Anti hypertensive agent for hypertension in very ederly (80 and more)

A systematic review and meta-analysis of randomized clinical trials

2017 - 6 - 14

This report should be referenced as follows:
TrialResults-center.org; Results of all major randomized clinical trials about Anti hypertensive agent for hypertension in very ederly (80 and more).

Contents

0.1 Synthesis of the meta-analysis results

In all 8 randomised controlled trials (RCTs) were included. These included 1 studie of **beta-blockers** involving 7 patients, 1 studie of **beta-blockers + diuretics** involving 97 patients, 1 studie of **beta-blockers or diuretics** involving 235 patients, 1 studie of **calcium-channel blockers** involving 441 patients and 4 studies of **diuretics** involving 4,735 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 Beta-blockers

Only one trials including 7 patients was found.
Among these comparisons, one trial 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 1.

Table 1: *Results summary - Atenolol*

Benefit	Harmful	No evidence
	Atenolol versus control	
		→ cardiovascular events RR=0.67^{NS} [0.03;14.03] k=1 → cardiovascular death RR=1.33^{NS} [0.04;49.93] k=1 → stroke (fatal and non fatal) RR=0.67^{NS} [0.03;14.03] k=1 → coronary event RR=1.33^{NS} [0.04;49.93] k=1 → coronary death RR=1.33^{NS} [0.04;49.93] k=1 → heart failure RR=1.33^{NS} [0.04;49.93] k=1 → all cause death RR=1.33^{NS} [0.04;49.93] k=1 → fatal stroke RR=1.33^{NS} [0.04;49.93] 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 + diuretics

Only one trials including 97 patients was found.
Among these comparisons, one trial are about beta-blockers + diuretics.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with beta-blockers + diuretics for all the endpoints with data in at least one trial are summarized table 2.

Table 2: *Results summary - Beta-blockers + diuretics*

Benefit	Harmful	No evidence
Beta-blockers + diuretics versus placebo		
		→ cardiovascular events RR=0.81^{NS} [0.58;1.13] k=1 → cardiovascular death RR=0.82^{NS} [0.56;1.18] k=1 → stroke (fatal and non fatal) RR=0.91^{NS} [0.33;2.52] k=1 → coronary event RR=0.43^{NS} [0.14;1.26] k=1 → coronary death RR=0.24^{NS} [0.05;1.04] k=1 → heart failure RR=0.68^{NS} [0.33;1.43] k=1 → all cause death RR=0.92^{NS} [0.76;1.10] k=1 → fatal stroke RR=1.28^{NS} [0.42;3.90] 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 Beta-blockers or diuretics

Only one trials including 235 patients was found.
Among these comparisons, one trial are about beta-blockers or diuretics.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with beta-blockers or diuretics for all the endpoints with data in at least one trial are summarized table 3.

Table 3: *Results summary - Beta-blockers or diuretics*

Benefit	Harmful	No evidence
Beta-blockers or diuretics versus placebo		
		→ cardiovascular events RR=0.69^{NS} [0.34;1.40] k=1 → cardiovascular death RR=2.16^{NS} [0.57;8.16] k=1 → stroke (fatal and non fatal) RR=1.16^{NS} [0.47;2.83] k=1 → coronary event RR=0.46^{NS} [0.02;13.67] k=1 → coronary death RR=1.85^{NS} [0.17;20.15] k=1 → heart failure RR=1.39^{NS} [0.24;8.16] k=1 → all cause death RR=1.27^{NS} [0.53;3.05] k=1 → fatal stroke RR=3.70^{NS} [0.42;32.66] 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 Calcium-channel blockers

Only one trials including 441 patients was found.
Among these comparisons, one trial are about nidrendipine.
During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with nidrendipine for all the endpoints with data in at least one trial are summarized table 4.

Table 4: *Results summary - Nidrendipine*

Benefit	Harmful	No evidence
	Nidrendipine versus placebo	
		→ cardiovascular events RR=0.95^{NS} [0.65;1.41] k=1 → cardiovascular death RR=1.08^{NS} [0.67;1.74] k=1 → stroke (fatal and non fatal) RR=0.77^{NS} [0.42;1.43] k=1 → coronary event RR=1.10^{NS} [0.56;2.18] k=1 → coronary death RR=1.16^{NS} [0.54;2.49] k=1 → heart failure RR=0.85^{NS} [0.42;1.72] k=1 → all cause death RR=1.23^{NS} [0.91;1.67] k=1 → fatal stroke RR=1.01^{NS} [0.42;2.44] k=1

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

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

0.1.5 Diuretics

Reports of 4 trials (including 4,735 patients) were identified .
Among these comparisons, two trials are about chlorthalidone,one about hydrochlorothiazide and one about indapamide.
During the selection 1 trials were excluded because of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Chlorthalidone

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

Table 5: *Results summary - Chlorthalidone*

Benefit	Harmful	No evidence
	Chlorthalidone versus placebo	

continued...

Benefit	Harmful	No evidence
↓ cardiovascular events RR=0.67* [0.48;0.93] k=2 ↓ stroke (fatal and non fatal) RR=0.45* [0.22;0.90] k=2 ↓ heart failure RR=0.40* [0.17;0.99] k=2		→ cardiovascular death RR=0.86^{NS} [0.52;1.43] k=2 → coronary event RR=0.72^{NS} [0.41;1.26] k=2 → coronary death RR=0.77^{NS} [0.40;1.50] k=2 → all cause death RR=1.04^{NS} [0.48;2.27] k=2 → fatal stroke RR=0.62^{NS} [0.15;2.48] k=2

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

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

Hydrochlorothiazide

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

Table 6: *Results summary - Hydrochlorothiazide*

Benefit	Harmful	No evidence
	Hydrochlorothiazide versus placebo	
		→ cardiovascular death RR=1.21^{NS} [0.85;1.73] k=1 → coronary death RR=1.37^{NS} [0.56;3.35] k=1 → all cause death RR=1.17^{NS} [0.99;1.40] k=1 → fatal stroke RR=1.48^{NS} [0.65;3.38] k=1

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

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

Indapamide

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

Table 7: *Results summary - Indapamide*

Benefit	Harmful	No evidence
	Indapamide versus placebo	
↓ heart failure RR=0.38¶ [0.23;0.62] k=1 ↓ all cause death RR=0.82* [0.69;0.99] k=1		→ cardiovascular death RR=0.81^{NS} [0.63;1.05] k=1 → stroke (fatal and non fatal) RR=0.73^{NS} [0.51;1.04] k=1 → coronary event RR=0.74^{NS} [0.31;1.76] k=1

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

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

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 very ederly (80 and more). The following classes of treatment are considered:

1. beta-blockers
2. beta-blockers + diuretics
3. beta-blockers or diuretics
4. calcium-channel blockers
5. 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 very ederly (80 and more).

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2017 - 6 - 14:

- 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 Fatal stroke, Cardiovascular death, Coronary death, Heart failure, stroke (fatal and non fatal), All cause death, cardiovascular events, Coronary event, .

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 beta-blockers, beta-blockers + diuretics, beta-blockers or diuretics, 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

Beta-blockers

2 Overview of beta-blockers

2.1 Included trials

Only one trial which randomized 7 patients was identified. In all, 1 randomized comparison concerned atenolol.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 21) for atenolol.

This trial included 7 patients and was published in 1986.
This trial was double blind in design.
It was reported in English language.
The table 2.1 (page 16) 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 beta-blockers provide the results listed in tables 2.2 to 2.2 (page 17) and in the following graphs.

2.2.1 Atenolol

No significant difference was found between **atenolol** and **control** in terms of cardiovascular events (RR=0.67, 95% CI 0.03 to 14.03, p=0.7942, 1 trial), cardiovascular death (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial), stroke (fatal and non fatal) (RR=0.67, 95% CI 0.03 to 14.03, p=0.7942, 1 trial), coronary event (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial), coronary death (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial), heart failure (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial), all cause death (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial)and fatal stroke (RR=1.33, 95% CI 0.04 to 49.93, p=0.8763, 1 trial).

Table 2.1: *Main study characteristics - beta-blockers*

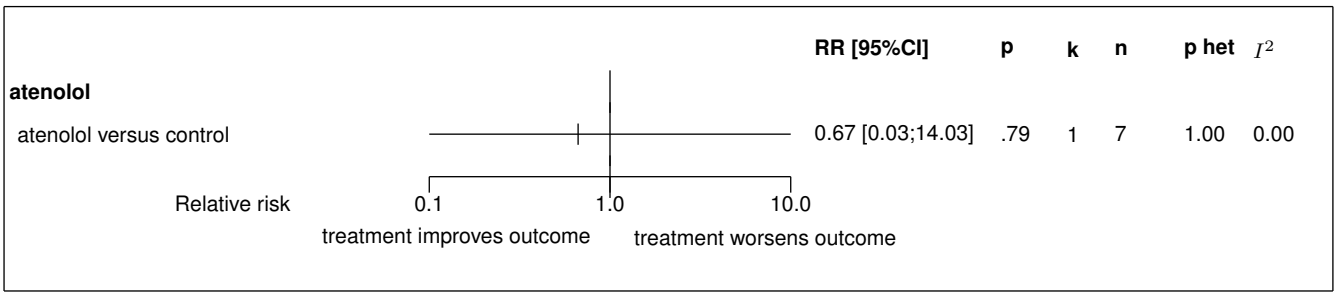
Trial	Patients	Treatments	Trial design and method
Atenolol			
Atenolol versus control			
Coope (subgroup), 1986 [1] n = 3 vs. 4	patients aged 60 to 79 years	atenolol and bendrofluazide **versus** control	double-blind

Table 2.2: *Summary of all results for atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atenolol versus control						
cardiovascular events	RR=0.67	0.03;14.03	0.7942	1.0000 (0.00)	1	7
cardiovascular death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
stroke (fatal and non fatal)	RR=0.67	0.03;14.03	0.7942	1.0000 (0.00)	1	7
coronary event	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
coronary death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
heart failure	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
all cause death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
fatal stroke	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7

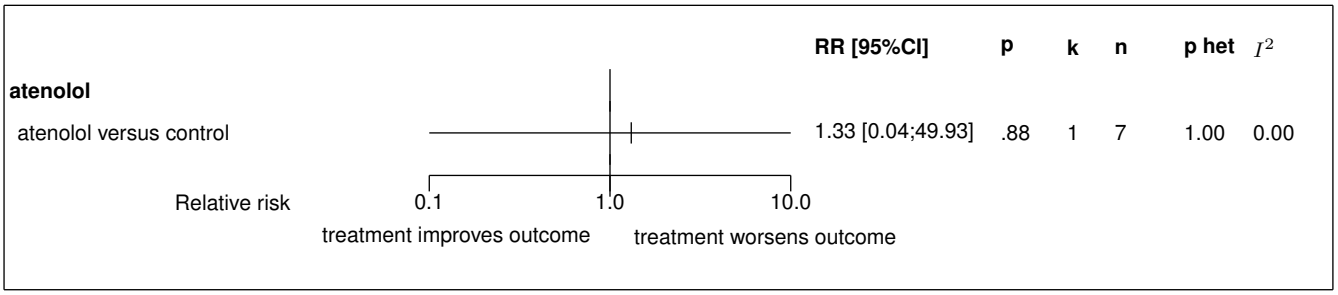
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



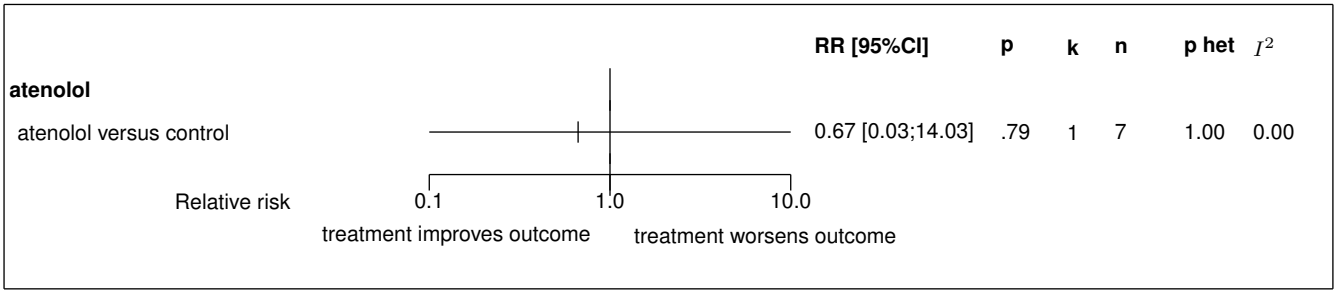
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



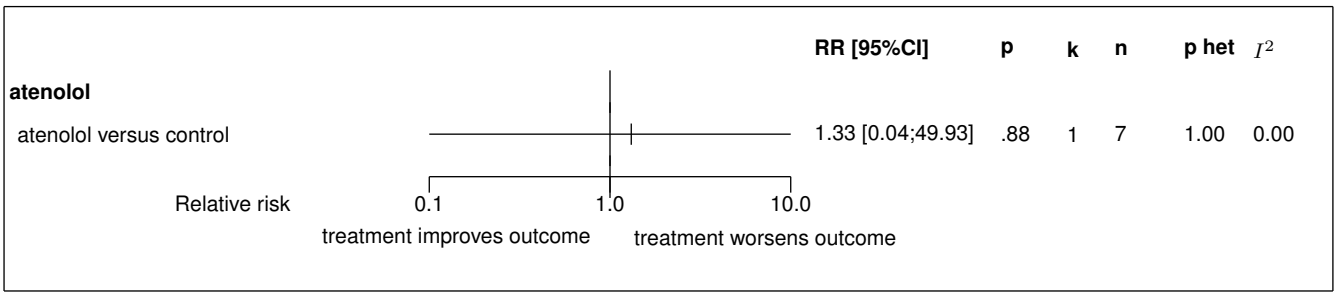
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



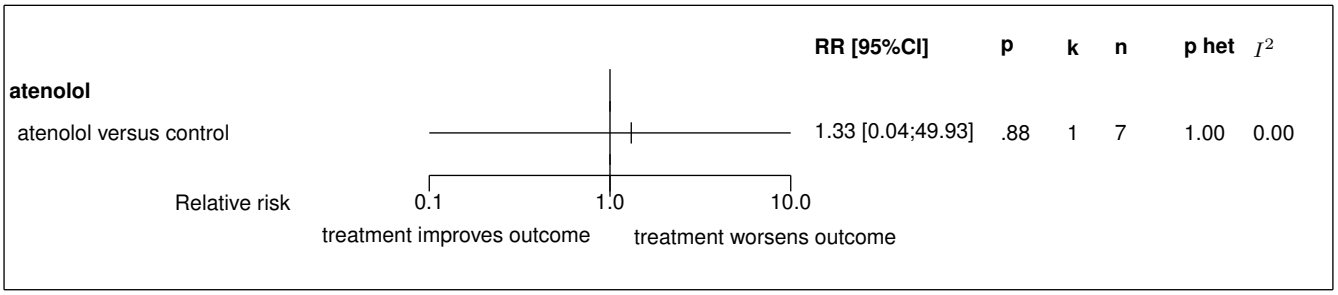
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



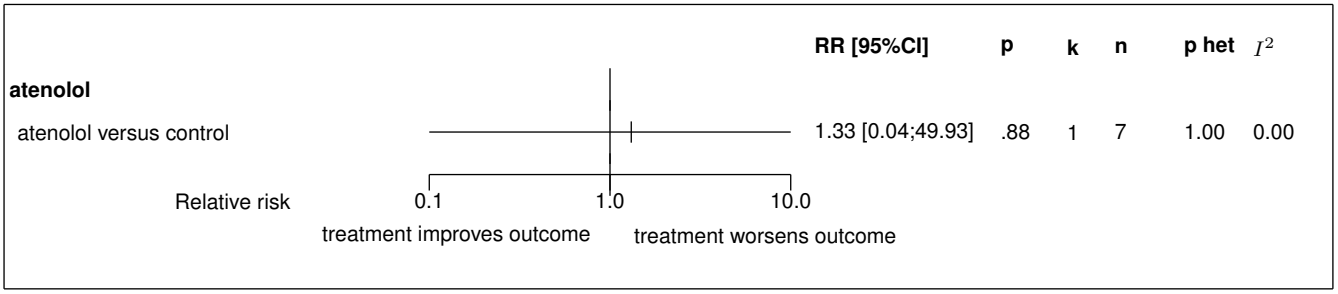
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *Forest's plot for coronary death*



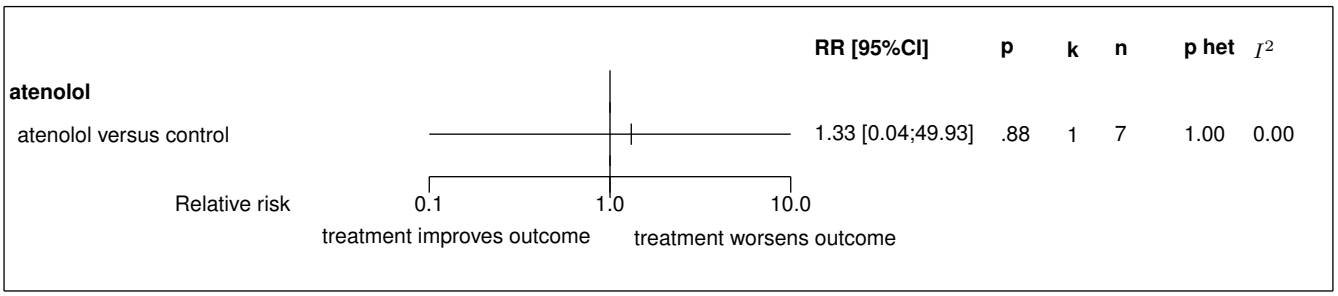
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.6: *Forest's plot for heart failure*



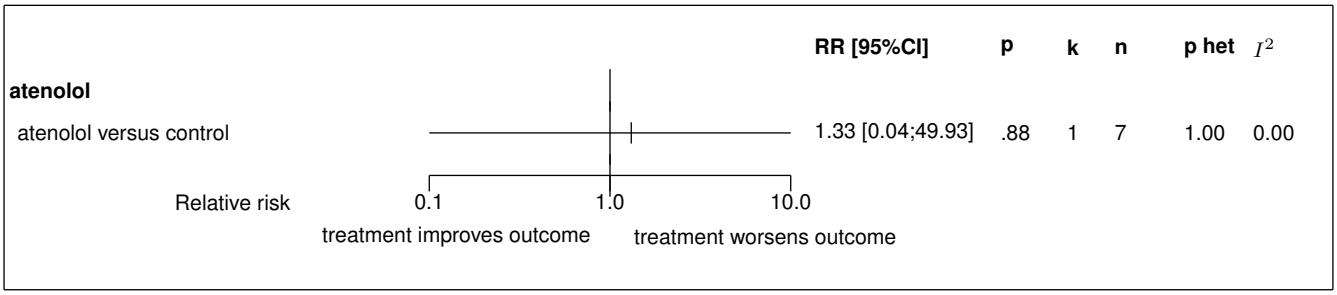
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.7: *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

Figure 2.8: *Forest's plot for fatal stroke*



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

3 Details

3.1 Available trials

Only one trial which randomized 7 patients was identified: it compared atenolol with control.
This trial included 7 patients and was published in 1986.
This trial was double blind in design.
It was reported in English language.
Fatal stroke data was reported in 1 trials; 1 trials reported data on cardiovascular death; 1 trials reported data on coronary death; 1 trials reported data on heart failure; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events; and 1 trials reported data on coronary event.
Following tables 3.1 (page 21), 3.2 (page 21), 3.4 (page 23), and 3.3 (page 21) summarized the main characteristics of the trial including in this systematic review of randomized trials of atenolol.

Table 3.1: *Treatment description - beta-blockers - atenolol*

Trial	Studied treatment	Control treatment
Atenolol versus control		
Coope (subgroup) (1986) [1]	atenolol and bendrofluazide	control

Table 3.2: *Descriptions of participants - beta-blockers - atenolol*

Trial	Patients
Atenolol versus control	
Coope (subgroup) (1986) [1]	Patients aged 60 to 79 years

Table 3.3: *Design and methodological quality of trials - beta-blockers - atenolol*

Trial	Design	Duration	Centre	Primary end-point
Atenolol versus control				

continued...

Trial	Design	Duration	Centre	Primary endpoint
Coope (subgroup), 1986 [1] n=7	double-blind	38y		

Table 3.4: *Trial characteristics - beta-blockers - atenolol*

Trial
Atenolol versus control
Coope (subgroup), 1986 [1]

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 24). This table is followed by the Forest's plot corresponding to each endpoint.

Atenolol versus control

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between atenolol and control, with a RR of 0.67 (95%CI 0.03 to 14.03, p=0.7942) in favour of atenolol. In other words, cardiovascular events was slightly lower in the atenolol 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 1.33 (95% CI 0.04 to 49.93, p=0.8763).
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 0.67 (95% CI 0.03 to 14.03, p=0.7942).
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 1.33 (95% CI 0.04 to 49.93, p=0.8763).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.33 (95% CI 0.04 to 49.93, p=0.8763).
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 1.33 (95% CI 0.04 to 49.93, p=0.8763).
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 1.33 (95% CI 0.04 to 49.93, p=0.8763).
The single study eligible for this comparison provided data on **fatal stroke**. No statistically significant difference between the groups was found in fatal stroke, with a RR of 1.33 (95% CI 0.04 to 49.93, p=0.8763).

