Anti hypertensive agent for hypertension in post stroke

A systematic review and meta-analysis of randomized clinical trials

2017 - 7 - 1

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

Contents

0.1 Synthesis of the meta-analysis results

In all 5 randomised controlled trials (RCTs) were included. These included 2 studies of **beta-blockers** involving 2,193 patients and 3 studies of **diuretics** involving 6,233 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

Reports of 2 trials (including 2,193 patients) were identified .
Among these comparisons, two trials are about atenolol.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with atenolol for all the endpoints with data in at least one trial are summarized table 1.

Table 1: *Results summary - Atenolol*

Benefit	Harmful	No evidence
	Atenolol versus placebo	
		→ cardiovascular events RR=1.01^{NS} [0.84;1.21] k=2 → cardiovascular death RR=0.61^{NS} [0.36;1.04] k=2 → myocardial infarction (fatal and non fatal) RR=0.94^{NS} [0.63;1.41] k=2 → stroke (fatal and non fatal) RR=0.95^{NS} [0.76;1.18] k=2 → all cause death RR=0.94^{NS} [0.68;1.32] k=2

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

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

0.1.2 Diuretics

Reports of 3 trials (including 6,233 patients) were identified .
Among these comparisons, one trial are about deserpidine +methylclothiazide,one about indapamide and one about thiazide diuretics.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

Deserpidine +methylclothiazide

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

Table 2: *Results summary - Deserpidine +methylclothiazide*

Benefit	Harmful	No evidence
	Deserpidine +methylclothiazide versus placebo	
		→ cardiovascular death RR=0.74^{NS} [0.39;1.42] k=1 → stroke (fatal and non fatal) RR=0.83^{NS} [0.55;1.24] k=1 → coronary event RR=0.94^{NS} [0.31;2.87] k=1 → heart failure RR=0.08^{NS} [0.00;1.39] k=1 → all cause death RR=1.02^{NS} [0.60;1.72] 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 3.

Table 3: *Results summary - Indapamide*

Benefit	Harmful	No evidence
	Indapamide versus placebo	
↓ stroke (fatal and non fatal) RR=0.73† [0.60;0.89] k=1		→ cardiovascular death RR=0.86^{NS} [0.65;1.14] k=1 → coronary event RR=1.19^{NS} [0.67;2.12] k=1 → all cause death RR=0.92^{NS} [0.74;1.15] k=1

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

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

Thiazide diuretics

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

Table 4: *Results summary - Thiazide diuretics*

Benefit	Harmful	No evidence
	Thiazide diuretics versus control	
↓ stroke (fatal and non fatal) RR=0.47* [0.25;0.89] k=1		→ cardiovascular death RR=0.61^{NS} [0.31;1.21] k=1 → coronary event RR=0.98^{NS} [0.14;6.68] k=1 → heart failure RR=0.74^{NS} [0.17;3.12] k=1 → all cause death RR=0.58^{NS} [0.33;1.01] k=1

continued...

Benefit	Harmful	No evidence

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

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

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 post stroke. The following classes of treatment are considered:

1. beta-blockers
2. 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 post stroke.

1.2.1 Sources searched

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

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

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

1.2.2 Search restrictions

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

1.3 Inclusion criteria

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

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

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

1.4 Exclusion criteria

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

1.5 Meta-analysis strategy

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

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, 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

A total of 2 randomized comparisons which enrolled 2193 patients were identified. In all, 2 randomized comparisons concerned atenolol.
The detailed descriptions of trials and meta-analysis results is given in section 3 (page 19) for atenolol.

The average study size was 1096 patients (range 720 to 1473). The first study was published in 1993, and the last study was published in 1995.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
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 **placebo** in terms of cardiovascular events (RR=1.01, 95% CI 0.84 to 1.21, p=0.9312, 2 trials), cardiovascular death (RR=0.61, 95% CI 0.36 to 1.04, p=0.0687, 2 trials), myocardial infarction (fatal and non fatal) (RR=0.94, 95% CI 0.63 to 1.41, p=0.7645, 2 trials), stroke (fatal and non fatal) (RR=0.95, 95% CI 0.76 to 1.18, p=0.6154, 2 trials)and all cause death (RR=0.94, 95% CI 0.68 to 1.32, p=0.7309, 2 trials).

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

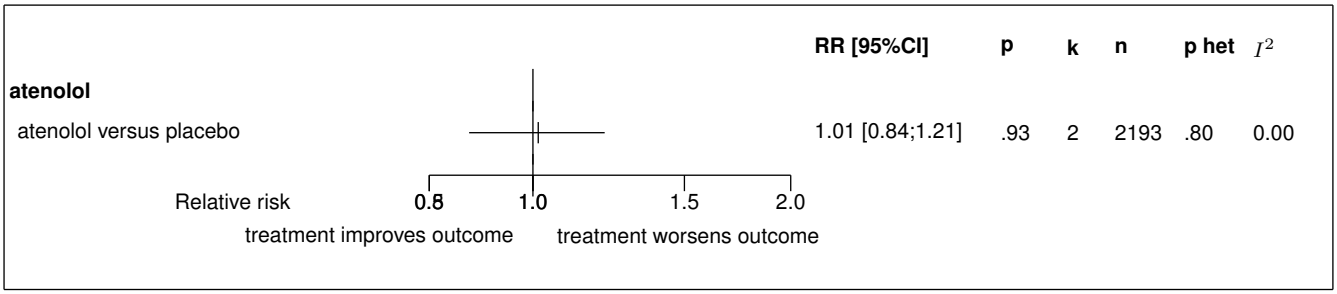
Trial	Patients	Treatments	Trial design and method
Atenolol			
Atenolol versus placebo			
Dutch TIA, 1993 [1] n = 732 vs. 741	aspirin-treated patients with transient ischemic attack or nondisabling ischemic stroke	atenolol 50mg/d **versus** placebo	double blind
TEST, 1995 [2] n = 372 vs. 348	post stroke	atenolol **versus** placebo	

Table 2.2: *Summary of all results for atenolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
atenolol versus placebo						
cardiovascular events	RR=1.01	0.84;1.21	0.9312	0.7988 (0.00)	2	2193
cardiovascular death	RR=0.61	0.36;1.04	0.0687	0.0622 (0.71)	2	2193
myocardial infarction (fatal and non fatal)	RR=0.94	0.63;1.41	0.7645	0.1943 (0.41)	2	2193
stroke (fatal and non fatal)	RR=0.95	0.76;1.18	0.6154	0.4489 (0.00)	2	2193
all cause death	RR=0.94	0.68;1.32	0.7309	0.1683 (0.47)	2	2193

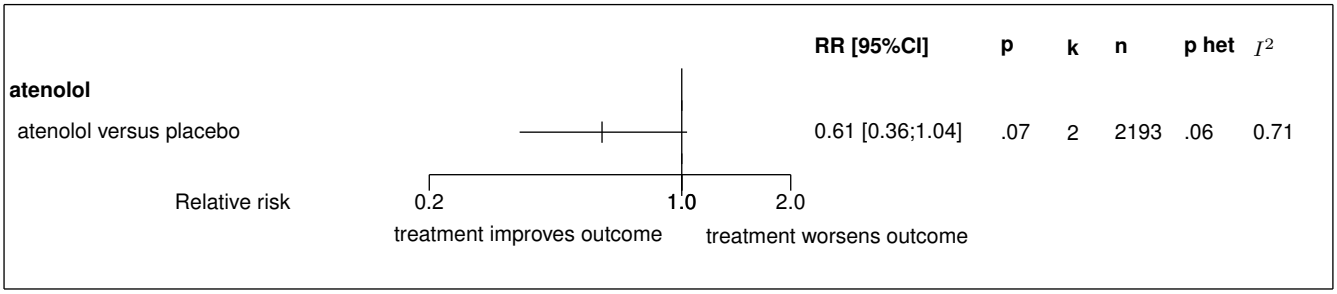
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



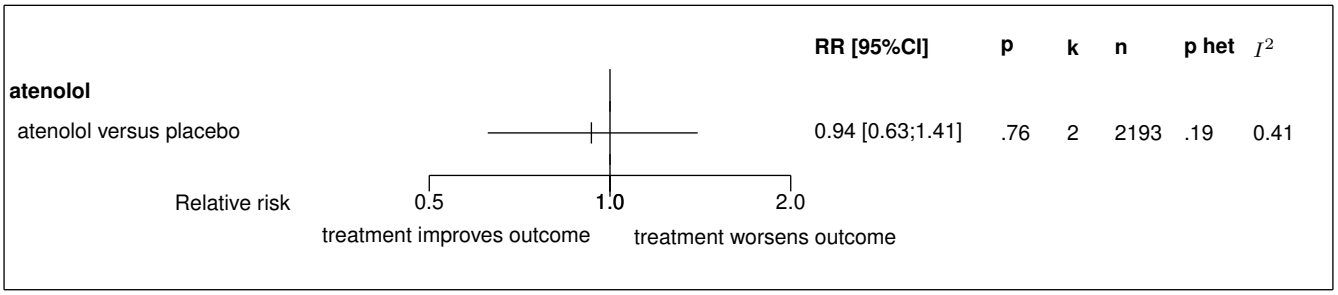
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



