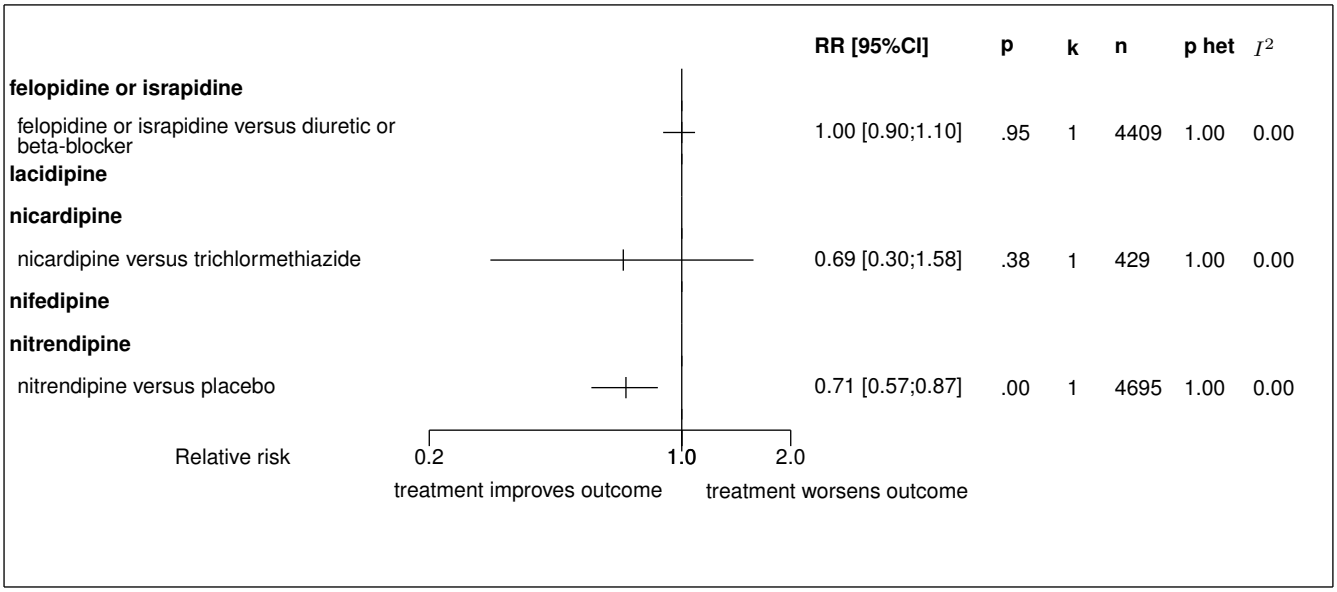
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 13.6: *Summary of all results for nitrendipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nitrendipine versus placebo						
cardiovascular events	RR=0.71	0.57;0.87	0.0000	1.0000 (0.00)	1	4695
cardiovascular death	RR=0.73	0.53;1.03	0.0697	1.0000 (0.00)	1	4695
stroke (fatal and non fatal)	RR=0.59	0.41;0.83	0.0029	1.0000 (0.00)	1	4695
coronary event	RR=0.75	0.50;1.13	0.1716	1.0000 (0.00)	1	4695
heart failure	RR=0.75	0.50;1.13	0.1716	1.0000 (0.00)	1	4695
all cause death	RR=0.86	0.68;1.09	0.2116	1.0000 (0.00)	1	4695

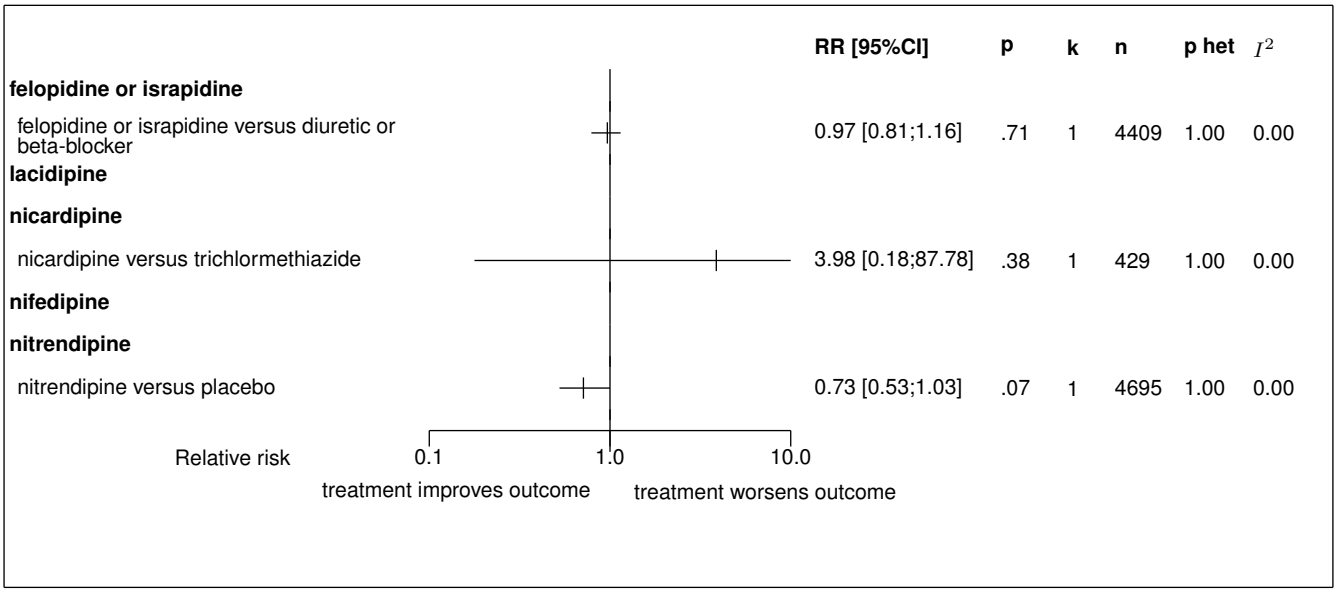
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 13.1: *Forest's plot for cardiovascular events*



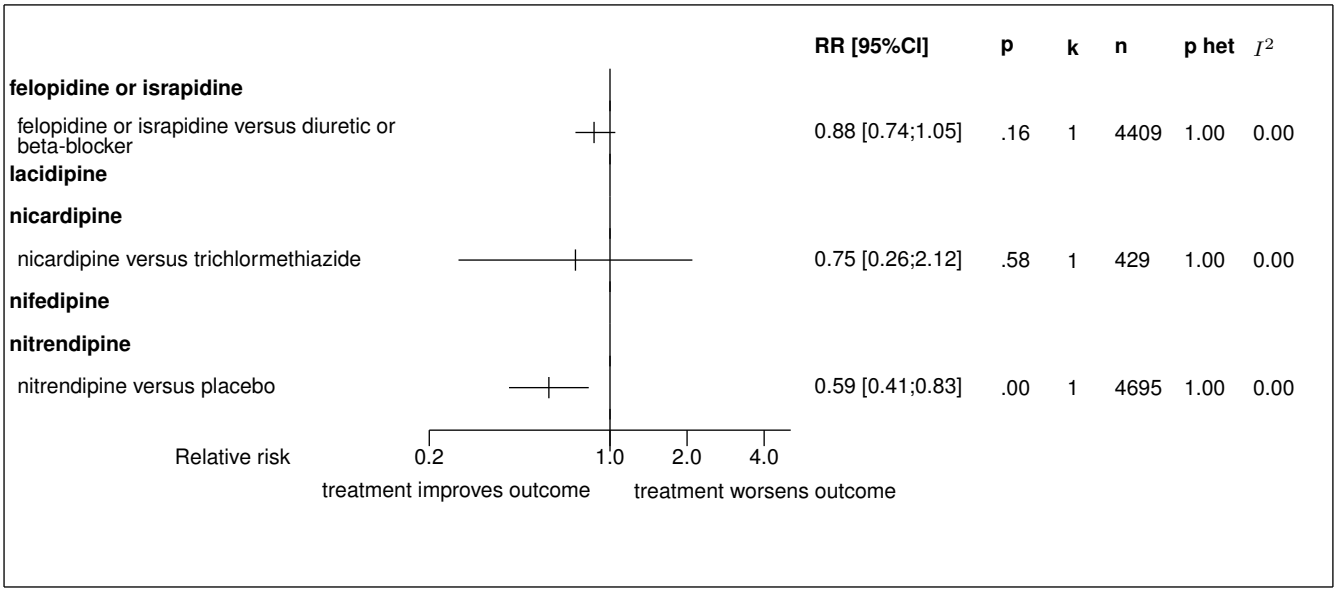
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 13.2: *Forest's plot for cardiovascular death*