Table 3.5: *Results details - beta-blockers - atenolol*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atenolol versus control						
cardiovascular events	RR=0.67	[0.03;14.03]	0.7942	1.0000 (I^2=0.00)	1	7
cardiovascular death	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7
stroke (fatal and non fatal)	RR=0.67	[0.03;14.03]	0.7942	1.0000 (I^2=0.00)	1	7
coronary event	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7
coronary death	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7
heart failure	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7
all cause death	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7
fatal stroke	RR=1.33	[0.04;49.93]	0.8763	1.0000 (I^2=0.00)	1	7

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 3.1: *Forest's plot for cardiovascular events*

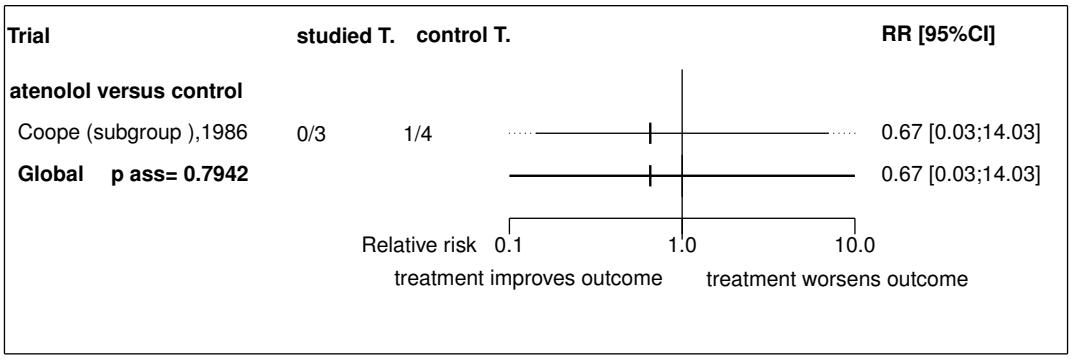


Figure 3.2: *Forest's plot for cardiovascular death*

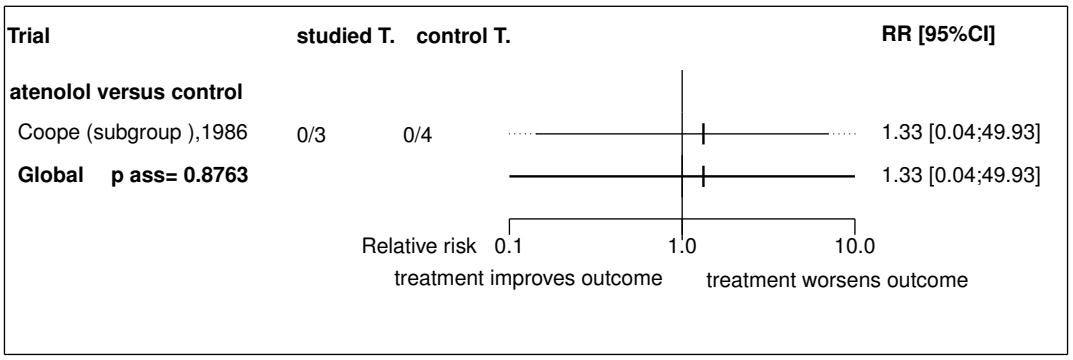


Figure 3.3: *Forest's plot for stroke (fatal and non fatal)*

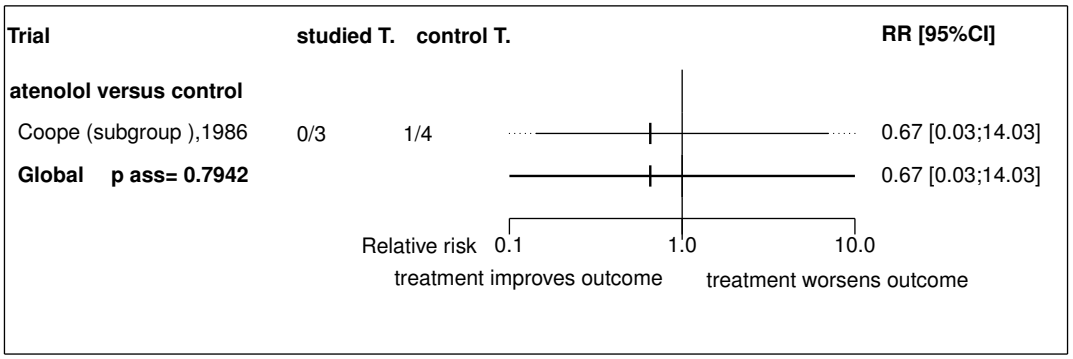


Figure 3.4: *Forest's plot for coronary event*

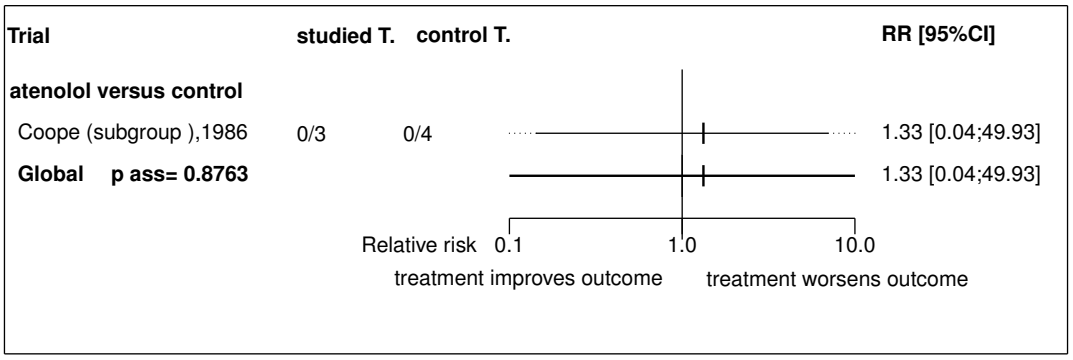


Figure 3.5: *Forest's plot for coronary death*

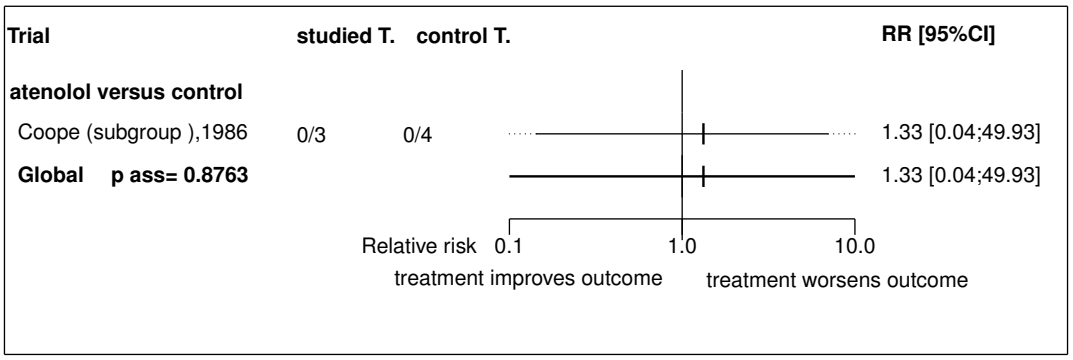


Figure 3.6: *Forest's plot for heart failure*

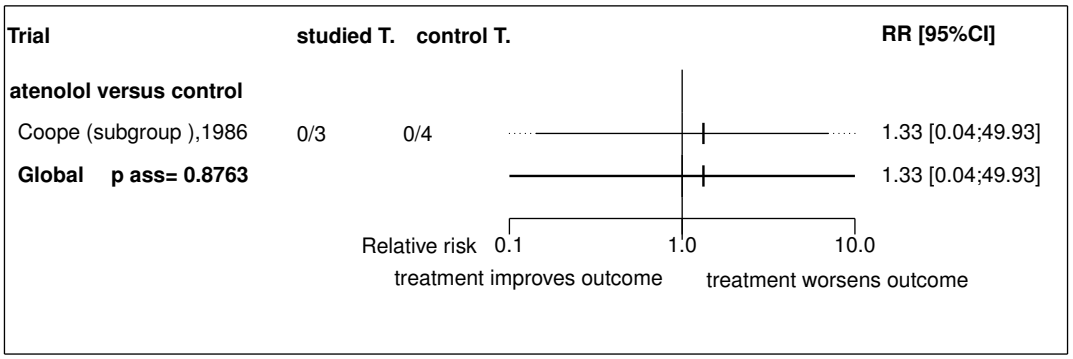


Figure 3.7: *Forest's plot for all cause death*

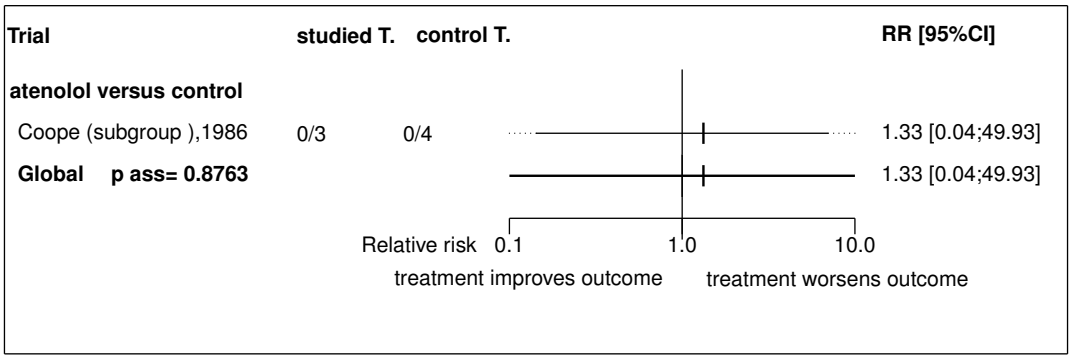
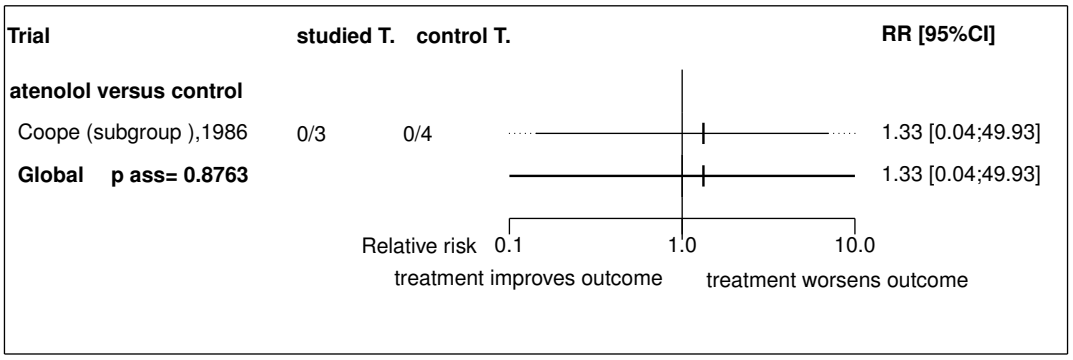


Figure 3.8: *Forest's plot for fatal stroke*



References

[1] Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed) 1986;293:1145-51. [PMID=3094811]

3.3 Individual trial summaries

Table 3.6: *Coope (subgroup), 1986 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=7 (3 vs. 4) **Follow-up duration:** 38y **Study design:** Randomized controlled trial Double-blind	Patients aged 60 to 79 years	**Studied treatment:** atenolol and bendrofluazide **Control treatment:** control	

Reference

Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed) 1986;293:1145-51 [PMID=3094811]

4 Global meta-analysis: all beta-blockers

4.1 Global meta-analysis: all beta-blockers versus control

Table 4.1: *All beta-blockersversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.67	0.03;14.03	0.7942	1.0000 (0.00)	1	7
cardiovascular death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
stroke (fatal and non fatal)	RR=0.67	0.03;14.03	0.7942	1.0000 (0.00)	1	7
coronary event	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
coronary death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
heart failure	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
all cause death	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7
fatal stroke	RR=1.33	0.04;49.93	0.8763	1.0000 (0.00)	1	7

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 Ongoing studies of beta-blockers

No ongoing trial was identified.

6 Excluded studies for beta-blockers

No trial was excluded.

References

Part II

Beta-blockers + diuretics

7 Overview of beta-blockers + diuretics

7.1 Included trials

Only one trial which randomized 97 patients was identified. In all, 1 randomized comparison concerned beta-blockers + diuretics.
The detailed descriptions of trials and meta-analysis results is given in section 8 (page 39) for beta-blockers + diuretics.

This trial included 97 patients and was published in 1994.
This trial was open-label in design.
It was reported in English language.
The table 7.1 (page 34) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

7.2 Summary of meta-analysis results

The meta-analysis of the available trials about beta-blockers + diuretics provide the results listed in tables 7.2 to 7.2 (page 35) and in the following graphs.

7.2.1 Beta-blockers + diuretics

No significant difference was found between **beta-blockers + diuretics** and **placebo** in terms of cardiovascular events (RR=0.81, 95% CI 0.58 to 1.13, p=0.2054, 1 trial), cardiovascular death (RR=0.82, 95% CI 0.56 to 1.18, p=0.2796, 1 trial), stroke (fatal and non fatal) (RR=0.91, 95% CI 0.33 to 2.52, p=0.8586, 1 trial), coronary event (RR=0.43, 95% CI 0.14 to 1.26, p=0.1241, 1 trial), coronary death (RR=0.24, 95% CI 0.05 to 1.04, p=0.0561, 1 trial), heart failure (RR=0.68, 95% CI 0.33 to 1.43, p=0.3121, 1 trial), all cause death (RR=0.92, 95% CI 0.76 to 1.10, p=0.3516, 1 trial)and fatal stroke (RR=1.28, 95% CI 0.42 to 3.90, p=0.6686, 1 trial).

Table 7.1: *Main study characteristics - beta-blockers + diuretics*

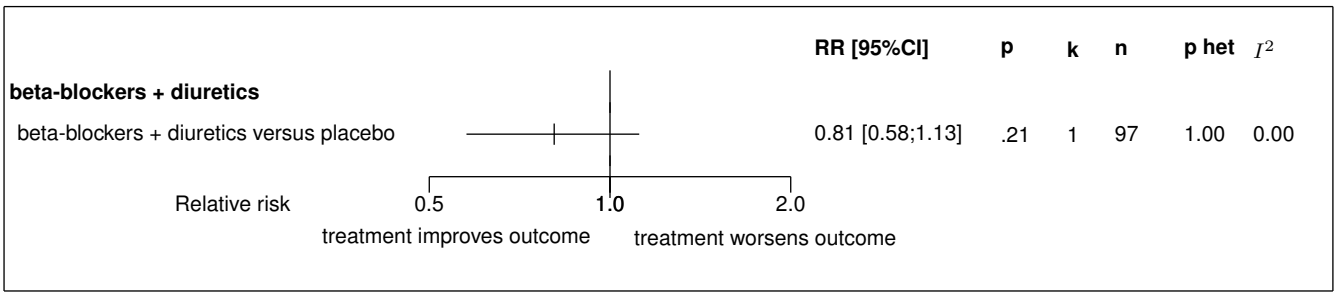
Trial	Patients	Treatments	Trial design and method
Beta-blockers + diuretics			
Beta-blockers + diuretics versus placebo			
CASTEL (subgroup), 1994 [1] n = 47 vs. 50		active antihypertensive therapy (thiazide or beta-blockers) **versus** control	open

Table 7.2: *Summary of all results for beta-blockers + diuretics*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
beta-blockers + diuretics versus placebo						
cardiovascular events	RR=0.81	0.58;1.13	0.2054	1.0000 (0.00)	1	97
cardiovascular death	RR=0.82	0.56;1.18	0.2796	1.0000 (0.00)	1	97
stroke (fatal and non fatal)	RR=0.91	0.33;2.52	0.8586	1.0000 (0.00)	1	97
coronary event	RR=0.43	0.14;1.26	0.1241	1.0000 (0.00)	1	97
coronary death	RR=0.24	0.05;1.04	0.0561	1.0000 (1.00)	1	97
heart failure	RR=0.68	0.33;1.43	0.3121	1.0000 (0.00)	1	97
all cause death	RR=0.92	0.76;1.10	0.3516	1.0000 (0.00)	1	97
fatal stroke	RR=1.28	0.42;3.90	0.6686	1.0000 (0.00)	1	97

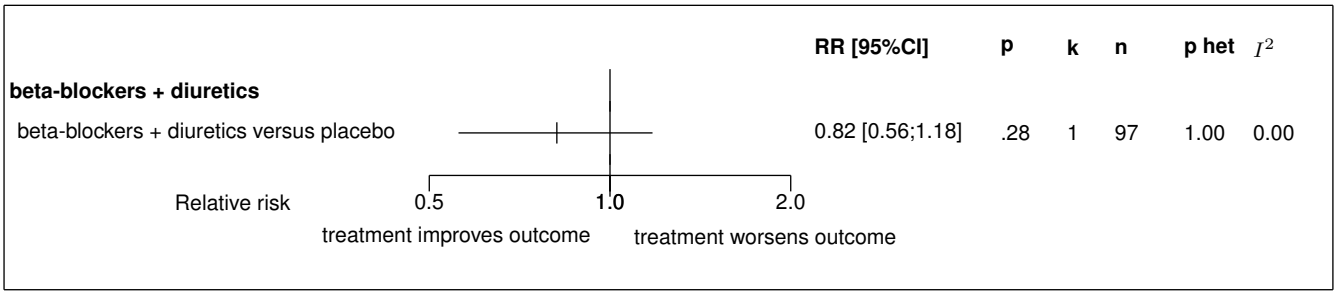
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 7.1: *Forest's plot for cardiovascular events*



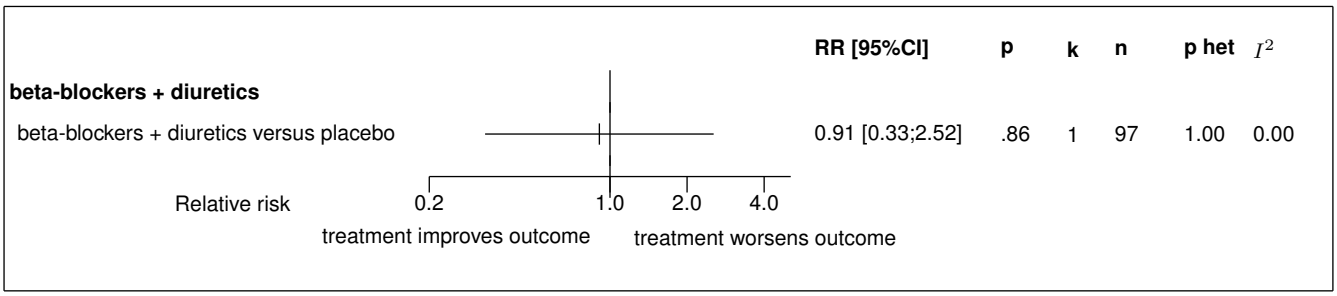
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.2: *Forest's plot for cardiovascular death*



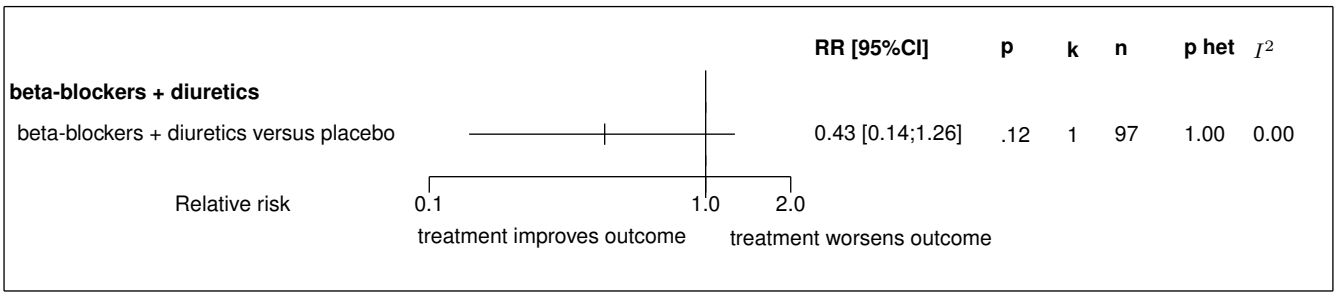
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.3: *Forest's plot for stroke (fatal and non fatal)*



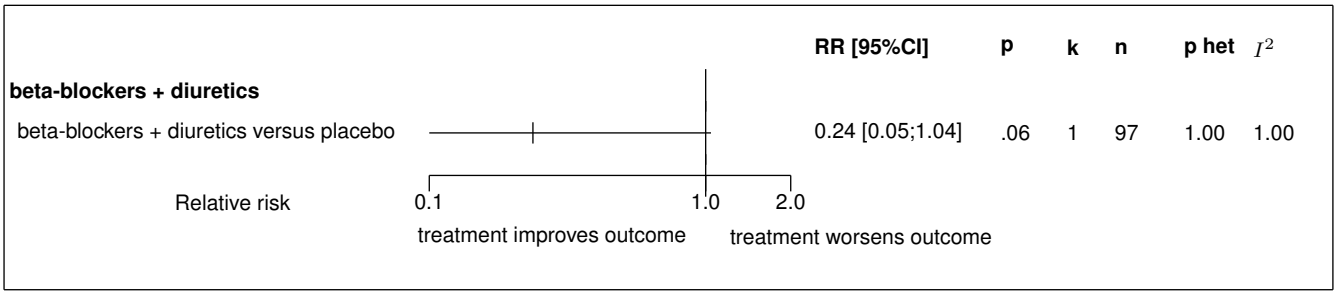
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for coronary event*



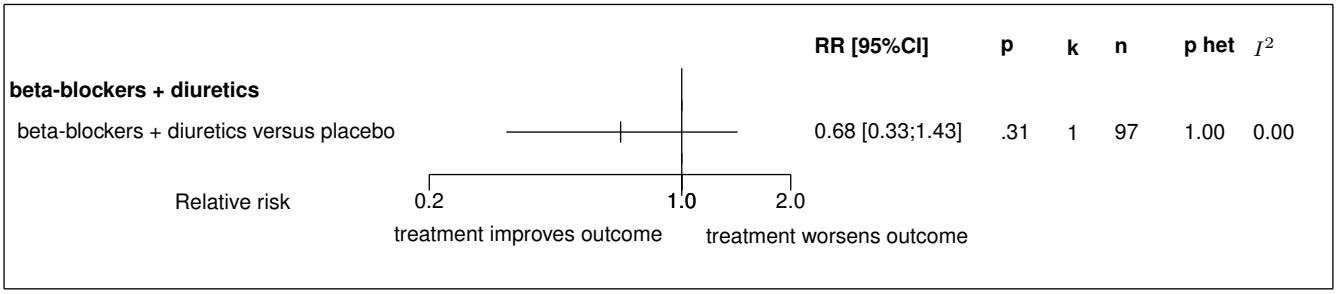
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.5: *Forest's plot for coronary death*



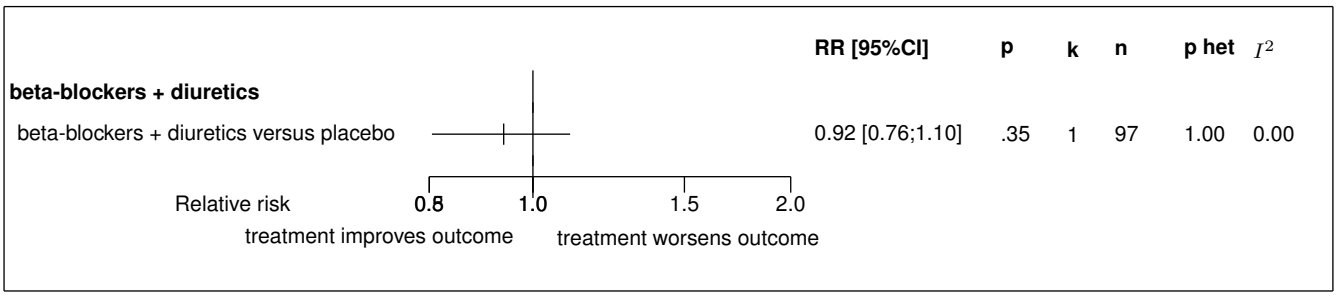
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.6: *Forest's plot for heart failure*



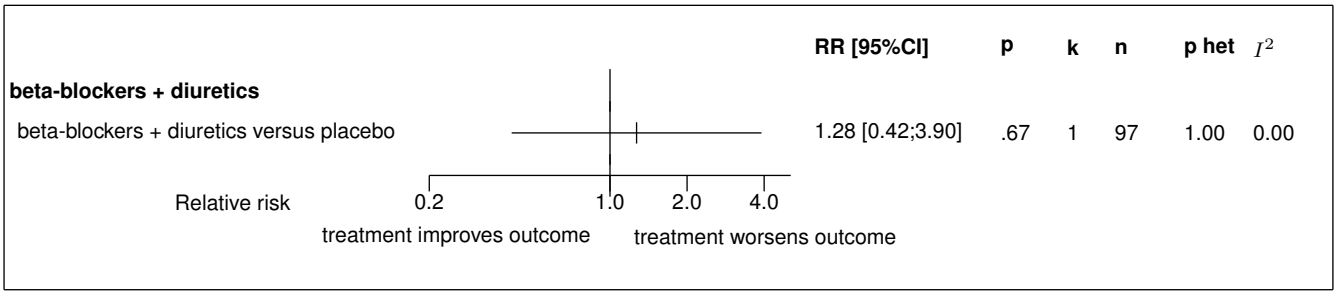
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.7: *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

Figure 7.8: *Forest's plot for fatal stroke*



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

8 Details

8.1 Available trials

Only one trial which randomized 97 patients was identified: it compared beta-blockers + diuretics with placebo.
This trial included 97 patients and was published in 1994.
This trial was open-label in design.
It was reported in English language.
Fatal stroke data was reported in 1 trials; 1 trials reported data on cardiovascular death; 1 trials reported data on coronary death; 1 trials reported data on heart failure; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events; and 1 trials reported data on coronary event.
Following tables 8.1 (page 39), 8.2 (page 39), 8.4 (page 41), and 8.3 (page 40) summarized the main characteristics of the trial including in this systematic review of randomized trials of beta-blockers + diuretics.

