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Anti hypertensive agent for hypertension in nephropathy

A systematic review and meta-analysis of randomized clinical trials

2017 - 7 - 1

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

Contents

0.1 Synthesis of the meta-analysis results

In all 12 randomised controlled trials (RCTs) were included. These included 6 studies of **angiotensin receptor blocker** involving 3,131 patients, 2 studies of **angiotensin-converting enzyme inhibitors** involving 1,530 patients, 3 studies of **calcium-channel blockers** involving 2,447 patients and 1 studie of **direct renin inhibitor** involving 599 patients. Results obtained by the meta-analysis are reported in the following tables, with the endpoints categorized according their results. Three classes are considered: endpoints for wich a benefit effect was detected, endpoints revealing a harmful effect and the other for wich no statistically significant difference was obtained (no evidence).

0.1.1 Angiotensin receptor blocker

Reports of 5 trials (including 3,131 patients) were identified .
Among these comparisons, one trial are about ARBs,two about candesartan,two about irbesartan and one about telmisartan.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.

ARBs

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

Table 1: *Results summary - ARBs*

Benefit	Harmful	No evidence
	ARBs versus control	
↓ heart failure RR=0.48* [0.26;0.88] k=1		→ cardiovascular death RR=0.60^{NS} [0.30;1.19] k=1 → myocardial infarction (fatal and non fatal) RR=0.80^{NS} [0.22;2.93] k=1 → stroke (fatal and non fatal) RR=0.75^{NS} [0.27;2.12] k=1 → all cause death RR=0.66^{NS} [0.41;1.04] k=1

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

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

Candesartan

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

Table 2: *Results summary - Candesartan*

Benefit	Harmful	No evidence
	Candesartan versus control	

continued...

Benefit	Harmful	No evidence
		→ heart failure RR=0.39^{NS} [0.15;1.02] k=1 → all cause death RR=0.06^{NS} [0.00;1.05] k=1
	Candesartan versus conventional treatment	
		→ cardiovascular death RR=1.04^{NS} [0.27;4.01] k=1 → myocardial infarction (fatal and non fatal) RR=2.09^{NS} [0.39;11.03] k=1 → stroke (fatal and non fatal) RR=0.89^{NS} [0.51;1.55] k=1 → heart failure RR=0.68^{NS} [0.34;1.34] k=1 → all cause death RR=1.04^{NS} [0.27;4.01] k=1

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

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

Irbesartan

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

Table 3: *Results summary - Irbesartan*

Benefit	Harmful	No evidence
	Irbesartan versus placebo	
		→ myocardial infarction (fatal and non fatal) RR=0.94^{NS} [0.63;1.40] k=1 → stroke (fatal and non fatal) RR=1.06^{NS} [0.63;1.78] k=1 → coronary event RR=0.91^{NS} [0.72;1.15] k=1 → heart failure RR=0.82^{NS} [0.59;1.13] k=1 → all cause death RR=0.92^{NS} [0.70;1.20] k=1
	Irbesartan versus amlodipine	
↓ heart failure RR=0.63† [0.47;0.86] k=1	↑ myocardial infarction (fatal and non fatal) RR=1.60* [1.00;2.54] k=1	→ cardiovascular events RR=1.03^{NS} [0.81;1.31] k=1 → cardiovascular death RR=1.38^{NS} [0.92;2.06] k=1 → stroke (fatal and non fatal) RR=1.83^{NS} [0.99;3.39] k=1 → all cause death RR=1.03^{NS} [0.78;1.35] k=1

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

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

Telmisartan

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

Table 4: *Results summary - Telmisartan*

Benefit	Harmful	No evidence
	Telmisartan versus enalapril	
		→ cardiovascular death RR=1.63^{NS} [0.28;9.56] k=1 → myocardial infarction (fatal and non fatal) RR=1.63^{NS} [0.60;4.43] k=1 → stroke (fatal and non fatal) RR=1.08^{NS} [0.36;3.27] k=1 → heart failure RR=1.39^{NS} [0.54;3.62] k=1 → all cause death RR=1.08^{NS} [0.36;3.27] 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 Angiotensin-converting enzyme inhibitors

Reports of 1 trials (including 1,530 patients) were identified .
Among these comparisons, two trials are about ramipril.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with ramipril for all the endpoints with data in at least one trial are summarized table 5.

Table 5: *Results summary - Ramipril*

Benefit	Harmful	No evidence
	Ramipril versus amlodipine	
		→ cardiovascular events RR=1.37^{NS} [0.44;4.25] k=1 → cardiovascular death RR=0.50^{NS} [0.07;3.51] k=1 → all cause death RR=1.11^{NS} [0.59;2.09] k=1
	Ramipril versus metoprolol	
		→ all cause death RR=0.77^{NS} [0.48;1.23] k=1

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

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

0.1.3 Calcium-channel blockers

Reports of 2 trials (including 2,447 patients) were identified .
Among these comparisons, 3 trials are about amlodipine.

No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with amlodipine for all the endpoints with data in at least one trial are summarized table 6.

Table 6: *Results summary - Amlodipine*

Benefit	Harmful	No evidence
	Amlodipine versus placebo	
		→ all cause death RR=0.90^{NS} [0.68;1.18] k=1
	Amlodipine versus metoprolol	
		→ all cause death RR=0.70^{NS} [0.38;1.28] k=1
	Amlodipine versus ramipril	
		→ all cause death RR=0.90^{NS} [0.48;1.70] 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 Direct renin inhibitor

Only one trials including 599 patients was found.
Among these comparisons, one trial are about aliskiren.
No trial was excluded on grounds of potentially flawed methodology or incomplete presentation of results. No ongoing trial was found.
Results obtained with aliskiren for all the endpoints with data in at least one trial are summarized table 7.

Table 7: *Results summary - Aliskiren*

Benefit	Harmful	No evidence
	Aliskiren versus placebo	
		→ serious adverse event RR=0.95^{NS} [0.58;1.58] k=1 → any adverse event RR=0.99^{NS} [0.89;1.11] k=1 → all cause death RR=0.25^{NS} [0.01;5.47] k=1 → adverse events leading to treatment discontinuation RR=0.89^{NS} [0.47;1.67] 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 nephropathy. The following classes of treatment are considered:

1. angiotensin receptor blocker
2. angiotensin-converting enzyme inhibitors
3. calcium-channel blockers
4. direct renin inhibitor

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 nephropathy.

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 Heart failure, All cause death, stroke (fatal and non fatal), myocardial infarction (fatal and non fatal), Cardiovascular death, .

1.6 Structure of the report

Each of the eligible studies is summarised in part **??**. A summary of the studies together with an evaluation of their quality is given in part I to **??**, listed by therapeutic class. The therapeutic classes included angiotensin receptor blocker, angiotensin-converting enzyme inhibitors, calcium-channel blockers, direct renin inhibitor,
In these sections, studies in which an active intervention was compared with placebo or no treatment are discussed first, by intervention, followed by a discussion of those studies in which two or more active interventions were compared.

Part I

Angiotensin receptor blocker

2 Overview of angiotensin receptor blocker

2.1 Included trials

A total of 6 randomized comparisons which enrolled 3131 patients were identified. In all, 1 randomized comparison concerned ARBs , two candesartan , two irbesartan and one telmisartan. The detailed descriptions of trials and meta-analysis results is given in section 3 (page 26) for ARBs, in section 4 (page 33) for candesartan, in section 5 (page 43) for irbesartan and in section 6 (page 55) for telmisartan.

The average study size was 521 patients (range 80 to 1148). The first study was published in 2001, and the last study was published in 2008.
A total of 3 trials were double blind and 3 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 2.1 (page 17) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of meta-analysis results

The meta-analysis of the available trials about angiotensin receptor blocker provide the results listed in tables 2.2 to 2.5 (page 19) and in the following graphs.

2.2.1 ARBs

ARBs was superior to **control** in terms of heart failure (RR=0.48, 95% CI 0.26 to 0.88, p=0.0181, 1 trial). However, no significant difference was found on cardiovascular death (RR=0.60, 95% CI 0.30 to 1.19, p=0.1443, 1 trial), myocardial infarction (fatal and non fatal) (RR=0.80, 95% CI 0.22 to 2.93, p=0.7363, 1 trial), stroke (fatal and non fatal) (RR=0.75, 95% CI 0.27 to 2.12, p=0.5872, 1 trial)and all cause death (RR=0.66, 95% CI 0.41 to 1.04, p=0.0752, 1 trial).

2.2.2 Candesartan

No significant difference was found between **candesartan** and **control** in terms of heart failure (RR=0.39, 95% CI 0.15 to 1.02, p=0.0557, 1 trial)and all cause death (RR=0.06, 95% CI 0.00 to 1.05, p=0.0538, 1 trial).

No significant difference was found between **candesartan** and **conventional treatment** in terms of cardiovascular death (RR=1.04, 95% CI 0.27 to 4.01, p=0.9506, 1 trial), myocardial infarction (fatal and non fatal) (RR=2.09, 95% CI 0.39 to 11.03, p=0.3865, 1 trial), stroke (fatal and non fatal) (RR=0.89, 95% CI 0.51 to 1.55, p=0.6723, 1 trial), heart failure (RR=0.68, 95% CI 0.34 to 1.34, p=0.2595, 1 trial)and all cause death (RR=1.04, 95% CI 0.27 to 4.01, p=0.9506, 1 trial).

2.2.3 Irbesartan

No significant difference was found between **irbesartan** and **placebo** in terms of myocardial infarction (fatal and non fatal) (RR=0.94, 95% CI 0.63 to 1.40, p=0.7599, 1 trial), stroke (fatal and non fatal) (RR=1.06, 95% CI 0.63 to 1.78, p=0.8312, 1 trial), coronary event (RR=0.91,

95% CI 0.72 to 1.15, p=0.4211, 1 trial), heart failure (RR=0.82, 95% CI 0.59 to 1.13, p=0.2247, 1 trial)and all cause death (RR=0.92, 95% CI 0.70 to 1.20, p=0.5392, 1 trial).

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

2.2.4 Telmisartan

No significant difference was found between **telmisartan** and **enalapril** in terms of cardiovascular death (RR=1.63, 95% CI 0.28 to 9.56, p=0.5912, 1 trial), myocardial infarction (fatal and non fatal) (RR=1.63, 95% CI 0.60 to 4.43, p=0.3426, 1 trial), stroke (fatal and non fatal) (RR=1.08, 95% CI 0.36 to 3.27, p=0.8870, 1 trial), heart failure (RR=1.39, 95% CI 0.54 to 3.62, p=0.4969, 1 trial)and all cause death (RR=1.08, 95% CI 0.36 to 3.27, p=0.8870, 1 trial).

Table 2.1: *Main study characteristics - angiotensin receptor blocker*

Trial	Patients	Treatments	Trial design and method
ARBs			
ARBs versus control			
Suzuki, 2008 [1] n = 183 vs. 183	patients with diabetes and chronic kidney disease on dialysis	ARBs (valsartan, candesartan, and losartan) **versus** no ARBs	open parallel groups Primary endpoint: CVD events
Candesartan			
Candesartan versus control			
Takahashi, 2006 [1] n = 43 vs. 37	patients on chronic haemodialysis in stable condition and with no clinical evidence of cardiac disorders	candesartan **versus** control	open parallel groups Primary endpoint: cardiovascular events
Candesartan versus conventional treatment			
E-COST-R, 2005 [2] n = 69 vs. 72	hypertensive subjects 60 to 75 years old with non-diabetic chronic renal insufficiency	candesartan **versus** conventional treatment	open parallel groups Primary endpoint: cardiovascular event
Irbesartan			
Irbesartan versus placebo			
IDNT (vs placebo), 2001 [1, 2] n = 579 vs. 569	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300mg/d (target 135/85) **versus** placebo	double-blind parallel groups Primary endpoint: doubling of the base-line serum creatinine concentration, end-stage renal disease, or death 210 centres, worldwide
Irbesartan versus amlodipine			

continued...

Trial	Patients	Treatments	Trial design and method
IDNT (vs amlodipine), 2001 [3] n = 579 vs. 567	hypertensive patients with nephropathy due to type 2 diabetes	irbesartan 300mg/d (with a target of 135/85) **versus** amlodipine 10mg/d (with a target of 135/85)	double-blind parallel groups Primary endpoint: doubling of creatinine or endstage renal disease or death 210 centres, worldwide
Telmisartan			
Telmisartan versus enalapril			
DETAIL, 2004 [1] n = 120 vs. 130	subjects with type 2 diabetes and early nephropathy	telmisartan 80 mg daily **versus** enalapril 20 mg daily	double-blind parallel groups Primary endpoint: glomerular filtration rate

Table 2.2: *Summary of all results for ARBs*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ARBs versus control						
cardiovascular death	RR=0.60	0.30;1.19	0.1443	1.0000 (0.00)	1	366
myocardial infarction (fatal and non fatal)	RR=0.80	0.22;2.93	0.7363	1.0000 (0.00)	1	366
stroke (fatal and non fatal)	RR=0.75	0.27;2.12	0.5872	1.0000 (0.00)	1	366
heart failure	RR=0.48	0.26;0.88	0.0181	1.0000 (0.00)	1	366
all cause death	RR=0.66	0.41;1.04	0.0752	1.0000 (0.00)	1	366

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

Table 2.3: *Summary of all results for candesartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
candesartan versus control						
heart failure	RR=0.39	0.15;1.02	0.0557	1.0000 (0.00)	1	80
all cause death	RR=0.06	0.00;1.05	0.0538	1.0000 (0.00)	1	80
candesartan versus conventional treatment						
cardiovascular death	RR=1.04	0.27;4.01	0.9506	1.0000 (0.00)	1	141
myocardial infarction (fatal and non fatal)	RR=2.09	0.39;11.03	0.3865	1.0000 (0.00)	1	141
stroke (fatal and non fatal)	RR=0.89	0.51;1.55	0.6723	1.0000 (0.00)	1	141
heart failure	RR=0.68	0.34;1.34	0.2595	1.0000 (0.00)	1	141
all cause death	RR=1.04	0.27;4.01	0.9506	1.0000 (0.00)	1	141

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

Table 2.4: *Summary of all results for irbesartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
irbesartan versus placebo						
myocardial infarction (fatal and non fatal)	RR=0.94	0.63;1.40	0.7599	1.0000 (0.00)	1	1148
stroke (fatal and non fatal)	RR=1.06	0.63;1.78	0.8312	1.0000 (0.00)	1	1148
coronary event	RR=0.91	0.72;1.15	0.4211	1.0000 (0.00)	1	1148
heart failure	RR=0.82	0.59;1.13	0.2247	1.0000 (1.00)	1	1148

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=0.92	0.70;1.20	0.5392	1.0000 (0.00)	1	1148
irbesartan versus amlodipine						
cardiovascular events	RR=1.03	0.81;1.31	0.8095	1.0000 (0.00)	1	1146
cardiovascular death	RR=1.38	0.92;2.06	0.1225	1.0000 (0.00)	1	1146
myocardial infarction (fatal and non fatal)	RR=1.60	1.00;2.54	0.0488	1.0000 (0.00)	1	1146
stroke (fatal and non fatal)	RR=1.83	0.99;3.39	0.0551	1.0000 (0.00)	1	1146
heart failure	RR=0.63	0.47;0.86	0.0030	1.0000 (0.00)	1	1146
all cause death	RR=1.03	0.78;1.35	0.8536	1.0000 (0.00)	1	1146

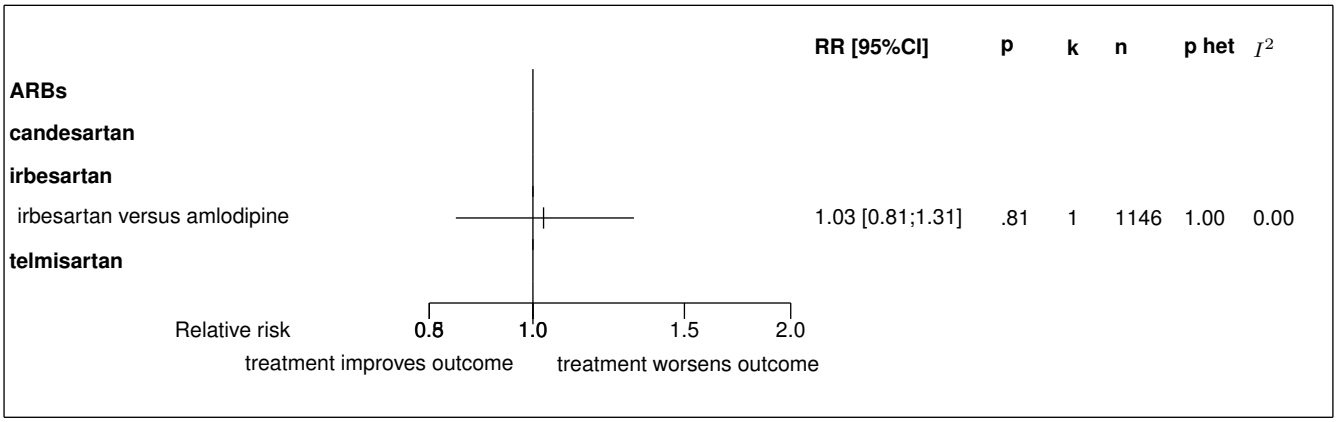
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.5: *Summary of all results for telmisartan*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
telmisartan versus enalapril						
cardiovascular death	RR=1.63	0.28;9.56	0.5912	1.0000 (0.00)	1	250
myocardial infarction (fatal and non fatal)	RR=1.63	0.60;4.43	0.3426	1.0000 (0.00)	1	250
stroke (fatal and non fatal)	RR=1.08	0.36;3.27	0.8870	1.0000 (0.00)	1	250
heart failure	RR=1.39	0.54;3.62	0.4969	1.0000 (0.00)	1	250
all cause death	RR=1.08	0.36;3.27	0.8870	1.0000 (0.00)	1	250