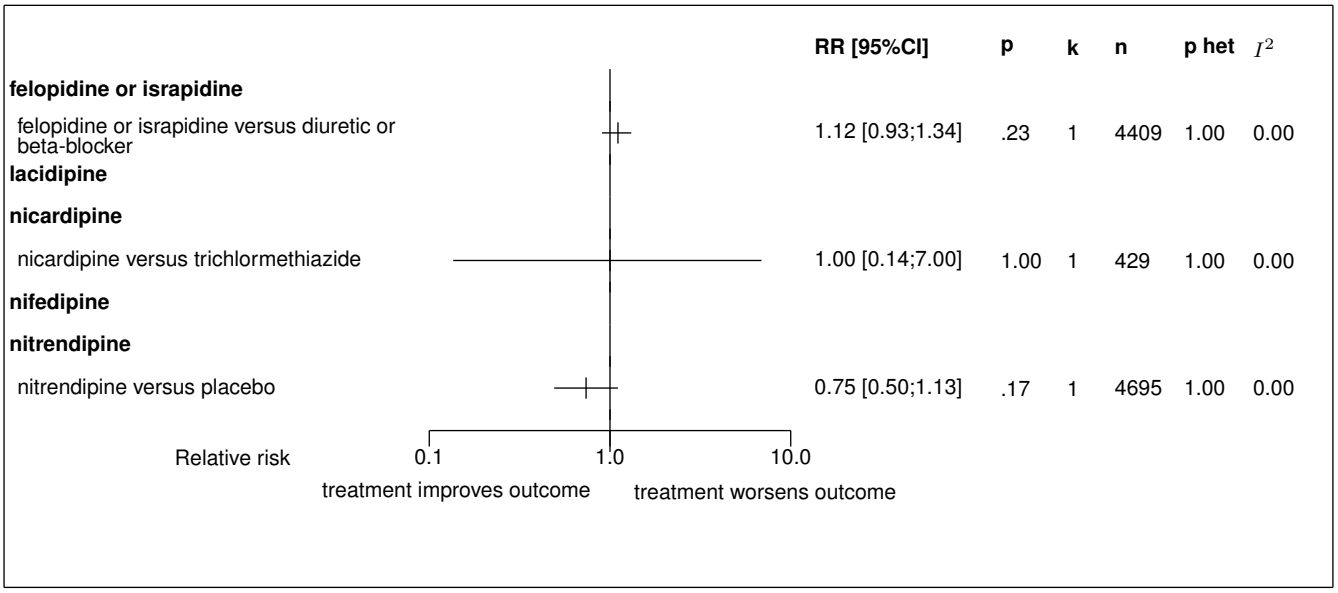
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 13.3: *Forest's plot for stroke (fatal and non fatal)*



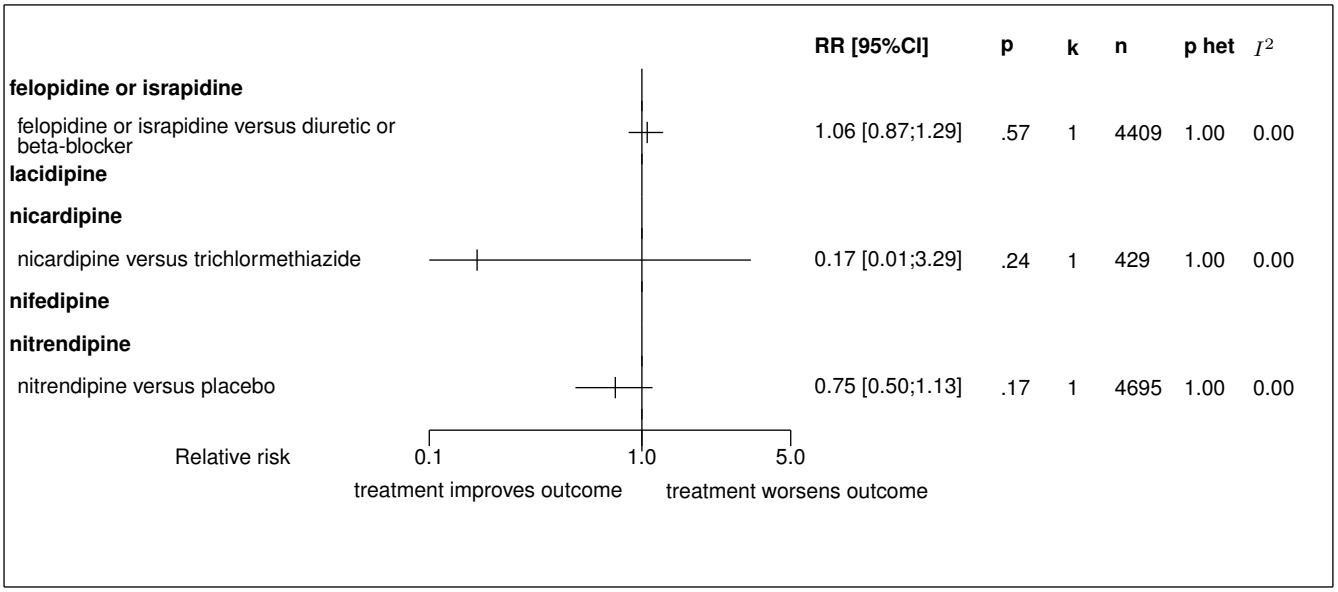
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 13.4: *Forest's plot for coronary event*



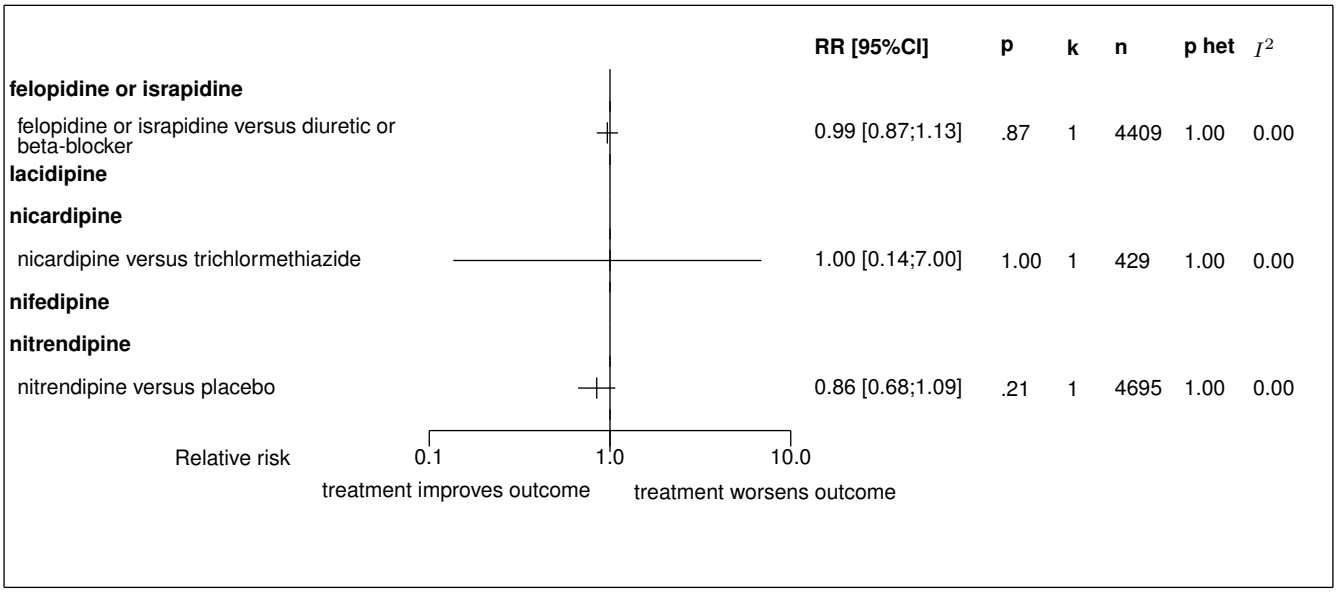
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 13.5: *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 13.6: *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; ˡ: random effect model used

14 Detailed results for felopidine or israpidine

14.1 Available trials

Only one trial which randomized 4409 patients was identified: it compared felopidine or israpidine with diuretic or beta-blocker.
This trial included 4409 patients and was published in 1999.
This trial was open-label in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on cardiovascular events; 1 trials reported data on coronary event; 1 trials reported data on cardiovascular death; 1 trials reported data on heart failure; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 14.1 (page 72), 14.2 (page 72), 14.4 (page 74), and 14.3 (page 73) summarized the main characteristics of the trial including in this systematic review of randomized trials of felopidine or israpidine.