Table 8.1: *Treatment description - beta-blockers + diuretics - beta-blockers + diuretics*

Trial	Studied treatment	Control treatment
Beta-blockers + diuretics versus placebo		
CASTEL (subgroup) (1994) [1]	active antihypertensive therapy (thiazide or beta-blockers)	control

Table 8.2: *Descriptions of participants - beta-blockers + diuretics - beta-blockers + diuretics*

Trial	Patients
Beta-blockers + diuretics versus placebo	
CASTEL (subgroup) (1994) [1]	

Table 8.3: *Design and methodological quality of trials - beta-blockers + diuretics - beta-blockers + diuretics*

Trial	Design	Duration	Centre	Primary end-point
Beta-blockers + diuretics versus placebo				
CASTEL (subgroup), 1994 [1] n=97	open	68y		

Table 8.4: *Trial characteristics - beta-blockers + diuretics - beta-blockers + diuretics*

Trial
Beta-blockers + diuretics versus placebo
CASTEL (subgroup), 1994 [1]

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 42). This table is followed by the Forest's plot corresponding to each endpoint.

Beta-blockers + diuretics versus placebo

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between beta-blockers + diuretics and placebo, with a RR of 0.81 (95%CI 0.58 to 1.13, p=0.2054) in favour of beta-blockers + diuretics. In other words, cardiovascular events was slightly lower in the beta-blockers + diuretics 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 0.82 (95% CI 0.56 to 1.18, p=0.2796).
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 0.91 (95% CI 0.33 to 2.52, p=0.8586).
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 0.43 (95% CI 0.14 to 1.26, p=0.1241).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 0.24 (95% CI 0.05 to 1.04, p=0.0561).
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 0.68 (95% CI 0.33 to 1.43, p=0.3121).
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 0.92 (95% CI 0.76 to 1.10, p=0.3516).
The single study eligible for this comparison provided data on **fatal stroke**. No statistically significant difference between the groups was found in fatal stroke, with a RR of 1.28 (95% CI 0.42 to 3.90, p=0.6686).

Table 8.5: *Results details - beta-blockers + diuretics - beta-blockers + diuretics*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
beta-blockers + diuretics versus placebo						
cardiovascular events	RR=0.81	[0.58;1.13]	0.2054	1.0000 (I^2=0.00)	1	97
cardiovascular death	RR=0.82	[0.56;1.18]	0.2796	1.0000 (I^2=0.00)	1	97
stroke (fatal and non fatal)	RR=0.91	[0.33;2.52]	0.8586	1.0000 (I^2=0.00)	1	97
coronary event	RR=0.43	[0.14;1.26]	0.1241	1.0000 (I^2=0.00)	1	97
coronary death	RR=0.24	[0.05;1.04]	0.0561	1.0000 (I^2=1.00)	1	97
heart failure	RR=0.68	[0.33;1.43]	0.3121	1.0000 (I^2=0.00)	1	97
all cause death	RR=0.92	[0.76;1.10]	0.3516	1.0000 (I^2=0.00)	1	97
fatal stroke	RR=1.28	[0.42;3.90]	0.6686	1.0000 (I^2=0.00)	1	97

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 8.1: *Forest's plot for cardiovascular events*

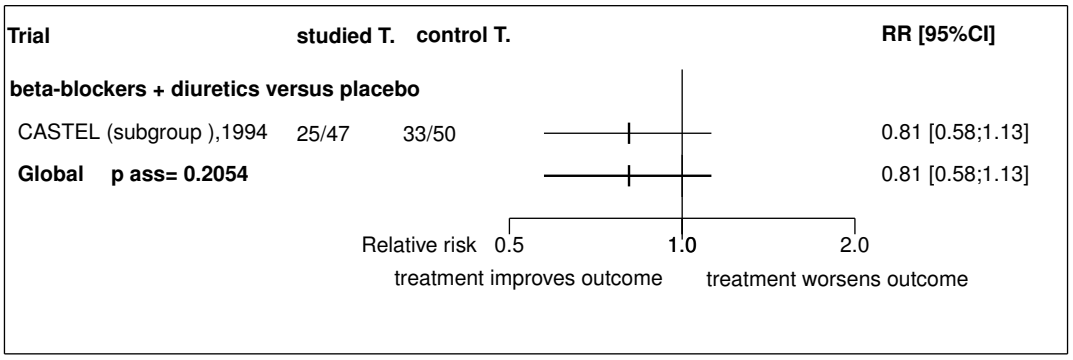


Figure 8.2: *Forest's plot for cardiovascular death*

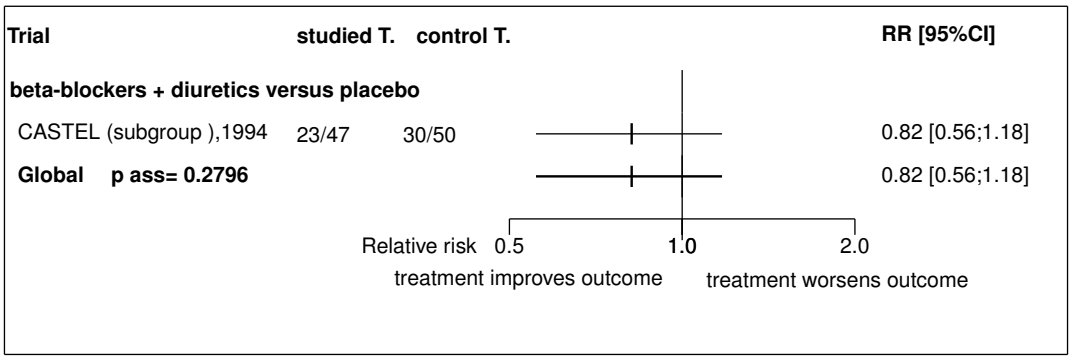


Figure 8.3: *Forest's plot for stroke (fatal and non fatal)*

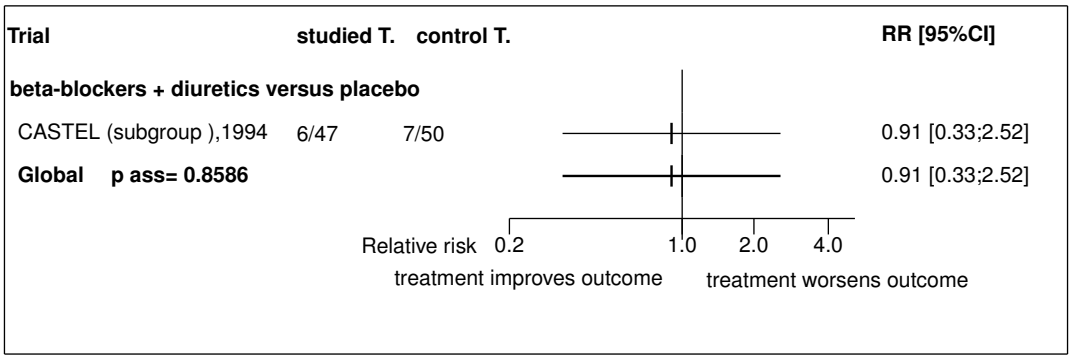


Figure 8.4: *Forest's plot for coronary event*

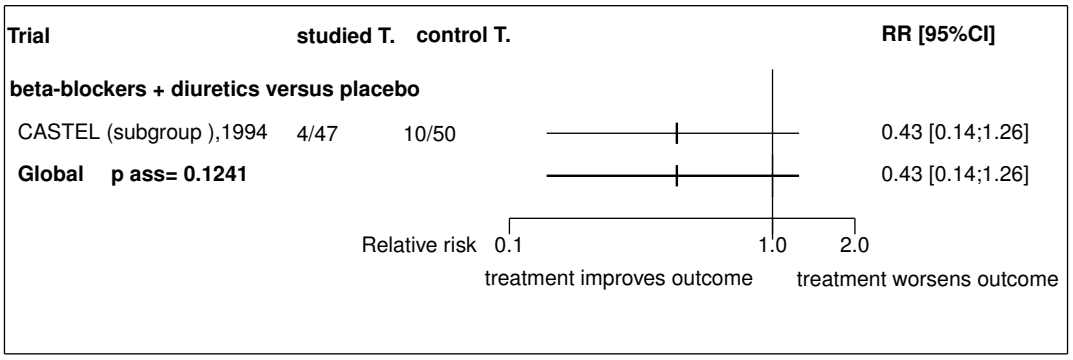


Figure 8.5: *Forest's plot for coronary death*

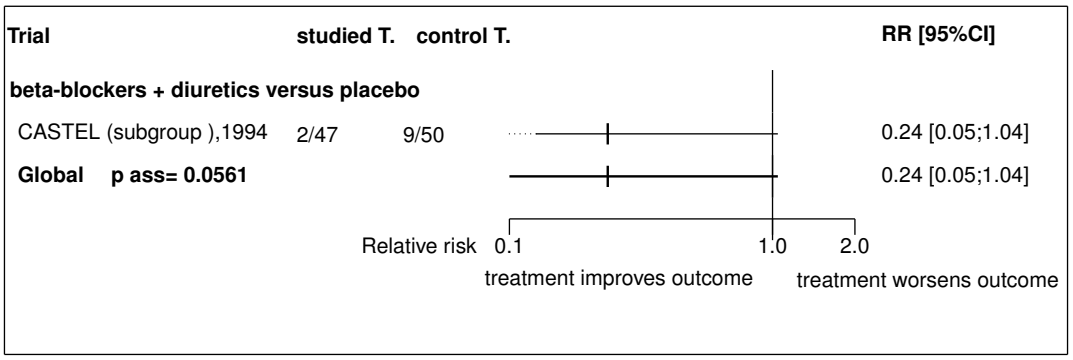


Figure 8.6: *Forest's plot for heart failure*

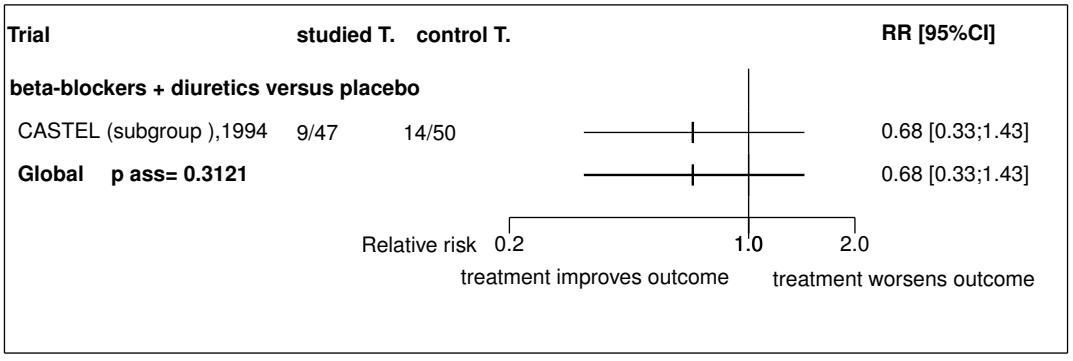


Figure 8.7: *Forest's plot for all cause death*

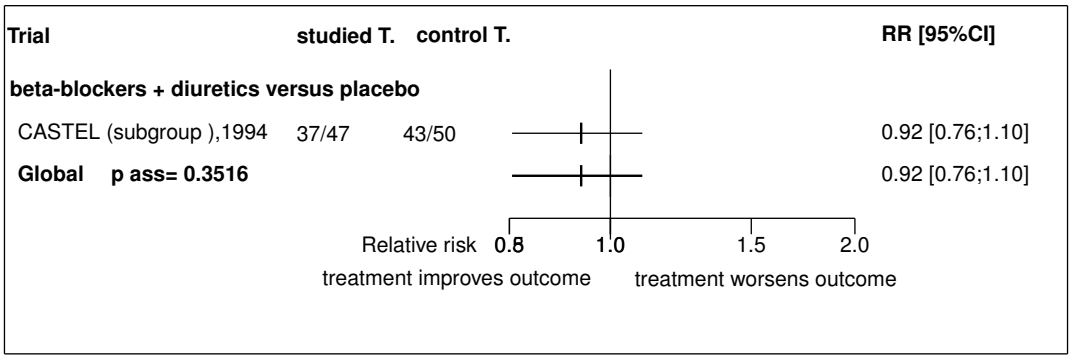
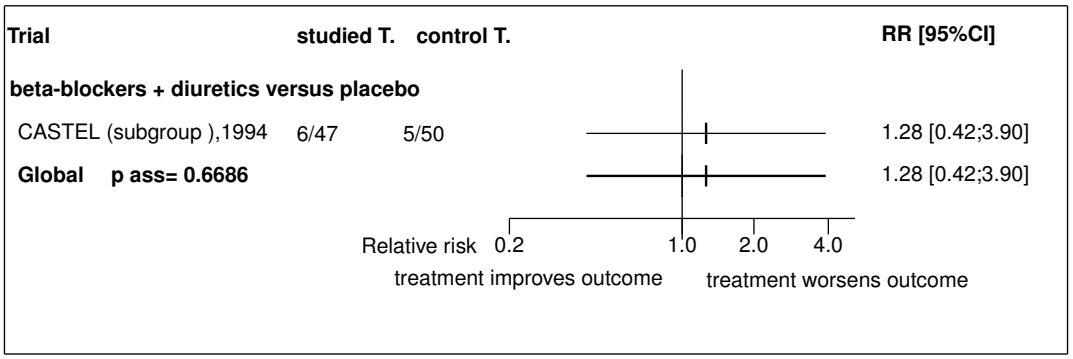


Figure 8.8: *Forest's plot for fatal stroke*



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]

8.3 Individual trial summaries

Table 8.6: *CASTEL (subgroup), 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=97 (47 vs. 50) **Follow-up duration:** 68y **Study design:** Randomized controlled trial Open		**Studied treatment:** active antihypertensive therapy (thiazide or beta-blockers) **Control treatment:** control	Cardiovascular events RR=0.81 [0.58;1.13] Cardiovascular death RR=0.82 [0.56;1.18] Stroke (fatal and non fatal) RR=0.91 [0.33;2.52] Coronary event RR=0.43 [0.14;1.26] Coronary death RR=0.24 [0.05;1.04] Heart failure RR=0.68 [0.33;1.43] All cause death RR=0.92 [0.76;1.10] Fatal stroke RR=1.28 [0.42;3.90]

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]

9 Global meta-analysis: all beta-blockers + diuretics

9.1 Global meta-analysis: all beta-blockers + diuretics versus placebo

Table 9.1: *All beta-blockers + diureticsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.81	0.58;1.13	0.2054	1.0000 (0.00)	1	97
cardiovascular death	RR=0.82	0.56;1.18	0.2796	1.0000 (0.00)	1	97
stroke (fatal and non fatal)	RR=0.91	0.33;2.52	0.8586	1.0000 (0.00)	1	97
coronary event	RR=0.43	0.14;1.26	0.1241	1.0000 (0.00)	1	97
coronary death	RR=0.24	0.05;1.04	0.0561	1.0000 (1.00)	1	97
heart failure	RR=0.68	0.33;1.43	0.3121	1.0000 (0.00)	1	97
all cause death	RR=0.92	0.76;1.10	0.3516	1.0000 (0.00)	1	97
fatal stroke	RR=1.28	0.42;3.90	0.6686	1.0000 (0.00)	1	97

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 Ongoing studies of beta-blockers + diuretics

No ongoing trial was identified.

11 Excluded studies for beta-blockers + diuretics

No trial was excluded.

References

Part III

Beta-blockers or diuretics

12 Overview of beta-blockers or diuretics

12.1 Included trials

Only one trial which randomized 235 patients was identified. In all, 1 randomized comparison concerned beta-blockers or diuretics.
The detailed descriptions of trials and meta-analysis results is given in section 13 (page 57) for beta-blockers or diuretics.

This trial included 235 patients and was published in 1991.
This trial was double blind in design.
It was reported in English language.
The table 12.1 (page 52) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

12.2 Summary of meta-analysis results

The meta-analysis of the available trials about beta-blockers or diuretics provide the results listed in tables 12.2 to 12.2 (page 53) and in the following graphs.

12.2.1 Beta-blockers or diuretics

No significant difference was found between **beta-blockers or diuretics** and **placebo** in terms of cardiovascular events (RR=0.69, 95% CI 0.34 to 1.40, p=0.3100, 1 trial), cardiovascular death (RR=2.16, 95% CI 0.57 to 8.16, p=0.2554, 1 trial), stroke (fatal and non fatal) (RR=1.16, 95% CI 0.47 to 2.83, p=0.7480, 1 trial), coronary event (RR=0.46, 95% CI 0.02 to 13.67, p=0.6558, 1 trial), coronary death (RR=1.85, 95% CI 0.17 to 20.15, p=0.6127, 1 trial), heart failure (RR=1.39, 95% CI 0.24 to 8.16, p=0.7159, 1 trial), all cause death (RR=1.27, 95% CI 0.53 to 3.05, p=0.5876, 1 trial)and fatal stroke (RR=3.70, 95% CI 0.42 to 32.66, p=0.2382, 1 trial).