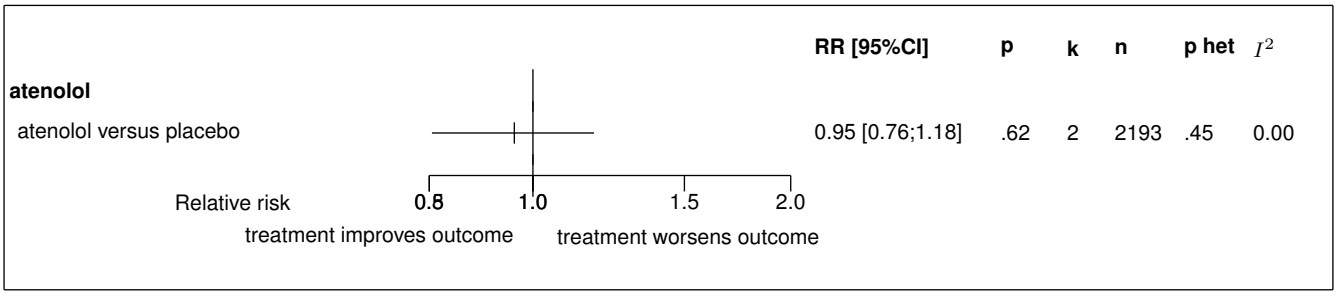
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



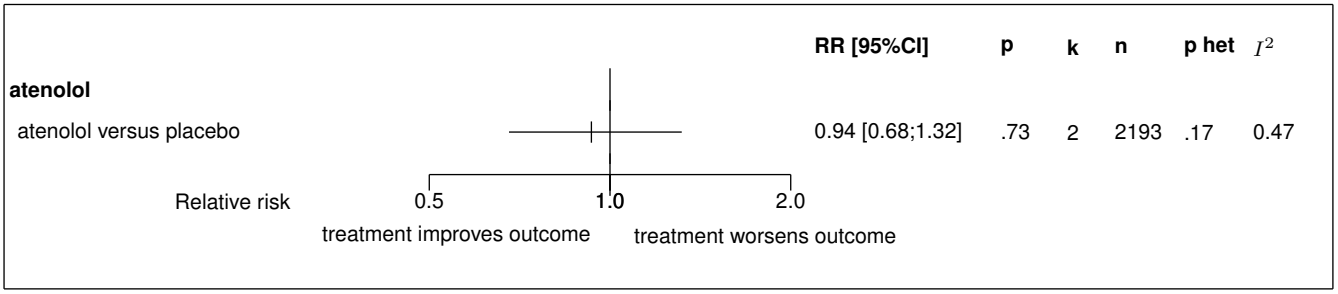
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for stroke (fatal and non fatal)*



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

Figure 2.5: *Forest's plot for all cause death*



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

3 Details

3.1 Available trials

A total of 2 RCTs which randomized 2193 patients were identified: all compared atenolol with placebo.
The average study size was 1096 patients (range 720 to 1473). The first study was published in 1993, and the last study was published in 1995.
This trial was double blind in design.
All included studies were reported in English language. We did not found any unpublished trial.
Cardiovascular death data was reported in 2 trials; 2 trials reported data on stroke (fatal and non fatal); 2 trials reported data on all cause death; 2 trials reported data on cardiovascular events; and 2 trials reported data on myocardial infarction (fatal and non fatal).
Following tables 3.1 (page 19), 3.2 (page 19), 3.4 (page 21), and 3.3 (page 20) summarized the main characteristics of the trials 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 placebo		
Dutch TIA (1993) [1]	Atenolol 50mg/d	Placebo
TEST (1995) [2]	Atenolol	Placebo

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

Trial	Patients
Atenolol versus placebo	
Dutch TIA (1993) [1]	Aspirin-treated patients with transient ischemic attack or nondisabling ischemic stroke
TEST (1995) [2]	Post stroke

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

Trial	Design	Duration	Centre	Primary end-point
Atenolol versus placebo				
Dutch TIA, 1993 [1] n=1473	double blind	26y		
TEST, 1995 [2] n=720		26y		

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

Trial
Atenolol versus placebo
Dutch TIA, 1993 [1]
TEST, 1995 [2]

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 22). This table is followed by the Forest's plot corresponding to each endpoint.

Atenolol versus placebo

All the 2 studies had extractable data about the number of participants with **cardiovascular events**. There was no statistically significant difference in cardiovascular events between atenolol and placebo, with a RR of 1.01 (95%CI 0.84 to 1.21, p=0.9312) in favour of placebo. In other words, cardiovascular events was slightly lower in the placebo group , but this was not statistically significant. No heterogeneity was detected (p = 0.7988, 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 0.61 (95% CI 0.36 to 1.04, p=0.0687). No heterogeneity was detected (p = 0.0622, I^2 = 0.71%).
All the 2 studies had extractable data about the number of participants with **myocardial infarction (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in myocardial infarction (fatal and non fatal), with a RR of 0.94 (95% CI 0.63 to 1.41, p=0.7645). No heterogeneity was detected (p = 0.1943, I^2 = 0.41%).
All the 2 studies had extractable data about the number of participants with **stroke (fatal and non fatal)**. When pooled together, there was no statistically significant difference between the groups in stroke (fatal and non fatal), with a RR of 0.95 (95% CI 0.76 to 1.18, p=0.6154). No heterogeneity was detected (p = 0.4489, I^2 = 0.00%).
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 0.94 (95% CI 0.68 to 1.32, p=0.7309). No heterogeneity was detected (p = 0.1683, I^2 = 0.47%).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
atenolol versus placebo						
cardiovascular events	RR=1.01	[0.84;1.21]	0.9312	0.7988 (I^2=0.00)	2	2193
cardiovascular death	RR=0.61	[0.36;1.04]	0.0687	0.0622 (I^2=0.71)	2	2193
myocardial infarction (fatal and non fatal)	RR=0.94	[0.63;1.41]	0.7645	0.1943 (I^2=0.41)	2	2193
stroke (fatal and non fatal)	RR=0.95	[0.76;1.18]	0.6154	0.4489 (I^2=0.00)	2	2193
all cause death	RR=0.94	[0.68;1.32]	0.7309	0.1683 (I^2=0.47)	2	2193