Table 14.1: *Treatment description - calcium-channel blockers - felopidine or israpidine*

Trial	Studied treatment	Control treatment
Felopidine or israpidine versus diuretic or beta-blocker		
STOP 2 (vs diurectic or beta-blocker) (1999) [1]	felodipine 25 mg or isradipine 25 mg daily	conventional antihypertensivedrugs (atenolol 50 mg, metoprolol 100 mg,pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride2.5 mg daily

Table 14.2: *Descriptions of participants - calcium-channel blockers - felopidine or israpidine*

Trial	Patients
Felopidine or israpidine versus diuretic or beta-blocker	
STOP 2 (vs diurectic or beta-blocker) (1999) [1]	Patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).

Table 14.3: *Design and methodological quality of trials - calcium-channel blockers - felopidine or israpidine*

Trial	Design	Duration	Centre	Primary end-point
Felopidine or israpidine versus diuretic or beta-blocker				
STOP 2 (vs diurectic or beta-blocker), 1999 [1] n=4409	Parallel groups Open	up to 6 years		Fatal CV disease

Table 14.4: *Trial characteristics - calcium-channel blockers - felopidine or israpidine*

Trial
Felopidine or israpidine versus diuretic or beta-blocker
STOP 2 (vs diurectic or beta-blocker), 1999 [1]

14.2 Meta-analysis results

The results are detailed in table 14.5 (page 75). This table is followed by the Forest's plot corresponding to each endpoint.

Felopidine or israpidine versus diuretic or beta-blocker

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between felopidine or israpidine and diuretic or beta-blocker, with a RR of 1.00 (95%CI 0.90 to 1.10, p=0.9548) in favour of felopidine or israpidine. In other words, cardiovascular events was slightly lower in the felopidine or israpidine group , but this was not statistically significant.
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 0.97 (95% CI 0.81 to 1.16, p=0.7107).
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 0.88 (95% CI 0.74 to 1.05, p=0.1573).
The single study 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 1.12 (95% CI 0.93 to 1.34, p=0.2259).
The single study 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 1.06 (95% CI 0.87 to 1.29, p=0.5689).
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 0.99 (95% CI 0.87 to 1.13, p=0.8655).

Table 14.5: *Results details - calcium-channel blockers - felopidine or israpidine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
felopidine or israpidine versus diuretic or beta-blocker						
cardiovascular events	RR=1.00	[0.90;1.10]	0.9548	1.0000 (I^2=0.00)	1	4409
cardiovascular death	RR=0.97	[0.81;1.16]	0.7107	1.0000 (I^2=0.00)	1	4409
stroke (fatal and non fatal)	RR=0.88	[0.74;1.05]	0.1573	1.0000 (I^2=0.00)	1	4409
coronary event	RR=1.12	[0.93;1.34]	0.2259	1.0000 (I^2=0.00)	1	4409
heart failure	RR=1.06	[0.87;1.29]	0.5689	1.0000 (I^2=0.00)	1	4409
all cause death	RR=0.99	[0.87;1.13]	0.8655	1.0000 (I^2=0.00)	1	4409