Table 12.1: *Main study characteristics - beta-blockers or diuretics*

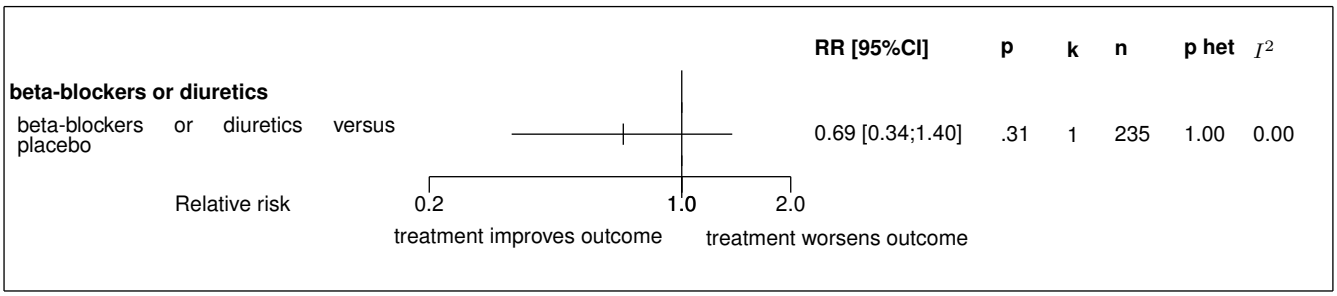
Trial	Patients	Treatments	Trial design and method
Beta-blockers or diuretics			
Beta-blockers or diuretics versus placebo			
STOP (subgroup), 1991 [1] n = 122 vs. 113	hypertensive Swedish men and women aged 70-84 years	active antihypertensive therapy (three beta-blockers and one diuretic) **versus** placebo	double-blind 116 centres, Sweden

Table 12.2: *Summary of all results for beta-blockers or diuretics*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
beta-blockers or diuretics versus placebo						
cardiovascular events	RR=0.69	0.34;1.40	0.3100	1.0000 (0.00)	1	235
cardiovascular death	RR=2.16	0.57;8.16	0.2554	1.0000 (0.00)	1	235
stroke (fatal and non fatal)	RR=1.16	0.47;2.83	0.7480	1.0000 (0.00)	1	235
coronary event	RR=0.46	0.02;13.67	0.6558	1.0000 (0.00)	1	235
coronary death	RR=1.85	0.17;20.15	0.6127	1.0000 (0.00)	1	235
heart failure	RR=1.39	0.24;8.16	0.7159	1.0000 (0.00)	1	235
all cause death	RR=1.27	0.53;3.05	0.5876	1.0000 (0.00)	1	235
fatal stroke	RR=3.70	0.42;32.66	0.2382	1.0000 (0.00)	1	235

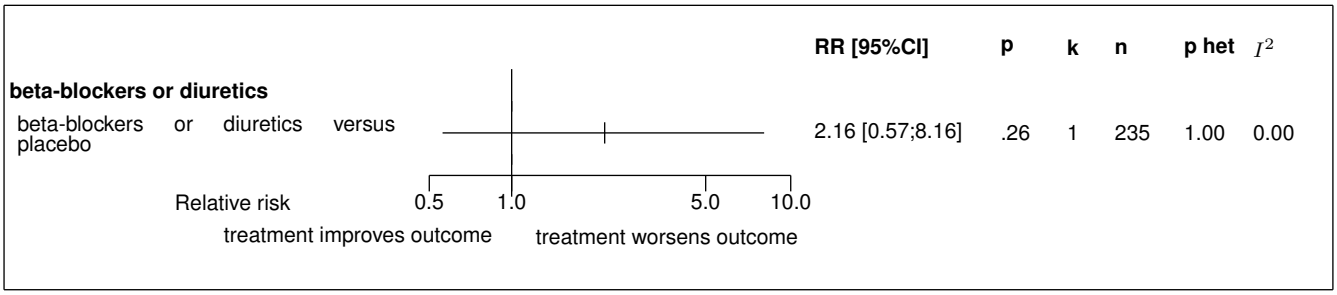
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



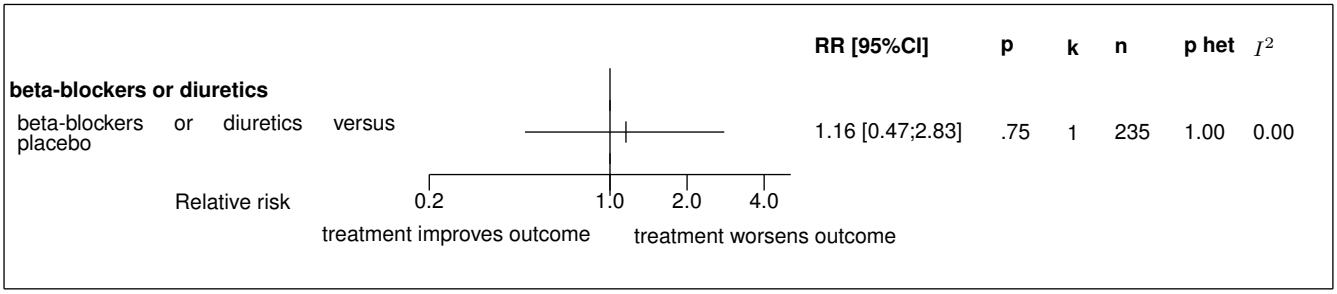
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



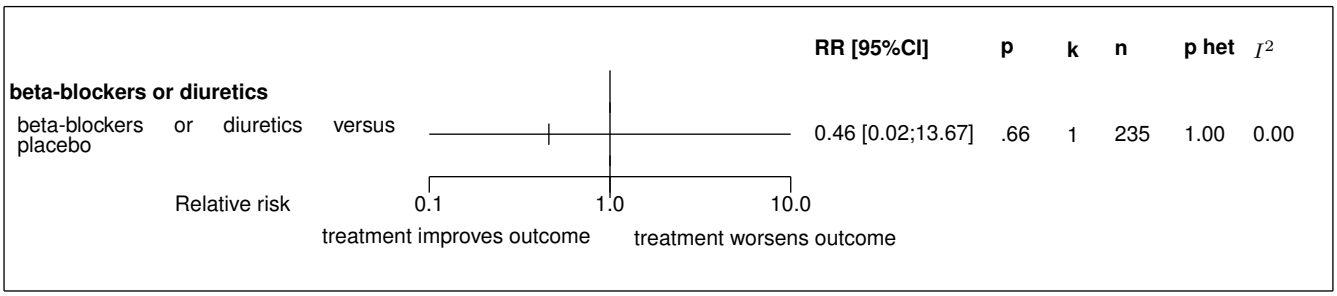
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 12.3: *Forest's plot for stroke (fatal and non fatal)*



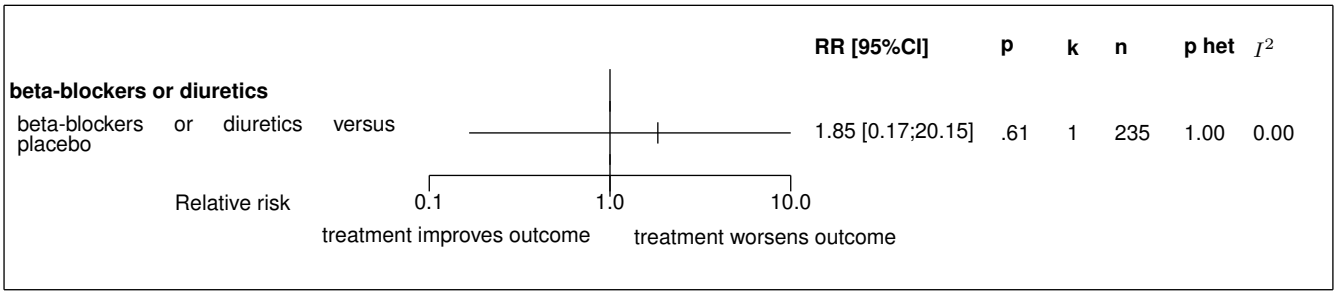
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 12.4: *Forest's plot for coronary event*



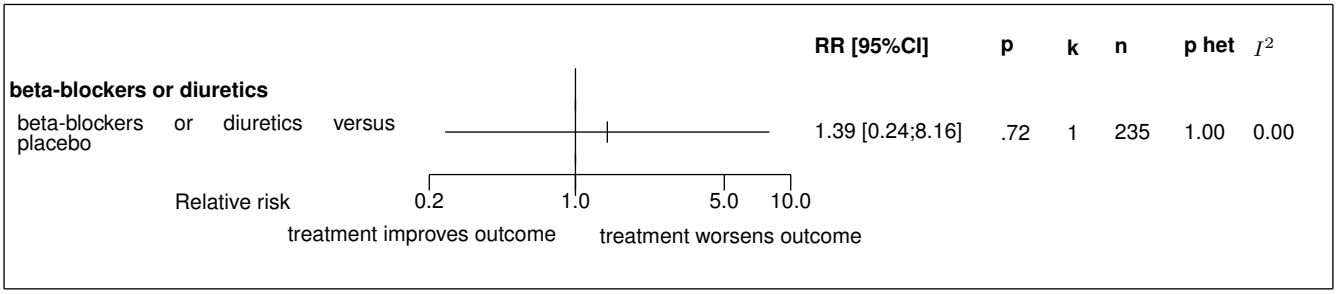
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 12.5: *Forest's plot for coronary death*



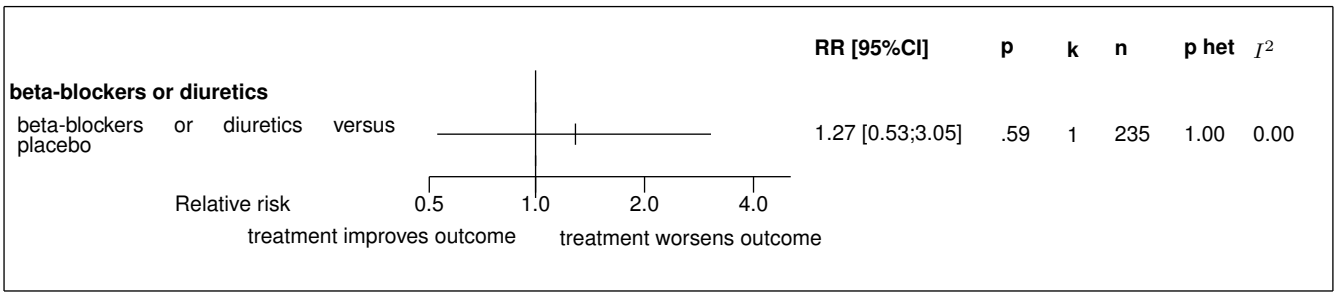
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 12.6: *Forest's plot for heart failure*



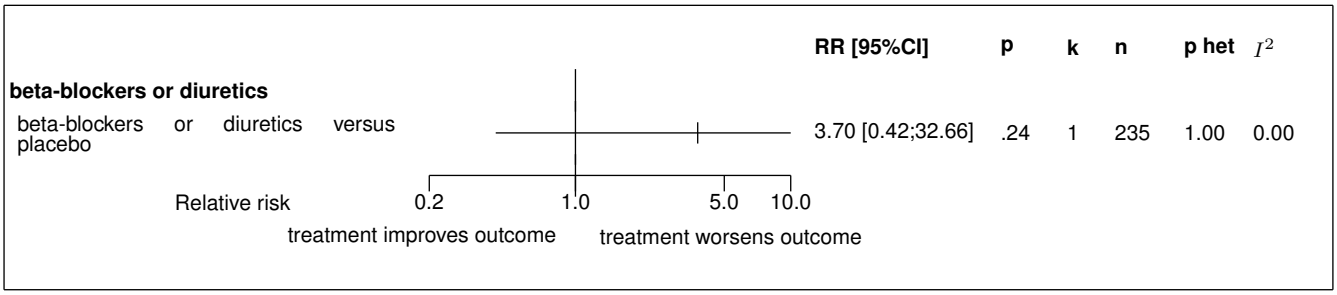
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 12.7: *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

Figure 12.8: *Forest's plot for fatal stroke*



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

13 Details

13.1 Available trials

Only one trial which randomized 235 patients was identified: it compared beta-blockers or diuretics with placebo.
This trial included 235 patients and was published in 1991.
This trial was double blind in design.
It was reported in English language.
Fatal stroke data was reported in 1 trials; 1 trials reported data on cardiovascular death; 1 trials reported data on coronary death; 1 trials reported data on heart failure; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events; and 1 trials reported data on coronary event.
Following tables 13.1 (page 57), 13.2 (page 57), 13.4 (page 59), and 13.3 (page 58) summarized the main characteristics of the trial including in this systematic review of randomized trials of beta-blockers or diuretics.

Table 13.1: *Treatment description - beta-blockers or diuretics - beta-blockers or diuretics*

Trial	Studied treatment	Control treatment
Beta-blockers or diuretics versus placebo		
STOP (subgroup) (1991) [1]	active antihypertensive therapy (three beta-blockers and one diuretic)	placebo

Table 13.2: *Descriptions of participants - beta-blockers or diuretics - beta-blockers or diuretics*

Trial	Patients
Beta-blockers or diuretics versus placebo	
STOP (subgroup) (1991) [1]	Hypertensive Swedish men and women aged 70-84 years

Table 13.3: *Design and methodological quality of trials - beta-blockers or diuretics - beta-blockers or diuretics*

Trial	Design	Duration	Centre	Primary end-point
Beta-blockers or diuretics versus placebo				
STOP (subgroup), 1991 [1] n=235	double-blind	21 y	Sweden 116 centres	

Table 13.4: *Trial characteristics - beta-blockers or diuretics - beta-blockers or diuretics*

Trial
Beta-blockers or diuretics versus placebo
STOP (subgroup), 1991 [1]

13.2 Meta-analysis results

The results are detailed in table 13.5 (page 60). This table is followed by the Forest's plot corresponding to each endpoint.

Beta-blockers or diuretics versus placebo

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between beta-blockers or diuretics and placebo, with a RR of 0.69 (95%CI 0.34 to 1.40, p=0.3100) in favour of beta-blockers or diuretics. In other words, cardiovascular events was slightly lower in the beta-blockers or diuretics 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 2.16 (95% CI 0.57 to 8.16, p=0.2554).
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 1.16 (95% CI 0.47 to 2.83, p=0.7480).
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 0.46 (95% CI 0.02 to 13.67, p=0.6558).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.85 (95% CI 0.17 to 20.15, p=0.6127).
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 1.39 (95% CI 0.24 to 8.16, p=0.7159).
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 1.27 (95% CI 0.53 to 3.05, p=0.5876).
The single study eligible for this comparison provided data on **fatal stroke**. No statistically significant difference between the groups was found in fatal stroke, with a RR of 3.70 (95% CI 0.42 to 32.66, p=0.2382).

Table 13.5: *Results details - beta-blockers or diuretics - beta-blockers or diuretics*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
beta-blockers or diuretics versus placebo						
cardiovascular events	RR=0.69	[0.34;1.40]	0.3100	1.0000 (I^2=0.00)	1	235
cardiovascular death	RR=2.16	[0.57;8.16]	0.2554	1.0000 (I^2=0.00)	1	235
stroke (fatal and non fatal)	RR=1.16	[0.47;2.83]	0.7480	1.0000 (I^2=0.00)	1	235
coronary event	RR=0.46	[0.02;13.67]	0.6558	1.0000 (I^2=0.00)	1	235
coronary death	RR=1.85	[0.17;20.15]	0.6127	1.0000 (I^2=0.00)	1	235
heart failure	RR=1.39	[0.24;8.16]	0.7159	1.0000 (I^2=0.00)	1	235
all cause death	RR=1.27	[0.53;3.05]	0.5876	1.0000 (I^2=0.00)	1	235
fatal stroke	RR=3.70	[0.42;32.66]	0.2382	1.0000 (I^2=0.00)	1	235

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 13.1: *Forest's plot for cardiovascular events*

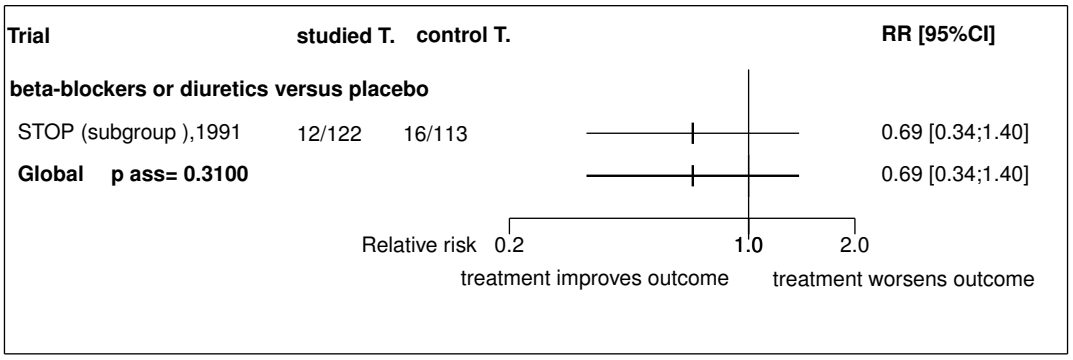


Figure 13.2: *Forest's plot for cardiovascular death*

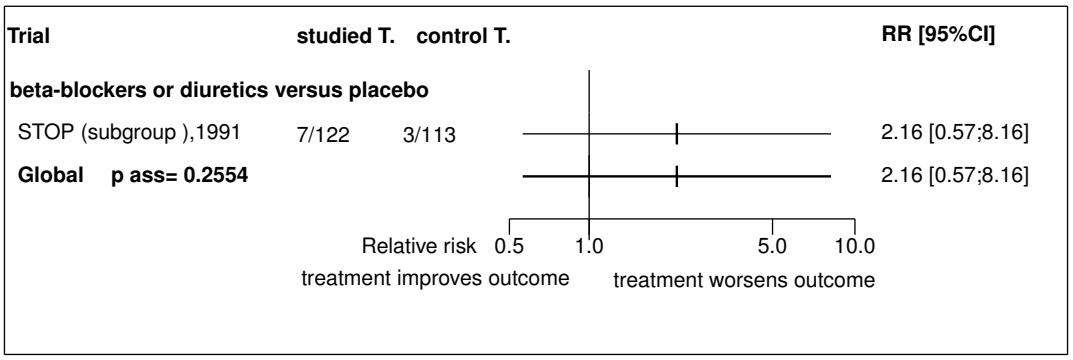


Figure 13.3: *Forest's plot for stroke (fatal and non fatal)*

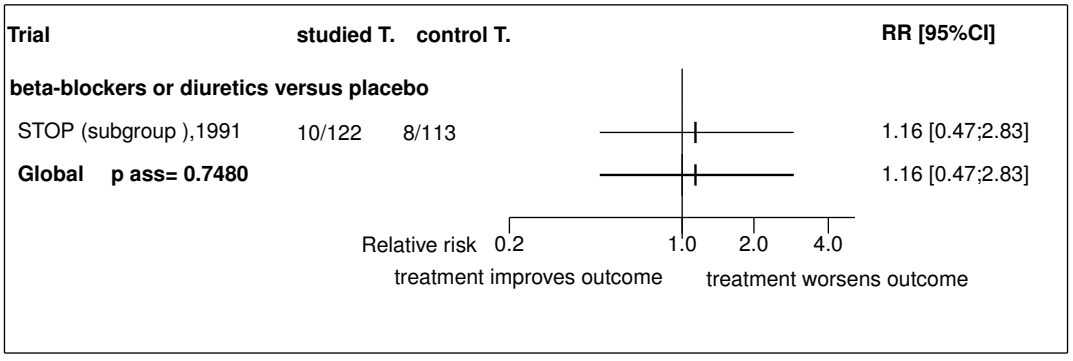


Figure 13.4: *Forest's plot for coronary event*

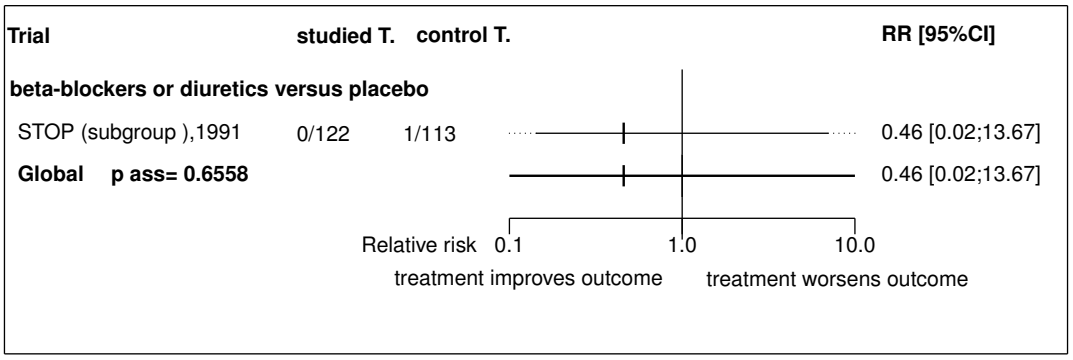


Figure 13.5: *Forest's plot for coronary death*

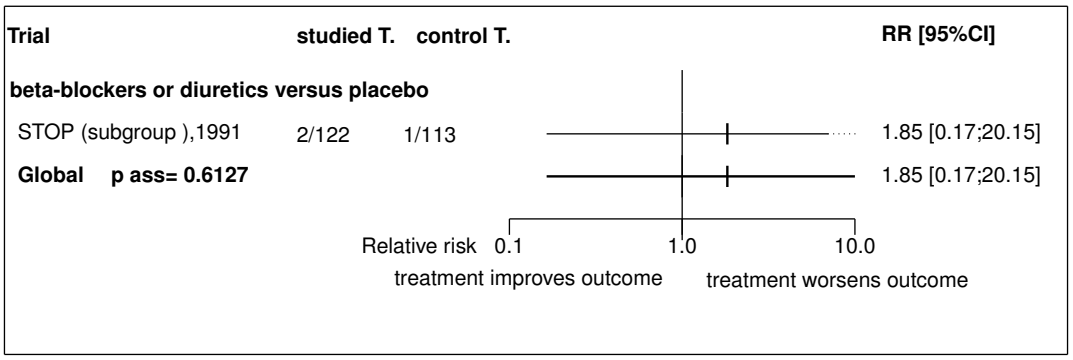


Figure 13.6: *Forest's plot for heart failure*

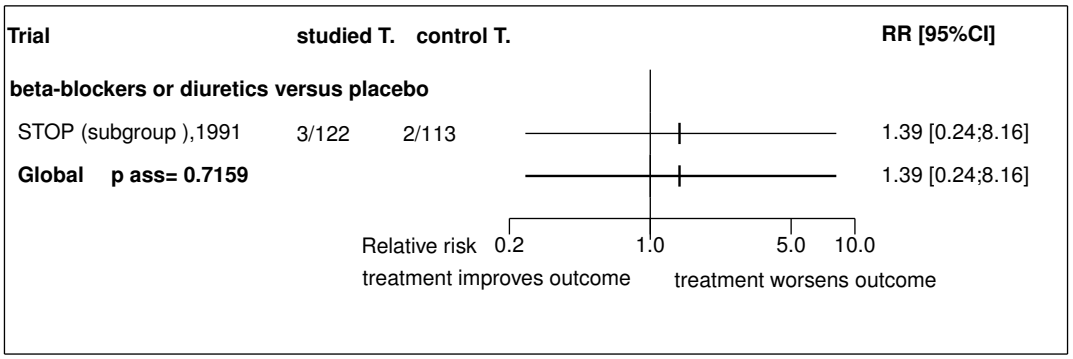


Figure 13.7: *Forest's plot for all cause death*

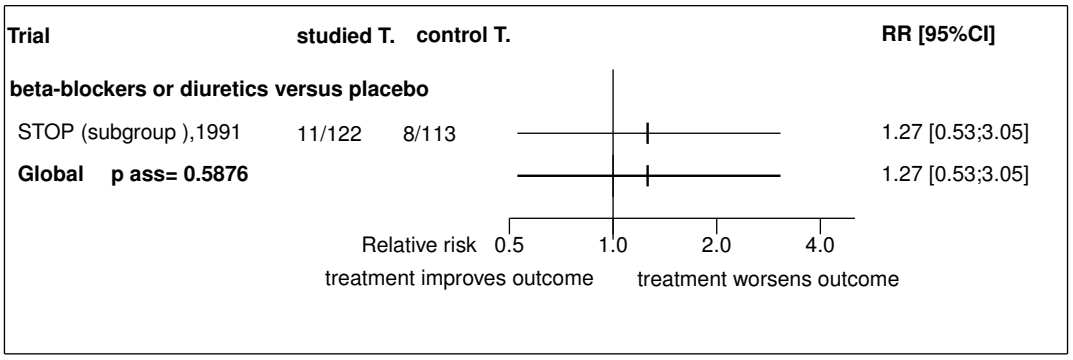
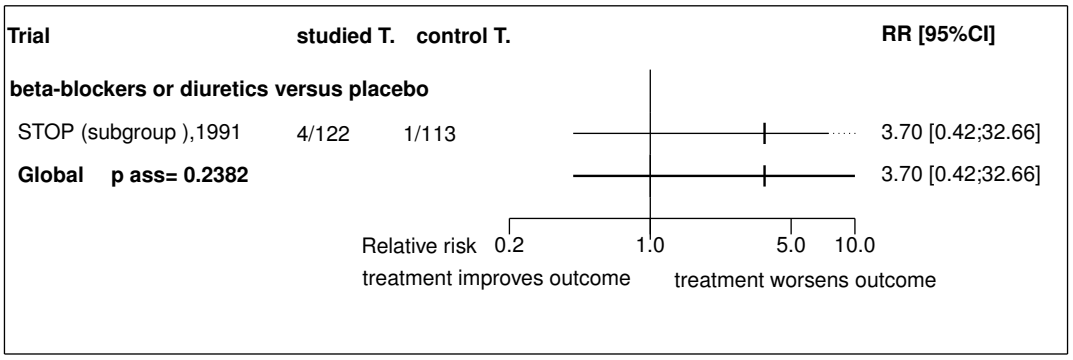


Figure 13.8: *Forest's plot for fatal stroke*



References

[1] Dahlöf B, Lindholm LH, Hansson L, Scherstn B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281-5. [PMID=1682683]

13.3 Individual trial summaries

Table 13.6: *STOP (subgroup), 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=235 (122 vs. 113) **Follow-up duration:** 21 y **Study design:** Randomized controlled trial Double-blind Sweden, 116 centres	Hypertensive Swedish men and women aged 70-84 years	**Studied treatment:** active antihypertensive therapy (three beta-blockers and one diuretic) **Control treatment:** placebo	Cardiovascular events RR=0.69 [0.34;1.40] Cardiovascular death RR=2.16 [0.57;8.16] Stroke (fatal and non fatal) RR=1.16 [0.47;2.83] Coronary death RR=1.85 [0.17;20.15] Heart failure RR=1.39 [0.24;8.16] All cause death RR=1.27 [0.53;3.05] Fatal stroke RR=3.70 [0.42;32.66]

Reference

Dahlöf B, Lindholm LH, Hansson L, Scherstn B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281-5 [PMID=1682683]

14 Global meta-analysis: all beta-blockers or diuretics

14.1 Global meta-analysis: all beta-blockers or diuretics versus placebo

Table 14.1: *All beta-blockers or diureticsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.69	0.34;1.40	0.3100	1.0000 (0.00)	1	235
cardiovascular death	RR=2.16	0.57;8.16	0.2554	1.0000 (0.00)	1	235
stroke (fatal and non fatal)	RR=1.16	0.47;2.83	0.7480	1.0000 (0.00)	1	235
coronary event	RR=0.46	0.02;13.67	0.6558	1.0000 (0.00)	1	235
coronary death	RR=1.85	0.17;20.15	0.6127	1.0000 (0.00)	1	235
heart failure	RR=1.39	0.24;8.16	0.7159	1.0000 (0.00)	1	235
all cause death	RR=1.27	0.53;3.05	0.5876	1.0000 (0.00)	1	235
fatal stroke	RR=3.70	0.42;32.66	0.2382	1.0000 (0.00)	1	235

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

15 Ongoing studies of beta-blockers or diuretics

No ongoing trial was identified.