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*

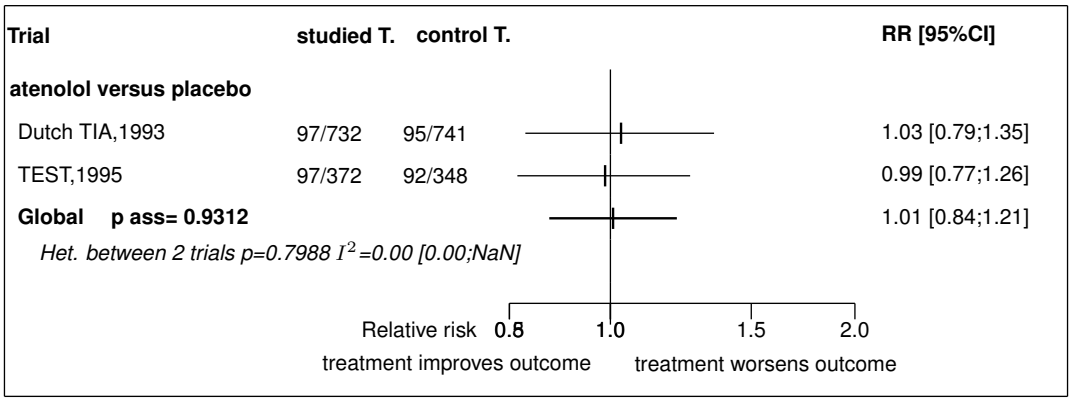


Figure 3.2: *Forest's plot for cardiovascular death*

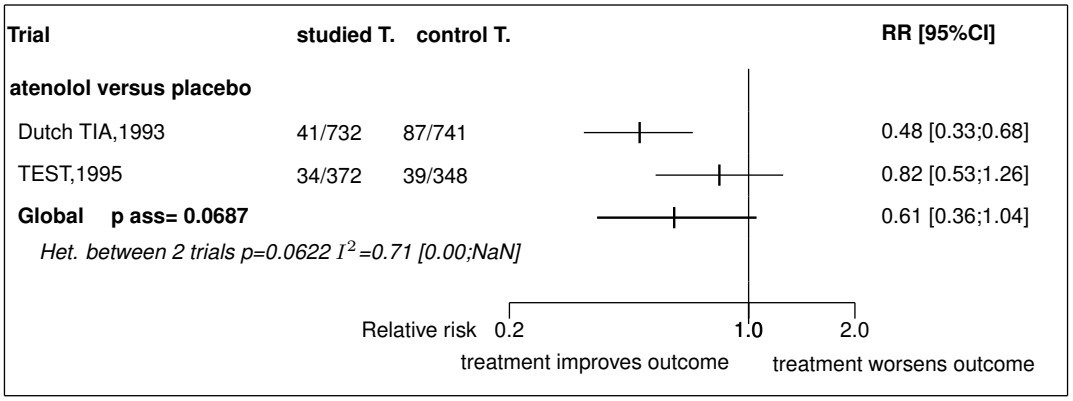


Figure 3.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

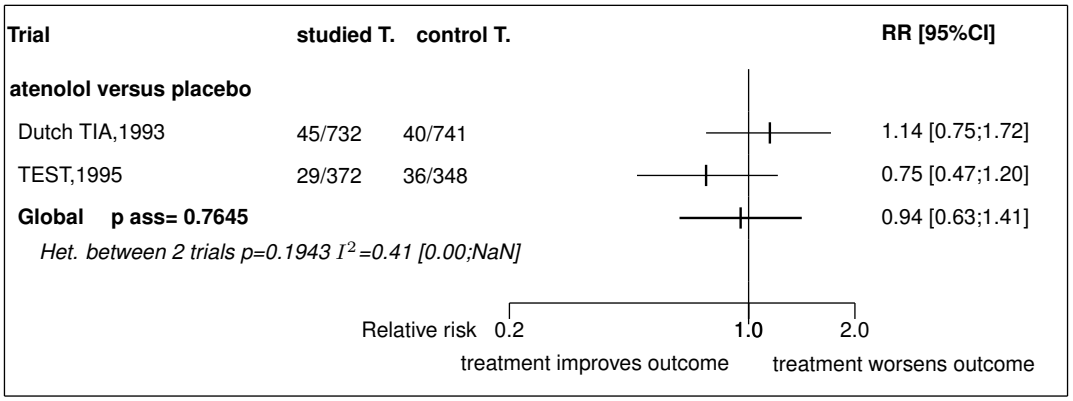


Figure 3.4: *Forest's plot for stroke (fatal and non fatal)*

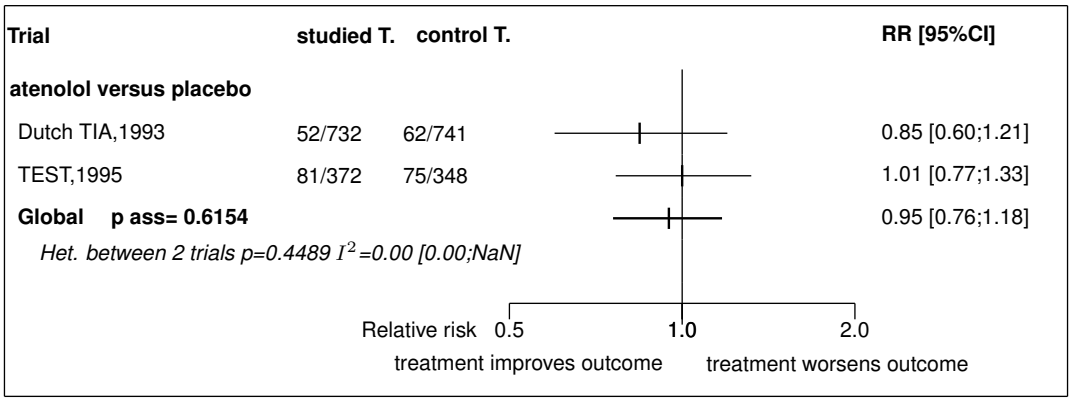
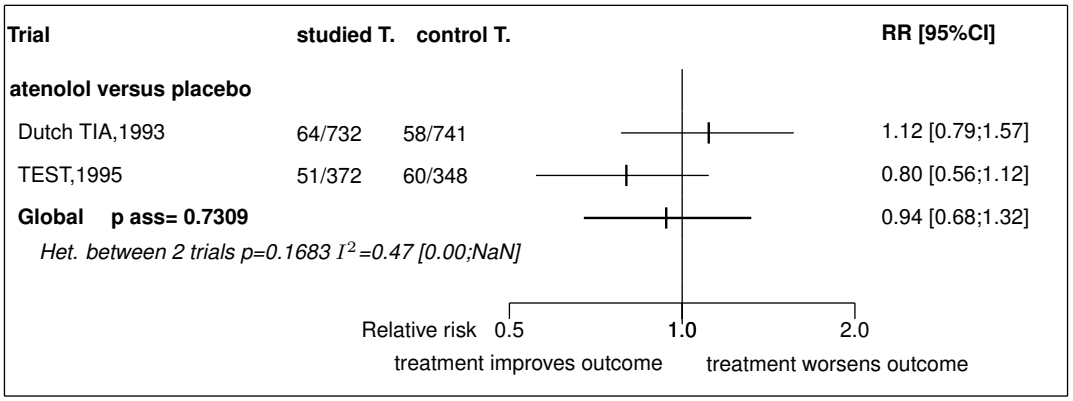


Figure 3.5: *Forest's plot for all cause death*



References

[1] . Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group. Stroke 1993 Apr;24:543-8. [PMID=8465360]

[2] Eriksson S, Olofsson BO, Wester PO. imag. Atenolol in the secondaryprevention after stroke. Cerebrovasc Dis 1995; 5: 2125.

3.3 Individual trial summaries

Table 3.6: *Dutch TIA, 1993 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1473 (732 vs. 741) **Follow-up duration:** 26y **Study design:** Randomized controlled trial Double blind	Aspirin-treated patients with transient ischemic attack or nondisabling ischemic stroke	**Studied treatment:** Atenolol 50mg/d **Control treatment:** Placebo	Cardiovascular events RR=1.03 [0.79;1.35] Cardiovascular death RR=0.48 [0.33;0.68] Myocardial infarction (fatal and non fatal) RR=1.14 [0.75;1.72] Stroke (fatal and non fatal) RR=0.85 [0.60;1.21] All cause death RR=1.12 [0.79;1.57]

Reference

. Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group. Stroke 1993 Apr;24:543-8 [PMID=8465360]

Table 3.7: *TEST, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=720 (372 vs. 348) **Follow-up duration:** 26y **Study design:** Randomized controlled trial	Post stroke	**Studied treatment:** Atenolol **Control treatment:** Placebo	Cardiovascular events RR=0.99 [0.77;1.26] Cardiovascular death RR=0.82 [0.53;1.26] Myocardial infarction (fatal and non fatal) RR=0.75 [0.47;1.20] Stroke (fatal and non fatal) RR=1.01 [0.77;1.33] All cause death RR=0.80 [0.56;1.12]

Reference

Eriksson S, Olofsson BO, Wester PO. imag. Atenolol in the secondaryprevention after stroke. Cerebrovasc Dis 1995; 5: 2125

4 Global meta-analysis: all beta-blockers

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

Table 4.1: *All beta-blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.01	0.84;1.21	0.9312	0.7988 (0.00)	2	2193
cardiovascular death	RR=0.61	0.36;1.04	0.0687	0.0622 (0.71)	2	2193
myocardial infarction (fatal and non fatal)	RR=0.94	0.63;1.41	0.7645	0.1943 (0.41)	2	2193
stroke (fatal and non fatal)	RR=0.95	0.76;1.18	0.6154	0.4489 (0.00)	2	2193
all cause death	RR=0.94	0.68;1.32	0.7309	0.1683 (0.47)	2	2193

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

Diuretics

7 Overview of diuretics

7.1 Included trials

A total of 3 randomized comparisons which enrolled 6233 patients were identified. In all, 1 randomized comparison concerned deserpidine +methylclothiazide , one indapamide and one thiazide diuretics.
The detailed descriptions of trials and meta-analysis results is given in section 8 (page 37) for deserpidine +methylclothiazide, in section 9 (page 45) for indapamide and in section 10 (page 53) for thiazide diuretics.

The average study size was 2077 patients (range 99 to 5682). The first study was published in 1970, and the last study was published in 1995.
A total of 2 trials were double blind and 1 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 7.1 (page 32) 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 diuretics provide the results listed in tables 7.2 to 7.4 (page 33) and in the following graphs.

7.2.1 Deserpidine +methylclothiazide

No significant difference was found between **deserpidine +methylclothiazide** and **placebo** in terms of cardiovascular death (RR=0.74, 95% CI 0.39 to 1.42, p=0.3693, 1 trial), stroke (fatal and non fatal) (RR=0.83, 95% CI 0.55 to 1.24, p=0.3570, 1 trial), coronary event (RR=0.94, 95% CI 0.31 to 2.87, p=0.9134, 1 trial), heart failure (RR=0.08, 95% CI 0.00 to 1.39, p=0.0830, 1 trial)and all cause death (RR=1.02, 95% CI 0.60 to 1.72, p=0.9460, 1 trial).

7.2.2 Indapamide

Indapamide was superior to **placebo** in terms of stroke (fatal and non fatal) (RR=0.73, 95% CI 0.60 to 0.89, p=0.0021, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.86, 95% CI 0.65 to 1.14, p=0.2996, 1 trial), coronary event (RR=1.19, 95% CI 0.67 to 2.12, p=0.5543, 1 trial)and all cause death (RR=0.92, 95% CI 0.74 to 1.15, p=0.4794, 1 trial).