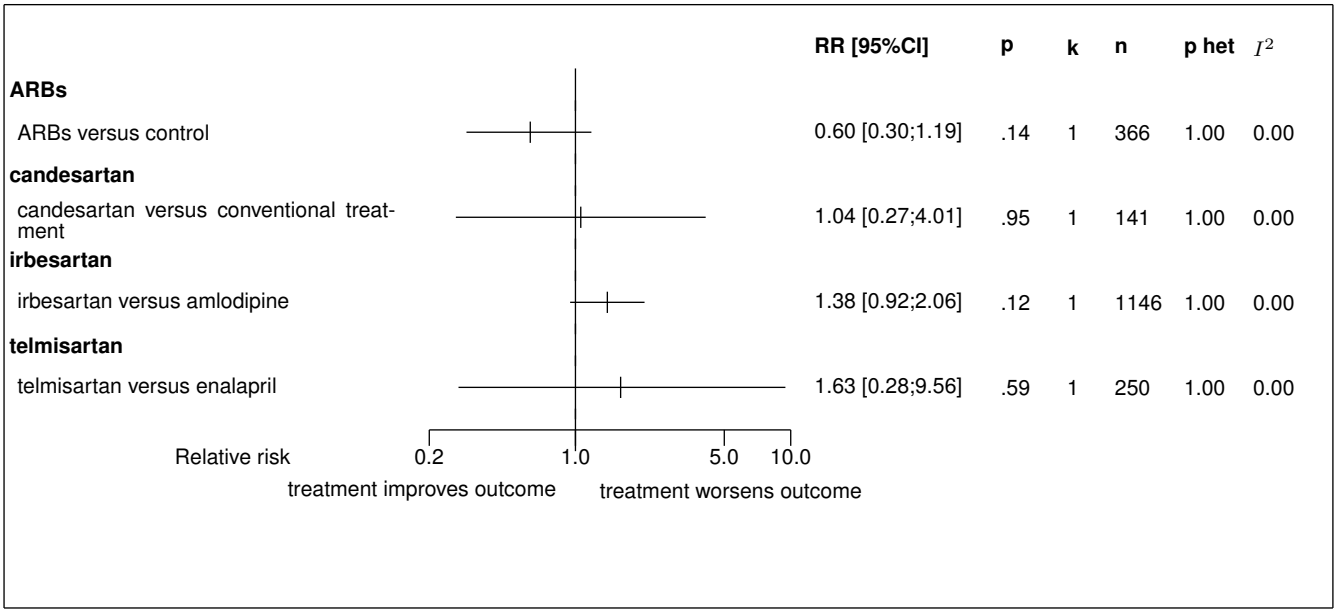
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



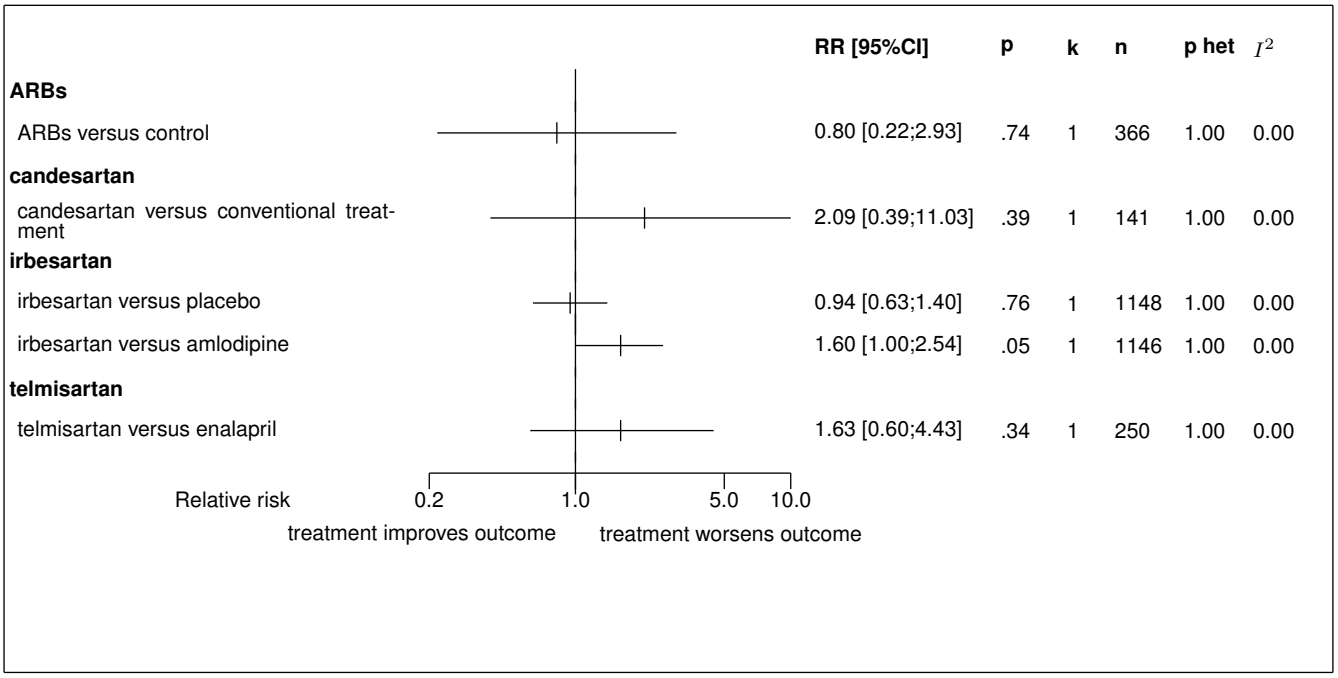
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



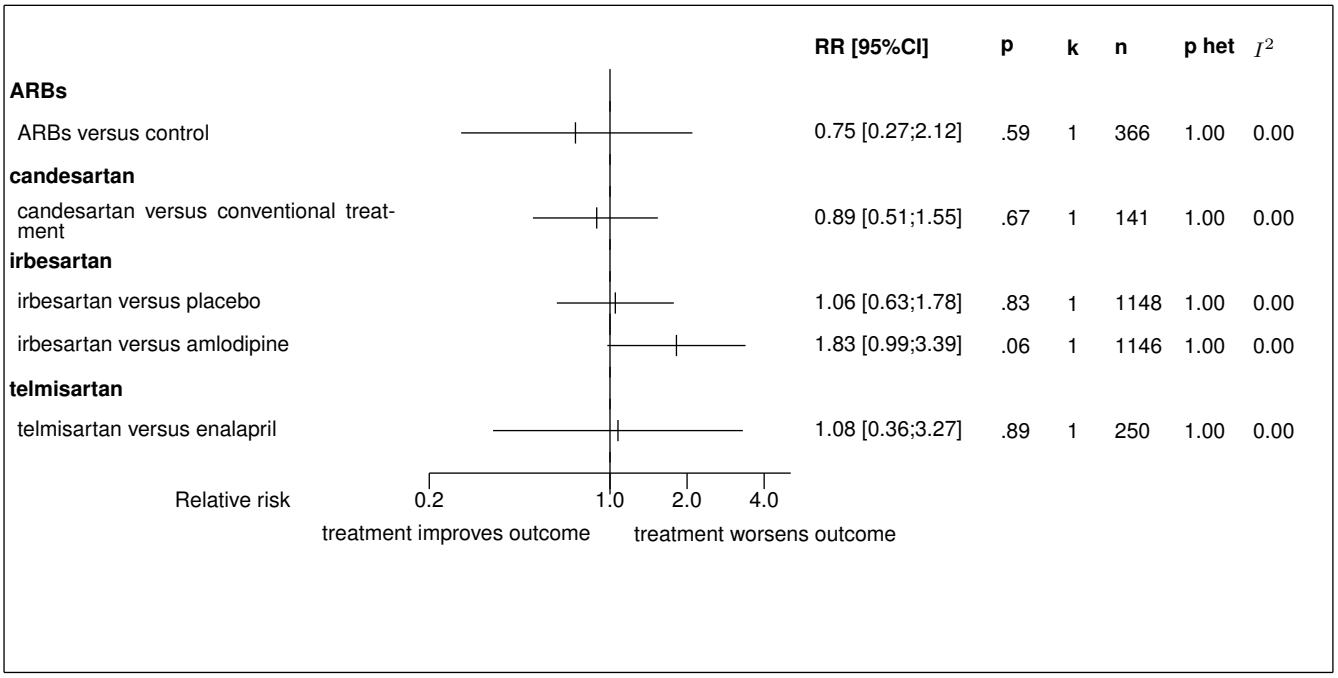
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



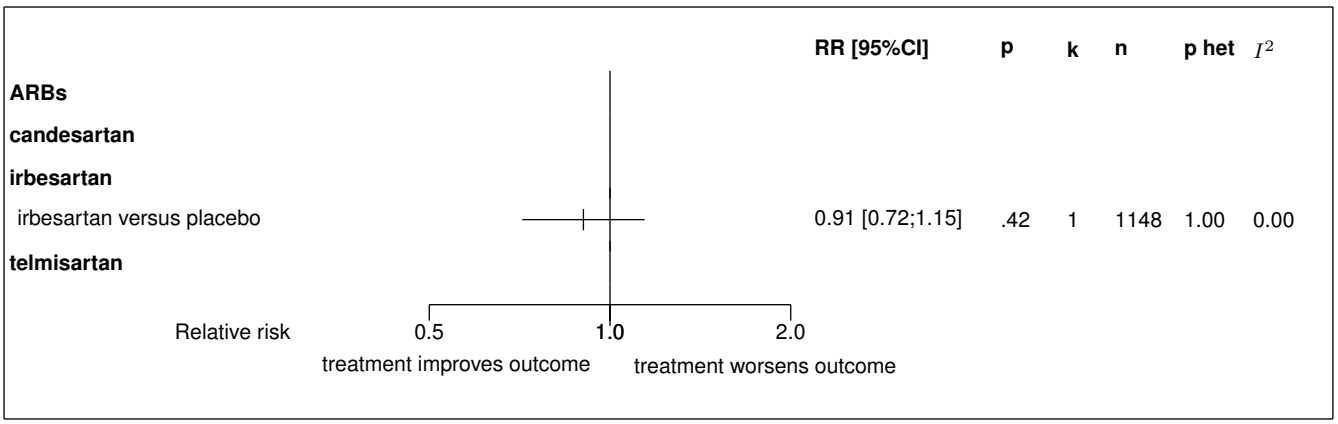
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



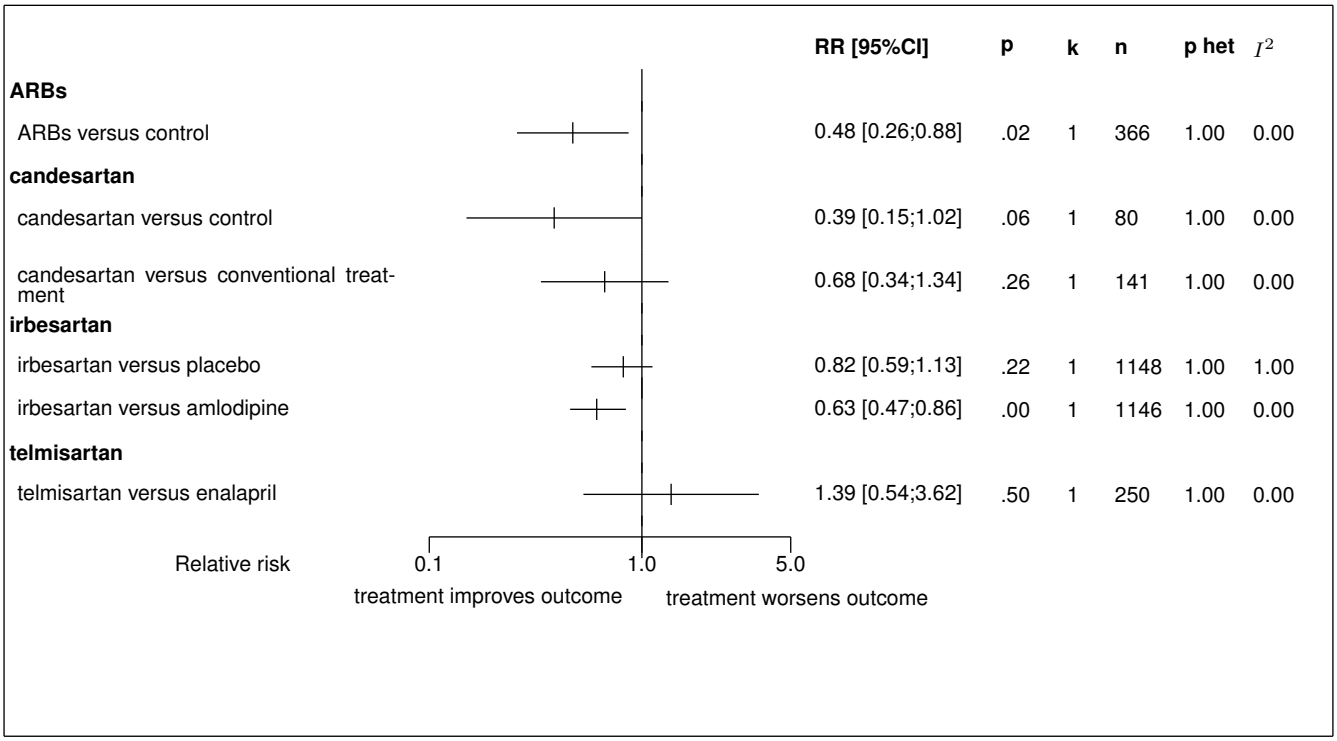
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



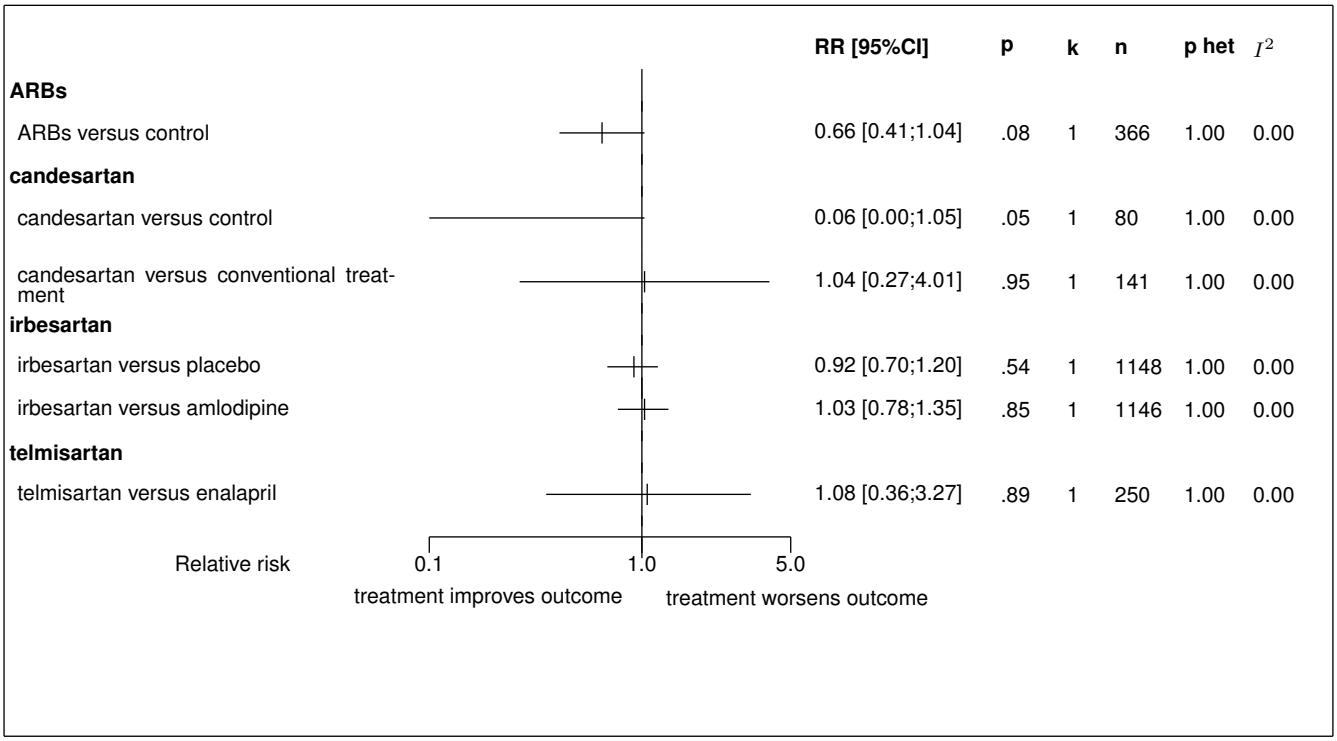
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.6: *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

3 Detailed results for ARBs

3.1 Available trials

Only one trial which randomized 366 patients was identified: it compared ARBs with control.
This trial included 366 patients and was published in 2008.
This trial was open-label in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on cardiovascular death; 1 trials reported data on heart failure; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 3.1 (page 26), 3.2 (page 26), 3.4 (page 27), and 3.3 (page 26) summarized the main characteristics of the trial including in this systematic review of randomized trials of ARBs.