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*

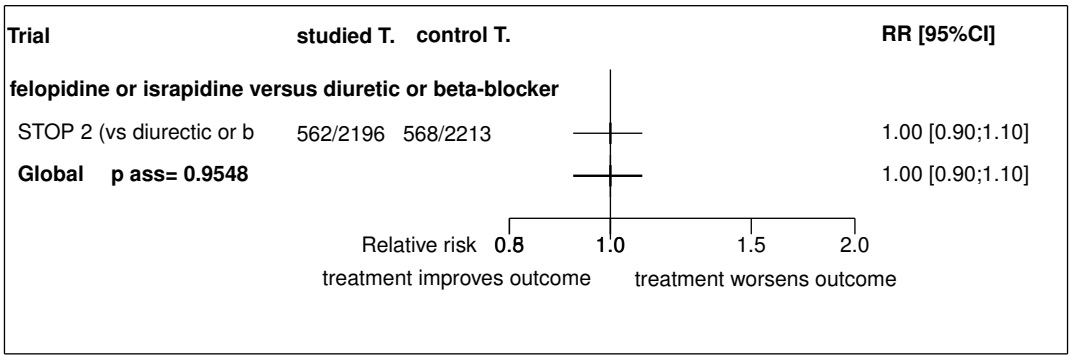


Figure 14.2: *Forest's plot for cardiovascular death*

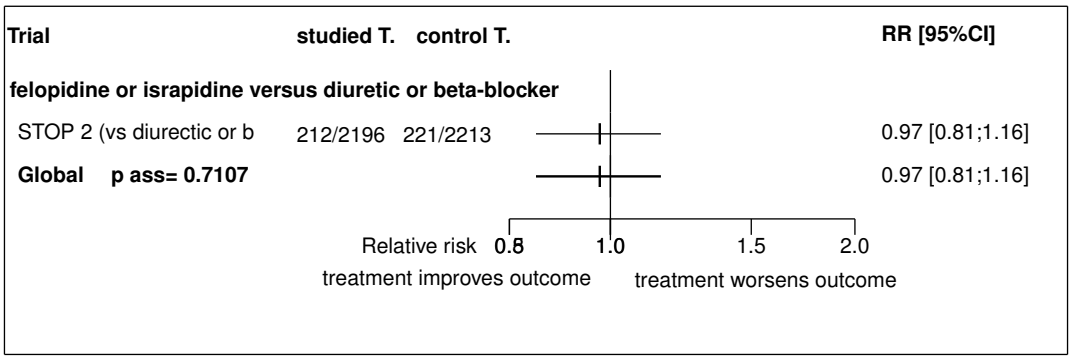


Figure 14.3: *Forest's plot for stroke (fatal and non fatal)*

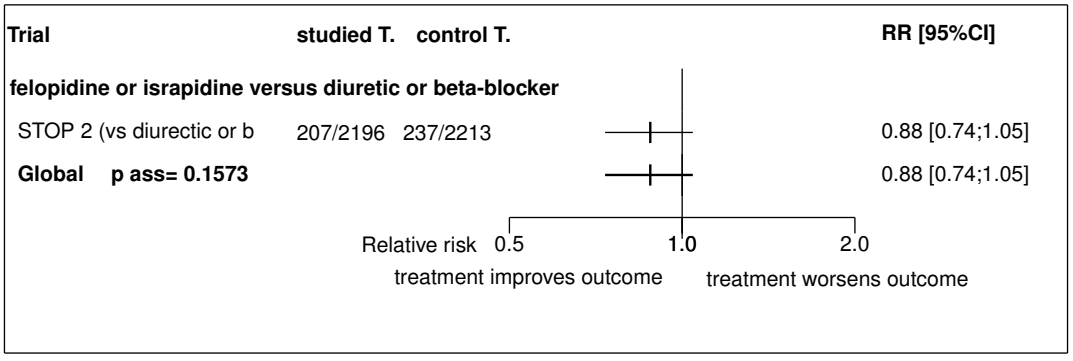


Figure 14.4: *Forest's plot for coronary event*

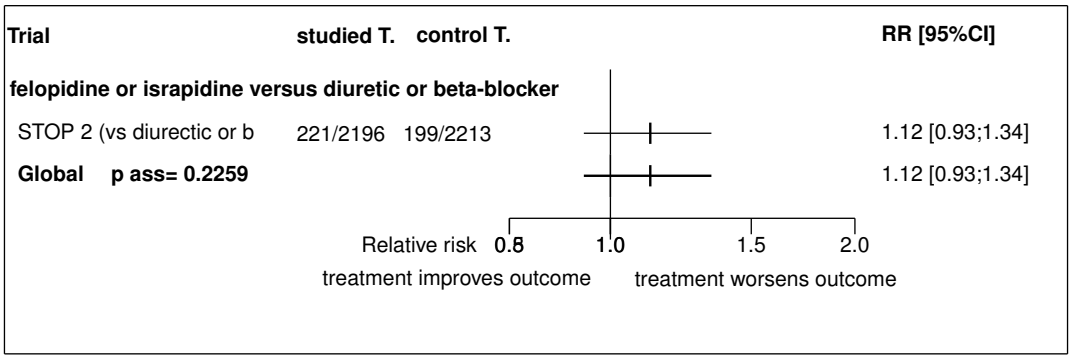


Figure 14.5: *Forest's plot for heart failure*

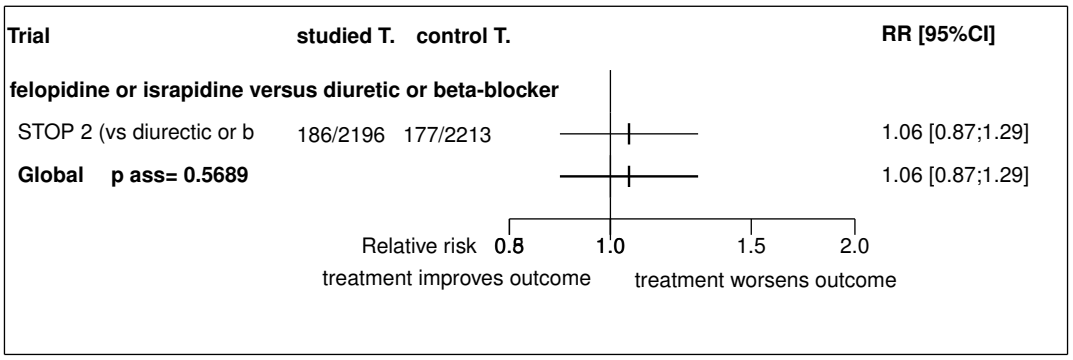
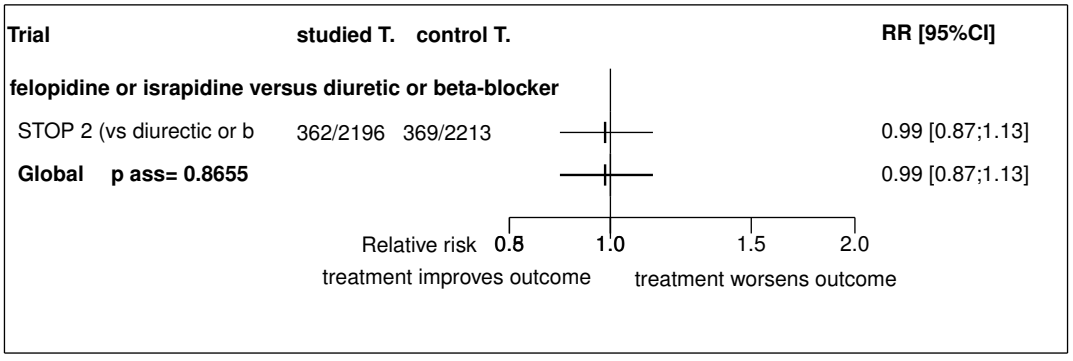


Figure 14.6: *Forest's plot for all cause death*



References

[1] Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten 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 Nov 20;354:1751-6. [PMID=10577635]

14.3 Individual trial summaries

Table 14.6: *STOP 2 (vs diurectic or beta-blocker), 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4409 (2196 vs. 2213) **Follow-up duration:** up to 6 years **Study design:** Randomized controlled trial Parallel groups Open	Patients aged 7084 years with hypertension (blood pressure >180 mm Hg systolic, >105 mm Hg diastolic, or both).	**Studied treatment:** felodipine 25 mg or isradipine 25 mg daily **Control treatment:** conventional antihypertensivedrugs (atenolol 50 mg, metoprolol 100 mg,pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride2.5 mg daily	Cardiovascular events RR=1.00 [0.90;1.10] Cardiovascular death RR=0.97 [0.81;1.16] Stroke (fatal and non fatal) RR=0.88 [0.74;1.05] Coronary event RR=1.12 [0.93;1.34] Heart failure RR=1.06 [0.87;1.29] All cause death RR=0.99 [0.87;1.13]

Reference

Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten 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 Nov 20;354:1751-6 [PMID=10577635]

15 Detailed results for lacidipine

15.1 Available trials

Only one trial which randomized 0 patients was identified: it compared lacidipine with chlorthalidone.
This trial included NaN patients and was published in 2003.
Erreur ??? 0 et 0.
It was reported in English language.
data was reported in trials;
Following tables 15.1 (page 81), 15.2 (page 81), 15.4 (page 82), and 15.3 (page 81) summarized the main characteristics of the trial including in this systematic review of randomized trials of lacidipine.

Table 15.1: *Treatment description - calcium-channel blockers - lacidipine*

Trial	Studied treatment	Control treatment
Lacidipine versus chlorthalidone		
SHELL (2003) [1]	lacidipine 4 mg/d	chlorthalidone 12.5 mg/d

Table 15.2: *Descriptions of participants - calcium-channel blockers - lacidipine*

Trial	Patients
Lacidipine versus chlorthalidone	
SHELL (2003) [1]	Elderly patients with isolated systolic hypertension >or = 60 years **Inclusion criteria:** sitting systolic blood pressure was >or = 160 mmHg with a diastolic blood pressure equal or lower than 95 mmHg **Exclusion criteria:**

Table 15.3: *Design and methodological quality of trials - calcium-channel blockers - lacidipine*

Trial	Design	Duration	Centre	Primary endpoint
Lacidipine versus chlorthalidone				
SHELL, 2003 [1] n=NaN		36?y		cardiovascular and cerebrovascular events

Table 15.4: *Trial characteristics - calcium-channel blockers - lacidipine*

Trial
Lacidipine versus chlorthalidone
SHELL, 2003 [1]

15.2 Meta-analysis results

The results are detailed in table 15.5 (page 83). This table is followed by the Forest's plot corresponding to each endpoint.

Lacidipine versus chlorthalidone

No data were presented in the 1 trial identified

Table 15.5: *Results details - calcium-channel blockers - lacidipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
lacidipine 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] Malacco E, Mancia G, Rappelli A, Menotti A, Zuccaro MS, Coppini A. Treatment of isolated systolic hypertension: the SHELL study results. Blood Press 2003;12:160-7. [PMID=12875478]

15.3 Individual trial summaries

Table 15.6: *SHELL, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=NA (NA vs. NA) **Follow-up duration:** 36?y **Study design:** Randomized controlled trial	Elderly patients with isolated systolic hypertension >or = 60 years **Inclusion criteria:** sitting systolic blood pressure was >or = 160 mmHg with a diastolic blood pressure equal or lower than 95 mmHg	**Studied treatment:** lacidipine 4 mg/d **Control treatment:** chlorthalidone 12.5 mg/d	

Reference

Malacco E, Mancia G, Rappelli A, Menotti A, Zuccaro MS, Coppini A. Treatment of isolated systolic hypertension: the SHELL study results. Blood Press 2003;12:160-7 [PMID=12875478]

16 Detailed results for nicardipine

16.1 Available trials

Only one trial which randomized 429 patients was identified: it compared nicardipine with trichlormethiazide.
This trial included 429 patients and was published in 1999.
This trial was double blind in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on cardiovascular events; 1 trials reported data on coronary event; 1 trials reported data on cardiovascular death; 1 trials reported data on heart failure; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 16.1 (page 86), 16.2 (page 86), 16.4 (page 88), and 16.3 (page 86) summarized the main characteristics of the trial including in this systematic review of randomized trials of nicardipine.

Table 16.1: *Treatment description - calcium-channel blockers - nicardipine*

Trial	Studied treatment	Control treatment
Nicardipine versus trichlormethiazide		
NICS-EH (1999) [1]	Nicardipine SR 20mg twice daily	trichlormethiazide 2mg once daily

Table 16.2: *Descriptions of participants - calcium-channel blockers - nicardipine*

Trial	Patients
Nicardipine versus trichlormethiazide	
NICS-EH (1999) [1]	>=60 years of age with systolic blood pressure of 160 to 220 mm Hg and diastolic blood pressure <115 mm Hg

Table 16.3: *Design and methodological quality of trials - calcium-channel blockers - nicardipine*

Trial	Design	Duration	Centre	Primary end-point
Nicardipine versus trichlormethiazide				
NICS-EH, 1999 [1] n=429	Parallel groups Double blind	4.5 years		CV events

continued...