7.2.3 Thiazide diuretics

Thiazide diuretics was superior to **control** in terms of stroke (fatal and non fatal) (RR=0.47, 95% CI 0.25 to 0.89, p=0.0199, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.61, 95% CI 0.31 to 1.21, p=0.1606, 1 trial), coronary event (RR=0.98, 95% CI 0.14 to 6.68, p=0.9835, 1 trial), heart failure (RR=0.74, 95% CI 0.17 to 3.12, p=0.6761, 1 trial)and all cause death (RR=0.58, 95% CI 0.33 to 1.01, p=0.0564, 1 trial).

Table 7.1: *Main study characteristics - Diuretics*

Trial	Patients	Treatments	Trial design and method
Deserpidine +methylclothiazide			
Deserpidine +methylclothiazide versus placebo			
HSCS, 1974 [1, 2] n = 233 vs. 219	stroke	deserpidine 1mg/d + methylclothiazide 10mg/d **versus** placebo	double blind parallel groups USA
Indapamide			
Indapamide versus placebo			
PATS, 1995 [1] n = 2841 vs. 2841		indapamide 2.5 mg/d **versus** placebo	double blind parallel groups China
Thiazide diuretics			
Thiazide diuretics versus control			
Carter, 1970 [1] n = 50 vs. 49		thiazide **versus** ?	open NA NA

Table 7.2: *Summary of all results for deserpidine +methylclothiazide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
deserpidine +methylclothiazide versus placebo						
cardiovascular death	RR=0.74	0.39;1.42	0.3693	1.0000 (1.00)	1	452
stroke (fatal and non fatal)	RR=0.83	0.55;1.24	0.3570	1.0000 (0.00)	1	452
coronary event	RR=0.94	0.31;2.87	0.9134	1.0000 (0.00)	1	452
heart failure	RR=0.08	0.00;1.39	0.0830	1.0000 (0.00)	1	452
all cause death	RR=1.02	0.60;1.72	0.9460	1.0000 (0.00)	1	452

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 7.3: *Summary of all results for indapamide*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
indapamide versus placebo						
cardiovascular death	RR=0.86	0.65;1.14	0.2996	1.0000 (0.00)	1	5682
stroke (fatal and non fatal)	RR=0.73	0.60;0.89	0.0021	1.0000 (0.00)	1	5682
coronary event	RR=1.19	0.67;2.12	0.5543	1.0000 (0.00)	1	5682
all cause death	RR=0.92	0.74;1.15	0.4794	1.0000 (0.00)	1	5682

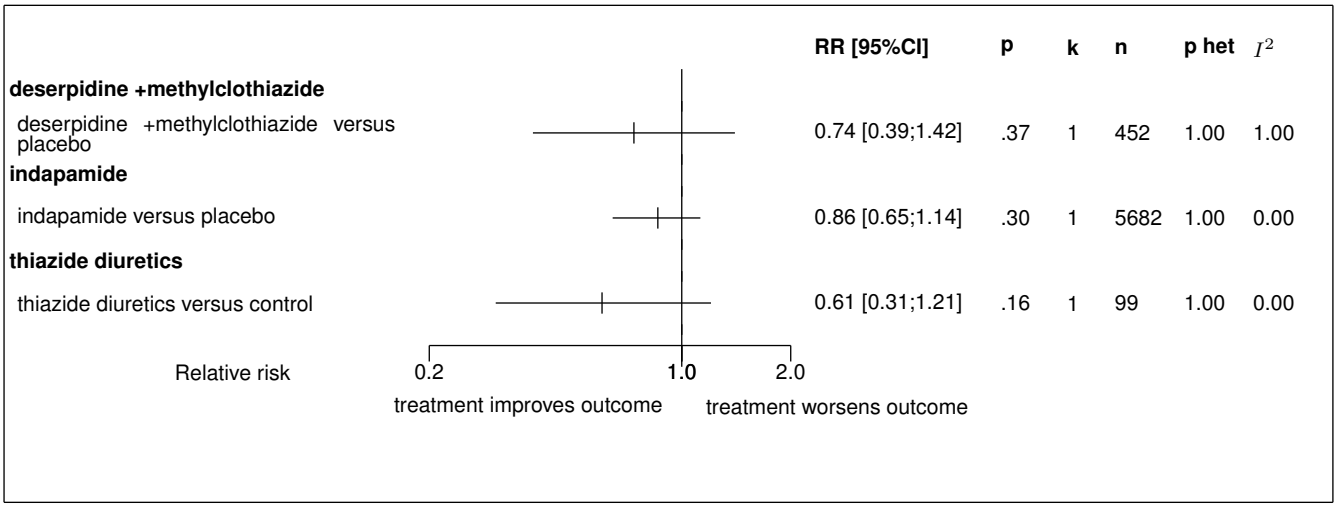
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 7.4: *Summary of all results for thiazide diuretics*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
thiazide diuretics versus control						
cardiovascular death	RR=0.61	0.31;1.21	0.1606	1.0000 (0.00)	1	99
stroke (fatal and non fatal)	RR=0.47	0.25;0.89	0.0199	1.0000 (0.00)	1	99
coronary event	RR=0.98	0.14;6.68	0.9835	1.0000 (0.00)	1	99
heart failure	RR=0.74	0.17;3.12	0.6761	1.0000 (0.00)	1	99
all cause death	RR=0.58	0.33;1.01	0.0564	1.0000 (0.00)	1	99

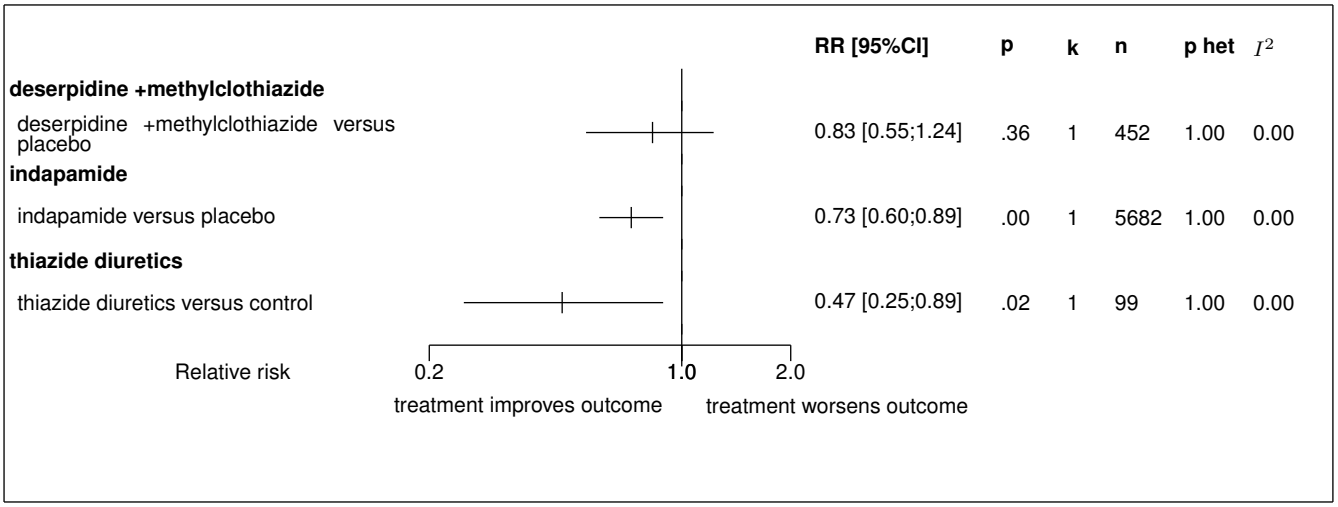
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



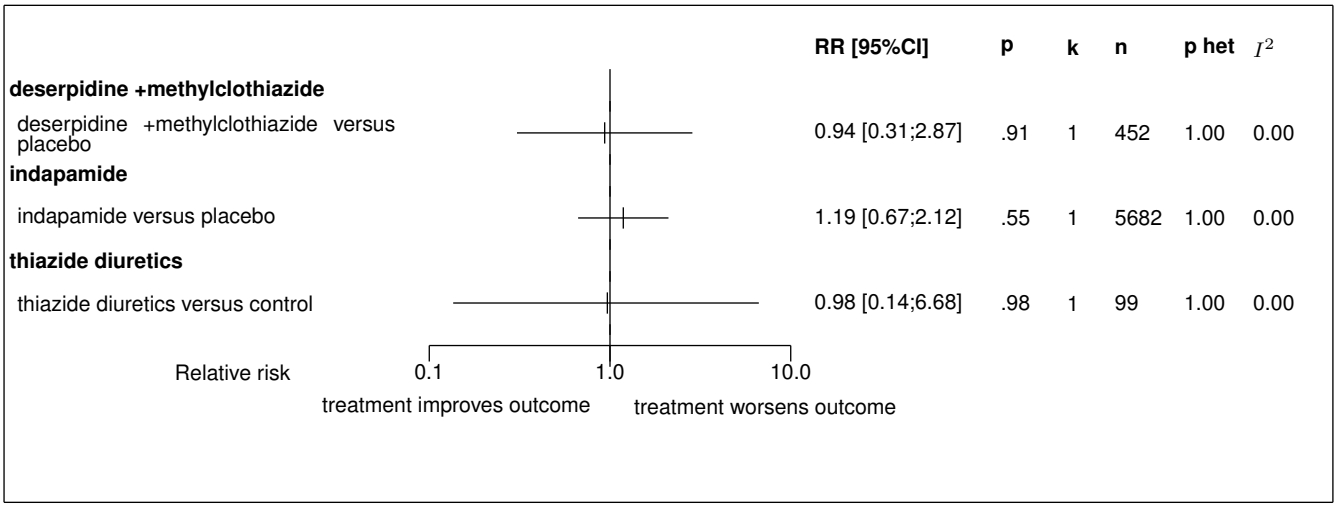
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.2: *Forest's plot for stroke (fatal and non fatal)*