Table 3.1: *Treatment description - angiotensin receptor blocker - ARBs*

Trial	Studied treatment	Control treatment
ARBs versus control		
Suzuki (2008) [1]	ARBs (valsartan, candesartan, and losartan)	no ARBs

Table 3.2: *Descriptions of participants - angiotensin receptor blocker - ARBs*

Trial	Patients
ARBs versus control	
Suzuki (2008) [1]	Patients with diabetes and chronic kidney disease on dialysis

Table 3.3: *Design and methodological quality of trials - angiotensin receptor blocker - ARBs*

Trial	Design	Duration	Centre	Primary end-point
ARBs versus control				
Suzuki, 2008 [1] n=366	Parallel groups open confirmatory trial at risk of bias			CVD events

Table 3.4: *Trial characteristics - angiotensin receptor blocker - ARBs*

Trial	target blood pressure
ARBs versus control	
Suzuki, 2008 [1]	

3.2 Meta-analysis results

The results are detailed in table 3.5 (page 28). This table is followed by the Forest's plot corresponding to each endpoint.

ARBs 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 0.60 (95% CI 0.30 to 1.19, p=0.1443).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.80 (95% CI 0.22 to 2.93, p=0.7363).
The single study eligible for this comparison provided data on **stroke (fatal and non fatal)**. No statistically significant difference between the groups was found in stroke (fatal and non fatal), with a RR of 0.75 (95% CI 0.27 to 2.12, p=0.5872).
The single study eligible for this comparison provided data on **heart failure**. The analysis detected a statistically significant difference in favor of ARBs in heart failure, with a RR of 0.48 (95% CI 0.26 to 0.88, p=0.0181).
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 0.66 (95% CI 0.41 to 1.04, p=0.0752).

Table 3.5: *Results details - angiotensin receptor blocker - ARBs*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ARBs versus control						
cardiovascular death	RR=0.60	[0.30;1.19]	0.1443	1.0000 (I^2=0.00)	1	366
myocardial infarction (fatal and non fatal)	RR=0.80	[0.22;2.93]	0.7363	1.0000 (I^2=0.00)	1	366
stroke (fatal and non fatal)	RR=0.75	[0.27;2.12]	0.5872	1.0000 (I^2=0.00)	1	366
heart failure	RR=0.48	[0.26;0.88]	0.0181	1.0000 (I^2=0.00)	1	366
all cause death	RR=0.66	[0.41;1.04]	0.0752	1.0000 (I^2=0.00)	1	366

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 death*

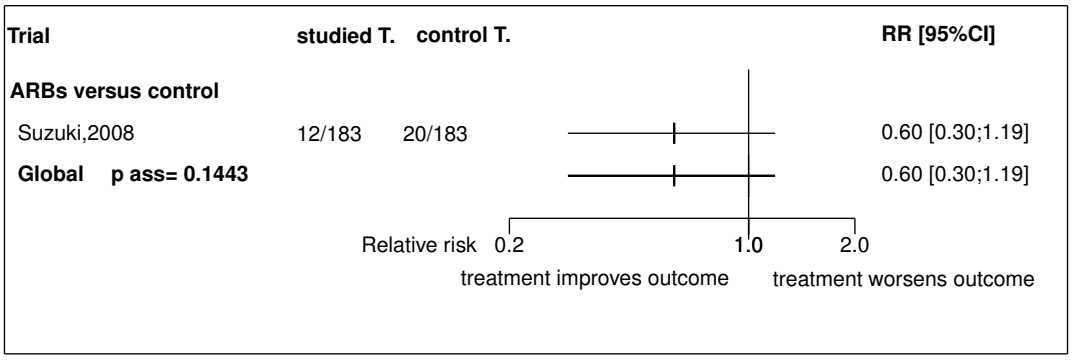


Figure 3.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

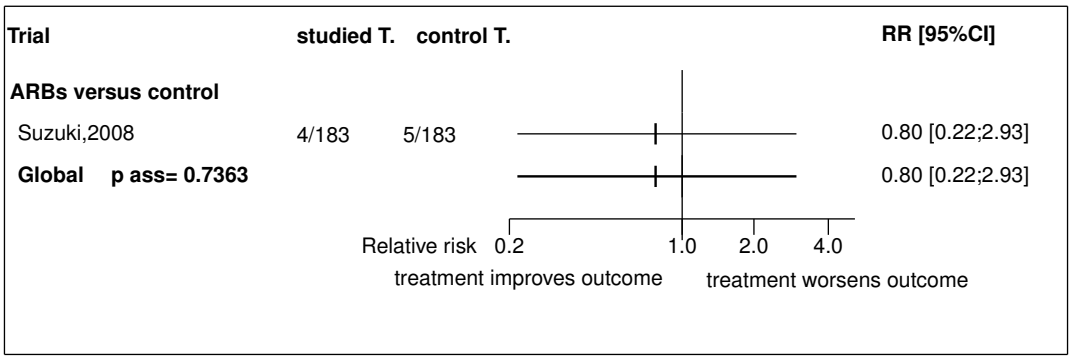


Figure 3.3: *Forest's plot for stroke (fatal and non fatal)*

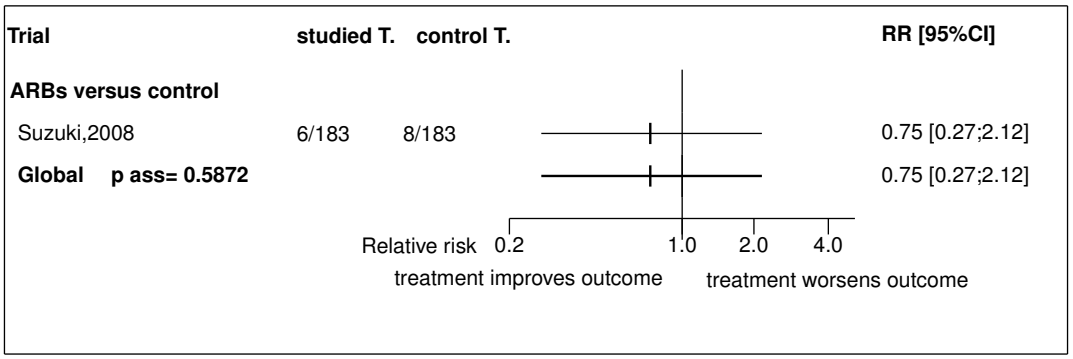


Figure 3.4: *Forest's plot for heart failure*

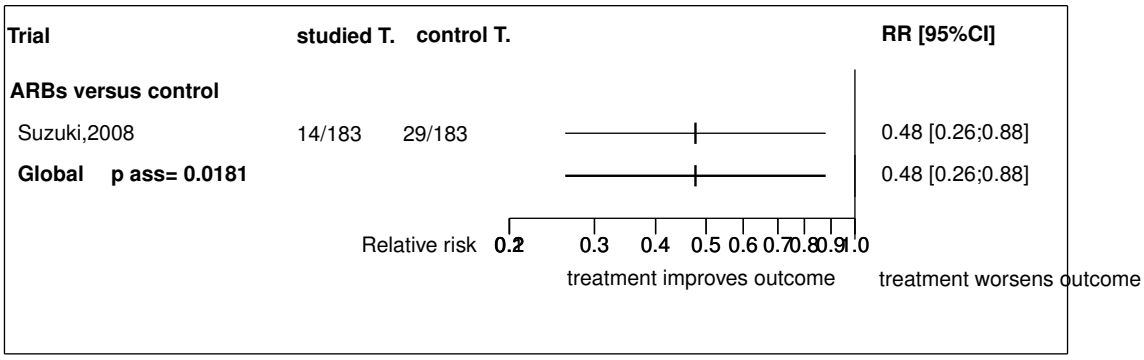
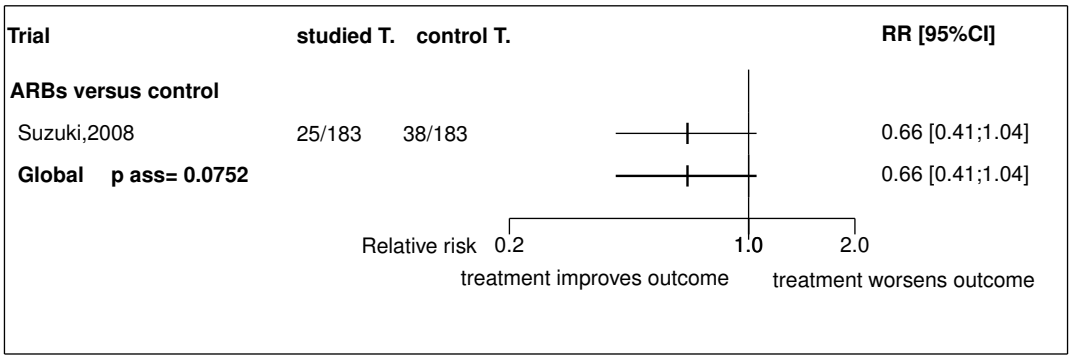


Figure 3.5: *Forest's plot for all cause death*



References

[1] Suzuki H, Kanno Y, Sugahara S, Ikeda N, Shoda J, Takenaka T, Inoue T, Araki R. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 2008;52:501-6. [PMID=18653268]

3.3 Individual trial summaries

Table 3.6: *Suzuki, 2008 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=366 (183 vs. 183) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias	Patients with diabetes and chronic kidney disease on dialysis	**Studied treatment:** ARBs (valsartan, candesartan, and losartan) **Control treatment:** no ARBs	Cardiovascular death RR=0.60 [0.30;1.19] Myocardial infarction (fatal and non fatal) RR=0.80 [0.22;2.93] Stroke (fatal and non fatal) RR=0.75 [0.27;2.12]

Reference

Suzuki H, Kanno Y, Sugahara S, Ikeda N, Shoda J, Takenaka T, Inoue T, Araki R. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 2008;52:501-6 [PMID=18653268]

4 Detailed results for candesartan

4.1 Available trials

A total of 2 RCTs which randomized 221 patients were identified: it compared candesartan with control and it compared candesartan with conventional treatment.
The average study size was 110 patients (range 80 to 141). The first study was published in 2005, and the last study was published in 2006.
All trials were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 2 trials; 2 trials reported data on heart failure; 1 trials reported data on myocardial infarction (fatal and non fatal); 1 trials reported data on cardiovascular death; and 1 trials reported data on stroke (fatal and non fatal).
Following tables 4.1 (page 33), 4.2 (page 33), 4.4 (page 35), and 4.3 (page 34) summarized the main characteristics of the trials including in this systematic review of randomized trials of candesartan.

Table 4.1: *Treatment description - angiotensin receptor blocker - candesartan*

Trial	Studied treatment	Control treatment
Candesartan versus control		
Takahashi (2006) [1]	candesartan	control
Candesartan versus conventional treatment		
E-COST-R (2005) [2]	candesartan	conventional treatment

Table 4.2: *Descriptions of participants - angiotensin receptor blocker - candesartan*

Trial	Patients
Candesartan versus control	
Takahashi (2006) [1]	Patients on chronic haemodialysis in stable condition and with no clinical evidence of cardiac disorders
Candesartan versus conventional treatment	
E-COST-R (2005) [2]	Hypertensive subjects 60 to 75 years old with non-diabetic chronic renal insufficiency

Table 4.3: *Design and methodological quality of trials - angiotensin receptor blocker - candesartan*

Trial	Design	Duration	Centre	Primary endpoint
Candesartan versus control				
Takahashi, 2006 [1] n=80	Parallel groups open exploratory trial	19.4 months		cardiovascular events
Candesartan versus conventional treatment				
E-COST-R, 2005 [2] n=141	Parallel groups open confirmatory trial at risk of bias			cardiovascular event

Table 4.4: *Trial characteristics - angiotensin receptor blocker - candesartan*

Trial	target blood pressure
Candesartan versus control	
Takahashi, 2006 [1]	
Candesartan versus conventional treatment	
E-COST-R, 2005 [2]	

4.2 Meta-analysis results

The results are detailed in table 4.5 (page 36). This table is followed by the Forest's plot corresponding to each endpoint.

Candesartan versus control

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 0.39 (95% CI 0.15 to 1.02, p=0.0557).
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 0.06 (95% CI 0.00 to 1.05, p=0.0538).

Candesartan versus conventional treatment

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 1.04 (95% CI 0.27 to 4.01, p=0.9506).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 2.09 (95% CI 0.39 to 11.03, p=0.3865).
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 0.89 (95% CI 0.51 to 1.55, p=0.6723).
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 0.34 to 1.34, p=0.2595).
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 1.04 (95% CI 0.27 to 4.01, p=0.9506).