Trial	Design	Duration	Centre	Primary end-point

Table 16.4: *Trial characteristics - calcium-channel blockers - nicardipine*

Trial
Nicardipine versus trichlormethiazide
NICS-EH, 1999 [1]

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 89). This table is followed by the Forest's plot corresponding to each endpoint.

Nicardipine versus trichlormethiazide

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between nicardipine and trichlormethiazide, with a RR of 0.69 (95%CI 0.30 to 1.58, p=0.3784) in favour of nicardipine. In other words, cardiovascular events was slightly lower in the nicardipine group , but this was not statistically significant.
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 3.98 (95% CI 0.18 to 87.78, p=0.3813).
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 0.75 (95% CI 0.26 to 2.12, p=0.5822).
The single study 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 1.00 (95% CI 0.14 to 7.00, p=0.9963).
The single study 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 0.17 (95% CI 0.01 to 3.29, p=0.2386).
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 1.00 (95% CI 0.14 to 7.00, p=0.9963).

Table 16.5: *Results details - calcium-channel blockers - nicardipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nicardipine versus trichlormethiazide						
cardiovascular events	RR=0.69	[0.30;1.58]	0.3784	1.0000 (I^2=0.00)	1	429
cardiovascular death	RR=3.98	[0.18;87.78]	0.3813	1.0000 (I^2=0.00)	1	429
stroke (fatal and non fatal)	RR=0.75	[0.26;2.12]	0.5822	1.0000 (I^2=0.00)	1	429
coronary event	RR=1.00	[0.14;7.00]	0.9963	1.0000 (I^2=0.00)	1	429
heart failure	RR=0.17	[0.01;3.29]	0.2386	1.0000 (I^2=0.00)	1	429
all cause death	RR=1.00	[0.14;7.00]	0.9963	1.0000 (I^2=0.00)	1	429

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 16.1: *Forest's plot for cardiovascular events*