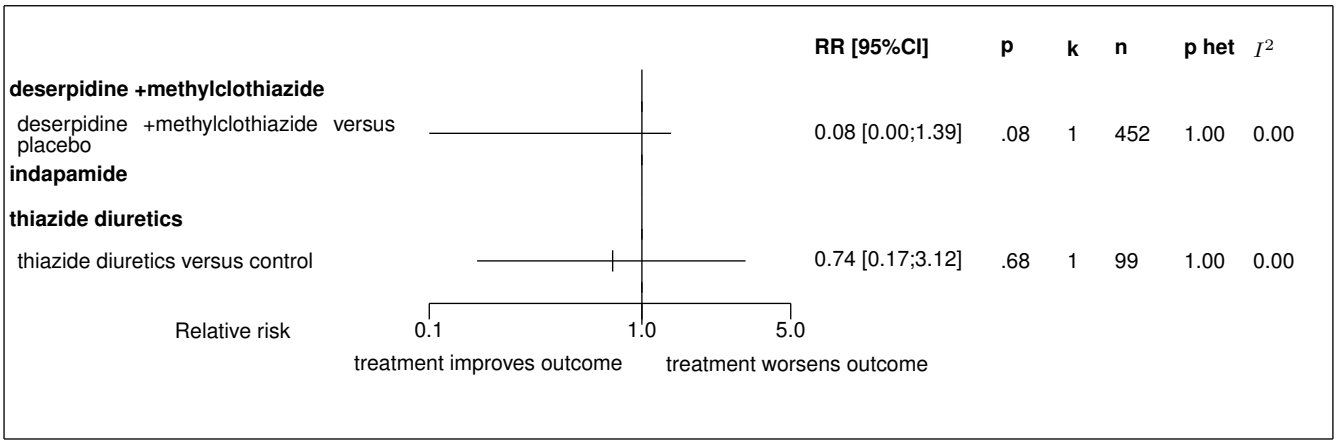
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.3: *Forest's plot for coronary event*



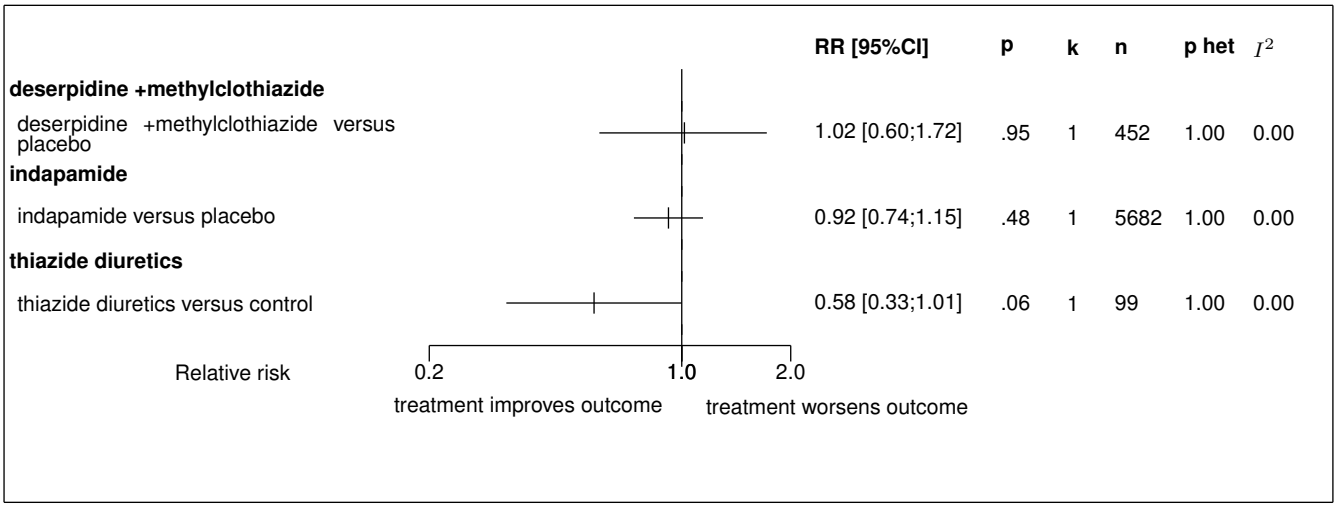
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 7.4: *Forest's plot for heart failure*



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

Figure 7.5: *Forest's plot for all cause death*



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

8 Detailed results for deserpidine +methylclothiazide

8.1 Available trials

Only one trial which randomized 452 patients was identified: it compared deserpidine +methylclothiazide with placebo.
This trial included 452 patients and was published in 1974.
This trial was double blind in design.
It was reported in English language.
Heart failure data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on coronary event; and 1 trials reported data on cardiovascular death.
Following tables 8.1 (page 37), 8.2 (page 37), 8.4 (page 39), and 8.3 (page 38) summarized the main characteristics of the trial including in this systematic review of randomized trials of deserpidine +methylclothiazide.

Table 8.1: *Treatment description - Diuretics - deserpidine +methylclothiazide*

Trial	Studied treatment	Control treatment
Deserpidine +methylclothiazide versus placebo		
HSCS (1974) [1, 2]	deserpidine 1mg/d + methylclothiazide 10mg/d **Concomittant treatment:** NA	placebo

Table 8.2: *Descriptions of participants - Diuretics - deserpidine +methylclothiazide*

Trial	Patients	
Deserpidine +methylclothiazide versus placebo		
HSCS (1974) [1, 2]	Stroke **Inclusion criteria:** stroke or TIA within the previous year	**Exclusion criteria:** NA

Table 8.3: *Design and methodological quality of trials - Diuretics - deserpidine +methylclothiazide*

Trial	Design	Duration	Centre	Primary endpoint
Deserpidine +methylclothiazide versus placebo				
HSCS, 1974 [1, 2] n=452	Parallel groups Double blind	2.3y	USA	

Table 8.4: *Trial characteristics - Diuretics - deserpidine +methylclothiazide*

Trial
Deserpidine +methylclothiazide versus placebo
HSCS, 1974 [1, 2]

8.2 Meta-analysis results

The results are detailed in table 8.5 (page 40). This table is followed by the Forest's plot corresponding to each endpoint.

Deserpidine +methylclothiazide 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 0.74 (95% CI 0.39 to 1.42, p=0.3693).
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 0.83 (95% CI 0.55 to 1.24, p=0.3570).
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 0.94 (95% CI 0.31 to 2.87, p=0.9134).
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 0.08 (95% CI 0.00 to 1.39, p=0.0830).
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 1.02 (95% CI 0.60 to 1.72, p=0.9460).

Table 8.5: *Results details - Diuretics - deserpidine +methylclothiazide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
deserpidine +methylclothiazide versus placebo						
cardiovascular death	RR=0.74	[0.39;1.42]	0.3693	1.0000 (I^2=1.00)	1	452
stroke (fatal and non fatal)	RR=0.83	[0.55;1.24]	0.3570	1.0000 (I^2=0.00)	1	452
coronary event	RR=0.94	[0.31;2.87]	0.9134	1.0000 (I^2=0.00)	1	452
heart failure	RR=0.08	[0.00;1.39]	0.0830	1.0000 (I^2=0.00)	1	452
all cause death	RR=1.02	[0.60;1.72]	0.9460	1.0000 (I^2=0.00)	1	452