Table 4.5: *Results details - angiotensin receptor blocker - candesartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
candesartan versus control						
heart failure	RR=0.39	[0.15;1.02]	0.0557	1.0000 (I^2=0.00)	1	80
all cause death	RR=0.06	[0.00;1.05]	0.0538	1.0000 (I^2=0.00)	1	80
candesartan versus conventional treatment						
cardiovascular death	RR=1.04	[0.27;4.01]	0.9506	1.0000 (I^2=0.00)	1	141
myocardial infarction (fatal and non fatal)	RR=2.09	[0.39;11.03]	0.3865	1.0000 (I^2=0.00)	1	141
stroke (fatal and non fatal)	RR=0.89	[0.51;1.55]	0.6723	1.0000 (I^2=0.00)	1	141
heart failure	RR=0.68	[0.34;1.34]	0.2595	1.0000 (I^2=0.00)	1	141
all cause death	RR=1.04	[0.27;4.01]	0.9506	1.0000 (I^2=0.00)	1	141

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

Figure 4.1: *Forest's plot for cardiovascular death*

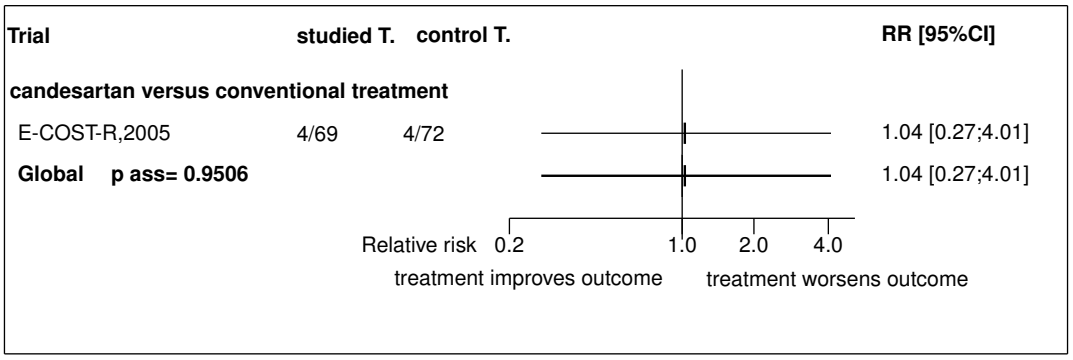


Figure 4.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

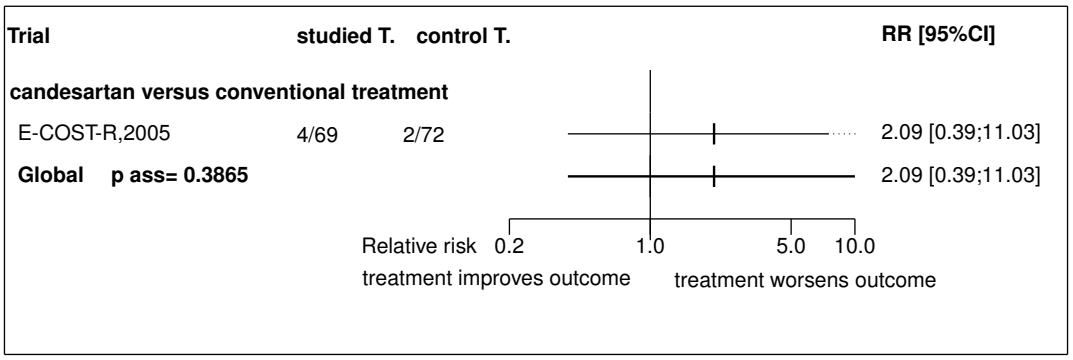


Figure 4.3: *Forest's plot for stroke (fatal and non fatal)*

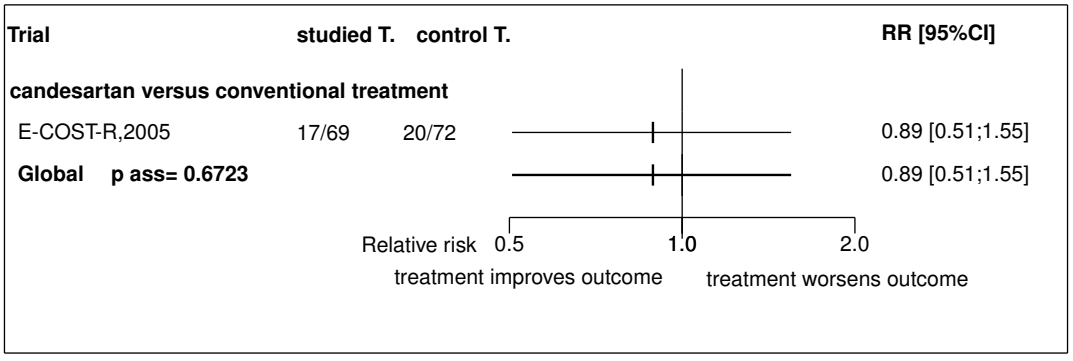


Figure 4.4: *Forest's plot for heart failure*

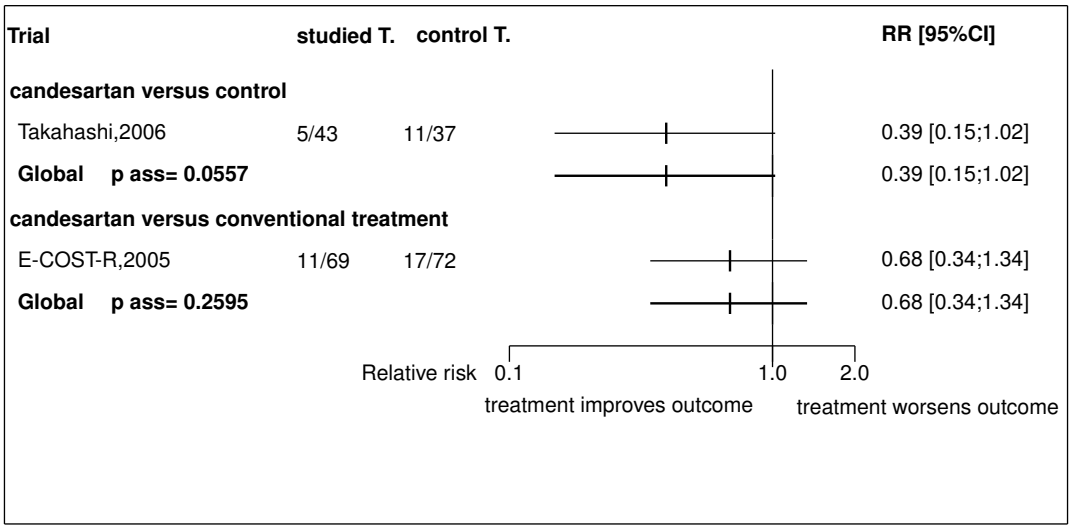
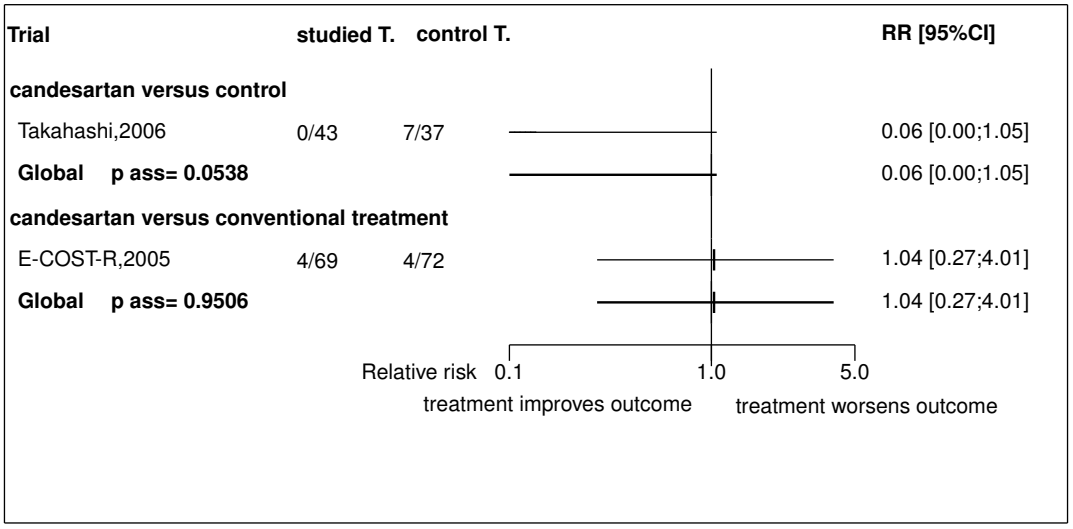


Figure 4.5: *Forest's plot for all cause death*



References

[1] Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R, Dohi Y. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis–a randomized study. Nephrol Dial Transplant 2006;21:2507-12. [PMID=16766543]

[2] Nakamura T, Kanno Y, Takenaka T, Suzuki H. An angiotensin receptor blocker reduces the risk of congestive heart failure in elderly hypertensive patients with renal insufficiency. Hypertens Res 2005;28:415-23.

[PMID=16156505]

4.3 Individual trial summaries

Table 4.6: *Takahashi, 2006 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=80 (43 vs. 37) **Follow-up duration:** 19.4 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Patients on chronic haemodialysis in stable condition and with no clinical evidence of cardiac disorders	**Studied treatment:** candesartan **Control treatment:** control	

Reference

Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R, Dohi Y. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis–a randomized study. Nephrol Dial Transplant 2006;21:2507-12 [PMID=16766543]

Table 4.7: *E-COST-R, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=141 (69 vs. 72) **Follow-up duration:** **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias	Hypertensive subjects 60 to 75 years old with non-diabetic chronic renal insufficiency	**Studied treatment:** candesartan **Control treatment:** conventional treatment	Cardiovascular death RR=1.04 [0.27;4.01] Myocardial infarction (fatal and non fatal) RR=2.09 [0.39;11.03] Stroke (fatal and non fatal) RR=0.89 [0.51;1.55]

Reference

Nakamura T, Kanno Y, Takenaka T, Suzuki H. An angiotensin receptor blocker reduces the risk of congestive heart failure in elderly hypertensive patients with renal insufficiency. Hypertens Res 2005;28:415-23 [PMID=16156505]

5 Detailed results for irbesartan

5.1 Available trials

A total of 2 RCTs which randomized 2294 patients were identified: it compared irbesartan with placebo and it compared irbesartan with amlodipine.
The average study size was 1147 patients (range 1146 to 1148). The first study was published in 2001, and the last study was published in 2001.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 2 trials; 2 trials reported data on myocardial infarction (fatal and non fatal); 2 trials reported data on cardiovascular death; 2 trials reported data on heart failure; and 2 trials reported data on stroke (fatal and non fatal).
Following tables 5.1 (page 43), 5.2 (page 43), 5.4 (page 45), and 5.3 (page 44) summarized the main characteristics of the trials including in this systematic review of randomized trials of irbesartan.

Table 5.1: *Treatment description - angiotensin receptor blocker - irbesartan*

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

Table 5.2: *Descriptions of participants - angiotensin receptor blocker - irbesartan*

Trial	Patients
Irbesartan versus placebo	
IDNT (vs placebo) (2001) [1, 2]	Hypertensive patients with nephropathy due to type 2 diabetes
Irbesartan versus amlodipine	
IDNT (vs amlodipine) (2001) [3]	Hypertensive patients with nephropathy due to type 2 diabetes

Table 5.3: *Design and methodological quality of trials - angiotensin receptor blocker - irbesartan*

Trial	Design	Duration	Centre	Primary end-point
Irbesartan versus placebo				
IDNT (vs placebo), 2001 [1, 2] n=1148	Parallel groups double-blind confirmatory trial at low risk of bias	2.6 y inclusion period: mar 1996 - feb 1999	worldwide 210 centres	doubling of the base-line serum creatinine concentration, end-stage renal disease, or death
Irbesartan versus amlodipine				
IDNT (vs amlodipine), 2001 [3] n=1146	Parallel groups double-blind confirmatory trial at low risk of bias	26y inclusion period: mar 1996 - feb 1999	worldwide 210 centres	doubling of creatinine or endstage renal disease or death

Table 5.4: *Trial characteristics - angiotensin receptor blocker - irbesartan*

Trial	target blood pressure
Irbesartan versus placebo	
IDNT (vs placebo), 2001 [1, 2]	
Irbesartan versus amlodipine	
IDNT (vs amlodipine), 2001 [3]	

5.2 Meta-analysis results

The results are detailed in table 5.5 (page 47). This table is followed by the Forest's plot corresponding to each endpoint.

Irbesartan versus placebo

The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 0.94 (95% CI 0.63 to 1.40, p=0.7599).
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 1.06 (95% CI 0.63 to 1.78, p=0.8312).
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 0.91 (95% CI 0.72 to 1.15, p=0.4211).
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 0.82 (95% CI 0.59 to 1.13, p=0.2247).
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 0.70 to 1.20, p=0.5392).

Irbesartan versus amlodipine

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

Table 5.5: *Results details - angiotensin receptor blocker - irbesartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
irbesartan versus placebo						
myocardial infarction (fatal and non fatal)	RR=0.94	[0.63;1.40]	0.7599	1.0000 (I^2=0.00)	1	1148
stroke (fatal and non fatal)	RR=1.06	[0.63;1.78]	0.8312	1.0000 (I^2=0.00)	1	1148
coronary event	RR=0.91	[0.72;1.15]	0.4211	1.0000 (I^2=0.00)	1	1148
heart failure	RR=0.82	[0.59;1.13]	0.2247	1.0000 (I^2=1.00)	1	1148
all cause death	RR=0.92	[0.70;1.20]	0.5392	1.0000 (I^2=0.00)	1	1148
irbesartan versus amlodipine						
cardiovascular events	RR=1.03	[0.81;1.31]	0.8095	1.0000 (I^2=0.00)	1	1146
cardiovascular death	RR=1.38	[0.92;2.06]	0.1225	1.0000 (I^2=0.00)	1	1146
myocardial infarction (fatal and non fatal)	RR=1.60	[1.00;2.54]	0.0488	1.0000 (I^2=0.00)	1	1146
stroke (fatal and non fatal)	RR=1.83	[0.99;3.39]	0.0551	1.0000 (I^2=0.00)	1	1146
heart failure	RR=0.63	[0.47;0.86]	0.0030	1.0000 (I^2=0.00)	1	1146
all cause death	RR=1.03	[0.78;1.35]	0.8536	1.0000 (I^2=0.00)	1	1146