16 Excluded studies for beta-blockers or diuretics

No trial was excluded.

References

Part IV

Calcium-channel blockers

17 Overview of calcium-channel blockers

17.1 Included trials

Only one trial which randomized 441 patients was identified. In all, 1 randomized comparison concerned nidrendipine.
The detailed descriptions of trials and meta-analysis results is given in section 18 (page 77) for nidrendipine.

This trial included 441 patients and was published in 1997.
This trial was double blind in design.
It was reported in English language.
The table 17.1 (page 72) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

17.2 Summary of meta-analysis results

The meta-analysis of the available trials about calcium-channel blockers provide the results listed in tables 17.2 to 17.2 (page 73) and in the following graphs.

17.2.1 Nidrendipine

No significant difference was found between **nidrendipine** and **placebo** in terms of cardiovascular events (RR=0.95, 95% CI 0.65 to 1.41, p=0.8154, 1 trial), cardiovascular death (RR=1.08, 95% CI 0.67 to 1.74, p=0.7592, 1 trial), stroke (fatal and non fatal) (RR=0.77, 95% CI 0.42 to 1.43, p=0.4143, 1 trial), coronary event (RR=1.10, 95% CI 0.56 to 2.18, p=0.7764, 1 trial), coronary death (RR=1.16, 95% CI 0.54 to 2.49, p=0.7095, 1 trial), heart failure (RR=0.85, 95% CI 0.42 to 1.72, p=0.6473, 1 trial), all cause death (RR=1.23, 95% CI 0.91 to 1.67, p=0.1701, 1 trial)and fatal stroke (RR=1.01, 95% CI 0.42 to 2.44, p=0.9822, 1 trial).

Table 17.1: *Main study characteristics - calcium-channel blockers*

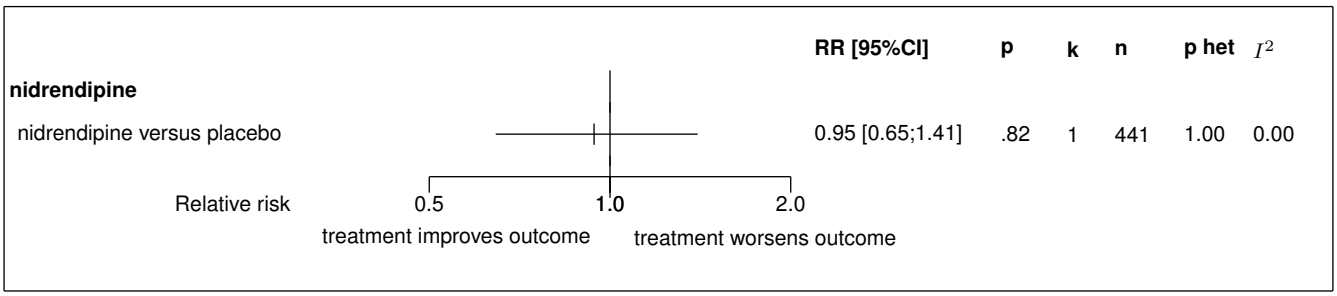
Trial	Patients	Treatments	Trial design and method
Nidrendipine			
Nidrendipine versus placebo			
Syst-Eur (subgroup), 1997 [1] n = 231 vs. 210	patients aged 60 years or older	nitrendipine 10-40 mg daily in first step **versus** placebo	double blind

Table 17.2: *Summary of all results for nidrendipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
nidrendipine versus placebo						
cardiovascular events	RR=0.95	0.65;1.41	0.8154	1.0000 (0.00)	1	441
cardiovascular death	RR=1.08	0.67;1.74	0.7592	1.0000 (0.00)	1	441
stroke (fatal and non fatal)	RR=0.77	0.42;1.43	0.4143	1.0000 (1.00)	1	441
coronary event	RR=1.10	0.56;2.18	0.7764	1.0000 (0.00)	1	441
coronary death	RR=1.16	0.54;2.49	0.7095	1.0000 (0.00)	1	441
heart failure	RR=0.85	0.42;1.72	0.6473	1.0000 (0.00)	1	441
all cause death	RR=1.23	0.91;1.67	0.1701	1.0000 (0.00)	1	441
fatal stroke	RR=1.01	0.42;2.44	0.9822	1.0000 (0.00)	1	441

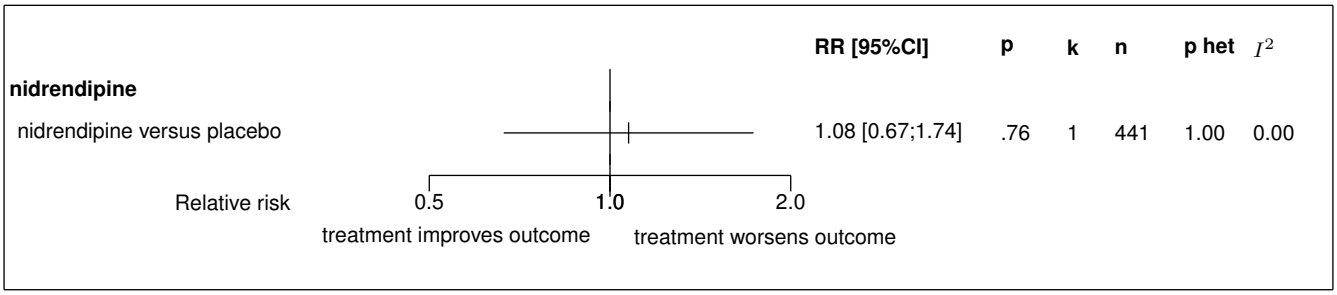
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 17.1: *Forest's plot for cardiovascular events*



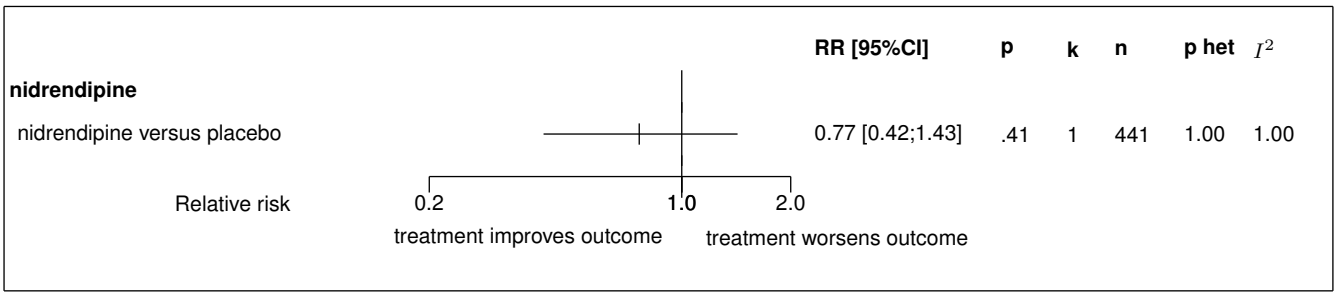
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.2: *Forest's plot for cardiovascular death*



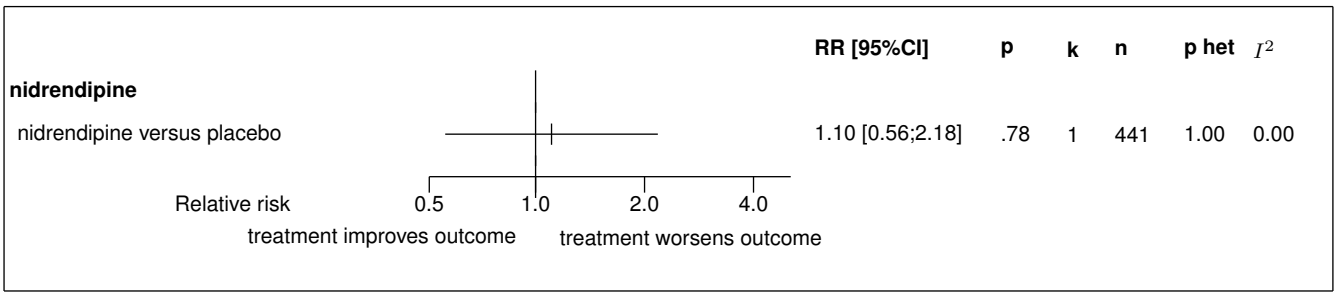
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.3: *Forest's plot for stroke (fatal and non fatal)*



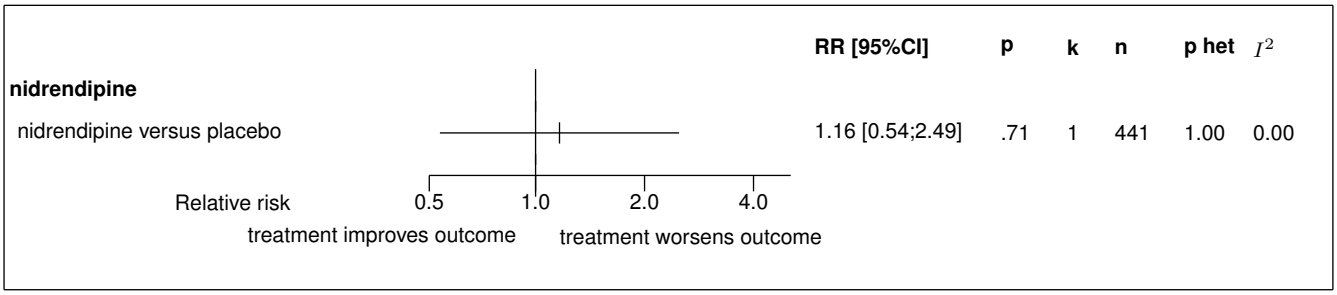
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.4: *Forest's plot for coronary event*



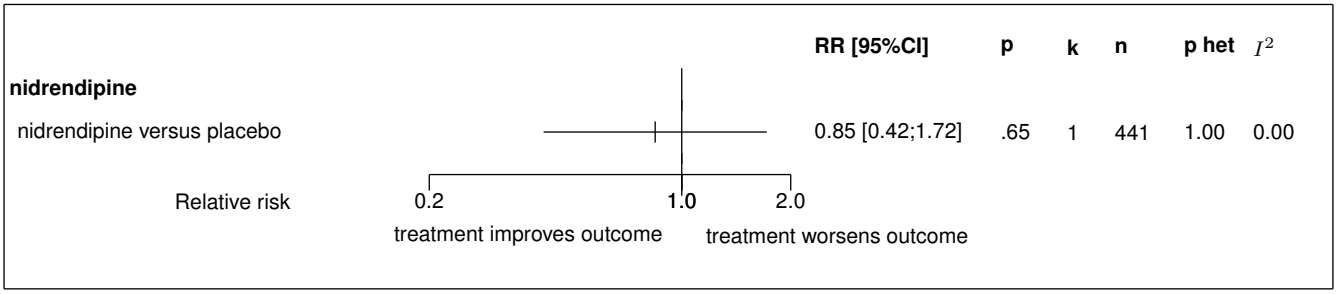
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.5: *Forest's plot for coronary death*



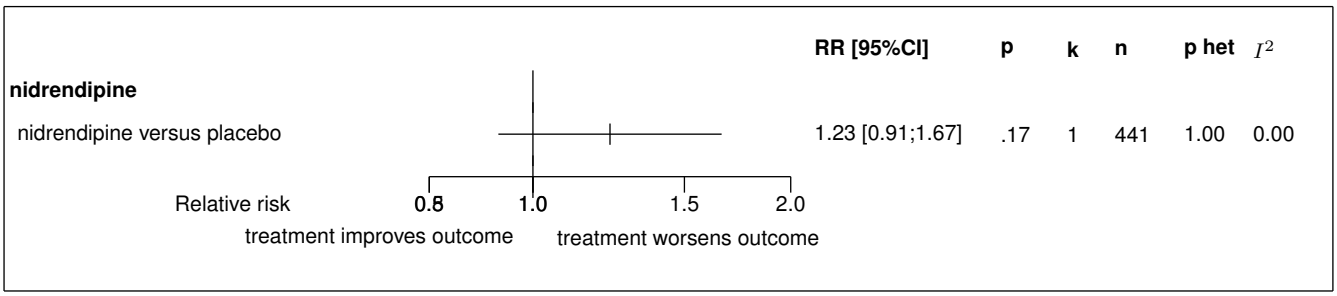
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.6: *Forest's plot for heart failure*



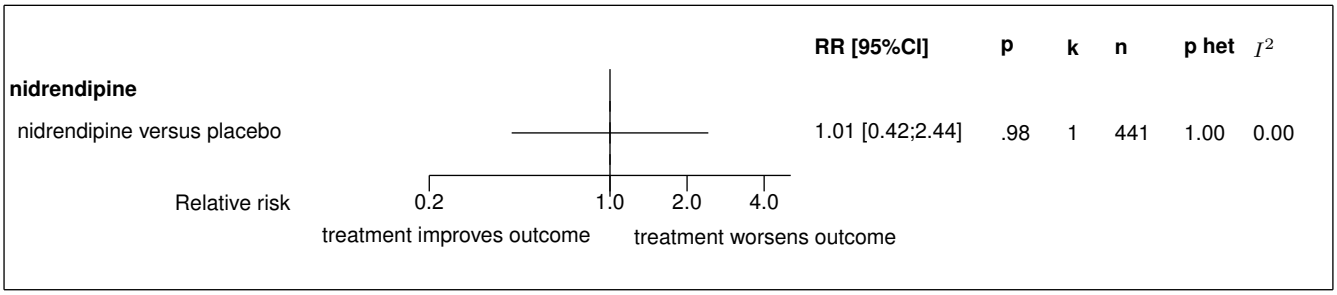
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 17.7: *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

Figure 17.8: *Forest's plot for fatal stroke*



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

18 Details

18.1 Available trials

Only one trial which randomized 441 patients was identified: it compared nidrendipine with placebo.
This trial included 441 patients and was published in 1997.
This trial was double blind in design.
It was reported in English language.
Fatal stroke data was reported in 1 trials; 1 trials reported data on cardiovascular death; 1 trials reported data on coronary death; 1 trials reported data on heart failure; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on cardiovascular events; and 1 trials reported data on coronary event.
Following tables 18.1 (page 77), 18.2 (page 77), 18.4 (page 79), and 18.3 (page 78) summarized the main characteristics of the trial including in this systematic review of randomized trials of nidrendipine.

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

Trial	Studied treatment	Control treatment
Nidrendipine versus placebo		
Syst-Eur (subgroup) (1997) [1]	nitrendipine 10-40 mg daily in first step	placebo

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

Trial	Patients
Nidrendipine versus placebo	
Syst-Eur (subgroup) (1997) [1]	Patients aged 60 years or older

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

Trial	Design	Duration	Centre	Primary endpoint
Nidrendipine versus placebo				
Syst-Eur (subgroup), 1997 [1] n=441	double blind	29 y		

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

Trial
Nidrendipine versus placebo
Syst-Eur (subgroup), 1997 [1]

18.2 Meta-analysis results

The results are detailed in table 18.5 (page 80). This table is followed by the Forest's plot corresponding to each endpoint.

Nidrendipine versus placebo

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between nidrendipine and placebo, with a RR of 0.95 (95%CI 0.65 to 1.41, p=0.8154) in favour of nidrendipine. In other words, cardiovascular events was slightly lower in the nidrendipine 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 1.08 (95% CI 0.67 to 1.74, p=0.7592).
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 0.77 (95% CI 0.42 to 1.43, p=0.4143).
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 1.10 (95% CI 0.56 to 2.18, p=0.7764).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.16 (95% CI 0.54 to 2.49, p=0.7095).
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 0.85 (95% CI 0.42 to 1.72, p=0.6473).
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 1.23 (95% CI 0.91 to 1.67, p=0.1701).
The single study eligible for this comparison provided data on **fatal stroke**. No statistically significant difference between the groups was found in fatal stroke, with a RR of 1.01 (95% CI 0.42 to 2.44, p=0.9822).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
nidrendipine versus placebo						
cardiovascular events	RR=0.95	[0.65;1.41]	0.8154	1.0000 (I^2=0.00)	1	441
cardiovascular death	RR=1.08	[0.67;1.74]	0.7592	1.0000 (I^2=0.00)	1	441
stroke (fatal and non fatal)	RR=0.77	[0.42;1.43]	0.4143	1.0000 (I^2=1.00)	1	441
coronary event	RR=1.10	[0.56;2.18]	0.7764	1.0000 (I^2=0.00)	1	441
coronary death	RR=1.16	[0.54;2.49]	0.7095	1.0000 (I^2=0.00)	1	441
heart failure	RR=0.85	[0.42;1.72]	0.6473	1.0000 (I^2=0.00)	1	441
all cause death	RR=1.23	[0.91;1.67]	0.1701	1.0000 (I^2=0.00)	1	441
fatal stroke	RR=1.01	[0.42;2.44]	0.9822	1.0000 (I^2=0.00)	1	441