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 death*

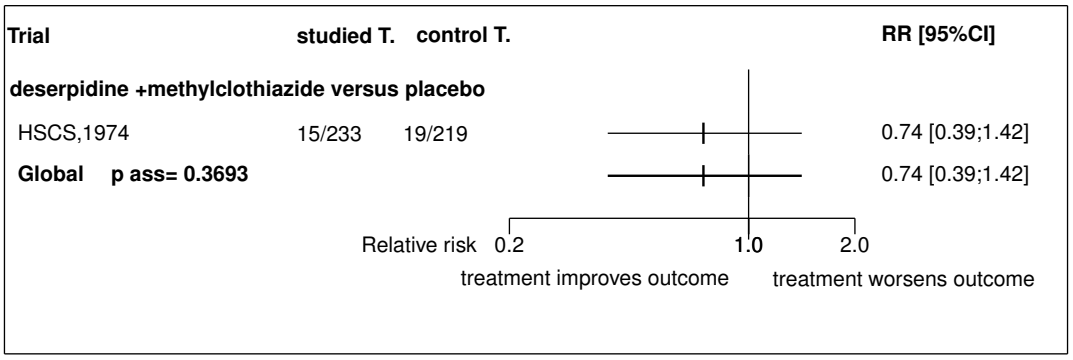


Figure 8.2: *Forest's plot for stroke (fatal and non fatal)*

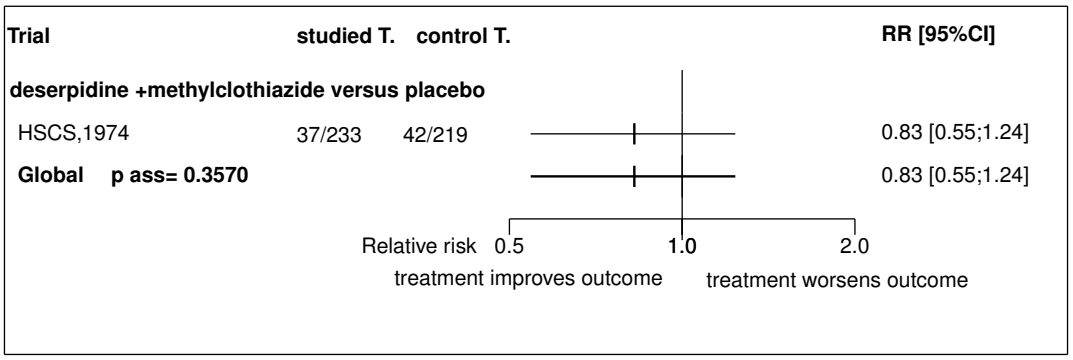


Figure 8.3: *Forest's plot for coronary event*

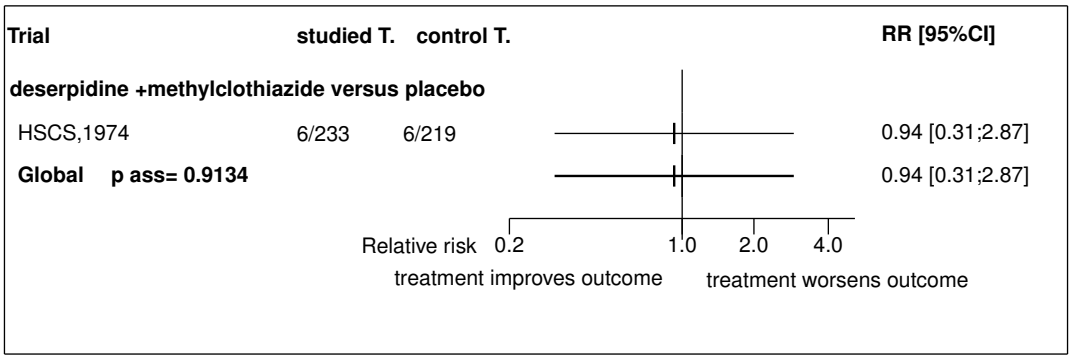


Figure 8.4: *Forest's plot for heart failure*

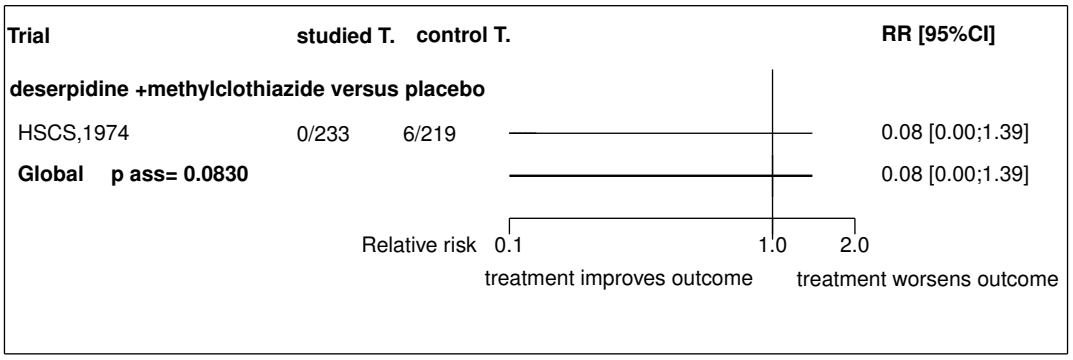
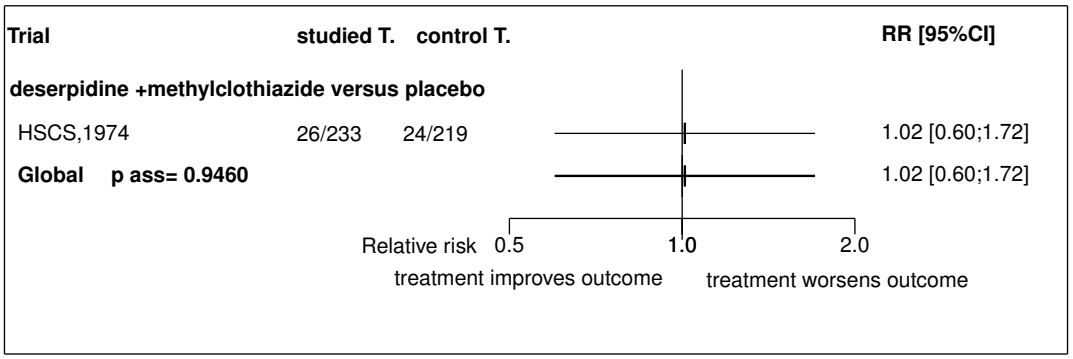


Figure 8.5: *Forest's plot for all cause death*



References

[1] . Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. JAMA 1974 Jul 22;229:409-18. [PMID=4599980]

[2] . Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. JAMA 1974;229:409-18. [PMID=4599980]

8.3 Individual trial summaries

Table 8.6: *HSCS, 1974 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=452 (233 vs. 219) **Follow-up duration:** 2.3y **Study design:** Randomized controlled trial Parallel groups Double blind USA	Stroke **Inclusion criteria:** stroke or TIA within the previous year **Exclusion criteria:** NA	**Studied treatment:** deserpidine 1mg/d + methylclothiazide 10mg/d **Control treatment:** placebo **Concomittant treat.:**NA	Cardiovascular death RR=0.74 [0.39;1.42] Stroke (fatal and non fatal) RR=0.83 [0.55;1.24] Coronary event RR=0.94 [0.31;2.87] All cause death RR=1.02 [0.60;1.72]

References

. Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. JAMA 1974 Jul 22;229:409-18 [PMID=4599980]

. Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. JAMA 1974;229:409-18 [PMID=4599980]

9 Detailed results for indapamide

9.1 Available trials

Only one trial which randomized 5682 patients was identified: it compared indapamide with placebo.
This trial included 5682 patients and was published in 1995.
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 coronary event; and 1 trials reported data on cardiovascular death.
Following tables 9.1 (page 45), 9.2 (page 45), 9.4 (page 47), and 9.3 (page 46) summarized the main characteristics of the trial including in this systematic review of randomized trials of indapamide.

Table 9.1: *Treatment description - Diuretics - indapamide*

Trial	Studied treatment	Control treatment
Indapamide versus placebo		
PATS (1995) [1]	indapamide 2.5 mg/d	placebo

Table 9.2: *Descriptions of participants - Diuretics - indapamide*

Trial	Patients	
Indapamide versus placebo		
PATS (1995) [1]	**Inclusion criteria:** men and women with history of TIA or stroke not severely disabled, irrespective of their blood pressure	**Exclusion criteria:** neoplasm, rheumatic valvular disease, congestive cardiomyopathy, atrial fibrillation, secondary hypertension, hyperthyroidism, renal and hepatic disease, haemorrhagic disease, insulin dependent diabetes

Table 9.3: *Design and methodological quality of trials - Diuretics - indapamide*

Trial	Design	Duration	Centre	Primary end-point
Indapamide versus placebo				
PATS, 1995 [1] n=5682	Parallel groups Double blind	2y	China	

Table 9.4: *Trial characteristics - Diuretics - indapamide*

Trial
Indapamide versus placebo
PATS, 1995 [1]

9.2 Meta-analysis results

The results are detailed in table 9.5 (page 48). 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 0.86 (95% CI 0.65 to 1.14, p=0.2996).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of indapamide in stroke (fatal and non fatal), with a RR of 0.73 (95% CI 0.60 to 0.89, p=0.0021).
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 1.19 (95% CI 0.67 to 2.12, p=0.5543).
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 0.74 to 1.15, p=0.4794).