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

Figure 5.1: *Forest's plot for cardiovascular events*

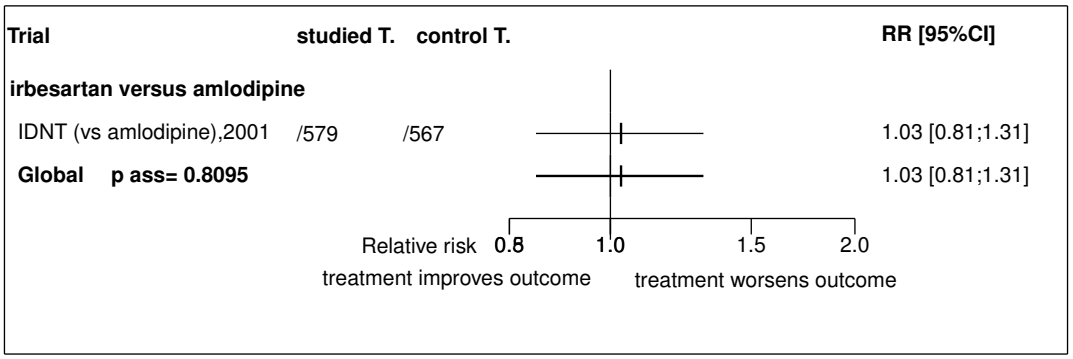


Figure 5.2: *Forest's plot for cardiovascular death*

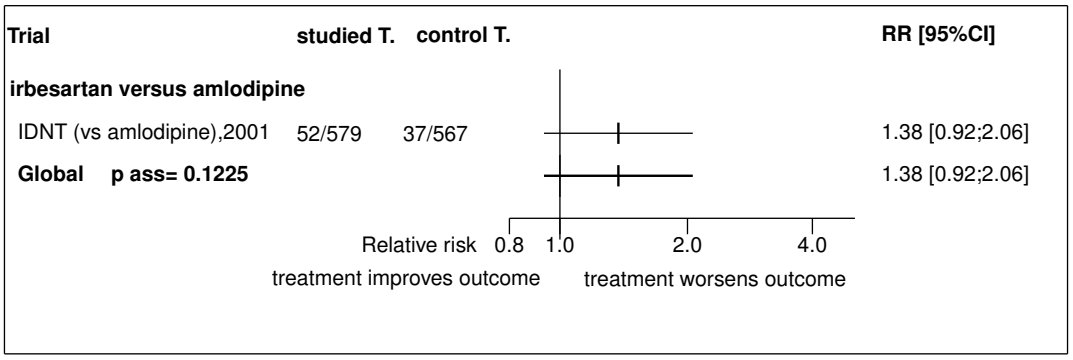


Figure 5.3: *Forest's plot for myocardial infarction (fatal and non fatal)*

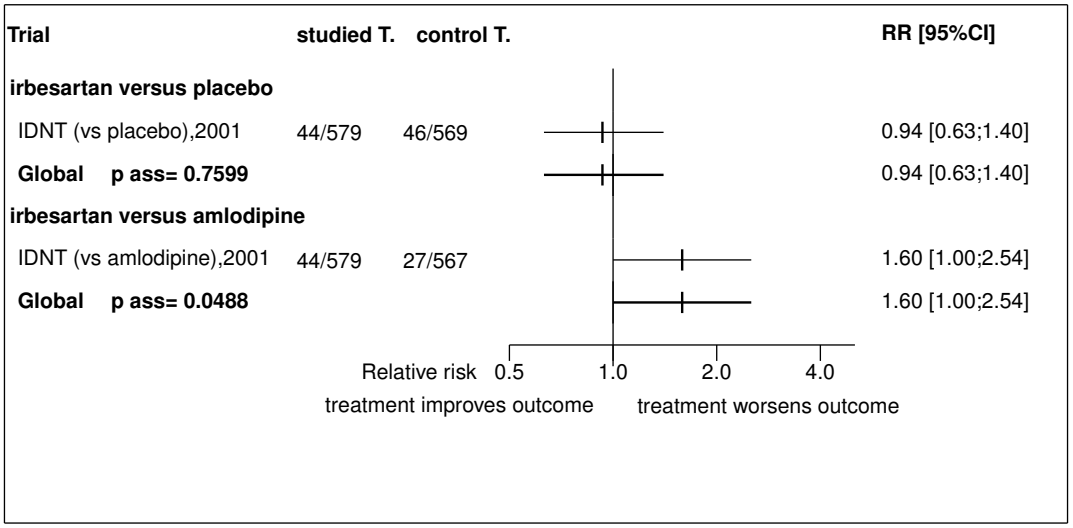


Figure 5.4: *Forest's plot for stroke (fatal and non fatal)*

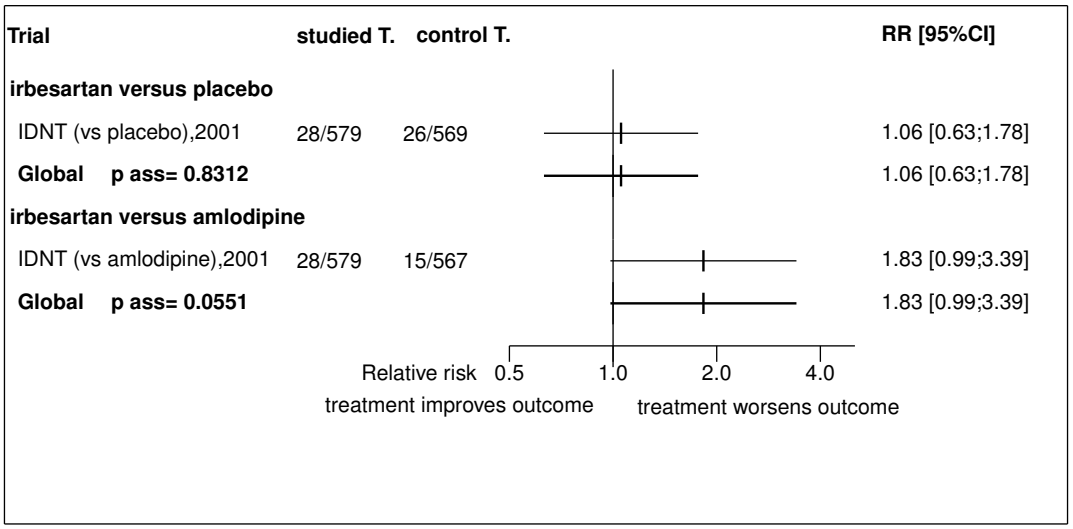


Figure 5.5: *Forest's plot for coronary event*

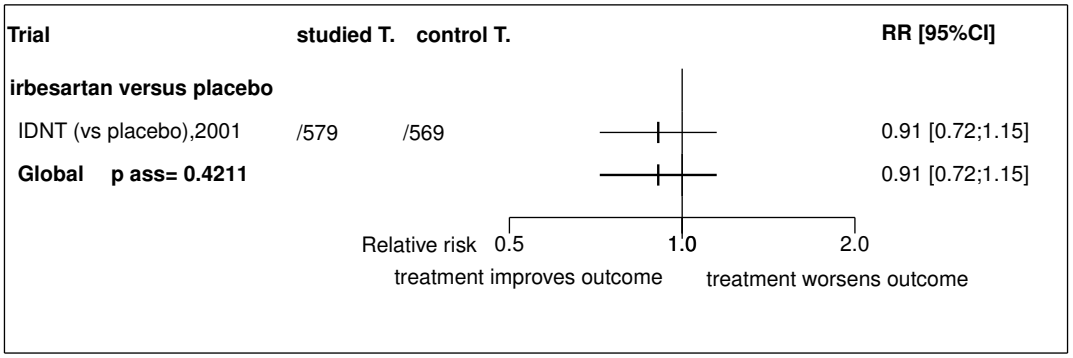


Figure 5.6: *Forest's plot for heart failure*

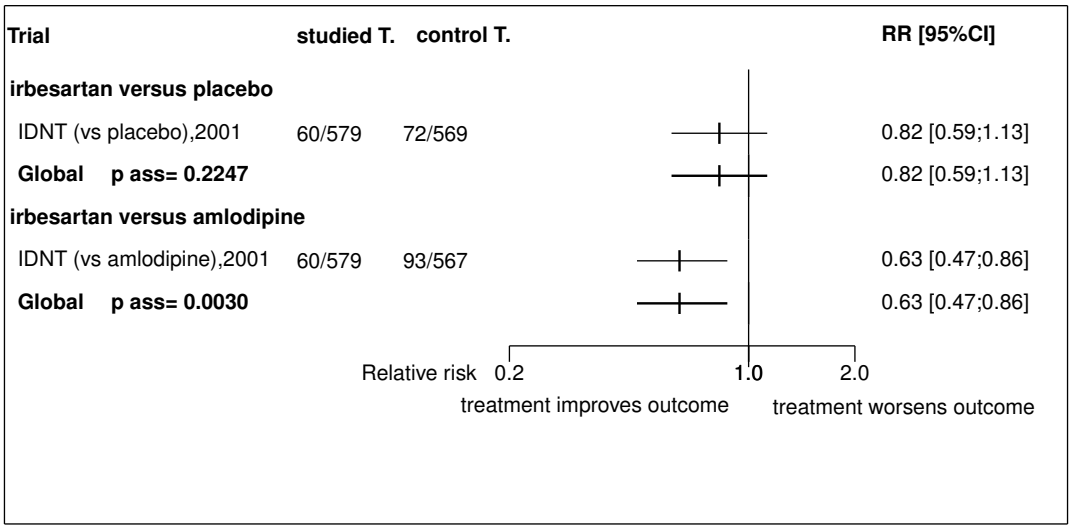
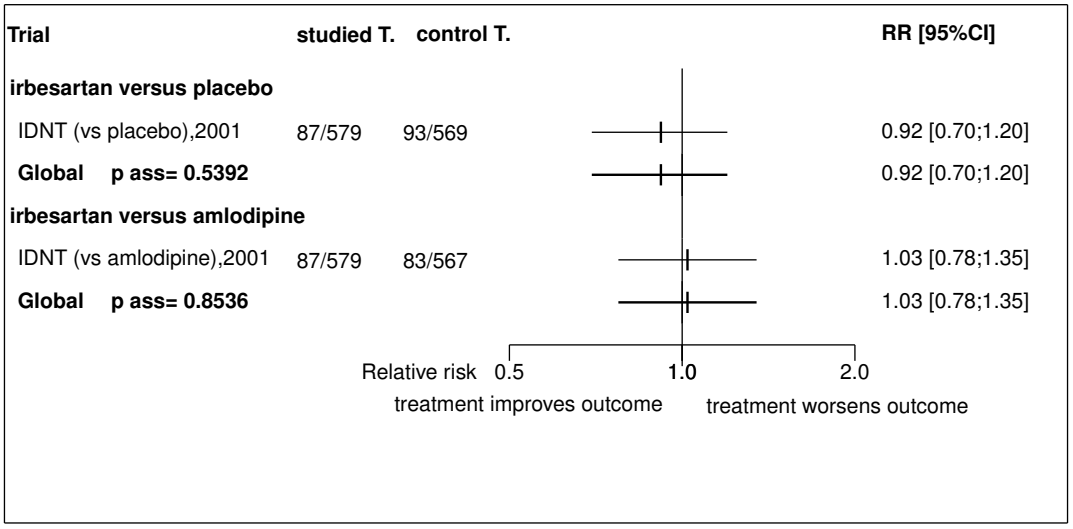


Figure 5.7: *Forest's plot for all cause death*



References

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

[2] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2

diabetes. N Engl J Med 2001;345:851-60. [PMID=11565517]

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

5.3 Individual trial summaries

Table 5.6: *IDNT (vs placebo), 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1148 (579 vs. 569) **Follow-up duration:** 2.6 y **Study design:** Randomized controlled trial Parallel groups Double-blind Confirmatory trial at low risk of bias worldwide, 210 centres **Inclusion period:** mar 1996 - feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes	**Studied treatment:** Irbesartan 300mg/d (target 135/85) target blood pressure: 135/85 mm Hg or less **Control treatment:** placebo	Myocardial infarction (fatal and non fatal) RR=0.94 [0.63;1.40] Stroke (fatal and non fatal) RR=1.06 [0.63;1.78]

References

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

Table 5.7: *IDNT (vs amlodipine), 2001 - Trial synopsis*

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

Reference

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

6 Detailed results for telmisartan

6.1 Available trials

Only one trial which randomized 250 patients was identified: it compared telmisartan with enalapril.
This trial included 250 patients and was published in 2004.
This trial was double blind in design.
It was reported in English language.
Heart failure data was reported in 1 trials; 1 trials reported data on stroke (fatal and non fatal); 1 trials reported data on all cause death; 1 trials reported data on myocardial infarction (fatal and non fatal); and 1 trials reported data on cardiovascular death.
Following tables 6.1 (page 55), 6.2 (page 55), 6.4 (page 57), and 6.3 (page 55) summarized the main characteristics of the trial including in this systematic review of randomized trials of telmisartan.

Table 6.1: *Treatment description - angiotensin receptor blocker - telmisartan*

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

Table 6.2: *Descriptions of participants - angiotensin receptor blocker - telmisartan*

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

Table 6.3: *Design and methodological quality of trials - angiotensin receptor blocker - telmisartan*

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

continued...

Trial	Design	Duration	Centre	Primary endpoint

Table 6.4: *Trial characteristics - angiotensin receptor blocker - telmisartan*

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

6.2 Meta-analysis results

The results are detailed in table 6.5 (page 58). This table is followed by the Forest's plot corresponding to each endpoint.

Telmisartan versus enalapril

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 1.63 (95% CI 0.28 to 9.56, p=0.5912).
The single study eligible for this comparison provided data on **myocardial infarction (fatal and non fatal)**. No statistically significant difference between the groups was found in myocardial infarction (fatal and non fatal), with a RR of 1.63 (95% CI 0.60 to 4.43, p=0.3426).
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 1.08 (95% CI 0.36 to 3.27, p=0.8870).
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 0.54 to 3.62, p=0.4969).
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 1.08 (95% CI 0.36 to 3.27, p=0.8870).

Table 6.5: *Results details - angiotensin receptor blocker - telmisartan*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
telmisartan versus enalapril						
cardiovascular death	RR=1.63	[0.28;9.56]	0.5912	1.0000 (I^2=0.00)	1	250
myocardial infarction (fatal and non fatal)	RR=1.63	[0.60;4.43]	0.3426	1.0000 (I^2=0.00)	1	250
stroke (fatal and non fatal)	RR=1.08	[0.36;3.27]	0.8870	1.0000 (I^2=0.00)	1	250
heart failure	RR=1.39	[0.54;3.62]	0.4969	1.0000 (I^2=0.00)	1	250
all cause death	RR=1.08	[0.36;3.27]	0.8870	1.0000 (I^2=0.00)	1	250

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 6.1: *Forest's plot for cardiovascular death*

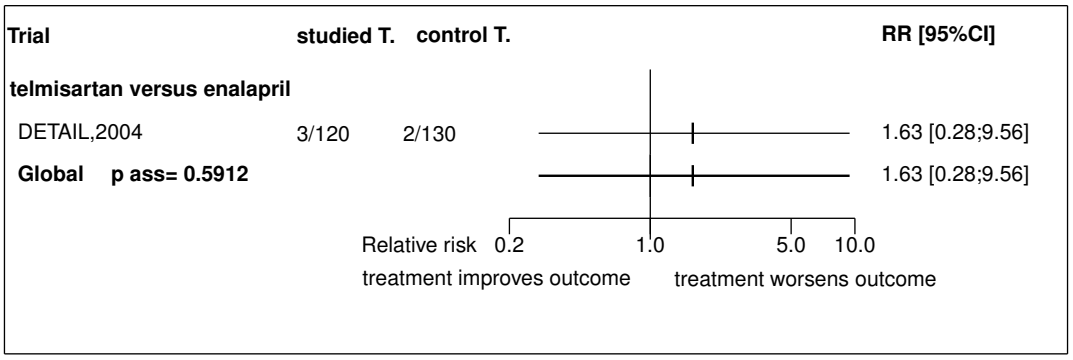


Figure 6.2: *Forest's plot for myocardial infarction (fatal and non fatal)*

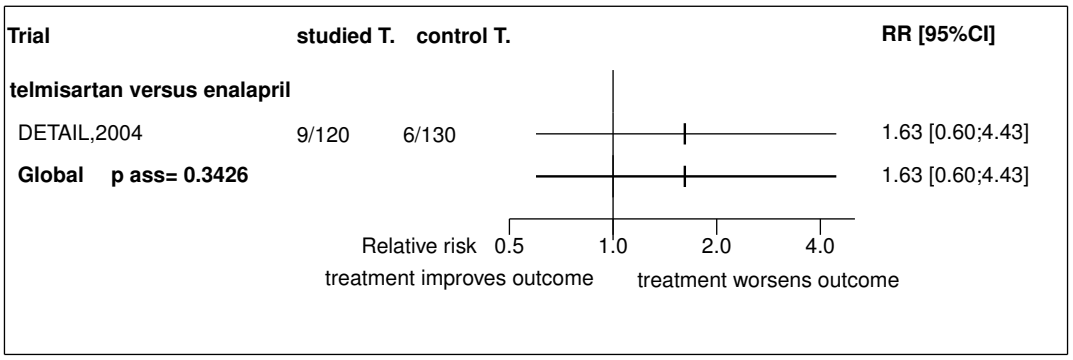


Figure 6.3: *Forest's plot for stroke (fatal and non fatal)*

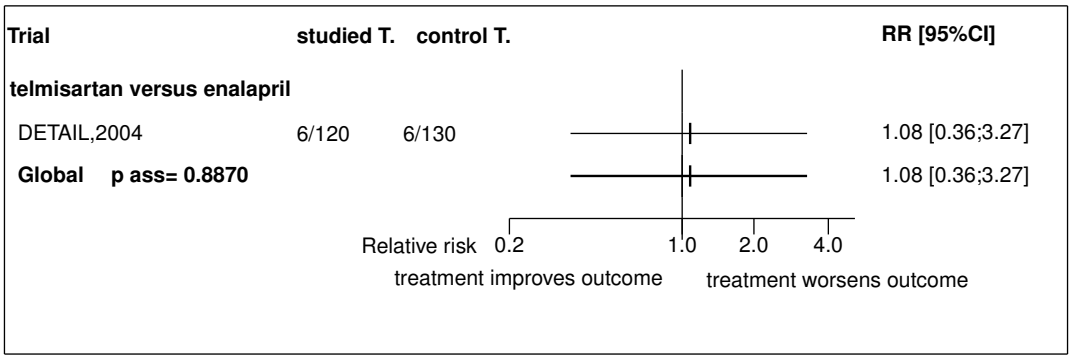


Figure 6.4: *Forest's plot for heart failure*

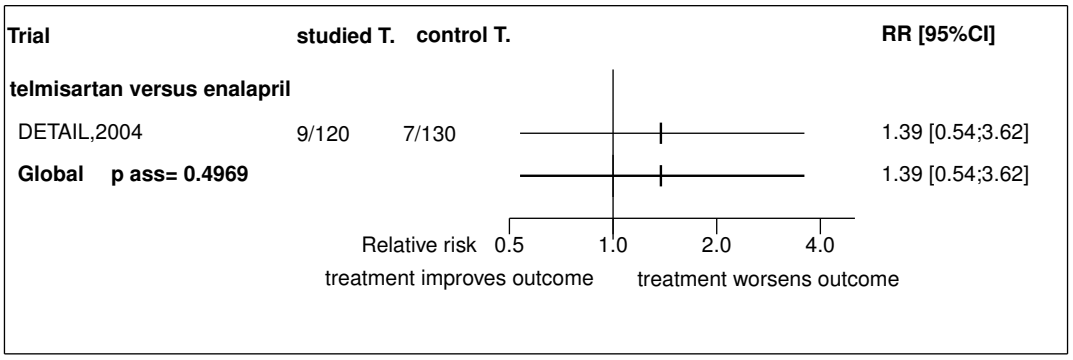
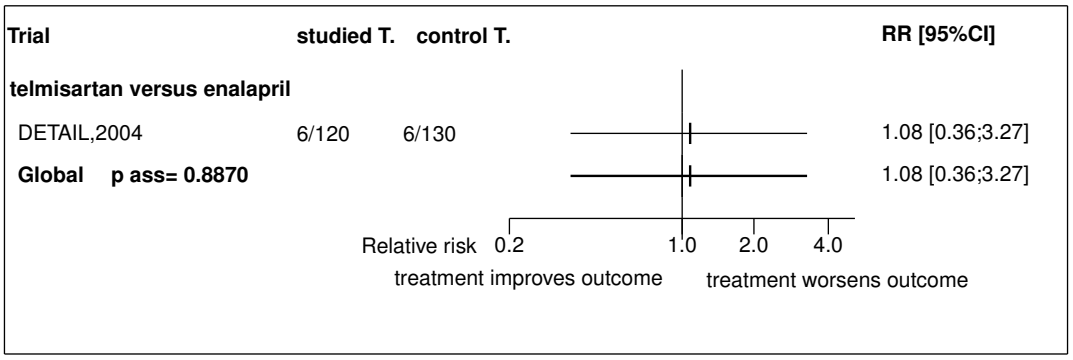