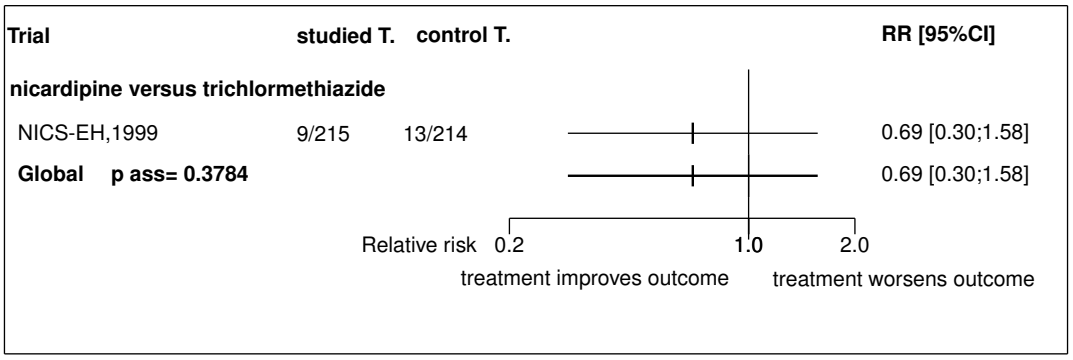


Figure 16.2: *Forest's plot for cardiovascular death*

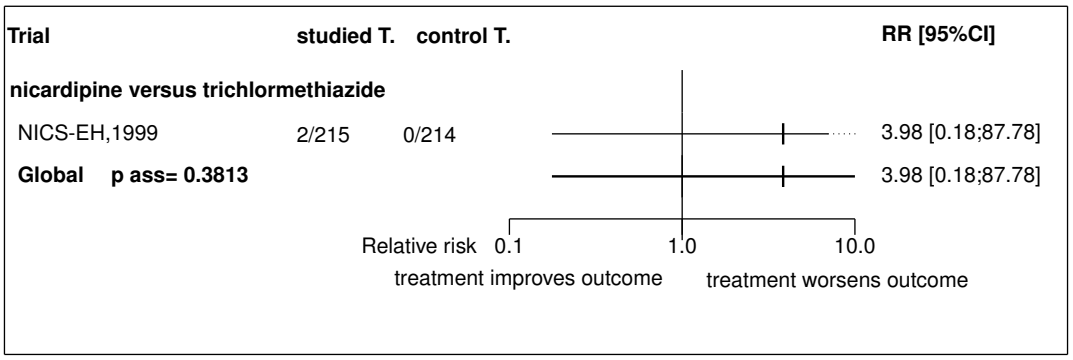


Figure 16.3: *Forest's plot for stroke (fatal and non fatal)*

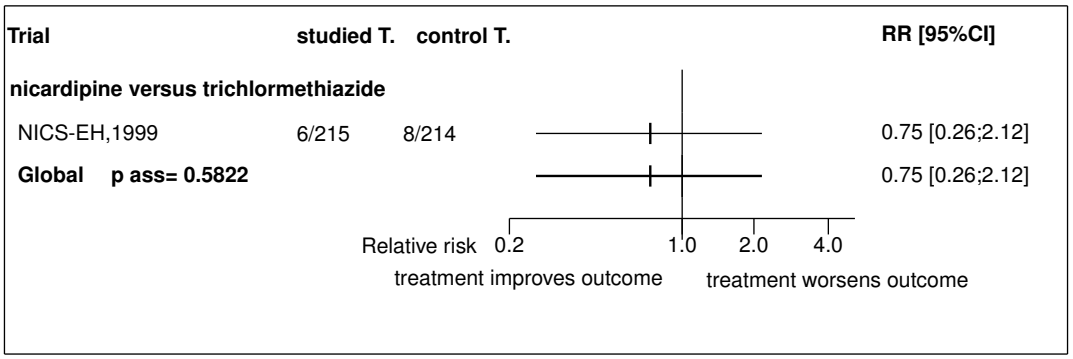


Figure 16.4: *Forest's plot for coronary event*

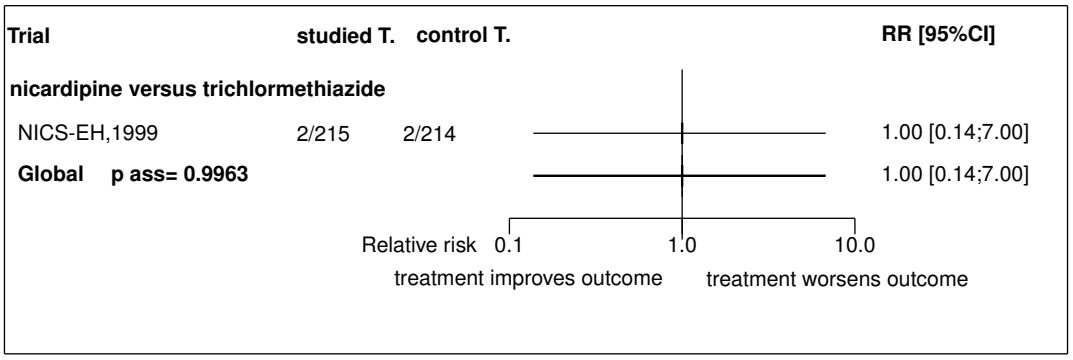


Figure 16.5: *Forest's plot for heart failure*

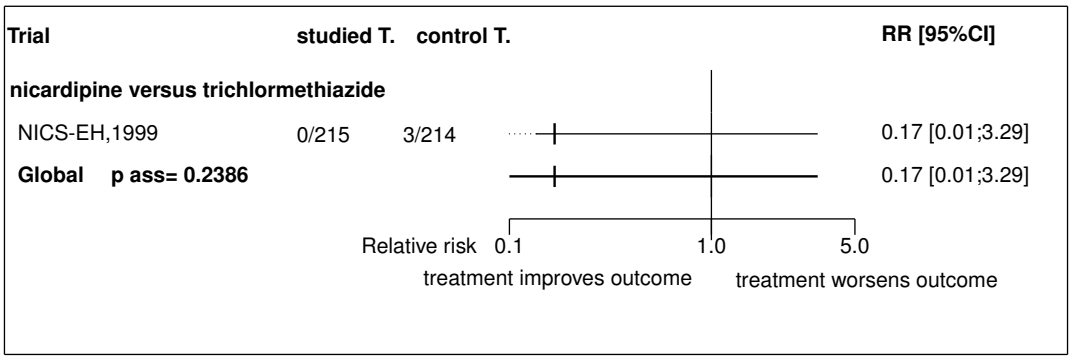
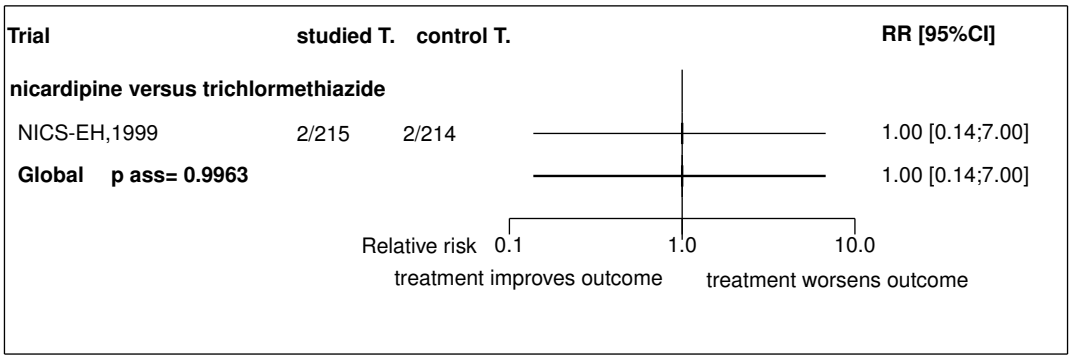


Figure 16.6: *Forest's plot for all cause death*



References

[1] . Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension 1999 Nov;34:1129-33. [PMID=10567194]

16.3 Individual trial summaries

Table 16.6: *NICS-EH, 1999 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=429 (215 vs. 214) **Follow-up duration:** 4.5 years **Study design:** Randomized controlled trial Parallel groups Double blind	>=60 years of age with systolic blood pressure of 160 to 220 mm Hg and diastolic blood pressure <115 mm Hg	**Studied treatment:** Nicardipine SR 20mg twice daily **Control treatment:** trichlormethiazide 2mg once daily	Cardiovascular events RR=0.69 [0.30;1.58] Stroke (fatal and non fatal) RR=0.75 [0.26;2.12] Coronary event RR=1.00 [0.14;7.00] All cause death RR=1.00 [0.14;7.00]

Reference

. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension 1999 Nov;34:1129-33 [PMID=10567194]

17 Detailed results for nifedipine

17.1 Available trials

Only one trial which randomized 351 patients was identified: it compared nifedipine with atenolol+chlorthalidon
This trial included 351 patients and was published in 1994.
Erreur ??? 0 et 0.
It was reported in English language.
data was reported in trials;
Following tables 17.1 (page 95), 17.2 (page 95), 17.4 (page 96), and 17.3 (page 95) summarized the main characteristics of the trial including in this systematic review of randomized trials of nifedipine.

Table 17.1: *Treatment description - calcium-channel blockers - nifedipine*

Trial	Studied treatment	Control treatment
Nifedipine versus atenolol+chlorthalidone		
Castel (1994) [1]	Nifedipine 20mg/d	Clonidine 0.15mg/d (n=61) or atenolol 100mg/d + chlorthalidone 25mg/d

Table 17.2: *Descriptions of participants - calcium-channel blockers - nifedipine*

Trial	Patients
Nifedipine versus atenolol+chlorthalidone	
Castel (1994) [1]	

Table 17.3: *Design and methodological quality of trials - calcium-channel blockers - nifedipine*

Trial	Design	Duration	Centre	Primary endpoint
Nifedipine versus atenolol+chlorthalidone				
Castel, 1994 [1] n=351				

Table 17.4: *Trial characteristics - calcium-channel blockers - nifedipine*

Trial
Nifedipine versus atenolol+chlorthalidone
Castel, 1994 [1]

17.2 Meta-analysis results

The results are detailed in table 17.5 (page 97). This table is followed by the Forest's plot corresponding to each endpoint.

Nifedipine versus atenolol+chlorthalidone

No data were presented in the 1 trial identified

Table 17.5: *Results details - calcium-channel blockers - nifedipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nifedipine versus atenolol+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] Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C, Di Menza G, Pegoraro L, Ambrosio GB. Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). Jpn Heart J 1994;35:589-600. [PMID=7830324]

17.3 Individual trial summaries

Table 17.6: *Castel, 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=351 (146 vs. 205) **Follow-up duration:** **Study design:** Randomized controlled trial		**Studied treatment:** Nifedipine 20mg/d **Control treatment:** Clonidine 0.15mg/d (n=61) or atenolol 100mg/d + chlorthalidone 25mg/d	

Reference

Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C, Di Menza G, Pegoraro L, Ambrosio GB. Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). Jpn Heart J 1994;35:589-600 [PMID=7830324]

18 Detailed results for nitrendipine

18.1 Available trials

Only one trial which randomized 4695 patients was identified: it compared nitrendipine with placebo.
This trial included 4695 patients and was published in 1997.
This trial was double blind in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on cardiovascular events; 1 trials reported data on coronary event; 1 trials reported data on cardiovascular death; 1 trials reported data on heart failure; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 18.1 (page 100), 18.2 (page 100), 18.4 (page 102), and 18.3 (page 100) summarized the main characteristics of the trial including in this systematic review of randomized trials of nitrendipine.

Table 18.1: *Treatment description - calcium-channel blockers - nitrendipine*

Trial	Studied treatment	Control treatment
Nitrendipine versus placebo		
SYST-EUR (1997) [1]	nitrendipine 10-40 mg daily , nitrendipine 10-40 mg daily	placebo

Table 18.2: *Descriptions of participants - calcium-channel blockers - nitrendipine*

Trial	Patients
Nitrendipine versus placebo	
SYST-EUR (1997) [1]	HBP, >=60 years

Table 18.3: *Design and methodological quality of trials - calcium-channel blockers - nitrendipine*

Trial	Design	Duration	Centre	Primary endpoint
Nitrendipine versus placebo				
SYST-EUR, 1997 [1] n=4695	Parallel groups Double aveugle	26y	23 countries across Europe 198 centres	

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 18.4: *Trial characteristics - calcium-channel blockers - nitrendipine*

Trial
Nitrendipine versus placebo
SYST-EUR, 1997 [1]

18.2 Meta-analysis results

The results are detailed in table 18.5 (page 103). This table is followed by the Forest's plot corresponding to each endpoint.

Nitrendipine versus placebo

The single study eligible for this comparison provided data on **cardiovascular events**. The analysis detected a statistically significant difference in favor of nitrendipine in cardiovascular events, with a RR of 0.71 (95% CI 0.57 to 0.87, 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 0.73 (95% CI 0.53 to 1.03, p=0.0697).
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 nitrendipine in stroke (fatal and non fatal), with a RR of 0.59 (95% CI 0.41 to 0.83, p=0.0029).
The single study 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 0.75 (95% CI 0.50 to 1.13, p=0.1716).
The single study 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 0.75 (95% CI 0.50 to 1.13, p=0.1716).
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 0.86 (95% CI 0.68 to 1.09, p=0.2116).