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*

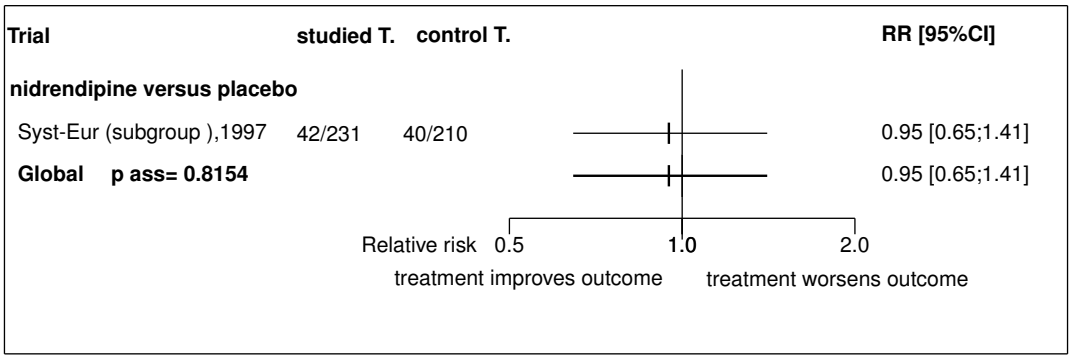


Figure 18.2: *Forest's plot for cardiovascular death*

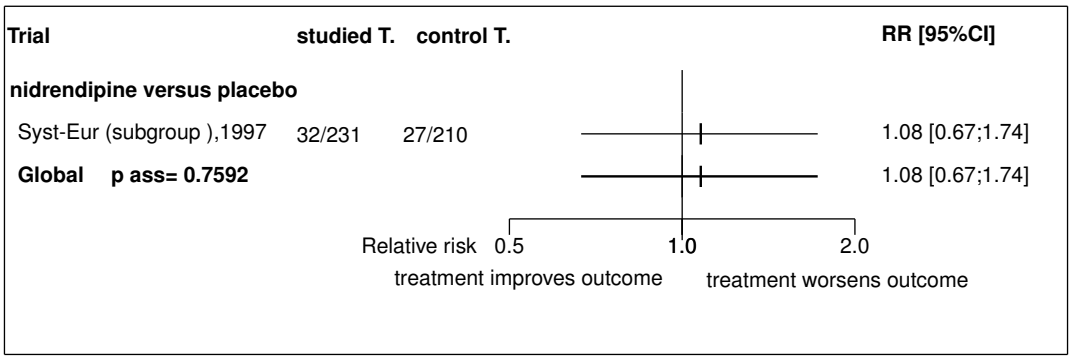


Figure 18.3: *Forest's plot for stroke (fatal and non fatal)*

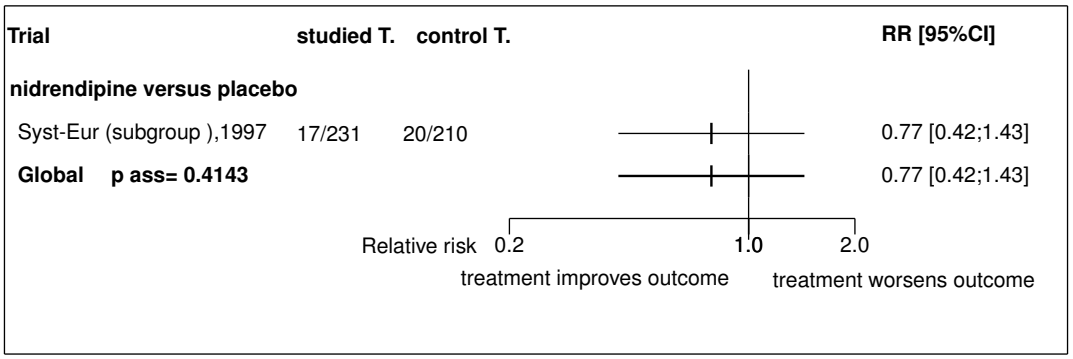


Figure 18.4: *Forest's plot for coronary event*

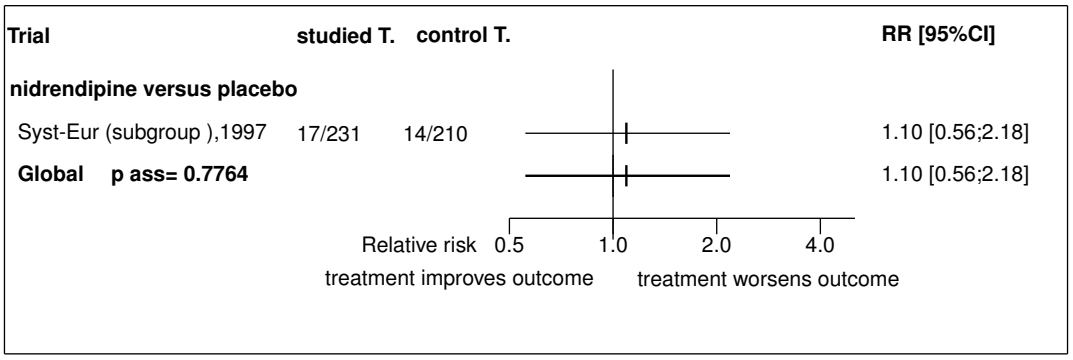


Figure 18.5: *Forest's plot for coronary death*

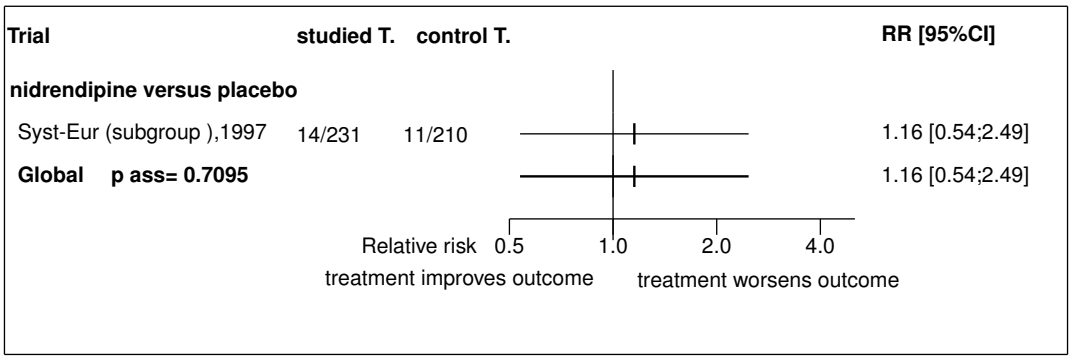


Figure 18.6: *Forest's plot for heart failure*

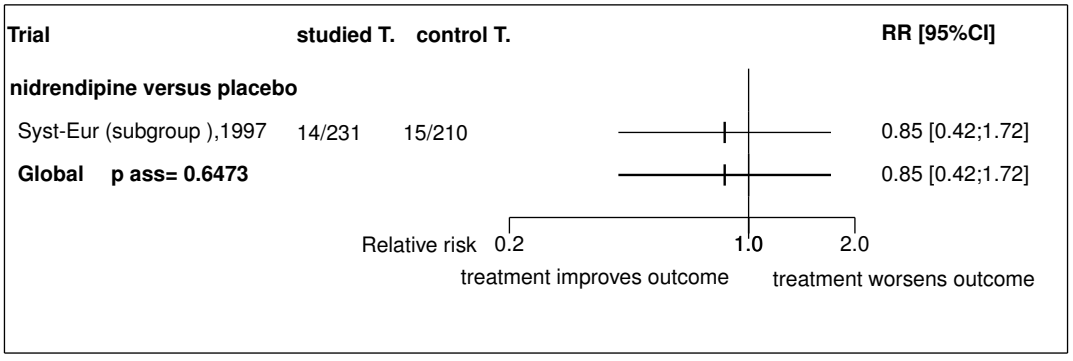


Figure 18.7: *Forest's plot for all cause death*

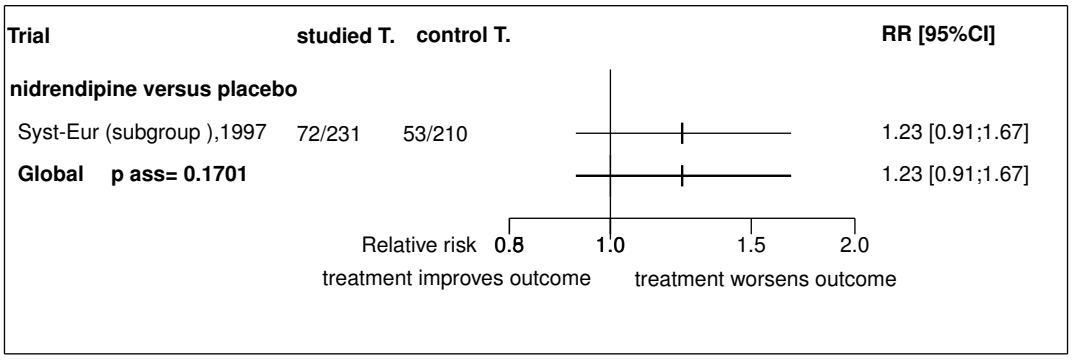
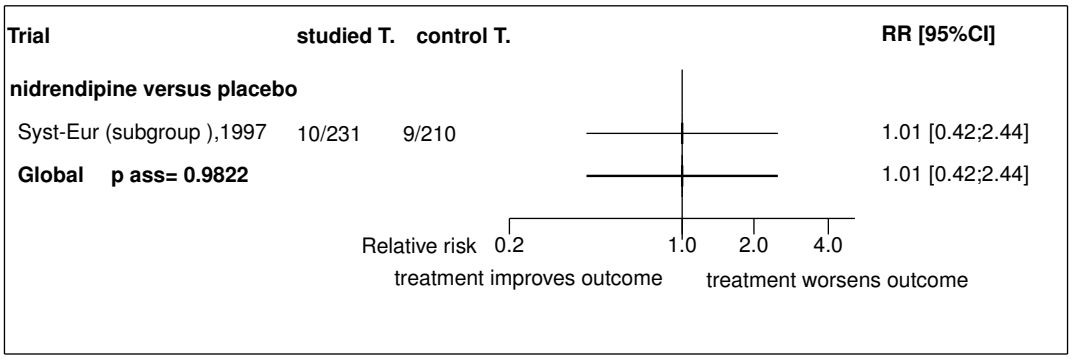


Figure 18.8: *Forest's plot for fatal stroke*



References

[1] Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhger 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;350:757-64. [PMID=9297994]

18.3 Individual trial summaries

Table 18.6: *Syst-Eur (subgroup), 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=441 (231 vs. 210) **Follow-up duration:** 29 y **Study design:** Randomized controlled trial Double blind	Patients aged 60 years or older	**Studied treatment:** nitrendipine 10-40 mg daily in first step **Control treatment:** placebo	Cardiovascular events RR=0.95 [0.65;1.41] Cardiovascular death RR=1.08 [0.67;1.74] Stroke (fatal and non fatal) RR=0.77 [0.42;1.43] Coronary event RR=1.10 [0.56;2.18] Coronary death RR=1.16 [0.54;2.49] Heart failure RR=0.85 [0.42;1.72] All cause death RR=1.23 [0.91;1.67] Fatal stroke RR=1.01 [0.42;2.44]

Reference

Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhger 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;350:757-64 [PMID=9297994]

19 Global meta-analysis: all calcium-channel blockers

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

Table 19.1: *All calcium-channel blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.95	0.65;1.41	0.8154	1.0000 (0.00)	1	441
cardiovascular death	RR=1.08	0.67;1.74	0.7592	1.0000 (0.00)	1	441
stroke (fatal and non fatal)	RR=0.77	0.42;1.43	0.4143	1.0000 (1.00)	1	441
coronary event	RR=1.10	0.56;2.18	0.7764	1.0000 (0.00)	1	441
coronary death	RR=1.16	0.54;2.49	0.7095	1.0000 (0.00)	1	441
heart failure	RR=0.85	0.42;1.72	0.6473	1.0000 (0.00)	1	441
all cause death	RR=1.23	0.91;1.67	0.1701	1.0000 (0.00)	1	441
fatal stroke	RR=1.01	0.42;2.44	0.9822	1.0000 (0.00)	1	441

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

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 21.1.

Table 21.1: *Excluded studies of calcium-channel blockers*

Study	Exclusion reason
Syst-China (1998) [1]	Non-randomised allocation (Patients were alternately assigned placebo or active medication)

References

[1] Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens 1998;16:1823-9. [PMID=9869017]

Part V

Diuretics

22 Overview of diuretics

22.1 Included trials

A total of 4 randomized comparisons which enrolled 4735 patients were identified. In all, 2 randomized comparisons concerned chlorthalidone , one hydrochlorothiazide and one indapamide.
The detailed descriptions of trials and meta-analysis results is given in section 23 (page 98) for chlorthalidone, in section 24 (page 109) for hydrochlorothiazide and in section 25 (page 117) for indapamide.

The average study size was 1183 patients (range 85 to 3845). The first study was published in 1985, and the last study was published in 2008.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 22.1 (page 92) 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 22.4 (page 93) and in the following graphs.

22.2.1 Chlorthalidone

Chlorthalidone was superior to **placebo** in terms of cardiovascular events (RR=0.67, 95% CI 0.48 to 0.93, p=0.0166, 2 trials), stroke (fatal and non fatal) (RR=0.45, 95% CI 0.22 to 0.90, p=0.0243, 2 trials)and heart failure (RR=0.40, 95% CI 0.17 to 0.99, p=0.0477, 2 trials). However, no significant difference was found on cardiovascular death (RR=0.86, 95% CI 0.52 to 1.43, p=0.5611, 2 trials), coronary event (RR=0.72, 95% CI 0.41 to 1.26, p=0.2506, 2 trials), coronary death (RR=0.77, 95% CI 0.40 to 1.50, p=0.4413, 2 trials), all cause death (RR=1.04, 95% CI 0.48 to 2.27, p=0.9198, 2 trials)and fatal stroke (RR=0.62, 95% CI 0.15 to 2.48, p=0.4980, 2 trials).

22.2.2 Hydrochlorothiazide

No significant difference was found between **hydrochlorothiazide** and **placebo** in terms of cardiovascular death (RR=1.21, 95% CI 0.85 to 1.73, p=0.2835, 1 trial), coronary death (RR=1.37, 95% CI 0.56 to 3.35, p=0.4961, 1 trial), all cause death (RR=1.17, 95% CI 0.99 to 1.40, p=0.0706, 1 trial)and fatal stroke (RR=1.48, 95% CI 0.65 to 3.38, p=0.3466, 1 trial).

22.2.3 Indapamide

Indapamide was superior to **placebo** in terms of heart failure (RR=0.38, 95% CI 0.23 to 0.62, p=0.0000, 1 trial)and all cause death (RR=0.82, 95% CI 0.69 to 0.99, p=0.0349, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.81, 95% CI 0.63 to 1.05, p=0.1079, 1 trial), stroke (fatal and non fatal) (RR=0.73, 95% CI 0.51 to 1.04, p=0.0850, 1 trial)and coronary event (RR=0.74, 95% CI 0.31 to 1.76, p=0.4971, 1 trial).

Table 22.1: *Main study characteristics - Diuretics*

Trial	Patients	Treatments	Trial design and method
Chlorthalidone			
Chlorthalidone versus placebo			
SHEP-P (subgroup), 1989 [1] n = 70 vs. 15	elderly participants with untreated blood pressures of greater than 160/less than 90 mm Hg	chlorthalidone **versus** placebo	double-blind
SHEP (subgroup), 1991 [2] n = 331 vs. 319	patients aged 60 years and above	chlorthalidone, 12.5 mg/d for step 1 **versus** placebo	double blind Primary endpoint: nonfatal and fatal (total) stroke
Hydrochlorothiazide			
Hydrochlorothiazide versus placebo			
EWPHE (subgroup), 1985 [1] n = 70 vs. 85	patients over the age of 60	hydrochlorothiazide + triamterene **versus** placebo	double-blind
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 chlorthalidone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
chlorthalidone versus placebo						
cardiovascular events	RR=0.67	0.48;0.93	0.0166	0.9528 (0.00)	2	735
cardiovascular death	RR=0.86	0.52;1.43	0.5611	0.4414 (0.00)	2	735
stroke (fatal and non fatal)	RR=0.45	0.22;0.90	0.0243	0.2601 (0.21)	2	735
coronary event	RR=0.72	0.41;1.26	0.2506	0.6938 (0.00)	2	735
coronary death	RR=0.77	0.40;1.50	0.4413	0.7262 (0.00)	2	735
heart failure	RR=0.40	0.17;0.99	0.0477	0.2927 (0.10)	2	735
all cause death	RR=1.04	0.48;2.27	0.9198	0.2860 (0.12)	2	735
fatal stroke	RR=0.62	0.15;2.48	0.4980	0.5664 (0.00)	2	735

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 22.3: *Summary of all results for hydrochlorothiazide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
hydrochlorothiazide versus placebo						
cardiovascular death	RR=1.21	0.85;1.73	0.2835	1.0000 (0.00)	1	155
coronary death	RR=1.37	0.56;3.35	0.4961	1.0000 (0.00)	1	155
all cause death	RR=1.17	0.99;1.40	0.0706	1.0000 (0.00)	1	155
fatal stroke	RR=1.48	0.65;3.38	0.3466	1.0000 (1.00)	1	155

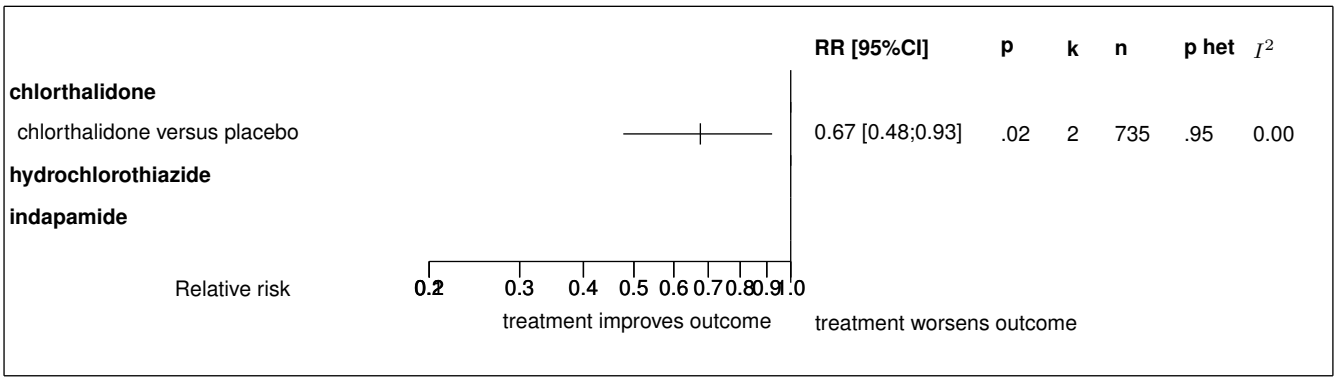
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 22.4: *Summary of all results for indapamide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
indapamide versus placebo						
cardiovascular death	RR=0.81	0.63;1.05	0.1079	1.0000 (0.00)	1	3845
stroke (fatal and non fatal)	RR=0.73	0.51;1.04	0.0850	1.0000 (0.00)	1	3845
coronary event	RR=0.74	0.31;1.76	0.4971	1.0000 (0.00)	1	3845
heart failure	RR=0.38	0.23;0.62	0.0000	1.0000 (0.00)	1	3845
all cause death	RR=0.82	0.69;0.99	0.0349	1.0000 (0.00)	1	3845

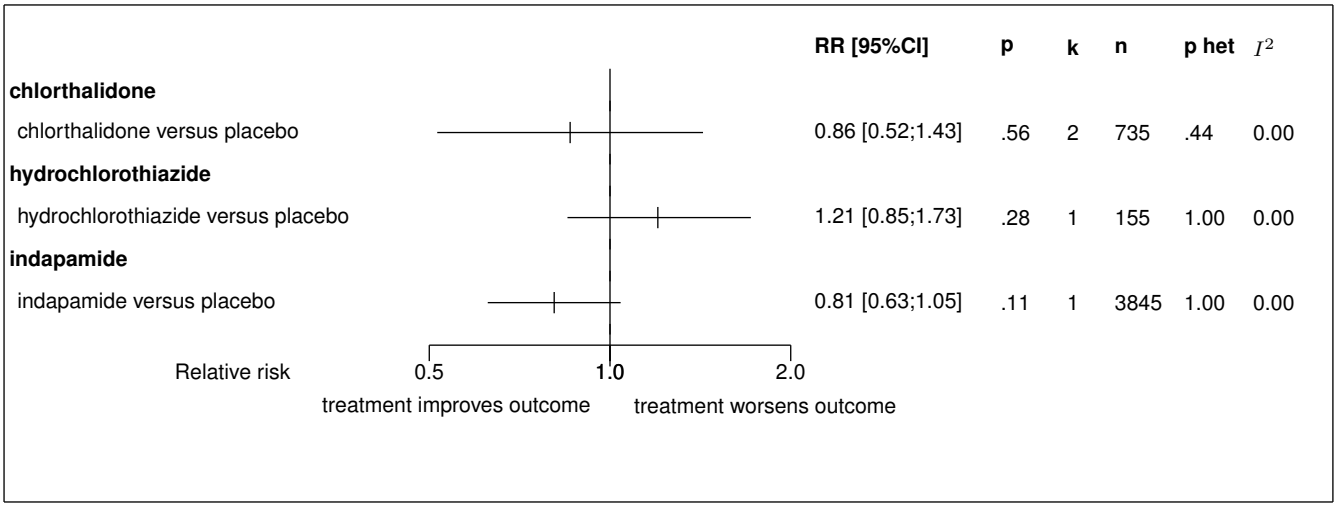
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 22.1: *Forest's plot for cardiovascular events*



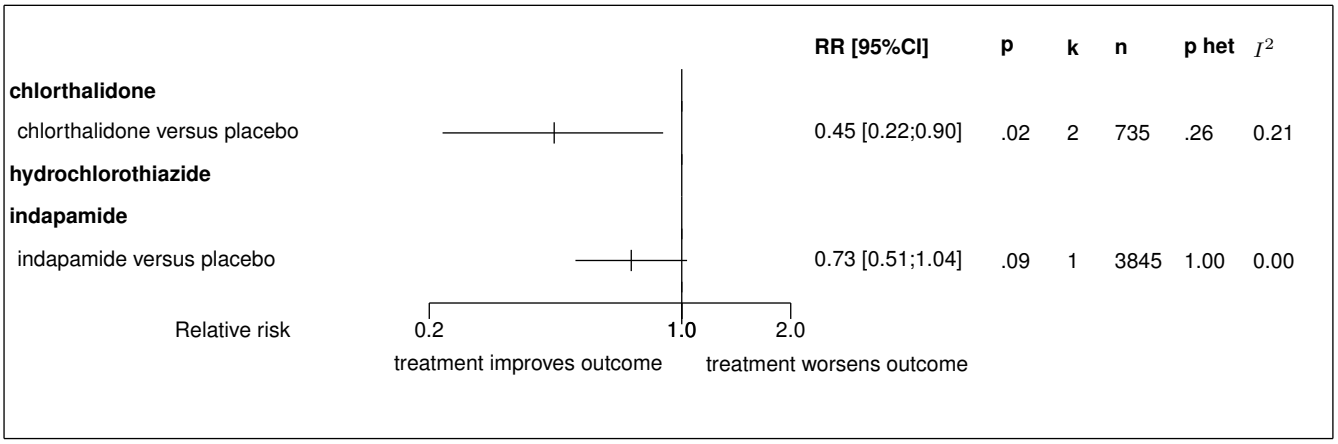
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.2: *Forest's plot for cardiovascular death*



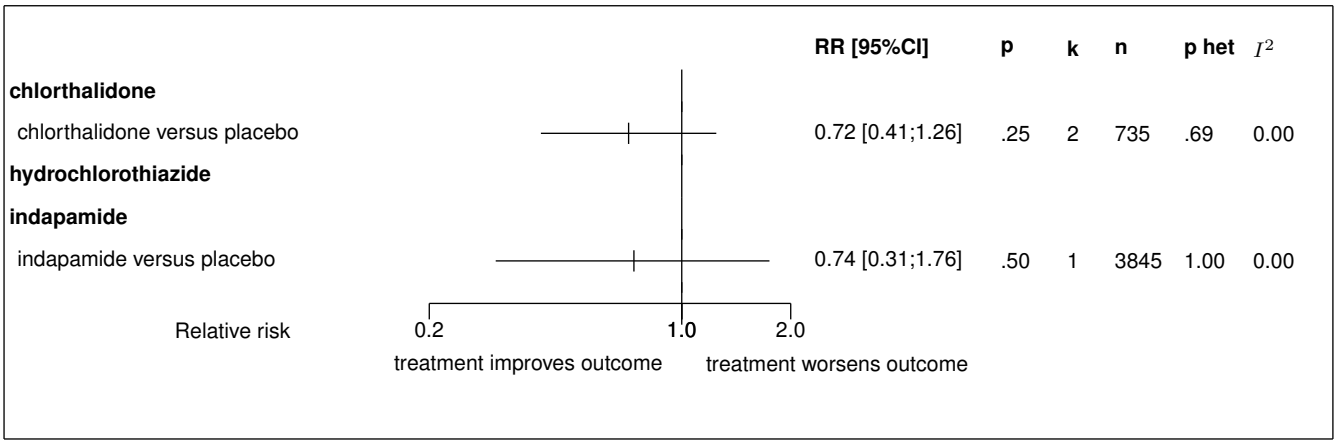
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.3: *Forest's plot for stroke (fatal and non fatal)*