Figure 6.5: *Forest's plot for all cause death*



References

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

6.3 Individual trial summaries

Table 6.6: *DETAIL, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=250 (120 vs. 130) **Follow-up duration:** 5 year **Study design:** Randomized controlled trial Parallel groups Double-blind Exploratory trial	Subjects with type 2 diabetes and early nephropathy	**Studied treatment:** telmisartan 80 mg daily **Control treatment:** enalapril 20 mg daily	Cardiovascular death RR=1.63 [0.28;9.56] Myocardial infarction (fatal and non fatal) RR=1.63 [0.60;4.43] Stroke (fatal and non fatal) RR=1.08 [0.36;3.27]

Reference

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

7 Global meta-analysis: all angiotensin receptor blocker

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

Table 7.1: *All angiotensin receptor blockerversus amlodipine*

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

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

7.2 Global meta-analysis: all angiotensin receptor blocker versus control

Table 7.2: *All angiotensin receptor blockerversus control*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular death	RR=0.60	0.30;1.19	0.1443	1.0000 (0.00)	1	366
myocardial infarction (fatal and non fatal)	RR=0.80	0.22;2.93	0.7363	1.0000 (0.00)	1	366
stroke (fatal and non fatal)	RR=0.75	0.27;2.12	0.5872	1.0000 (0.00)	1	366
heart failure	RR=0.45	0.27;0.76	0.0025	0.7163 (0.00)	2	446
all cause death	RR=0.31	0.04;2.69	0.2878	0.1058 (0.62)	2	446

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

7.3 Global meta-analysis: all angiotensin receptor blocker versus conventional treatment

Table 7.3: *All angiotensin receptor blockerversus conventional treatment*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular death	RR=1.04	0.27;4.01	0.9506	1.0000 (0.00)	1	141
myocardial infarction (fatal and non fatal)	RR=2.09	0.39;11.03	0.3865	1.0000 (0.00)	1	141
stroke (fatal and non fatal)	RR=0.89	0.51;1.55	0.6723	1.0000 (0.00)	1	141
heart failure	RR=0.68	0.34;1.34	0.2595	1.0000 (0.00)	1	141
all cause death	RR=1.04	0.27;4.01	0.9506	1.0000 (0.00)	1	141

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

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

Table 7.4: *All angiotensin receptor blockerversus enalapril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular death	RR=1.63	0.28;9.56	0.5912	1.0000 (0.00)	1	250
myocardial infarction (fatal and non fatal)	RR=1.63	0.60;4.43	0.3426	1.0000 (0.00)	1	250
stroke (fatal and non fatal)	RR=1.08	0.36;3.27	0.8870	1.0000 (0.00)	1	250
heart failure	RR=1.39	0.54;3.62	0.4969	1.0000 (0.00)	1	250
all cause death	RR=1.08	0.36;3.27	0.8870	1.0000 (0.00)	1	250

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

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

Table 7.5: *All angiotensin receptor blockerversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
myocardial infarction (fatal and non fatal)	RR=0.94	0.63;1.40	0.7599	1.0000 (0.00)	1	1148
stroke (fatal and non fatal)	RR=1.06	0.63;1.78	0.8312	1.0000 (0.00)	1	1148
coronary event	RR=0.91	0.72;1.15	0.4211	1.0000 (0.00)	1	1148
heart failure	RR=0.82	0.59;1.13	0.2247	1.0000 (1.00)	1	1148

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n
all cause death	RR=0.92	0.70;1.20	0.5392	1.0000 (0.00)	1	1148

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

8 Ongoing studies of angiotensin receptor blocker

No ongoing trial was identified.

9 Excluded studies for angiotensin receptor blocker

No trial was excluded.

References

Part II

Angiotensin-converting enzyme inhibitors

10 Overview of angiotensin-converting enzyme inhibitors

10.1 Included trials

A total of 2 randomized comparisons which enrolled 1530 patients were identified. In all, 2 randomized comparisons concerned ramipril.
The detailed descriptions of trials and meta-analysis results is given in section 11 (page 73) for ramipril.

The average study size was 765 patients (range 653 to 877). The first study was published in 2002, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 10.1 (page 70) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

10.2 Summary of meta-analysis results

The meta-analysis of the available trials about angiotensin-converting enzyme inhibitors provide the results listed in tables 10.2 to 10.2 (page 71) and in the following graphs.

10.2.1 Ramipril

No significant difference was found between **ramipril** and **amlodipine** in terms of cardiovascular events (RR=1.37, 95% CI 0.44 to 4.25, p=0.5871, 1 trial), cardiovascular death (RR=0.50, 95% CI 0.07 to 3.51, p=0.4838, 1 trial)and all cause death (RR=1.11, 95% CI 0.59 to 2.09, p=0.7463, 1 trial).

No significant difference was found between **ramipril** and **metoprolol** in terms of all cause death (RR=0.77, 95% CI 0.48 to 1.23, p=0.2750, 1 trial).

Table 10.1: *Main study characteristics - angiotensin-converting enzyme inhibitors*

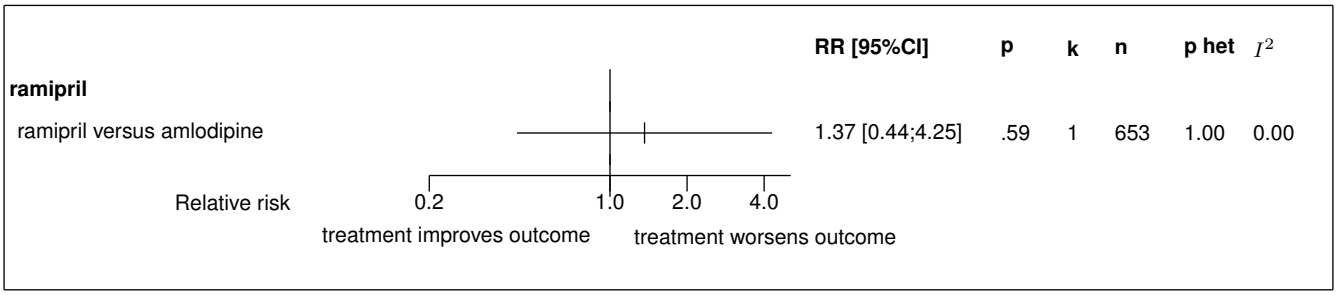
Trial	Patients	Treatments	Trial design and method
Ramipril			
Ramipril versus amlodipine			
AASK (vs amlodipine), 2002 [1] n = 436 vs. 217	african Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))	ramipril 2.5-10 mg/d **versus** amlodipine 5-10 mg/d	double blind parallel groups Primary endpoint: rate of change in GFR 21 centres, US
Ramipril versus metoprolol			
AASK (vs metoprolol), 2002 [2, 3] n = 436 vs. 441	african Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))	ramipril 2.5-10 mg/d **versus** metoprolol 50-200 mg/d	double blind parallel groups Primary endpoint: glomerular filtration rate (GFR) decline 21 centres, US

Table 10.2: *Summary of all results for ramipril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
ramipril versus amlodipine						
cardiovascular events	RR=1.37	0.44;4.25	0.5871	1.0000 (0.00)	1	653
cardiovascular death	RR=0.50	0.07;3.51	0.4838	1.0000 (0.00)	1	653
all cause death	RR=1.11	0.59;2.09	0.7463	1.0000 (0.00)	1	653
ramipril versus metoprolol						
all cause death	RR=0.77	0.48;1.23	0.2750	1.0000 (0.00)	1	877

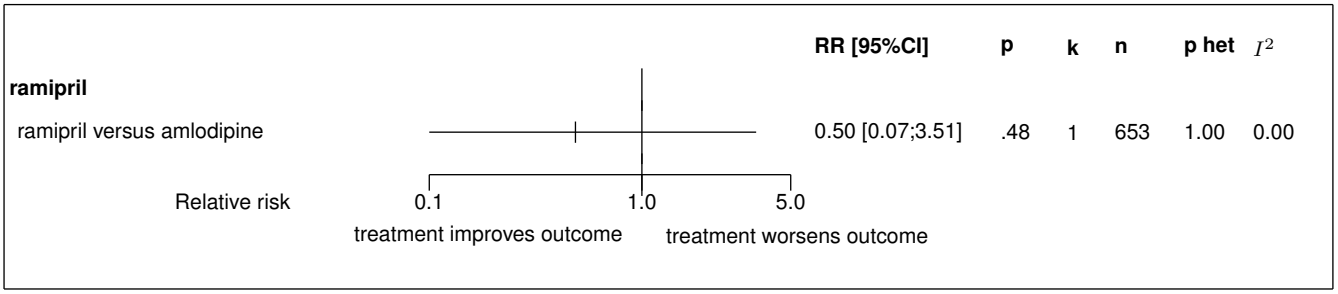
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

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



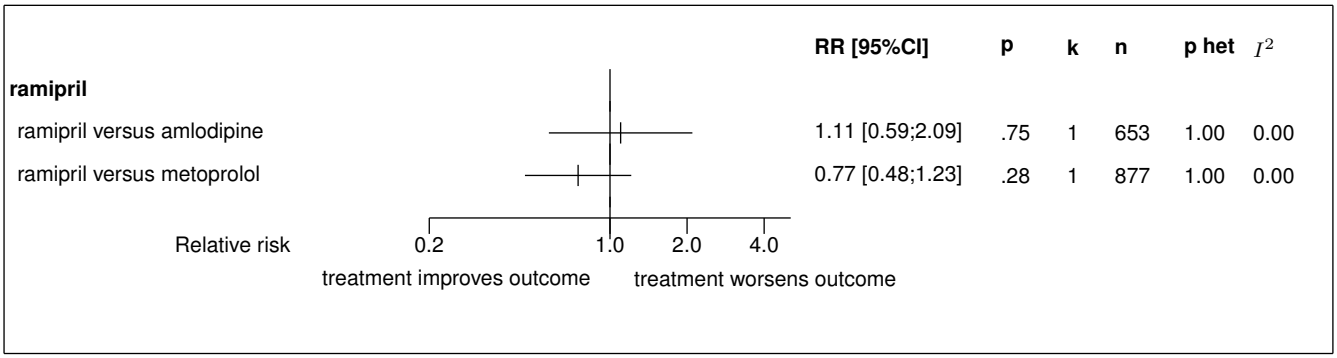
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

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



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

Figure 10.3: *Forest's plot for all cause death*



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

11 Details

11.1 Available trials

A total of 2 RCTs which randomized 1530 patients were identified: it compared ramipril with amlodipine and it compared ramipril with metoprolol.
The average study size was 765 patients (range 653 to 877). The first study was published in 2002, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
All cause death data was reported in 2 trials; 1 trials reported data on cardiovascular death; and 1 trials reported data on cardiovascular events.
Following tables 11.1 (page 73), 11.2 (page 73), 11.4 (page 75), and 11.3 (page 74) summarized the main characteristics of the trials including in this systematic review of randomized trials of ramipril.

Table 11.1: *Treatment description - angiotensin-converting enzyme inhibitors - ramipril*

Trial	Studied treatment	Control treatment
Ramipril versus amlodipine		
AASK (vs amlodipine) (2002) [1]	ramipril 2.5-10 mg/d	amlodipine 5-10 mg/d
Ramipril versus metoprolol		
AASK (vs metoprolol) (2002) [2, 3]	ramipril 2.5-10 mg/d	metoprolol 50-200 mg/d

Table 11.2: *Descriptions of participants - angiotensin-converting enzyme inhibitors - ramipril*

Trial	Patients
Ramipril versus amlodipine	
AASK (vs amlodipine) (2002) [1]	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))
Ramipril versus metoprolol	
AASK (vs metoprolol) (2002) [2, 3]	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))

Table 11.3: *Design and methodological quality of trials - angiotensin-converting enzyme inhibitors - ramipril*

Trial	Design	Duration	Centre	Primary endpoint
Ramipril versus amlodipine				
AASK (vs amlodipine), 2002 [1] n=653	Parallel groups Double blind	30 y	US 21 centres	Rate of change in GFR
Ramipril versus metoprolol				
AASK (vs metoprolol), 2002 [2, 3] n=877	Parallel groups Double blind	41 y	US 21 centres	glomerular filtration rate (GFR) decline

Table 11.4: *Trial characteristics - angiotensin-converting enzyme inhibitors - ramipril*

Trial
Ramipril versus amlodipine
AASK (vs amlodipine), 2002 [1]
Ramipril versus metoprolol
AASK (vs metoprolol), 2002 [2, 3]

11.2 Meta-analysis results

The results are detailed in table 11.5 (page 76). This table is followed by the Forest's plot corresponding to each endpoint.

Ramipril versus amlodipine

The single study eligible for this comparison provided data on **cardiovascular events**. There was no statistically significant difference in cardiovascular events between ramipril and amlodipine, with a RR of 1.37 (95%CI 0.44 to 4.25, p=0.5871) in favour of amlodipine. In other words, cardiovascular events was slightly lower in the amlodipine 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 0.50 (95% CI 0.07 to 3.51, p=0.4838).
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 1.11 (95% CI 0.59 to 2.09, p=0.7463).

Ramipril versus metoprolol

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 0.77 (95% CI 0.48 to 1.23, p=0.2750).

Table 11.5: *Results details - angiotensin-converting enzyme inhibitors - ramipril*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
ramipril versus amlodipine						
cardiovascular events	RR=1.37	[0.44;4.25]	0.5871	1.0000 (I^2=0.00)	1	653
cardiovascular death	RR=0.50	[0.07;3.51]	0.4838	1.0000 (I^2=0.00)	1	653
all cause death	RR=1.11	[0.59;2.09]	0.7463	1.0000 (I^2=0.00)	1	653
ramipril versus metoprolol						
all cause death	RR=0.77	[0.48;1.23]	0.2750	1.0000 (I^2=0.00)	1	877

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

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

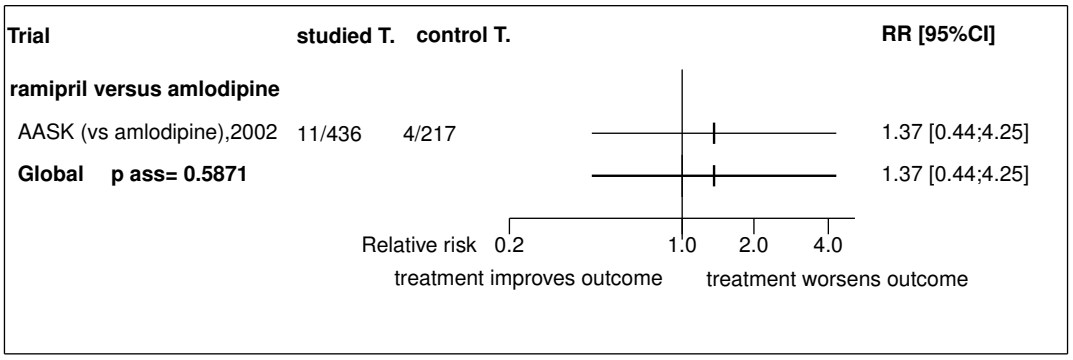


Figure 11.2: *Forest's plot for cardiovascular death*

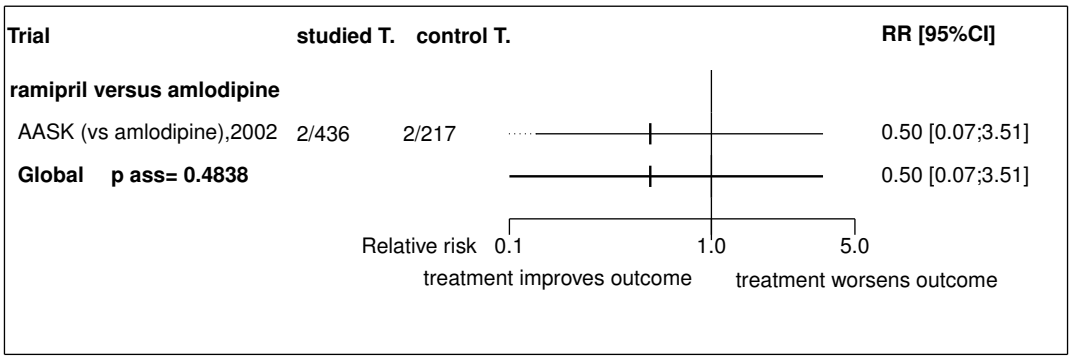
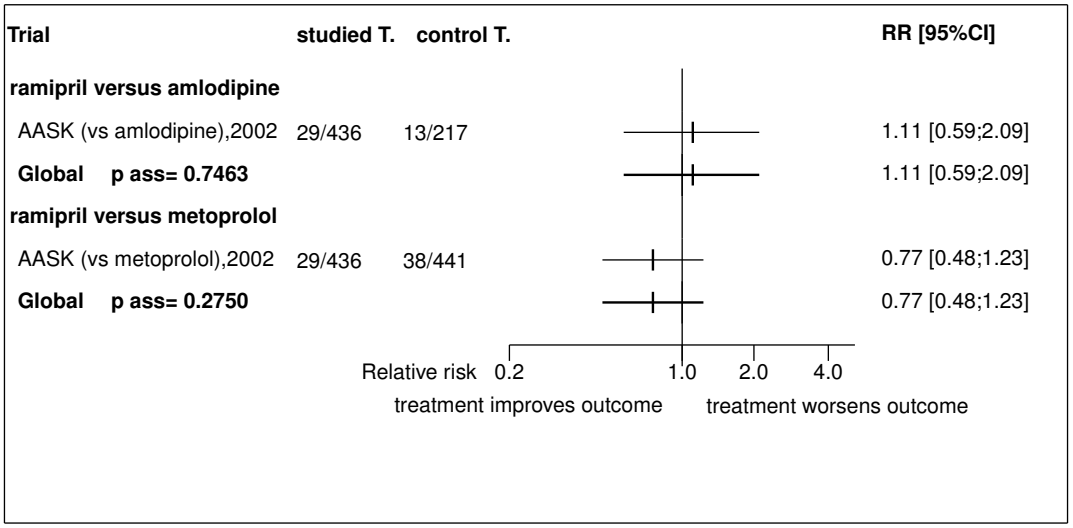