Table 18.5: *Results details - calcium-channel blockers - nitrendipine*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nitrendipine versus placebo						
cardiovascular events	RR=0.71	[0.57;0.87]	0.0000	1.0000 (I^2=0.00)	1	4695
cardiovascular death	RR=0.73	[0.53;1.03]	0.0697	1.0000 (I^2=0.00)	1	4695
stroke (fatal and non fatal)	RR=0.59	[0.41;0.83]	0.0029	1.0000 (I^2=0.00)	1	4695
coronary event	RR=0.75	[0.50;1.13]	0.1716	1.0000 (I^2=0.00)	1	4695
heart failure	RR=0.75	[0.50;1.13]	0.1716	1.0000 (I^2=0.00)	1	4695
all cause death	RR=0.86	[0.68;1.09]	0.2116	1.0000 (I^2=0.00)	1	4695

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 18.1: *Forest's plot for cardiovascular events*

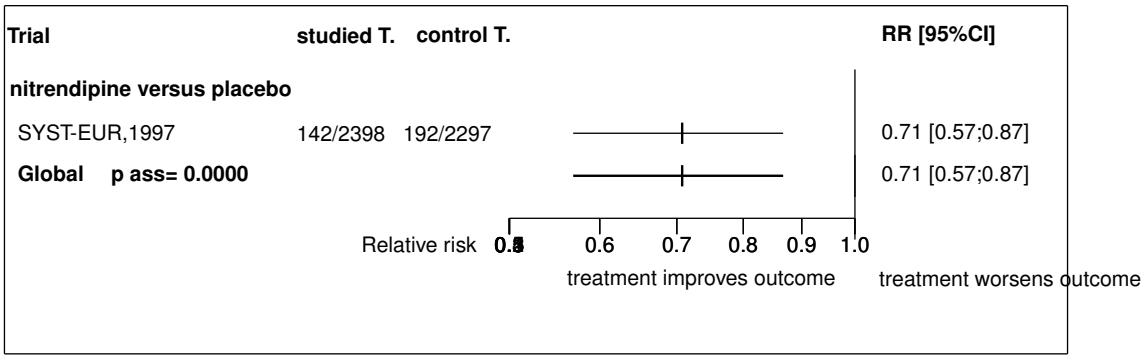


Figure 18.2: *Forest's plot for cardiovascular death*

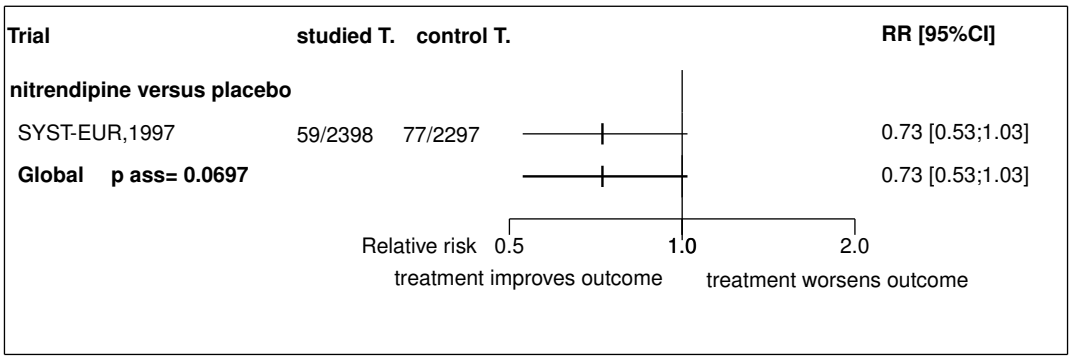


Figure 18.3: *Forest's plot for stroke (fatal and non fatal)*

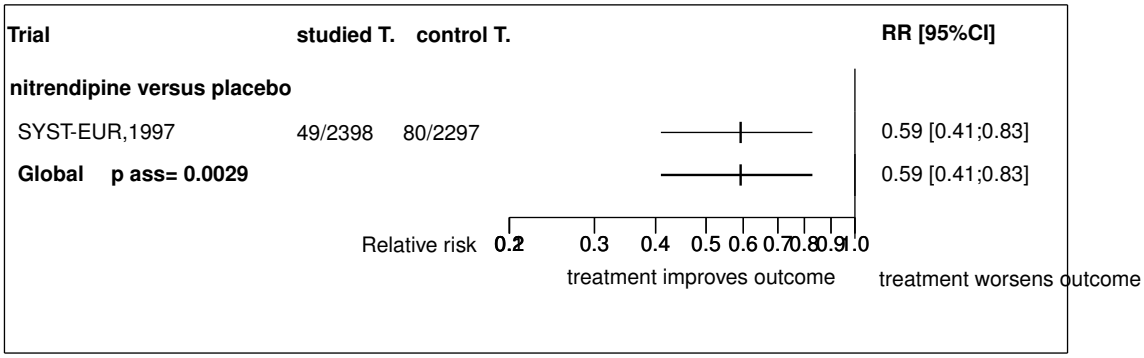


Figure 18.4: *Forest's plot for coronary event*

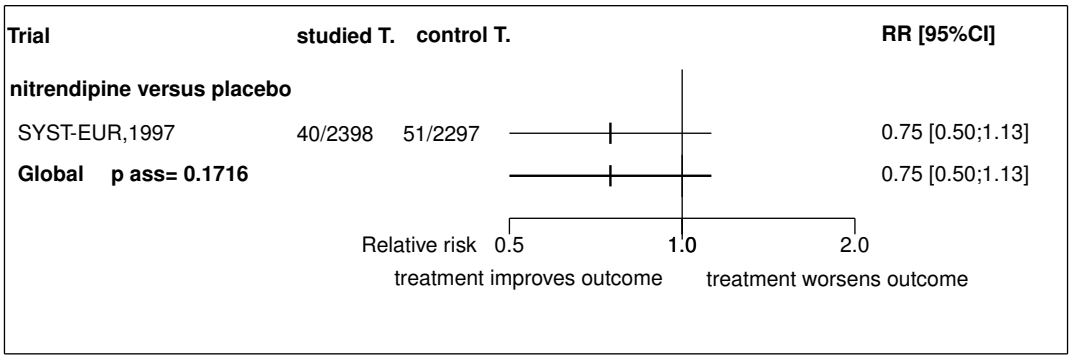


Figure 18.5: *Forest's plot for heart failure*

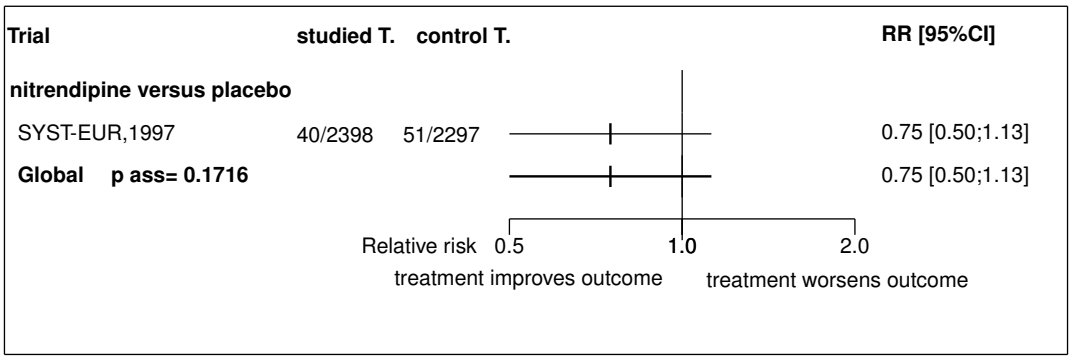
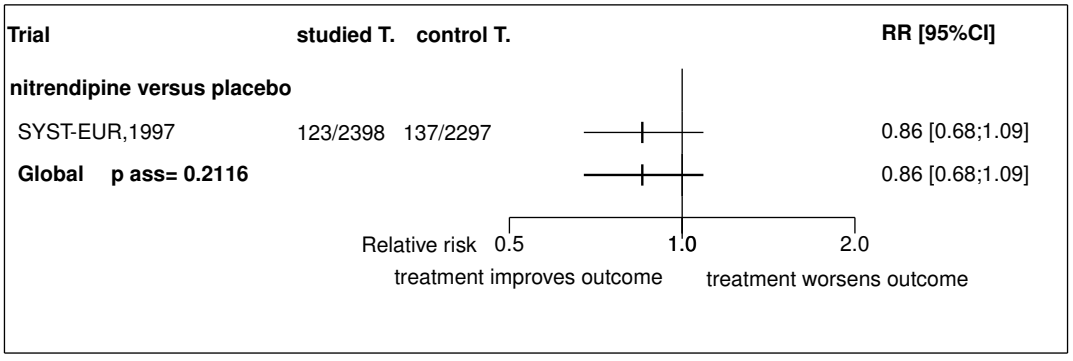


Figure 18.6: *Forest's plot for all cause death*



References

[1] Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997 Sep 13;350:757-64. [PMID=9297994]

18.3 Individual trial summaries

Table 18.6: *SYST-EUR, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=4695 (2398 vs. 2297) **Follow-up duration:** 26y **Study design:** Randomized controlled trial Parallel groups Double aveugle 23 countries across Europe, 198 centres	HBP, >=60 years	**Studied treatment:** nitrendipine 10-40 mg daily , nitrendipine 10-40 mg daily **Control treatment:** placebo	Cardiovascular events RR=0.71 [0.57;0.87] Cardiovascular death RR=0.73 [0.53;1.03] Stroke (fatal and non fatal) RR=0.59 [0.41;0.83] Coronary event RR=0.75 [0.50;1.13] Heart failure RR=0.75 [0.50;1.13] All cause death RR=0.86 [0.68;1.09]