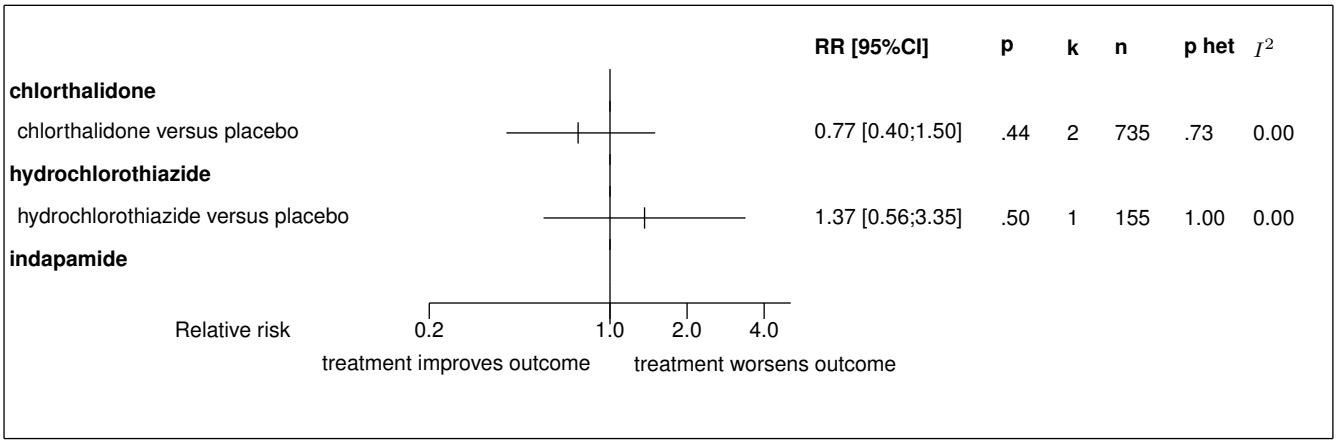
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.4: *Forest's plot for coronary event*



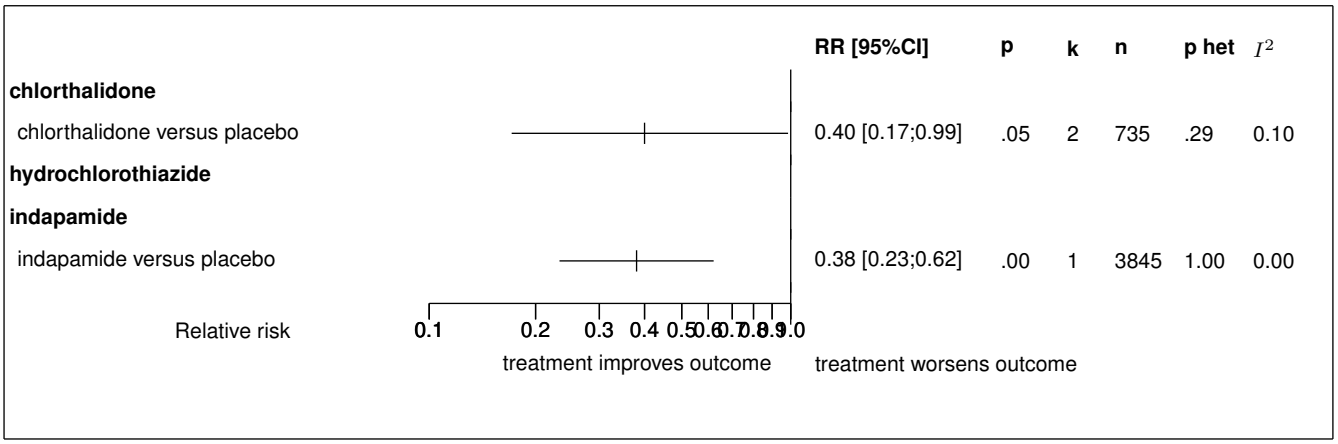
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.5: *Forest's plot for coronary death*



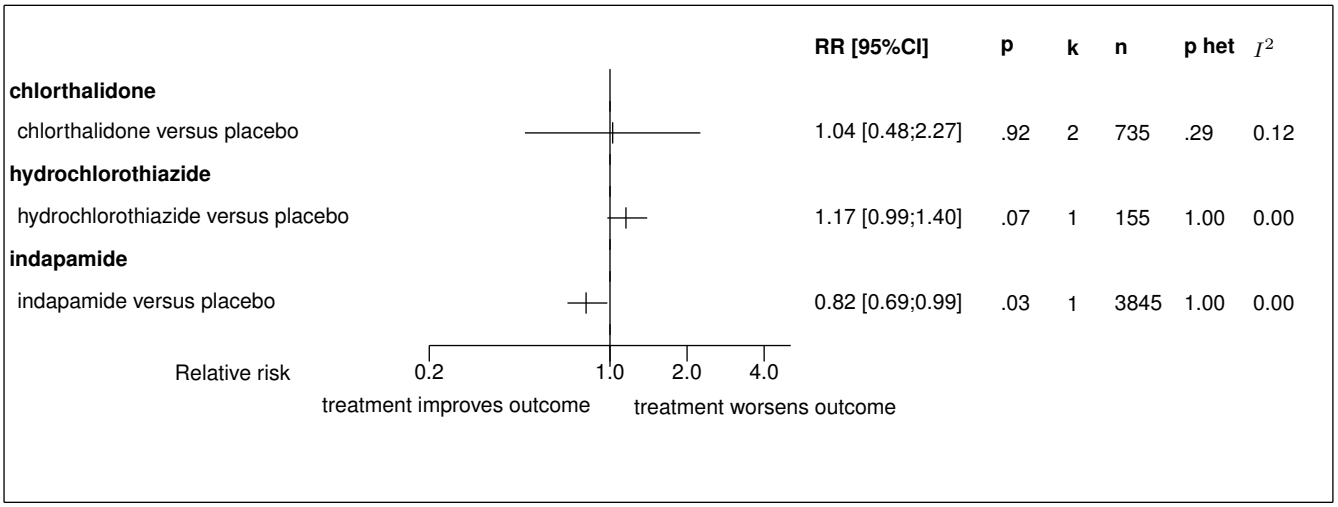
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.6: *Forest's plot for heart failure*



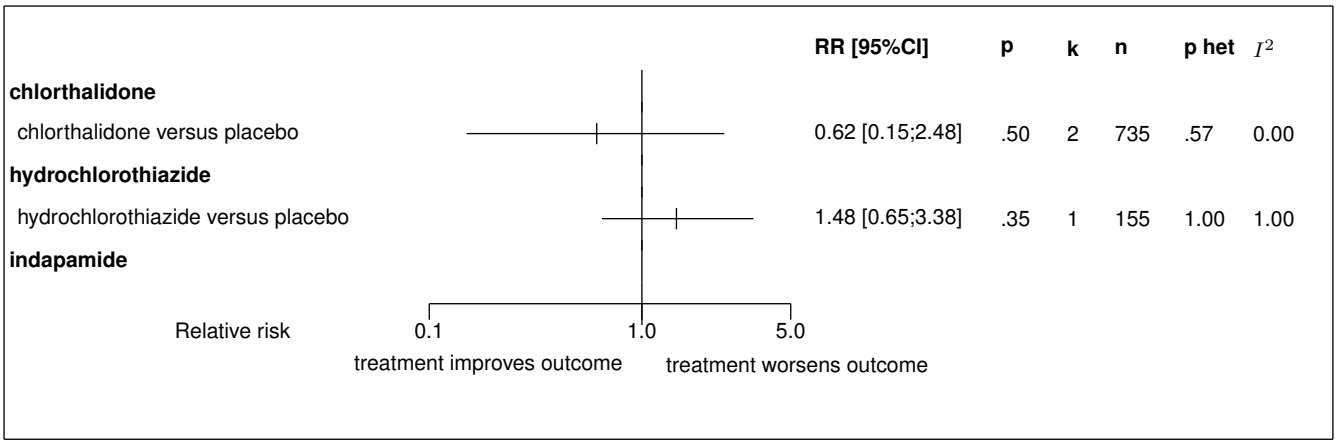
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 22.7: *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

Figure 22.8: *Forest's plot for fatal stroke*



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

23 Detailed results for chlorthalidone

23.1 Available trials

A total of 2 RCTs which randomized 735 patients were identified: all compared chlorthalidone with placebo.
The average study size was 367 patients (range 85 to 650). The first study was published in 1989, and the last study was published in 1991.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
Fatal stroke data was reported in 2 trials; 2 trials reported data on cardiovascular death; 2 trials reported data on coronary death; 2 trials reported data on heart failure; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on all cause death; 2 trials reported data on cardiovascular events; and 2 trials reported data on coronary event.
Following tables 23.1 (page 98), 23.2 (page 98), 23.4 (page 100), and 23.3 (page 99) summarized the main characteristics of the trials including in this systematic review of randomized trials of chlorthalidone.

Table 23.1: *Treatment description - Diuretics - chlorthalidone*

Trial	Studied treatment	Control treatment
Chlorthalidone versus placebo		
SHEP-P (subgroup) (1989) [1]	chlorthalidone	placebo
SHEP (subgroup) (1991) [2]	chlorthalidone, 12.5 mg/d for step 1	placebo

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

Trial	Patients
Chlorthalidone versus placebo	
SHEP-P (subgroup) (1989) [1]	Elderly participants with untreated blood pressures of greater than 160/less than 90 mm Hg
SHEP (subgroup) (1991) [2]	Patients aged 60 years and above

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

Trial	Design	Duration	Centre	Primary endpoint
Chlorthalidone versus placebo				
SHEP-P (subgroup), 1989 [1] n=85	double-blind	28y		
SHEP (subgroup), 1991 [2] n=650	double blind	42y		Nonfatal and fatal (total) stroke

Table 23.4: *Trial characteristics - Diuretics - chlorthalidone*

Trial
Chlorthalidone versus placebo
SHEP-P (subgroup), 1989 [1]
SHEP (subgroup), 1991 [2]

23.2 Meta-analysis results

The results are detailed in table 23.5 (page 101). This table is followed by the Forest's plot corresponding to each endpoint.

Chlorthalidone versus placebo

All the 2 studies had extractable data about the number of participants with **cardiovascular events**. The analysis detected a statistically significant difference in favor of chlorthalidone in cardiovascular events, with a RR of 0.67 (95% CI 0.48 to 0.93, p=0.0166). No heterogeneity was detected (p = 0.9528, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **cardiovascular death**. When pooled together, there was no statistically significant difference between the groups in cardiovascular death, with a RR of 0.86 (95% CI 0.52 to 1.43, p=0.5611). No heterogeneity was detected (p = 0.4414, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of chlorthalidone in stroke (fatal and non fatal), with a RR of 0.45 (95% CI 0.22 to 0.90, p=0.0243). No heterogeneity was detected (p = 0.2601, I^2 = 0.21%).
All the 2 studies had extractable data about the number of participants with **coronary event**. When pooled together, there was no statistically significant difference between the groups in coronary event, with a RR of 0.72 (95% CI 0.41 to 1.26, p=0.2506). No heterogeneity was detected (p = 0.6938, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **coronary death**. When pooled together, there was no statistically significant difference between the groups in coronary death, with a RR of 0.77 (95% CI 0.40 to 1.50, p=0.4413). No heterogeneity was detected (p = 0.7262, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **heart failure**. The analysis detected a statistically significant difference in favor of chlorthalidone in heart failure, with a RR of 0.40 (95% CI 0.17 to 0.99, p=0.0477). No heterogeneity was detected (p = 0.2927, I^2 = 0.10%).
All the 2 studies had extractable data about the number of participants with **all cause death**. When pooled together, there was no statistically significant difference between the groups in all cause death, with a RR of 1.04 (95% CI 0.48 to 2.27, p=0.9198). No heterogeneity was detected (p = 0.2860, I^2 = 0.12%).
All the 2 studies had extractable data about the number of participants with **fatal stroke**. When pooled together, there was no statistically significant difference between the groups in fatal stroke, with a RR of 0.62 (95% CI 0.15 to 2.48, p=0.4980). No heterogeneity was detected (p = 0.5664, I^2 = 0.00%).

Table 23.5: *Results details - Diuretics - chlorthalidone*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
chlorthalidone versus placebo						
cardiovascular events	RR=0.67	[0.48;0.93]	0.0166	0.9528 (I^2=0.00)	2	735
cardiovascular death	RR=0.86	[0.52;1.43]	0.5611	0.4414 (I^2=0.00)	2	735
stroke (fatal and non fatal)	RR=0.45	[0.22;0.90]	0.0243	0.2601 (I^2=0.21)	2	735

continued...

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
coronary event	RR=0.72	[0.41;1.26]	0.2506	0.6938 (I^2=0.00)	2	735
coronary death	RR=0.77	[0.40;1.50]	0.4413	0.7262 (I^2=0.00)	2	735
heart failure	RR=0.40	[0.17;0.99]	0.0477	0.2927 (I^2=0.10)	2	735
all cause death	RR=1.04	[0.48;2.27]	0.9198	0.2860 (I^2=0.12)	2	735
fatal stroke	RR=0.62	[0.15;2.48]	0.4980	0.5664 (I^2=0.00)	2	735

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 23.1: *Forest's plot for cardiovascular events*

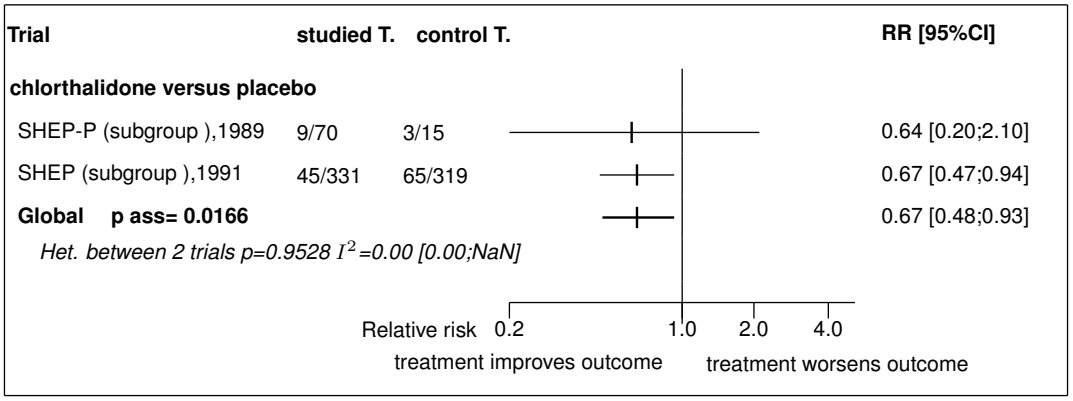


Figure 23.2: *Forest's plot for cardiovascular death*

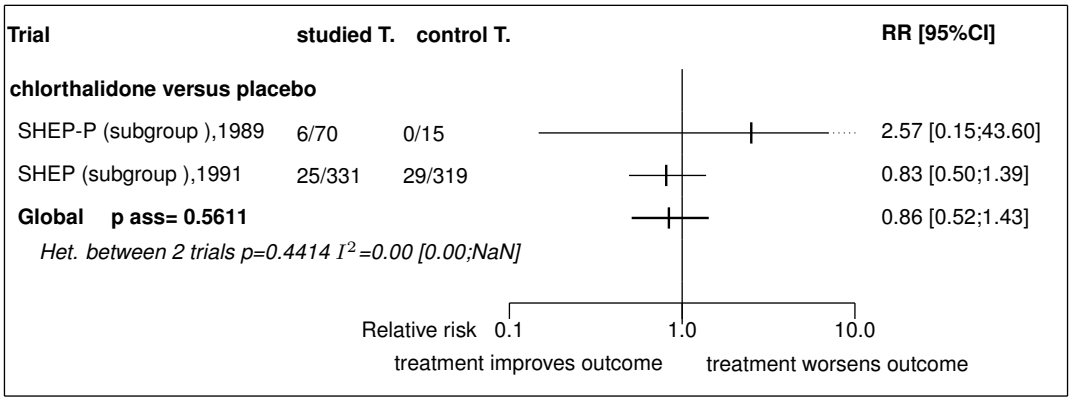


Figure 23.3: *Forest's plot for stroke (fatal and non fatal)*

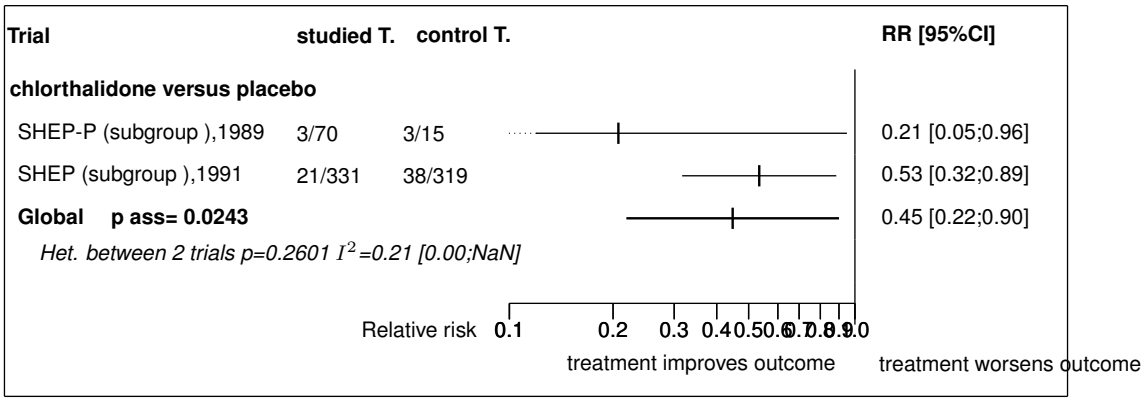


Figure 23.4: *Forest's plot for coronary event*

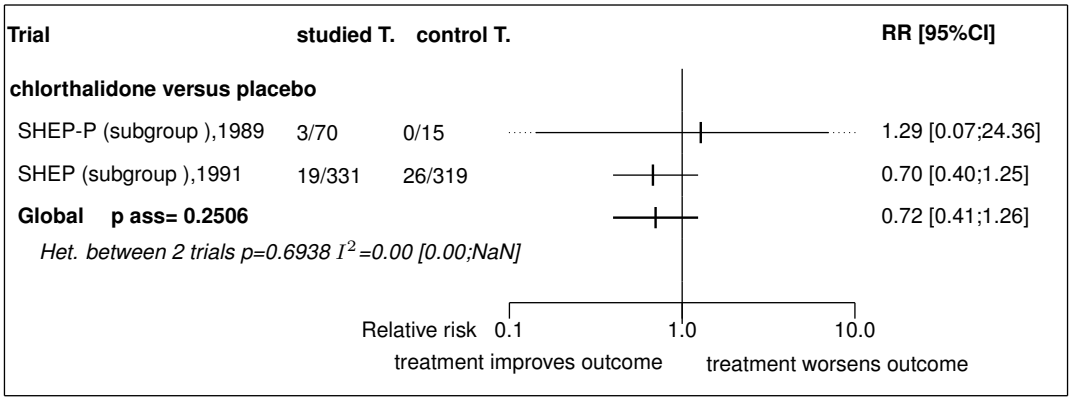


Figure 23.5: *Forest's plot for coronary death*

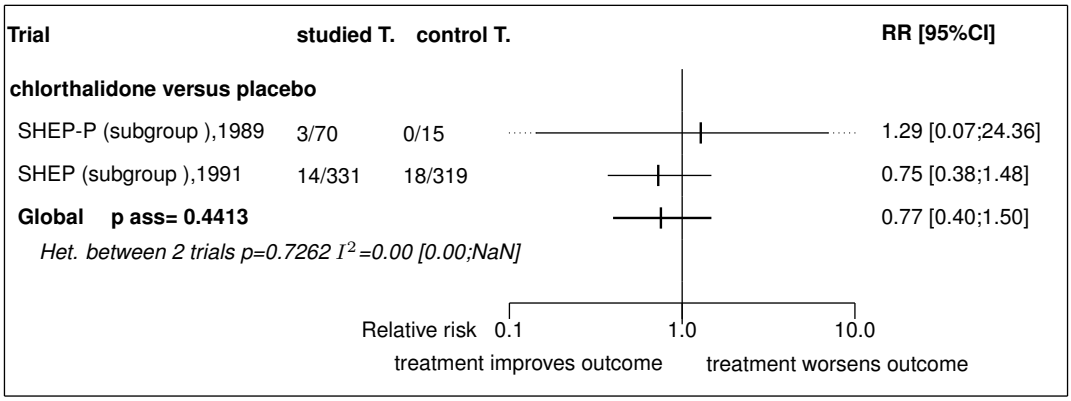


Figure 23.6: *Forest's plot for heart failure*

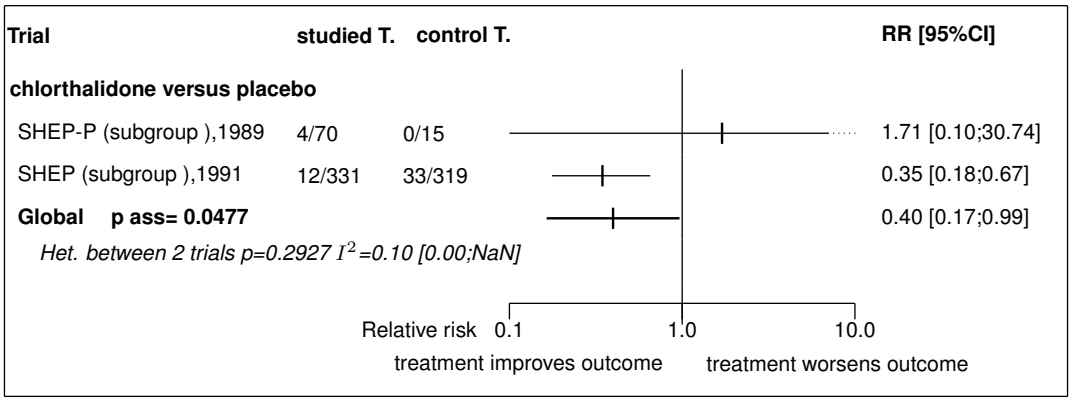


Figure 23.7: *Forest's plot for all cause death*

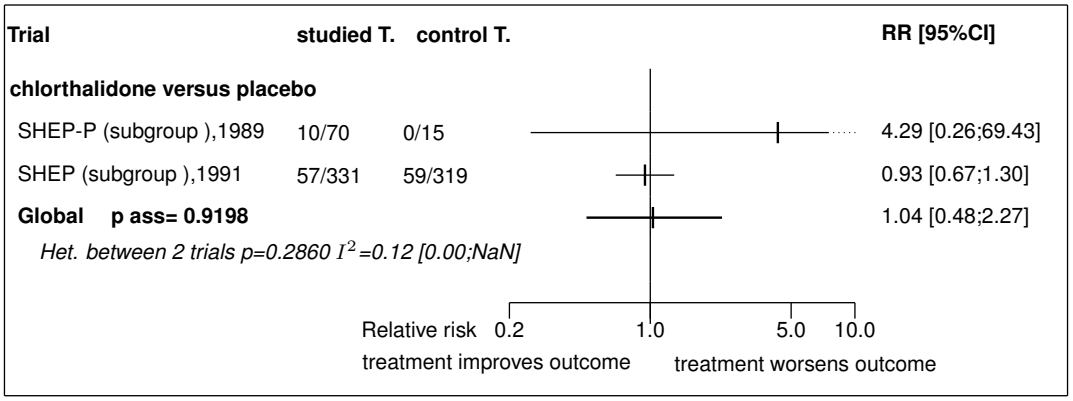
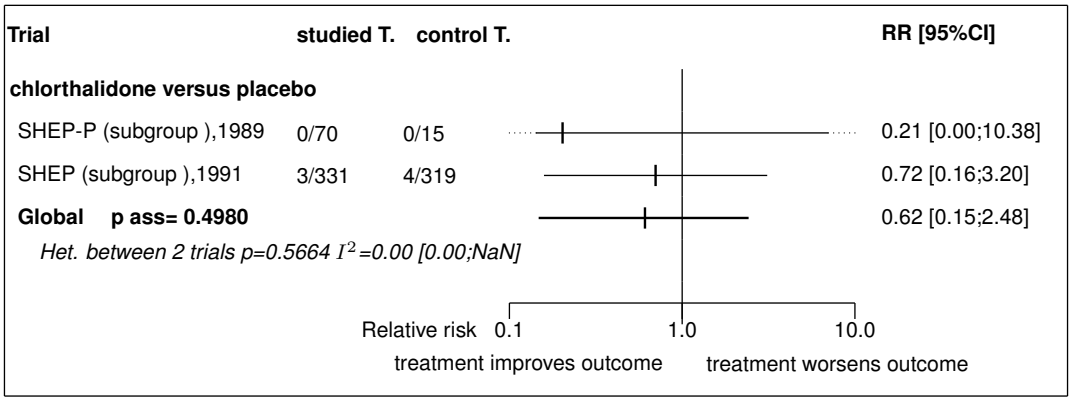