Figure 11.3: *Forest's plot for all cause death*



References

[1] Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31. [PMID=12435255]

[2] Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31. [PMID=12435255]

[3] Norris K, Bourgoigne J, Gassman J, Hebert L, Middleton J, Phillips RA, Randall O, Rostand S, Sherer S, Toto RD, Wright JT Jr, Wang X, Greene T, Appel LJ, Lewis J. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. Am J Kidney Dis 2006;48:739-51. [PMID=17059993]

11.3 Individual trial summaries

Table 11.6: *AASK (vs amlodipine), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=653 (436 vs. 217) **Follow-up duration:** 30 y **Study design:** Randomized controlled trial Parallel groups Double blind US, 21 centres	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))	**Studied treatment:** ramipril 2.5-10 mg/d **Control treatment:** amlodipine 5-10 mg/d	Cardiovascular events RR=1.37 [0.44;4.25] Cardiovascular death RR=0.50 [0.07;3.51]

Reference

Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31 [PMID=12435255]

Table 11.7: *AASK (vs metoprolol), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=877 (436 vs. 441) **Follow-up duration:** 41 y **Study design:** Randomized controlled trial Parallel groups Double blind US, 21 centres	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73 m(2))	**Studied treatment:** ramipril 2.5-10 mg/d **Control treatment:** metoprolol 50-200 mg/d	

References

Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31 [PMID=12435255]
Norris K, Bourgoigne J, Gassman J, Hebert L, Middleton J, Phillips RA, Randall O, Rostand S, Sherer S, Toto RD, Wright JT Jr, Wang X, Greene T, Appel LJ, Lewis J. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. Am J Kidney Dis 2006;48:739-51 [PMID=17059993]

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

12.1 Global meta-analysis: all angiotensin-converting enzyme inhibitors versus amlodipine

Table 12.1: *All angiotensin-converting enzyme inhibitorsversus amlodipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
cardiovascular events	RR=1.37	0.44;4.25	0.5871	1.0000 (0.00)	1	653
cardiovascular death	RR=0.50	0.07;3.51	0.4838	1.0000 (0.00)	1	653
all cause death	RR=1.11	0.59;2.09	0.7463	1.0000 (0.00)	1	653

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

12.2 Global meta-analysis: all angiotensin-converting enzyme inhibitors versus metoprolol

Table 12.2: *All angiotensin-converting enzyme inhibitorsversus metoprolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death	RR=0.77	0.48;1.23	0.2750	1.0000 (0.00)	1	877

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

13 Ongoing studies of angiotensin-converting enzyme inhibitors

No ongoing trial was identified.

14 Excluded studies for angiotensin-converting enzyme inhibitors

No trial was excluded.

References

Part III

Calcium-channel blockers

15 Overview of calcium-channel blockers

15.1 Included trials

A total of 3 randomized comparisons which enrolled 2447 patients were identified. In all, 3 randomized comparisons concerned amlodipine.
The detailed descriptions of trials and meta-analysis results is given in section 16 (page 90) for amlodipine.

The average study size was 815 patients (range 653 to 1136). The first study was published in 2001, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 15.1 (page 88) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

15.2 Summary of meta-analysis results

The meta-analysis of the available trials about calcium-channel blockers provide the results listed in tables 15.2 to 15.2 (page 89) and in the following graphs.

15.2.1 Amlodipine

No significant difference was found between **amlodipine** and **placebo** in terms of all cause death (RR=0.90, 95% CI 0.68 to 1.18, p=0.4272, 1 trial).

No significant difference was found between **amlodipine** and **metoprolol** in terms of all cause death (RR=0.70, 95% CI 0.38 to 1.28, p=0.2416, 1 trial).

No significant difference was found between **amlodipine** and **ramipril** in terms of all cause death (RR=0.90, 95% CI 0.48 to 1.70, p=0.7463, 1 trial).

Table 15.1: *Main study characteristics - calcium-channel blockers*

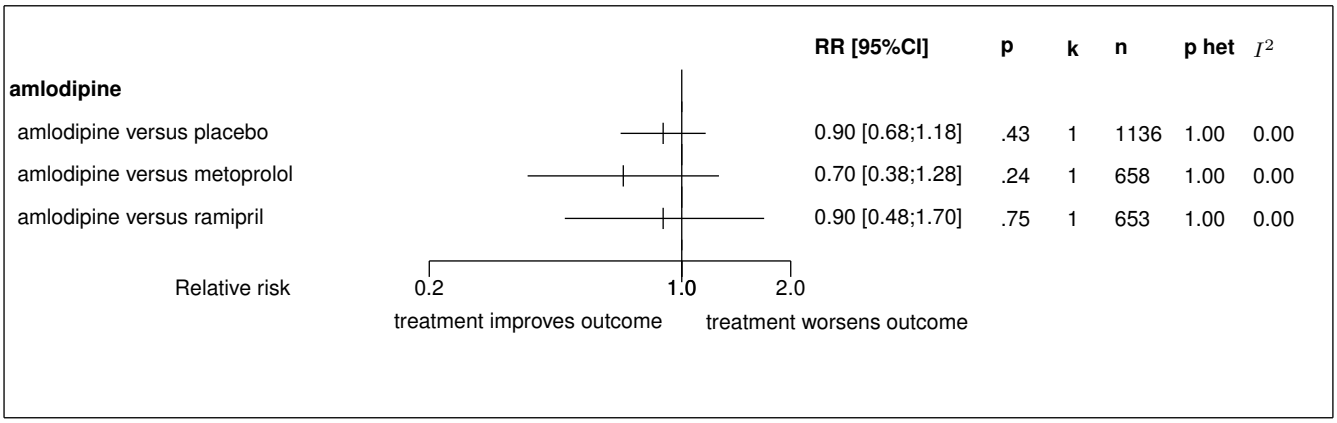
Trial	Patients	Treatments	Trial design and method
Amlodipine			
Amlodipine versus placebo			
IDNT, 2001 [1] n = 567 vs. 569	hypertensive patients with nephropathy due to type 2 diabetes	amlodipine 10mg/d **versus** placebo	double blind parallel groups 210 centres,
Amlodipine versus metoprolol			
AASK (vs metoprolol), 2002 [2] n = 217 vs. 441	african Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2)	amlodipine 5-10 mg/d **versus** metoprolol 50-200 mg/d	Primary endpoint: rate of change in GFR (GFR slope) 21 centres, US
Amlodipine versus ramipril			
AASK (vs ramipril), 2002 [3] n = 217 vs. 436	african Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2)	amlodipine 5-10 mg/d **versus** ramipril 2.5-10 mg/d	double blind factorial plan Primary endpoint: rate of change in GFR (GFR slope) 21 centres, US

Table 15.2: *Summary of all results for amlodipine*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
amlodipine versus placebo						
all cause death	RR=0.90	0.68;1.18	0.4272	1.0000 (0.00)	1	1136
amlodipine versus metoprolol						
all cause death	RR=0.70	0.38;1.28	0.2416	1.0000 (0.00)	1	658
amlodipine versus ramipril						
all cause death	RR=0.90	0.48;1.70	0.7463	1.0000 (0.00)	1	653

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 15.1: *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

16 Details

16.1 Available trials

A total of 3 RCTs which randomized 2447 patients were identified: it compared amlodipine with placebo , it compared amlodipine with metoprolol and it compared amlodipine with ramipril.
The average study size was 815 patients (range 653 to 1136). The first study was published in 2001, and the last study was published in 2002.
All trials were double blind in design. All included studies were reported in English language.
We did not found any unpublished trial.
All cause death data was reported in 3 trials;
Following tables 16.1 (page 90), 16.2 (page 90), 16.4 (page 93), and 16.3 (page 91) summarized the main characteristics of the trials including in this systematic review of randomized trials of amlodipine.

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

Trial	Studied treatment	Control treatment
Amlodipine versus placebo		
IDNT (2001) [1]	Amlodipine 10mg/d	placebo
Amlodipine versus metoprolol		
AASK (vs metoprolol) (2002) [2] [a]	Amlodipine 5-10 mg/d	metoprolol 50-200 mg/d
Amlodipine versus ramipril		
AASK (vs ramipril) (2002) [3] [a]	Amlodipine 5-10 mg/d	ramipril 2.5-10 mg/d

a) compare the effects of 2 levels of blood pressure (BP) control and 3 antihypertensive drug classe a) compare the effects of 2 levels of blood pressure (BP) control and 3 antihypertensive drug classe

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

Trial	Patients
Amlodipine versus placebo	

continued...

Trial	Patients	
IDNT (2001) [1]	Hypertensive patients with nephropathy due to type 2 diabetes	
	Inclusion criteria: age between 30 and 70 years;type 2 diabetes mellitus; hypertension(systolic blood pressure of more than 135 mm Hg whilesitting, a diastolic blood pressure of more than 85 mm Hg while sitting,or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per24 hours; serum creatinine between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter)in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol perliter) in men.	**Exclusion criteria:**
Amlodipine versus metoprolol		
AASK (vs metoprolol) (2002) [2]	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2)	
	Inclusion criteria: african Americans; hypertension; aged 18to 70 years; glomerular filtrationrate (GFR) between 20 and 65 mL/minper 1.73 m2; no other identifiedcauses of renal insufficiency	**Exclusion criteria:**
Amlodipine versus ramipril		
AASK (vs ramipril) (2002) [3]	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2)	
	Inclusion criteria: african Americans; hypertension; aged 18to 70 years; glomerular filtrationrate (GFR) between 20 and 65 mL/minper 1.73 m2; no other identifiedcauses of renal insufficiency	**Exclusion criteria:**

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

Trial	Design	Duration	Centre	Primary endpoint
Amlodipine versus placebo				
IDNT, 2001 [1] n=1136	Parallel groups Double blind	26 inclusion period: mar 1996 - feb 1999	210 centres	
Amlodipine versus metoprolol				
AASK (vs metoprolol), 2002 [2] n=658		30y inclusion period: Feb 1995 - sep 1998	US 21 centres	rate of change in GFR (GFR slope)
Amlodipine versus ramipril				

continued...

Trial	Design	Duration	Centre	Primary end-point
AASK (vs ramipril), 2002 [3] n=653	Factorial plan Double blind	30 inclusion period: Feb 1995 - sep 1998	US 21 centres	rate of change in GFR (GFR slope)

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

Trial
Amlodipine versus placebo
IDNT, 2001 [1]
Amlodipine versus metoprolol
AASK (vs metoprolol), 2002 [2]
Amlodipine versus ramipril
AASK (vs ramipril), 2002 [3]

16.2 Meta-analysis results

The results are detailed in table 16.5 (page 94). This table is followed by the Forest's plot corresponding to each endpoint.

Amlodipine versus placebo

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 0.90 (95% CI 0.68 to 1.18, p=0.4272).

Amlodipine versus metoprolol

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 0.70 (95% CI 0.38 to 1.28, p=0.2416).

Amlodipine versus ramipril

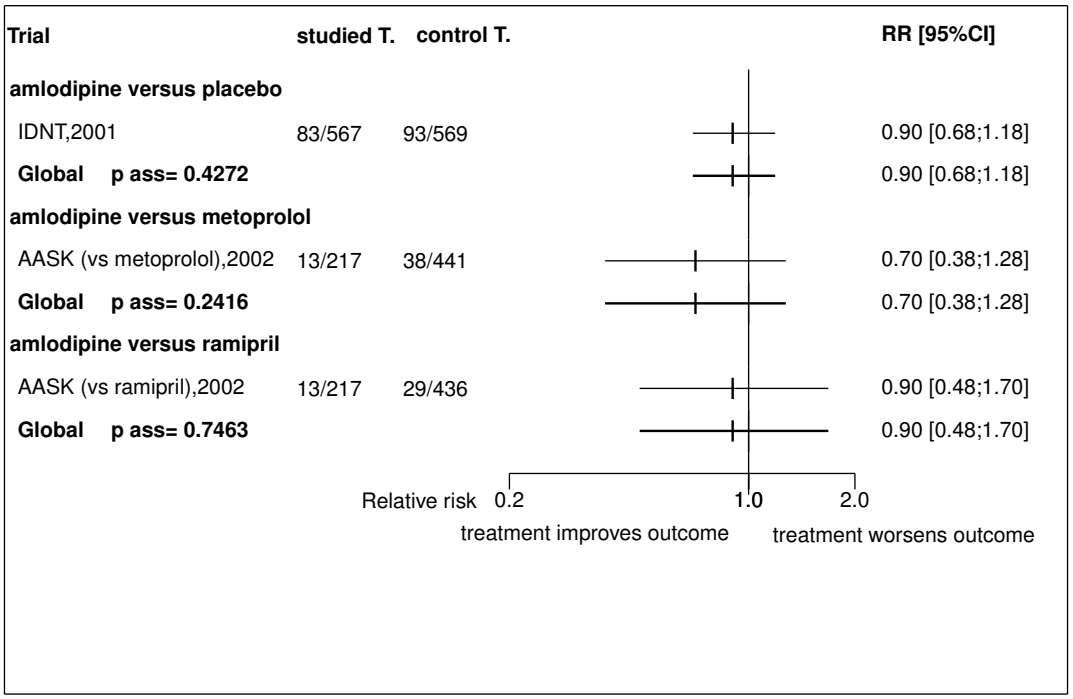
The single study eligible for this comparison provided data on **all cause death**. No statistically significant difference between the groups was found in all cause death, with a RR of 0.90 (95% CI 0.48 to 1.70, p=0.7463).