Reference

Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997 Sep 13;350:757-64 [PMID=9297994]

19 Global meta-analysis: all calcium-channel blockers

19.1 Global meta-analysis: all calcium-channel blockers versus atenolol+chlorthalidone

Table 19.1: *All calcium-channel blockersversus atenolol+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

19.2 Global meta-analysis: all calcium-channel blockers versus chlorthalidone

Table 19.2: *All calcium-channel 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

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

Table 19.3: *All calcium-channel blockersversus diuretic or beta-blocker*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.00	0.90;1.10	0.9548	1.0000 (0.00)	1	4409
cardiovascular death	RR=0.97	0.81;1.16	0.7107	1.0000 (0.00)	1	4409
stroke (fatal and non fatal)	RR=0.88	0.74;1.05	0.1573	1.0000 (0.00)	1	4409
coronary event	RR=1.12	0.93;1.34	0.2259	1.0000 (0.00)	1	4409
heart failure	RR=1.06	0.87;1.29	0.5689	1.0000 (0.00)	1	4409
all cause death	RR=0.99	0.87;1.13	0.8655	1.0000 (0.00)	1	4409

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

19.4 Global meta-analysis: all calcium-channel blockers versus placebo

Table 19.4: *All calcium-channel blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.71	0.57;0.87	0.0000	1.0000 (0.00)	1	4695
cardiovascular death	RR=0.73	0.53;1.03	0.0697	1.0000 (0.00)	1	4695
stroke (fatal and non fatal)	RR=0.59	0.41;0.83	0.0029	1.0000 (0.00)	1	4695
coronary event	RR=0.75	0.50;1.13	0.1716	1.0000 (0.00)	1	4695
heart failure	RR=0.75	0.50;1.13	0.1716	1.0000 (0.00)	1	4695
all cause death	RR=0.86	0.68;1.09	0.2116	1.0000 (0.00)	1	4695

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

19.5 Global meta-analysis: all calcium-channel blockers versus trichlormethiazide

Table 19.5: *All calcium-channel blockersversus trichlormethiazide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.69	0.30;1.58	0.3784	1.0000 (0.00)	1	429
cardiovascular death	RR=3.98	0.18;87.78	0.3813	1.0000 (0.00)	1	429
stroke (fatal and non fatal)	RR=0.75	0.26;2.12	0.5822	1.0000 (0.00)	1	429
coronary event	RR=1.00	0.14;7.00	0.9963	1.0000 (0.00)	1	429
heart failure	RR=0.17	0.01;3.29	0.2386	1.0000 (0.00)	1	429
all cause death	RR=1.00	0.14;7.00	0.9963	1.0000 (0.00)	1	429

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

20 Ongoing studies of calcium-channel blockers

No ongoing trial was identified.

21 Excluded studies for calcium-channel blockers

No trial was excluded.

References

Part IV

Diuretics

22 Overview of diuretics

22.1 Included trials

Only one trial which randomized 3845 patients was identified. In all, 1 randomized comparison concerned indapamide.
The detailed descriptions of trials and meta-analysis results is given in section 23 (page 118) for indapamide.

This trial included 3845 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
The table 22.1 (page 116) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

22.2 Summary of meta-analysis results

The meta-analysis of the available trials about diuretics provide the results listed in tables 22.2 to 22.2 (page 117) and in the following graphs.

22.2.1 Indapamide

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

Table 22.1: *Main study characteristics - Diuretics*

Trial	Patients	Treatments	Trial design and method
Indapamide			
Indapamide versus placebo			
HYVET, 2008 [1] n = 1933 vs. 1912	patients 80 years or older with persistent hypertension defined as a sustained systolic BP of 160 mm Hg or higher	indapamide sustained release 1.5 mg/d + perindopril 2-4mg/d to obtain SBP <150 and DBP <80 **versus** placebo	double blind parallel groups Primary endpoint: fatal and non fatal stroke 195 centres, Western and Eastern Europe, China, Australasia, and North Africa

Table 22.2: *Summary of all results for indapamide*

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

23 Details

23.1 Available trials

Only one trial which randomized 3845 patients was identified: it compared indapamide with placebo.
This trial included 3845 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 23.1 (page 118), 23.2 (page 118), 23.4 (page 120), and 23.3 (page 119) summarized the main characteristics of the trial including in this systematic review of randomized trials of indapamide.

Table 23.1: *Treatment description - Diuretics - indapamide*

Trial	Studied treatment	Control treatment
Indapamide versus placebo		
HYVET (2008) [1]	indapamide sustained release 1.5 mg/d + perindopril 2-4mg/d to obtain SBP $<$150 and DBP $<$80 At each visit, perindopril 2 or 4 mg could be added to achieve a target BP of less than 150 mm Hg systolic and less than 80 mm Hg diastolic	placebo
	Concomittant treatment: The angiotensin-convertingenzyme inhibitor perindopril(2 or 4 mg), or matching placebo, was added if necessary to achieve the target bloodpressure of 150/80 mm Hg.	

Table 23.2: *Descriptions of participants - Diuretics - indapamide*

Trial	Patients	
Indapamide versus placebo		
HYVET (2008) [1]	Patients 80 years or older with persistent hypertension defined as a sustained systolic BP of 160 mm Hg or higher	
	Inclusion criteria:	**Exclusion criteria:** accelerated or secondary hypertension, hemorrhagic stroke within 6 months, heart failure requiring treatment, creatinine level more than 1.7 mg/dL, potassium level less than 3.5 or more than 5.5 mmol/L, or dementia or in those requiring nursing care

Table 23.3: *Design and methodological quality of trials - Diuretics - indapamide*

Trial	Design	Duration	Centre	Primary endpoint
Indapamide versus placebo				
HYVET, 2008 [1] n=3845	Parallel groups Double blind	1.8y (median)	Western and Eastern Europe, China, Australasia, and North Africa 195 centres	fatal and non fatal stroke

Table 23.4: *Trial characteristics - Diuretics - indapamide*

Trial
Indapamide versus placebo
HYVET, 2008 [1]

23.2 Meta-analysis results

The results are detailed in table 23.5 (page 121). This table is followed by the Forest's plot corresponding to each endpoint.

Indapamide versus placebo

No data were presented in the 1 trial identified

Table 23.5: *Results details - Diuretics - indapamide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
indapamide 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] Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of Hypertension in Patients 80 Years of Age or Older. N Engl J Med 2008 Mar 31;:. [PMID=18378519]

23.3 Individual trial summaries

Table 23.6: *HYVET, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=3845 (1933 vs. 1912) **Follow-up duration:** 1.8y (median) **Study design:** Randomized controlled trial Parallel groups Double blind Western and Eastern Europe, China, Australasia, and North Africa, 195 centres	Patients 80 years or older with persistent hypertension defined as a sustained systolic BP of 160 mm Hg or higher **Exclusion criteria:** accelerated or secondary hypertension, hemorrhagic stroke within 6 months, heart failure requiring treatment, creatinine level more than 1.7 mg/dL, potassium level less than 3.5 or more than 5.5 mmol/L, or dementia or in those requiring nursing care	**Studied treatment:** indapamide sustained release 1.5 mg/d + perindopril 2-4mg/d to obtain SBP $<$150 and DBP $<$80 At each visit, perindopril 2 or 4 mg could be added to achieve a target BP of less than 150 mm Hg systolic and less than 80 mm Hg diastolic **Control treatment:** placebo **Concomittant treat.:**The angiotensin-convertingenzyme inhibitor perindopril(2 or 4 mg), or matching placebo, was added if necessary to achieve the target bloodpressure of 150/80 mm Hg.	

Reference

Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of Hypertension in Patients 80 Years of Age or Older. N Engl J Med 2008 Mar 31;: [PMID=18378519]

24 Global meta-analysis: all Diuretics

24.1 Global meta-analysis: all Diuretics versus placebo

Table 24.1: *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

25 Ongoing studies of Diuretics

No ongoing trial was identified.

26 Excluded studies for Diuretics

No trial was excluded.

References