Figure 23.8: *Forest's plot for fatal stroke*



References

[1] Perry HM Jr, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, Greenlick MR, Kuller LH, Schnaper HW, Schoenberger JA. Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. Stroke 1989;20:4-13. [PMID=2911834]

[2] . Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255-64. [PMID=2046107]

23.3 Individual trial summaries

Table 23.6: *SHEP-P (subgroup), 1989 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=85 (70 vs. 15) **Follow-up duration:** 28y **Study design:** Randomized controlled trial Double-blind	Elderly participants with untreated blood pressures of greater than 160/less than 90 mm Hg	**Studied treatment:** chlorthalidone **Control treatment:** placebo	Cardiovascular events RR=0.64 [0.20;2.10] Stroke (fatal and non fatal) RR=0.21 [0.05;0.96]

Reference

Perry HM Jr, Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, Greenlick MR, Kuller LH, Schnaper HW, Schoenberger JA. Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. Stroke 1989;20:4-13 [PMID=2911834]

Table 23.7: *SHEP (subgroup), 1991 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=650 (331 vs. 319) **Follow-up duration:** 42y **Study design:** Randomized controlled trial Double blind	Patients aged 60 years and above	**Studied treatment:** chlorthalidone, 12.5 mg/d for step 1 **Control treatment:** placebo	Cardiovascular events RR=0.67 [0.47;0.94] Cardiovascular death RR=0.83 [0.50;1.39] Stroke (fatal and non fatal) RR=0.53 [0.32;0.89] Coronary event RR=0.70 [0.40;1.25] Coronary death RR=0.75 [0.38;1.48] Heart failure RR=0.35 [0.18;0.67] All cause death RR=0.93 [0.67;1.30] Fatal stroke RR=0.72 [0.16;3.20]

Reference

. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255-64 [PMID=2046107]

24 Detailed results for hydrochlorothiazide

24.1 Available trials

Only one trial which randomized 155 patients was identified: it compared hydrochlorothiazide with placebo.
This trial included 155 patients and was published in 1985.
This trial was double blind in design.
It was reported in English language.
Coronary death data was reported in 1 trials; 1 trials reported data on cardiovascular death; 1 trials reported data on fatal stroke; and 1 trials reported data on all cause death.
Following tables 24.1 (page 109), 24.2 (page 109), 24.4 (page 111), and 24.3 (page 109) summarized the main characteristics of the trial including in this systematic review of randomized trials of hydrochlorothiazide.

Table 24.1: *Treatment description - Diuretics - hydrochlorothiazide*

Trial	Studied treatment	Control treatment
Hydrochlorothiazide versus placebo		
EWPHE (subgroup) (1985) [1]	hydrochlorothiazide + triamterene	placebo

Table 24.2: *Descriptions of participants - Diuretics - hydrochlorothiazide*

Trial	Patients
Hydrochlorothiazide versus placebo	
EWPHE (subgroup) (1985) [1]	Patients over the age of 60

Table 24.3: *Design and methodological quality of trials - Diuretics - hydrochlorothiazide*

Trial	Design	Duration	Centre	Primary end-point
Hydrochlorothiazide versus placebo				

continued...

Trial	Design	Duration	Centre	Primary end-point
EWPHE (subgroup), 1985 [1] n=155	double-blind	31y		

Table 24.4: *Trial characteristics - Diuretics - hydrochlorothiazide*

Trial
Hydrochlorothiazide versus placebo
EWPHE (subgroup), 1985 [1]

24.2 Meta-analysis results

The results are detailed in table 24.5 (page 112). This table is followed by the Forest's plot corresponding to each endpoint.

Hydrochlorothiazide versus placebo

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 1.21 (95% CI 0.85 to 1.73, p=0.2835).
The single study eligible for this comparison provided data on **coronary death**. No statistically significant difference between the groups was found in coronary death, with a RR of 1.37 (95% CI 0.56 to 3.35, p=0.4961).
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 1.17 (95% CI 0.99 to 1.40, p=0.0706).
The single study eligible for this comparison provided data on **fatal stroke**. No statistically significant difference between the groups was found in fatal stroke, with a RR of 1.48 (95% CI 0.65 to 3.38, p=0.3466).

Table 24.5: *Results details - Diuretics - hydrochlorothiazide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
hydrochlorothiazide versus placebo						
cardiovascular death	RR=1.21	[0.85;1.73]	0.2835	1.0000 (I^2=0.00)	1	155
coronary death	RR=1.37	[0.56;3.35]	0.4961	1.0000 (I^2=0.00)	1	155
all cause death	RR=1.17	[0.99;1.40]	0.0706	1.0000 (I^2=0.00)	1	155
fatal stroke	RR=1.48	[0.65;3.38]	0.3466	1.0000 (I^2=1.00)	1	155

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

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

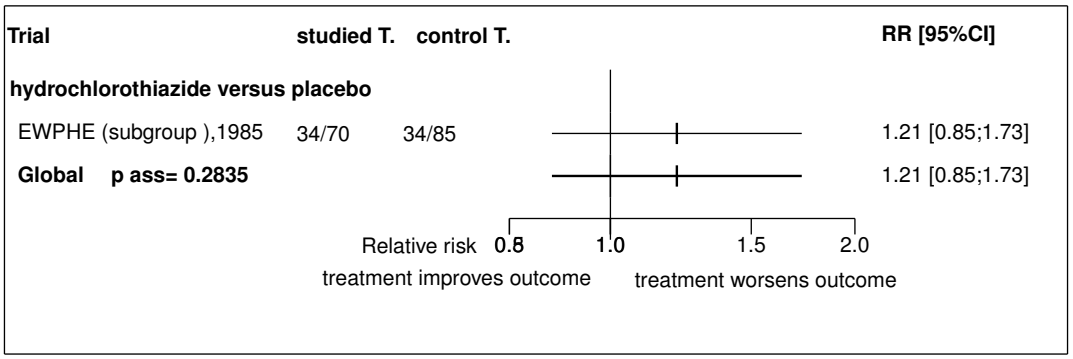


Figure 24.2: *Forest's plot for coronary death*

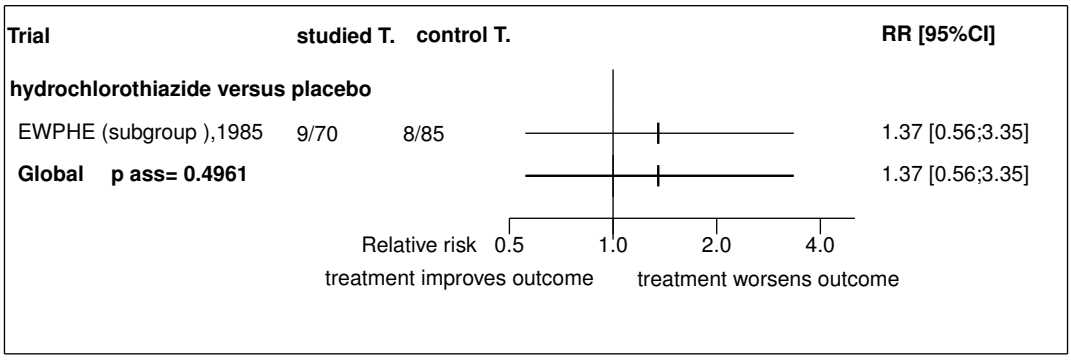


Figure 24.3: *Forest's plot for all cause death*

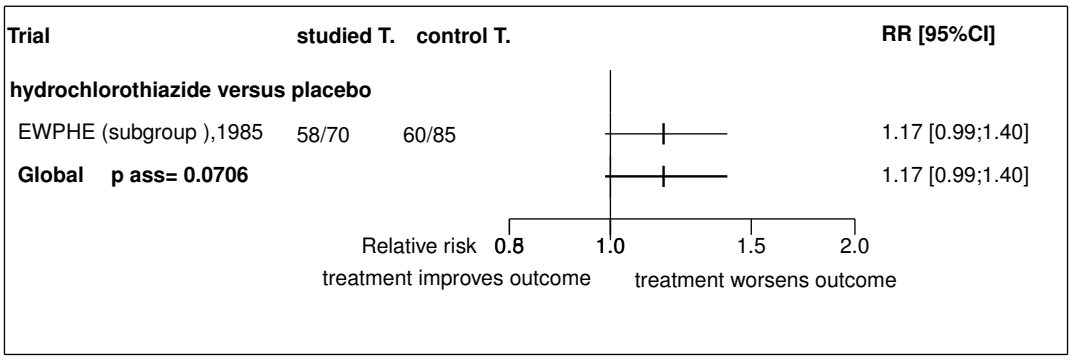
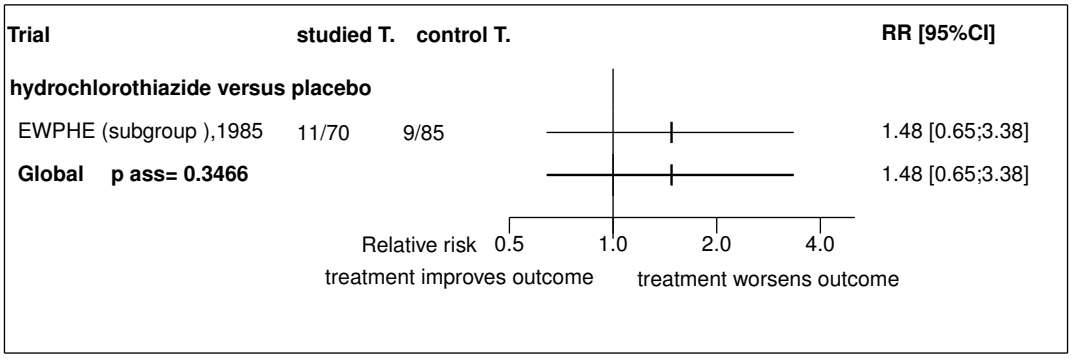


Figure 24.4: *Forest's plot for fatal stroke*



References

[1] Amery A, Birkenhger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985;1:1349-54. [PMID=2861311]

24.3 Individual trial summaries

Table 24.6: *EWPHE (subgroup), 1985 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=155 (70 vs. 85) **Follow-up duration:** 31y **Study design:** Randomized controlled trial Double-blind	Patients over the age of 60	**Studied treatment:** hydrochlorothiazide + triamterene **Control treatment:** placebo	Cardiovascular death RR=1.21 [0.85;1.73] Coronary death RR=1.37 [0.56;3.35] All cause death RR=1.17 [0.99;1.40] Fatal stroke RR=1.48 [0.65;3.38]

Reference

Amery A, Birkenhger W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985;1:1349-54 [PMID=2861311]

25 Detailed results for indapamide

25.1 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.
Stroke (fatal and non fatal) data was reported in 1 trials; 1 trials reported data on all cause death; 1 trials reported data on heart failure; 1 trials reported data on cardiovascular death; and 1 trials reported data on coronary event.
Following tables 25.1 (page 117), 25.2 (page 117), 25.4 (page 119), and 25.3 (page 118) summarized the main characteristics of the trial including in this systematic review of randomized trials of indapamide.

Table 25.1: *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 25.2: *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 25.3: *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 25.4: *Trial characteristics - Diuretics - indapamide*

Trial
Indapamide versus placebo
HYVET, 2008 [1]

25.2 Meta-analysis results

The results are detailed in table 25.5 (page 120). This table is followed by the Forest's plot corresponding to each endpoint.

Indapamide versus placebo

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 0.81 (95% CI 0.63 to 1.05, p=0.1079).
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 0.73 (95% CI 0.51 to 1.04, p=0.0850).
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 0.74 (95% CI 0.31 to 1.76, p=0.4971).
The single study eligible for this comparison provided data on **heart failure**. The analysis detected a statistically significant difference in favor of indapamide in heart failure, with a RR of 0.38 (95% CI 0.23 to 0.62, p=0.0000).
The single study eligible for this comparison provided data on **all cause death**. The analysis detected a statistically significant difference in favor of indapamide in all cause death, with a RR of 0.82 (95% CI 0.69 to 0.99, p=0.0349).

Table 25.5: *Results details - Diuretics - indapamide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
indapamide versus placebo						
cardiovascular death	RR=0.81	[0.63;1.05]	0.1079	1.0000 (I^2=0.00)	1	3845
stroke (fatal and non fatal)	RR=0.73	[0.51;1.04]	0.0850	1.0000 (I^2=0.00)	1	3845
coronary event	RR=0.74	[0.31;1.76]	0.4971	1.0000 (I^2=0.00)	1	3845
heart failure	RR=0.38	[0.23;0.62]	0.0000	1.0000 (I^2=0.00)	1	3845
all cause death	RR=0.82	[0.69;0.99]	0.0349	1.0000 (I^2=0.00)	1	3845

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 25.1: *Forest's plot for cardiovascular death*

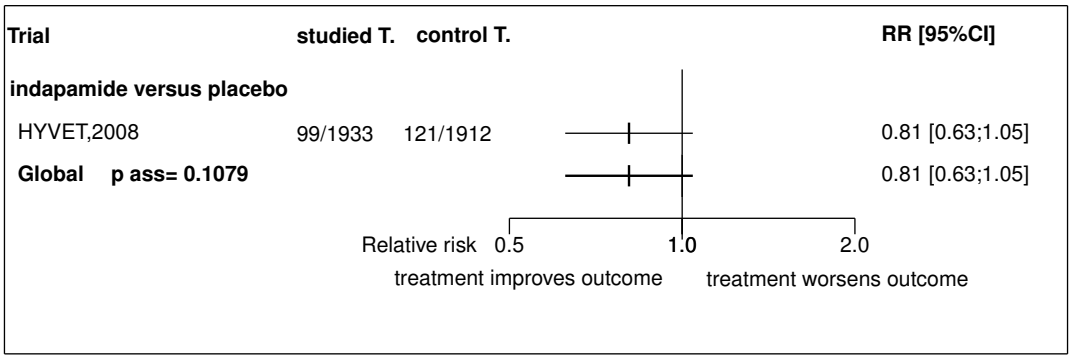


Figure 25.2: *Forest's plot for stroke (fatal and non fatal)*

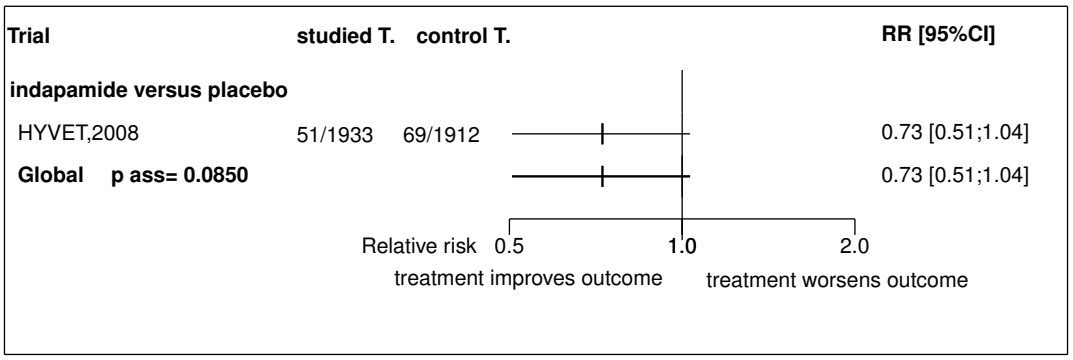


Figure 25.3: *Forest's plot for coronary event*

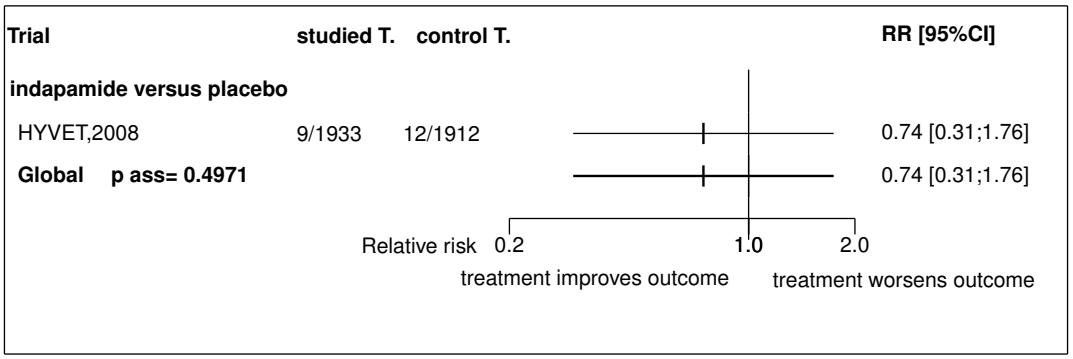


Figure 25.4: *Forest's plot for heart failure*

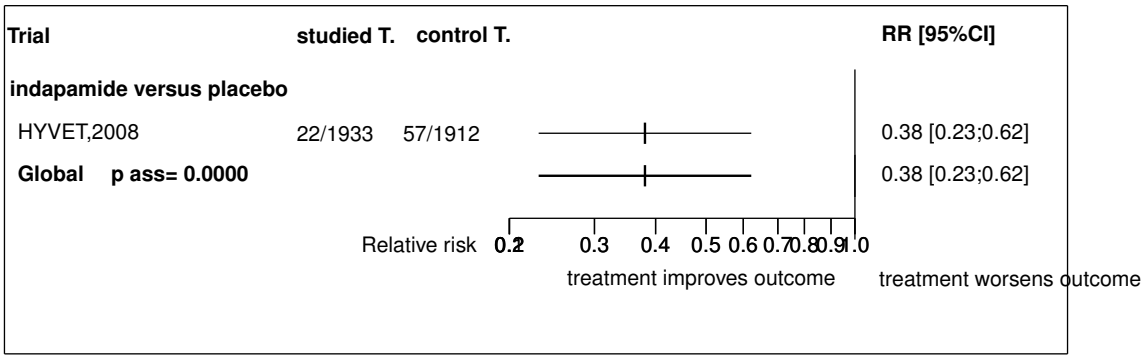
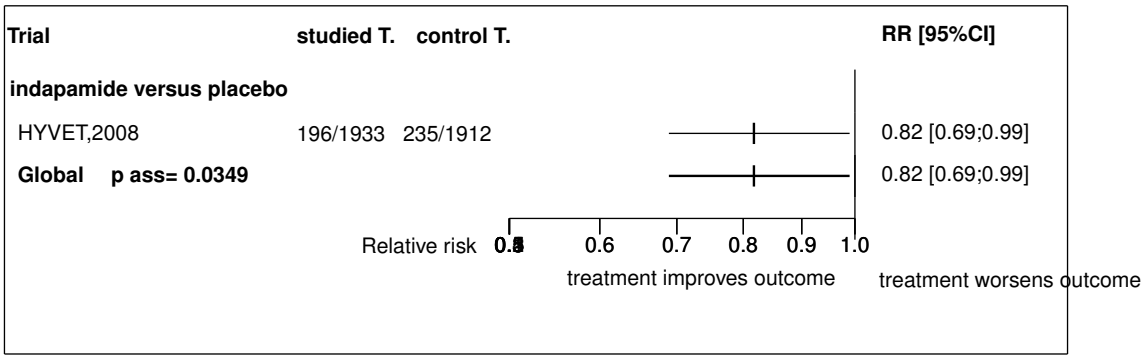


Figure 25.5: *Forest's plot for all cause death*



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]

25.3 Individual trial summaries

Table 25.6: *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.	Cardiovascular death RR=0.81 [0.63;1.05] Stroke (fatal and non fatal) RR=0.73 [0.51;1.04] Coronary event RR=0.74 [0.31;1.76] (MI) Heart failure RR=0.38 [0.23;0.62] All cause death RR=0.82 [0.69;0.99]

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]

26 Global meta-analysis: all Diuretics

26.1 Global meta-analysis: all Diuretics versus placebo

Table 26.1: *All Diureticsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=0.67	0.48;0.93	0.0166	0.9528 (0.00)	2	735
cardiovascular death	RR=0.94	0.73;1.20	0.6032	0.2661 (0.24)	4	4735
stroke (fatal and non fatal)	RR=0.59	0.39;0.90	0.0134	0.2153 (0.35)	3	4580
coronary event	RR=0.73	0.45;1.16	0.1824	0.9239 (0.00)	3	4580
coronary death	RR=0.94	0.55;1.61	0.8299	0.5676 (0.00)	3	890
heart failure	RR=0.38	0.26;0.56	0.0000	0.5747 (0.00)	3	4580
all cause death	RR=0.98 [1]	0.77;1.26	0.8862	0.0310 (0.66) †	4	4735
fatal stroke	RR=1.18	0.58;2.40	0.6418	0.4825 (0.00)	3	890

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

27 Ongoing studies of Diuretics

No ongoing trial was identified.

28 Excluded studies for Diuretics

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table 28.1.

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=0.98 95% CI 0.88;1.11

Table 28.1: *Excluded studies of Diuretics*

Study	Exclusion reason
HYVET (2008)	

References