Table 9.5: *Results details - Diuretics - indapamide*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
indapamide versus placebo						
cardiovascular death	RR=0.86	[0.65;1.14]	0.2996	1.0000 (I^2=0.00)	1	5682
stroke (fatal and non fatal)	RR=0.73	[0.60;0.89]	0.0021	1.0000 (I^2=0.00)	1	5682
coronary event	RR=1.19	[0.67;2.12]	0.5543	1.0000 (I^2=0.00)	1	5682
all cause death	RR=0.92	[0.74;1.15]	0.4794	1.0000 (I^2=0.00)	1	5682

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

Figure 9.1: *Forest's plot for cardiovascular death*

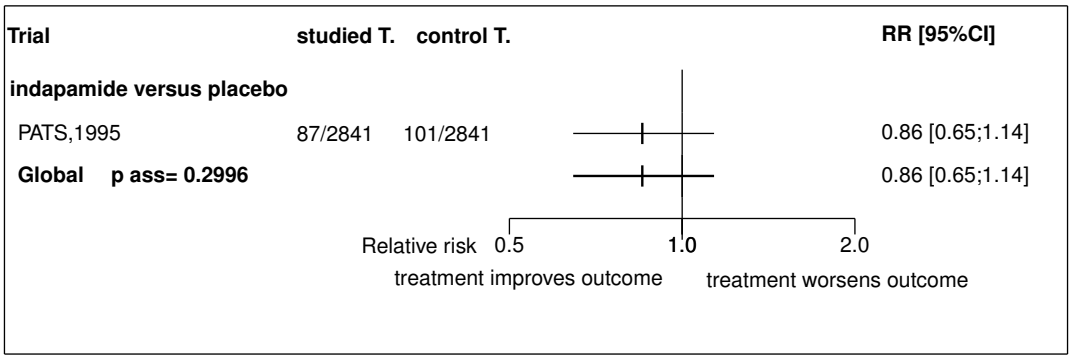


Figure 9.2: *Forest's plot for stroke (fatal and non fatal)*

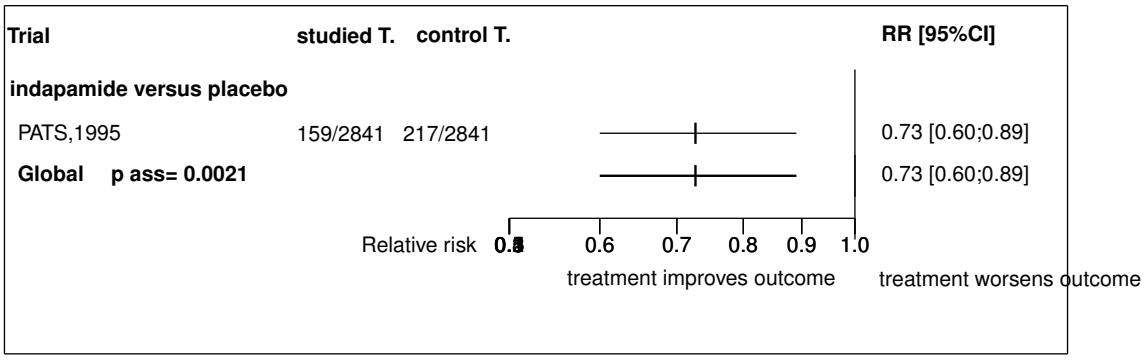


Figure 9.3: *Forest's plot for coronary event*

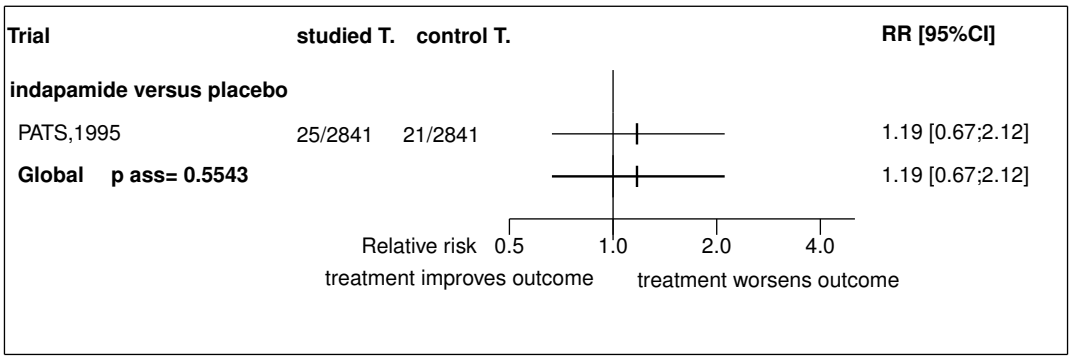
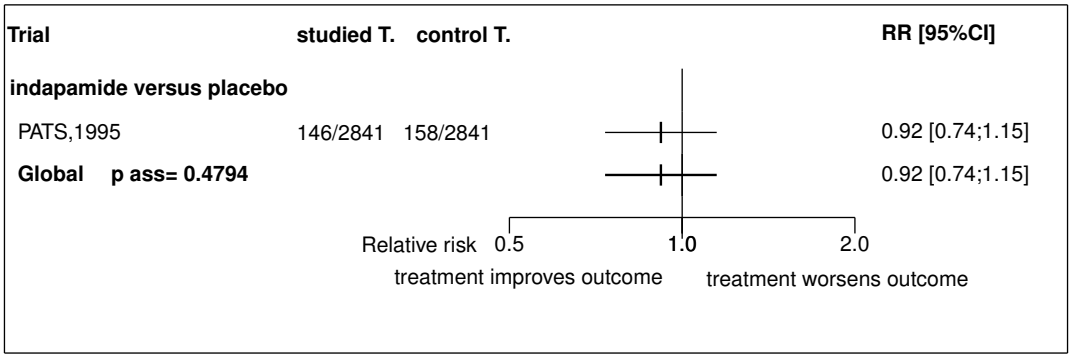


Figure 9.4: *Forest's plot for all cause death*



References

[1] . Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. Chin Med J (Engl) 1995;108:710-7. [PMID=8575241]

9.3 Individual trial summaries

Table 9.6: *PATS, 1995 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=5682 (2841 vs. 2841) **Follow-up duration:** 2y **Study design:** Randomized controlled trial Parallel groups Double blind China	**Inclusion criteria:** men and women with history of TIA or stroke not severely disabled, irrespective of their blood pressure **Exclusion criteria:** neoplasm, rheumatic valvular disease, congestive cardiomyopathy, atrial fibrillation, secondary hypertension, hyperthyroidism, renal and hepatic disease, haemorrhagic disease, insulin dependent diabetes	**Studied treatment:** indapamide 2.5 mg/d **Control treatment:** placebo	Cardiovascular death RR=0.86 [0.65;1.14] Stroke (fatal and non fatal) RR=0.73 [0.60;0.89] Coronary event RR=1.19 [0.67;2.12] All cause death RR=0.92 [0.74;1.15]

Reference

. Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. Chin Med J (Engl) 1995;108:710-7 [PMID=8575241]

10 Detailed results for thiazide diuretics

10.1 Available trials

Only one trial which randomized 99 patients was identified: it compared thiazide diuretics with control.
This trial included 99 patients and was published in 1970.
This trial was open-label in design.
It was reported in English language.
Heart failure data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on coronary event; and 1 trials reported data on cardiovascular death.
Following tables 10.1 (page 53), 10.2 (page 53), 10.4 (page 55), and 10.3 (page 53) summarized the main characteristics of the trial including in this systematic review of randomized trials of thiazide diuretics.

Table 10.1: *Treatment description - Diuretics - thiazide diuretics*

Trial	Studied treatment	Control treatment
Thiazide diuretics versus control		
Carter (1970) [1]	thiazide	?
	Concomittant treatment: NA	

Table 10.2: *Descriptions of participants - Diuretics - thiazide diuretics*

Trial	Patients	
Thiazide diuretics versus control		
Carter (1970) [1]	**Inclusion criteria:** NA	**Exclusion criteria:** NA

Table 10.3: *Design and methodological quality of trials - Diuretics - thiazide diuretics*

Trial	Design	Duration	Centre	Primary endpoint
Thiazide diuretics versus control				

continued...

Trial	Design	Duration	Centre	Primary end-point
Carter, 1970 [1] n=99	NA Open	3.6 y	NA	

Table 10.4: *Trial characteristics - Diuretics - thiazide diuretics*

Trial
Thiazide diuretics versus control
Carter, 1970 [1]

10.2 Meta-analysis results

The results are detailed in table 10.5 (page 56). This table is followed by the Forest's plot corresponding to each endpoint.

Thiazide diuretics versus control

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 0.61 (95% CI 0.31 to 1.21, p=0.1606).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. The analysis detected a statistically significant difference in favor of thiazide diuretics in stroke (fatal and non fatal), with a RR of 0.47 (95% CI 0.25 to 0.89, p=0.0199).
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 0.98 (95% CI 0.14 to 6.68, p=0.9835).
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 0.74 (95% CI 0.17 to 3.12, p=0.6761).
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 0.58 (95% CI 0.33 to 1.01, p=0.0564).