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

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
amlodipine versus placebo						
all cause death	RR=0.90	[0.68;1.18]	0.4272	1.0000 (I^2=0.00)	1	1136
amlodipine versus metoprolol						
all cause death	RR=0.70	[0.38;1.28]	0.2416	1.0000 (I^2=0.00)	1	658
amlodipine versus ramipril						
all cause death	RR=0.90	[0.48;1.70]	0.7463	1.0000 (I^2=0.00)	1	653

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

Figure 16.1: *Forest's plot for all cause death*



References

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

[2] Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31. [PMID=12435255]

[3] Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31. [PMID=12435255]

16.3 Individual trial summaries

Table 16.6: *IDNT, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1136 (567 vs. 569) **Follow-up duration:** 26 **Study design:** Randomized controlled trial Parallel groups Double blind 210 centres **Inclusion period:** mar 1996 - feb 1999	Hypertensive patients with nephropathy due to type 2 diabetes **Inclusion criteria:** age between 30 and 70 years;type 2 diabetes mellitus; hypertension(systolic blood pressure of more than 135 mm Hg whilesitting, a diastolic blood pressure of more than 85 mm Hg while sitting,or documented treatment with antihypertensive agents); proteinuria, with urinary protein excretion of at least 900 mg per24 hours; serum creatinine between 1.0 and 3.0 mg per deciliter (88 and 265 mol per liter)in women and 1.2 and 3.0 mg per deciliter (106 and 265 mol perliter) in men.	**Studied treatment:** Amlodipine 10mg/d **Control treatment:** placebo	

Reference

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

Table 16.7: *AASK (vs metoprolol), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=658 (217 vs. 441) **Follow-up duration:** 30y **Study design:** Randomized controlled trial US, 21 centres **Inclusion period:** Feb 1995 - sep 1998	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2) **Inclusion criteria:** African Americans; hypertension; aged 18to 70 years; glomerular filtrationrate (GFR) between 20 and 65 mL/minper 1.73 m2; no other identifiedcauses of renal insufficiency	**Studied treatment:** Amlodipine 5-10 mg/d **Control treatment:** metoprolol 50-200 mg/d **note:** compare the effects of 2 levels of blood pressure (BP) control and 3 antihypertensive drug classe	

Reference

Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31 [PMID=12435255]

Table 16.8: *AASK (vs ramipril), 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=653 (217 vs. 436) **Follow-up duration:** 30 **Study design:** Randomized controlled trial Factorial plan Double blind US, 21 centres **Inclusion period:** Feb 1995 - sep 1998	African Americans aged 18 to 70 years with hypertensive renal disease (GFR, 20-65 mL/min per 1.73m2) **Inclusion criteria:** African Americans; hypertension; aged 18to 70 years; glomerular filtrationrate (GFR) between 20 and 65 mL/minper 1.73 m2; no other identifiedcauses of renal insufficiency	**Studied treatment:** Amlodipine 5-10 mg/d **Control treatment:** ramipril 2.5-10 mg/d **note:** compare the effects of 2 levels of blood pressure (BP) control and 3 antihypertensive drug classe	

Reference

Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31 [PMID=12435255]

17 Global meta-analysis: all calcium-channel blockers

17.1 Global meta-analysis: all calcium-channel blockers versus metoprolol

Table 17.1: *All calcium-channel blockersversus metoprolol*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death	RR=0.70	0.38;1.28	0.2416	1.0000 (0.00)	1	658

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

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

Table 17.2: *All calcium-channel blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death	RR=0.90	0.68;1.18	0.4272	1.0000 (0.00)	1	1136

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

17.3 Global meta-analysis: all calcium-channel blockers versus ramipril

Table 17.3: *All calcium-channel blockersversus ramipril*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death	RR=0.90	0.48;1.70	0.7463	1.0000 (0.00)	1	653

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

18 Ongoing studies of calcium-channel blockers

No ongoing trial was identified.

19 Excluded studies for calcium-channel blockers

No trial was excluded.

References

Part IV

Direct renin inhibitor

20 Overview of direct renin inhibitor

20.1 Included trials

Only one trial which randomized 599 patients was identified. In all, 1 randomized comparison concerned aliskiren.
The detailed descriptions of trials and meta-analysis results is given in section 21 (page 109) for aliskiren.

This trial included 599 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
The table 20.1 (page 106) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

20.2 Summary of meta-analysis results

The meta-analysis of the available trials about direct renin inhibitor provide the results listed in tables 20.2 to 20.2 (page 107) and in the following graphs.

20.2.1 Aliskiren

No significant difference was found between **aliskiren** and **placebo** in terms of all cause death (RR=0.25, 95% CI 0.01 to 5.47, p=0.3765, 1 trial).

Table 20.1: *Main study characteristics - direct renin inhibitor*

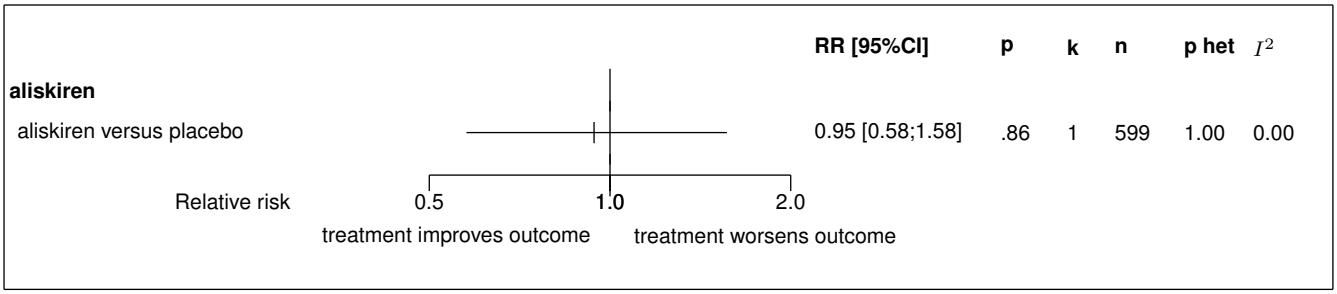
Trial	Patients	Treatments	Trial design and method
Aliskiren			
Aliskiren versus placebo			
AVOID, 2008 [1] n = 301 vs. 298	patients with hypertension and type 2 diabetes with nephropathy	aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months **versus**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

Table 20.2: *Summary of all results for aliskiren*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
aliskiren versus placebo						
serious adverse event	RR=0.95	0.58;1.58	0.8568	1.0000 (0.00)	1	599
any adverse event	RR=0.99	0.89;1.11	0.9302	1.0000 (0.00)	1	599
all cause death	RR=0.25	0.01;5.47	0.3765	1.0000 (0.00)	1	599
adverse events leading to treatment discontinuation	RR=0.89	0.47;1.67	0.7080	1.0000 (0.00)	1	599

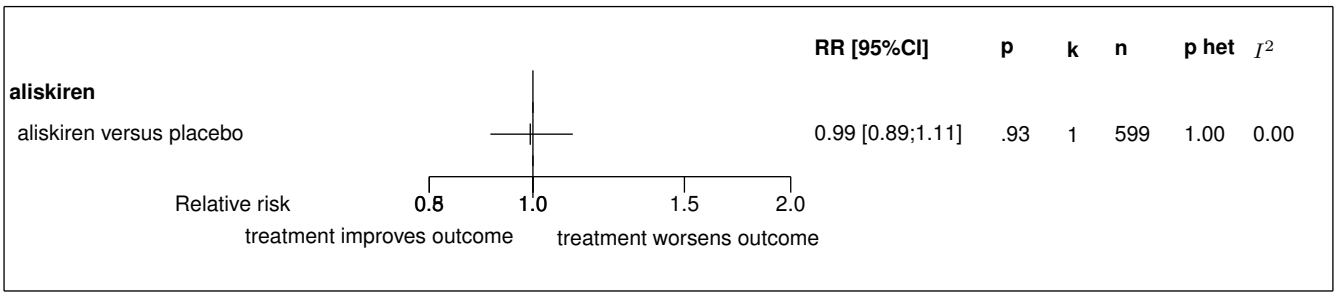
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 20.1: *Forest's plot for serious adverse event*



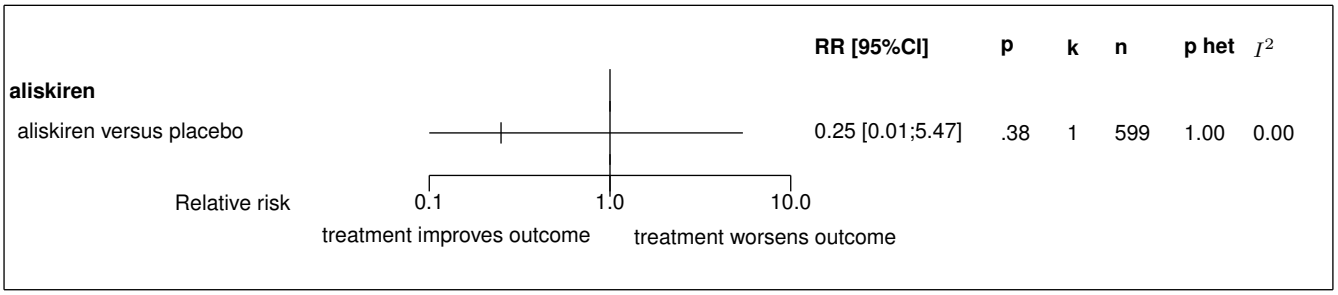
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 20.2: *Forest's plot for any adverse event*



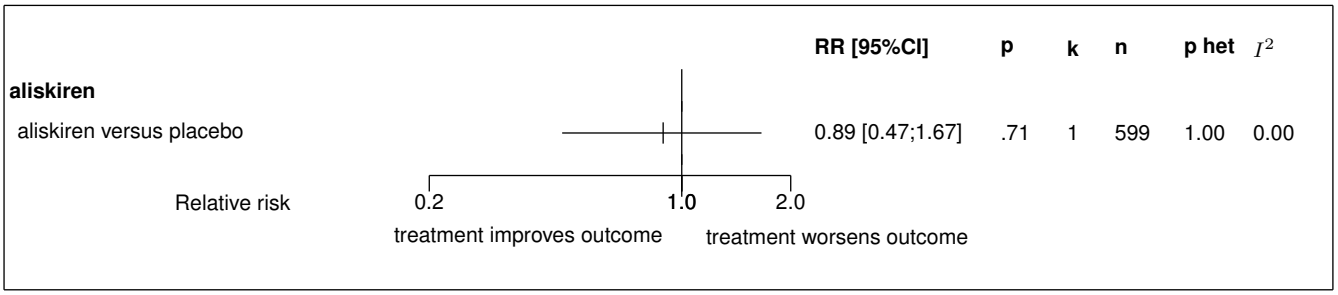
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 20.3: *Forest's plot for all cause death*



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

Figure 20.4: *Forest's plot for adverse events leading to treatment discontinuation*



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

21 Details

21.1 Available trials

Only one trial which randomized 599 patients was identified: it compared aliskiren with placebo.
This trial included 599 patients and was published in 2008.
This trial was double blind in design.
It was reported in English language.
All cause death data was reported in 1 trials; 1 trials reported data on any adverse event; 1 trials reported data on adverse events leading to treatment discontinuation; and 1 trials reported data on serious adverse event.
Following tables 21.1 (page 109), 21.2 (page 109), 21.4 (page 111), and 21.3 (page 110) summarized the main characteristics of the trial including in this systematic review of randomized trials of aliskiren.

Table 21.1: *Treatment description - direct renin inhibitor - aliskiren*

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

Table 21.2: *Descriptions of participants - direct renin inhibitor - aliskiren*

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

Table 21.3: *Design and methodological quality of trials - direct renin inhibitor - aliskiren*

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

Table 21.4: *Trial characteristics - direct renin inhibitor - aliskiren*

Trial
Aliskiren versus placebo
AVOID, 2008 [1]

21.2 Meta-analysis results

The results are detailed in table 21.5 (page 112). This table is followed by the Forest's plot corresponding to each endpoint.

Aliskiren versus placebo

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 0.25 (95% CI 0.01 to 5.47, p=0.3765).

Table 21.5: *Results details - direct renin inhibitor - aliskiren*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
aliskiren versus placebo						
serious adverse event	RR=0.95	[0.58;1.58]	0.8568	1.0000 (I^2=0.00)	1	599
any adverse event	RR=0.99	[0.89;1.11]	0.9302	1.0000 (I^2=0.00)	1	599
all cause death	RR=0.25	[0.01;5.47]	0.3765	1.0000 (I^2=0.00)	1	599
adverse events leading to treatment discontinuation	RR=0.89	[0.47;1.67]	0.7080	1.0000 (I^2=0.00)	1	599

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 21.1: *Forest's plot for serious adverse event*

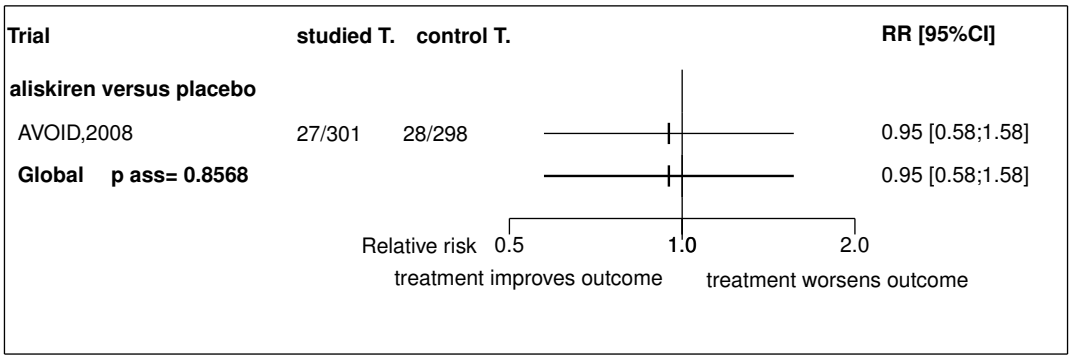


Figure 21.2: *Forest's plot for any adverse event*

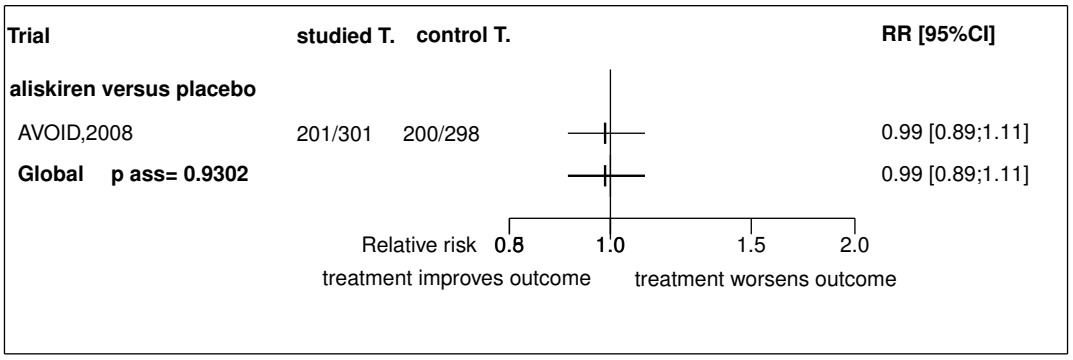


Figure 21.3: *Forest's plot for all cause death*

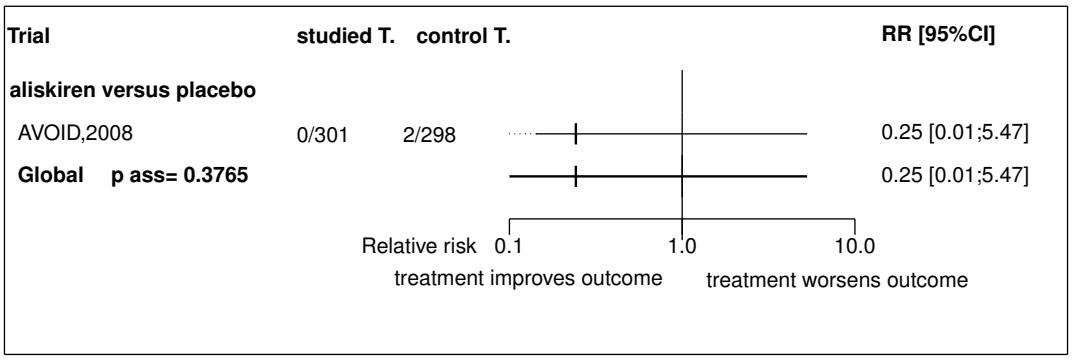
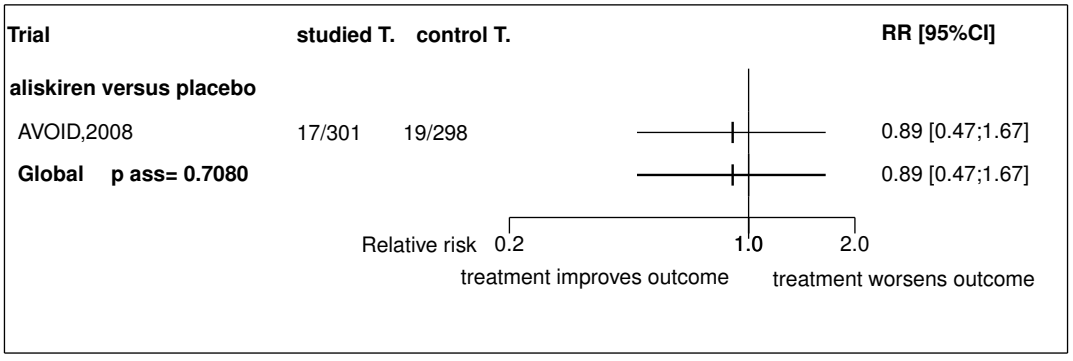


Figure 21.4: *Forest's plot for adverse events leading to treatment discontinuation*



References

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

21.3 Individual trial summaries

Table 21.6: *AVOID, 2008 - Trial synopsis*

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

Reference

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

22 Global meta-analysis: all direct renin inhibitor

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

Table 22.1: *All direct renin inhibitorversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
all cause death	RR=0.25	0.01;5.47	0.3765	1.0000 (0.00)	1	599

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

23 Ongoing studies of direct renin inhibitor

No ongoing trial was identified.

24 Excluded studies for direct renin inhibitor

No trial was excluded.

References