Table 10.5: *Results details - Diuretics - thiazide diuretics*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
thiazide diuretics versus control						
cardiovascular death	RR=0.61	[0.31;1.21]	0.1606	1.0000 (I^2=0.00)	1	99
stroke (fatal and non fatal)	RR=0.47	[0.25;0.89]	0.0199	1.0000 (I^2=0.00)	1	99
coronary event	RR=0.98	[0.14;6.68]	0.9835	1.0000 (I^2=0.00)	1	99
heart failure	RR=0.74	[0.17;3.12]	0.6761	1.0000 (I^2=0.00)	1	99
all cause death	RR=0.58	[0.33;1.01]	0.0564	1.0000 (I^2=0.00)	1	99

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 10.1: *Forest's plot for cardiovascular death*

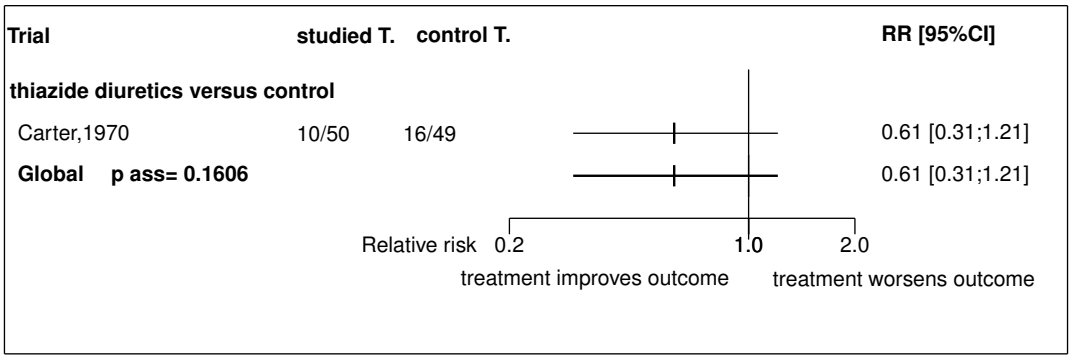


Figure 10.2: *Forest's plot for stroke (fatal and non fatal)*

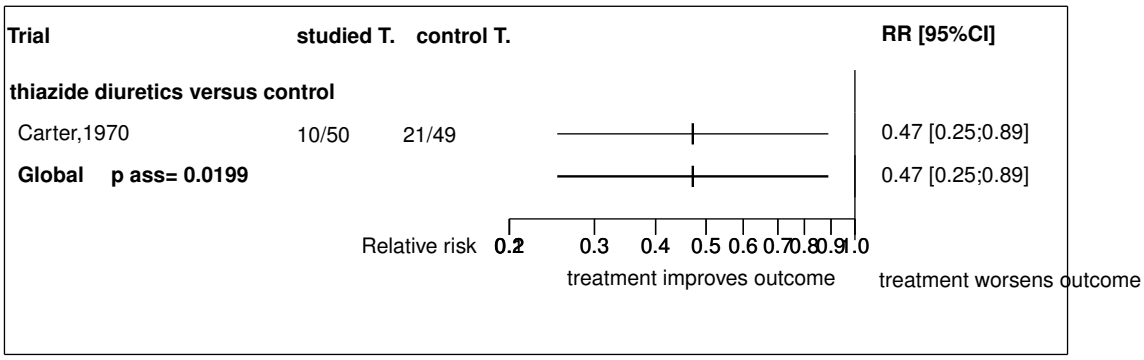


Figure 10.3: *Forest's plot for coronary event*

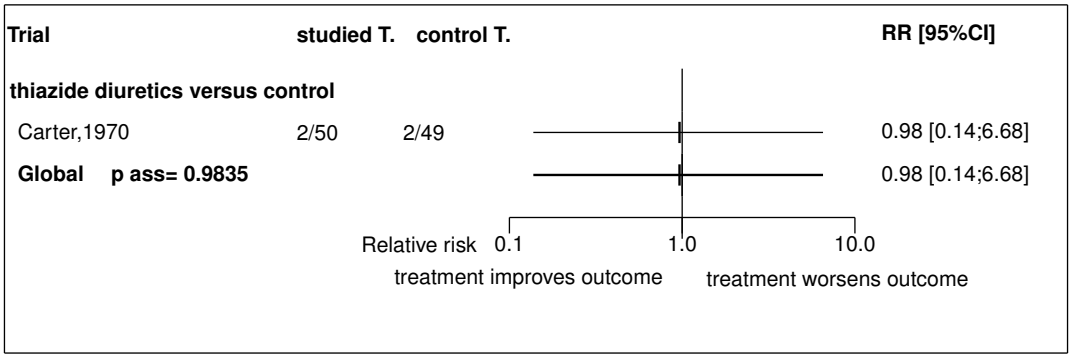


Figure 10.4: *Forest's plot for heart failure*

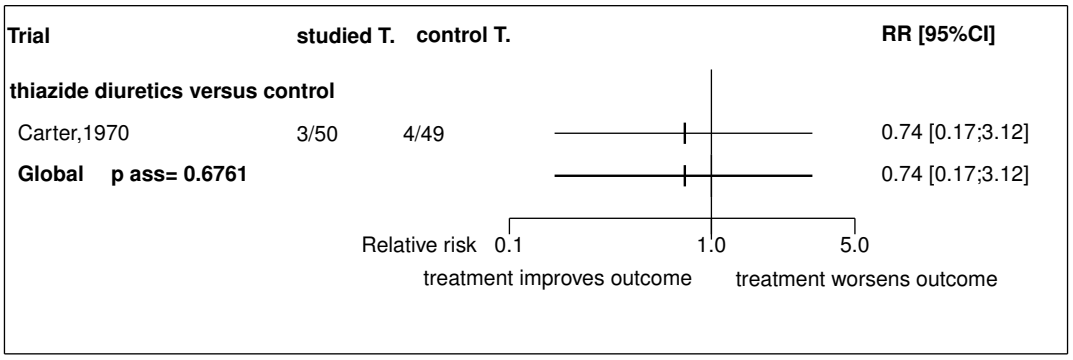
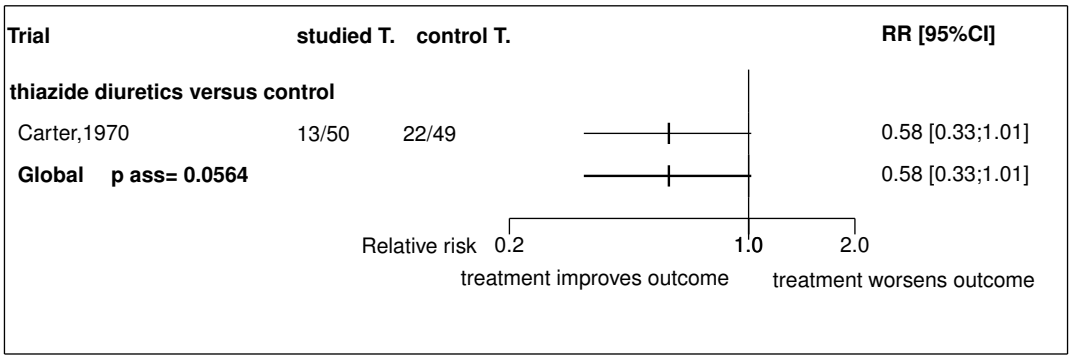


Figure 10.5: *Forest's plot for all cause death*



References

[1] Carter AB. Hypotensive therapy in stroke survivors. Lancet 1970;1:485-9. [PMID=4190177]

10.3 Individual trial summaries

Table 10.6: *Carter, 1970 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=99 (50 vs. 49) **Follow-up duration:** 3.6 y **Study design:** Randomized controlled trial NA Open NA	**Inclusion criteria:** NA **Exclusion criteria:** NA	**Studied treatment:** thiazide **Control treatment:** ? **Concomittant treat.:**NA	Cardiovascular death RR=0.61 [0.31;1.21] Stroke (fatal and non fatal) RR=0.47 [0.25;0.89] Coronary event RR=0.98 [0.14;6.68] Heart failure RR=0.74 [0.17;3.12] All cause death RR=0.58 [0.33;1.01]

Reference

Carter AB. Hypotensive therapy in stroke survivors. Lancet 1970;1:485-9 [PMID=4190177]

11 Global meta-analysis: all Diuretics

11.1 Global meta-analysis: all Diuretics versus control

Table 11.1: *All Diureticsversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular death	RR=0.61	0.31;1.21	0.1606	1.0000 (0.00)	1	99
stroke (fatal and non fatal)	RR=0.47	0.25;0.89	0.0199	1.0000 (0.00)	1	99
coronary event	RR=0.98	0.14;6.68	0.9835	1.0000 (0.00)	1	99
heart failure	RR=0.74	0.17;3.12	0.6761	1.0000 (0.00)	1	99
all cause death	RR=0.58	0.33;1.01	0.0564	1.0000 (0.00)	1	99

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

11.2 Global meta-analysis: all Diuretics versus placebo

Table 11.2: *All Diureticsversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular death	RR=0.84	0.65;1.09	0.1907	0.6804 (0.00)	2	6134
stroke (fatal and non fatal)	RR=0.75	0.63;0.90	0.0000	0.5924 (0.00)	2	6134
coronary event	RR=1.13	0.68;1.89	0.6346	0.7125 (0.00)	2	6134
heart failure	RR=0.08	0.00;1.39	0.0830	1.0000 (0.00)	1	452
all cause death	RR=0.94	0.77;1.15	0.5311	0.7373 (0.00)	2	6134

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

12 Ongoing studies of Diuretics

No ongoing trial was identified.

13 Excluded studies for Diuretics

No trial was excluded.

References