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Aldosterone blockade for heart failure

A systematic review and meta-analysis of randomized clinical trials

2011 - 2 - 22

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TrialResults-center.org; Results of all major randomized clinical trials about Aldosterone blockade for heart failure. Accessed at www.trialresultscenter.org godirect.asp q=488 c= on 2011 - 2 - 22

Contents

1 Introduction

1.1 Aim of the report

This report review all the randomized clinical trials of aldosterone blockade for the treatment of heart failure in all type of patients.

1.2 Search strategy

The search aimed to identify all randomized clinical trials relating to the clinical effectiveness of aldosterone blockade for the treatment of heart failure in all type of patients.

1.2.1 Sources searched

The following electronic databases were searched for relevant published literature for the period up to 2011 - 2 - 22:

- 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 heart failure.

Interventions studies in which aldosterone blockade was used.

Studies using other interventions in addition to aldosterone blockade therapy were included only if the treatment received by the intervention and control groups was identical in all respects other than the use of aldosterone blockade .

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 All cause death, serious hyperkalemia, Cardiovascular death, Sudden death, hospitalisation for cardiovascular causes, Hospitalization for any reason, death from cardiovascular causes or hospitalization for cardiovascular causes, exacerbation of heart failure, hospitalisation for heart failure, Death from any cause or hospitalization for heart failure, NYHA class improvement, Death from any cause or hospitalization for any reason, Adverse events, Adverse events leading to treatment discontinuation, .

1.6 Structure of the report

Each of the eligible studies is summarised in part I. A summary of the studies together with an evaluation of their quality is given in part **??** to **??**, listed by therapeutic class. The therapeutic classes included aldosterone-receptor blockers,

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.

2 Overview of aldosterone-receptor blockers16

2.1 Trials

A total of 16 randomized comparisons which enrolled 11639 patients were identified. In all, 1 randomized comparison concerned aldactone , two eplerenone , 11 spironolactone , one spironolactone+captopril and one spironolactone+furosemide.
The detailed descriptions of trials and meta-analysis results is given in section 4 (page 31) for aldactone, in section 5 (page 33) for eplerenone, in section 6 (page 41) for spironolactone, in section 7 (page 50) for spironolactone+captopril and in section 8 (page 52) for spironolactone+furosemide.

The average study size was 727 patients (range 20 to 6632). The first study was published in 1985, and the last study was published in 2010.
A total of 8 trials were double blind and 8 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
The table 3.1 (page 19) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

2.2 Summary of results

The meta-analysis of the available trials about aldosterone-receptor blockers provide the results listed in tables 3.2 to 3.6 (page 22) and in the following graphs.

2.2.1 Aldactone

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

2.2.2 Eplerenone

Eplerenone was superior to **placebo** in terms of death from cardiovascular causes or hospitalization for cardiovascular causes (RR=0.89, 95% CI 0.82 to 0.96, p=0.0028, 1 trial) , sudden death (RR=0.80, 95% CI 0.68 to 0.95, p=0.0118, 2 trials) , hospitalisation for heart failure (RR=0.65, 95% CI 0.54 to 0.78, p=0.0000, 1 trial) , death from any cause or hospitalization for any reason (RR=0.82, 95% CI 0.74 to 0.90, p=0.0000, 1 trial) , death from any cause or hospitalization for heart failure (RR=0.72, 95% CI 0.63 to 0.83, p=0.0000, 1 trial) , hospitalization for any reason (RR=0.84, 95% CI 0.75 to 0.93, p=0.0000, 1 trial) , cardiovascular death (RR=0.83, 95% CI 0.75 to 0.92, p=0.0000, 2 trials) and all cause death (RR=0.85, 95% CI 0.77 to 0.93, p=0.0000, 2 trials) .But eplerenone increased the risk of serious hyperkalemia (RR=1.74, 95% CI 1.14 to 2.65, p=0.0100, 2 trials) with a random effect model in reason of a heterogeneity (Het. p=0.0324) .However, no significant difference was found on hospitalisation for cardiovascular causes (RR=0.93, 95% CI 0.84 to 1.03, p=0.1666, 1 trial) .

2.2.3 Spironolactone

Data were insufficient to compare **spironolactone** to **control**. There were 3 eligible trials but none provided sufficient information about the endpoints considered by this meta-analysis.

Spironolactone was superior to **placebo** in terms of hospitalisation for cardiovascular causes (RR=0.79, 95% CI 0.70 to 0.90, p=0.0000, 1 trial) , sudden death (RR=0.76, 95% CI 0.58 to 1.00, p=0.0487, 1 trial) , exacerbation of heart failure (RR=0.79, 95% CI 0.71 to 0.88, p=0.0000, 1 trial) , cardiovascular death (RR=0.74, 95% CI 0.65 to 0.85, p=0.0000, 1 trial) and all cause death (RR=0.75, 95% CI 0.67 to 0.85, p=0.0000, 1 trial) .But spironolactone increased the risk of NYHA class improvement (RR=1.24, 95% CI 1.09 to 1.41, p=0.0000, 1 trial) .However, no significant difference was found on serious hyperkalemia (RR=2.05, 95% CI 0.19 to 22.52, p=0.5585, 1 trial) .Spironolactone appear to be associated with significantly greater risk of adverse events leading to treatment discontinuation (RR=1.59, 95% CI 1.08 to 2.33, p=0.0191, 1 trial) .

2.2.4 Spironolactone+captopril

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

2.2.5 Spironolactone+furosemide

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

Table 2.1: *Main study characteristics - aldosterone-receptor blockers*

Trial	Patients	Treatments	Trial design and method
Aldactone			
Aldactone versus furosemide			
Bednarz, 2000 [1, 2] n = 11 vs. 10	patients with NYHA class III to IV congestive heart failure	aldactone 200 mg i.v **versus** furosemide 20 mg i.v	open
Eplerenone			
Eplerenone versus placebo			
EMPHASIS-HF, 2010 [1, 2, 3] n = 1364 vs. 1373	patients withNew York Heart Association class II heart failure and an ejection fraction of nomore than 35%	eplerenone **versus** placebo	double blind parallel groups Primary endpoint: CV death, hospitalization for HF 278 centres,29 countries
EPHESUS, 2003 [4, 5] n = 3319 vs. 3313	patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure	eplerenone 25 mg per day initially, titrated to amaximum of 50 mg per day **versus** placebo	double blind parallel groups Primary endpoint: all cause death AND cardiovascular death or hospitalization for a CV event 674 centres,37 countries
Spironolactone			
Spironolactone versus control			
Cicoira, 2002 [1] n = 54 vs. 52	patients with chronic heart failure	spironolactone 12.5 to 50 mg/day **versus** control	open parallel groups Primary endpoint: ventricular Function and Exercise tolerance
Cicoira, 2004 [2] n = 47 vs. 46	chronic heart failure patients	spironolactone **versus** control	open Primary endpoint: ACE gene insertion/deletion polymorphism

continued...

Trial	Patients	Treatments	Trial design and method
Ramires, 2000 [3] n = 19 vs. 16	patients with systolic dysfunction and NYHA class III CHF secondary to dilated or ischemic cardiomyopathy	spironolactone **versus** standard medical treatment	open parallel groups Primary endpoint: none
Spironolactone versus placebo			
Agostoni, 2005 [4] n = 14 vs. 15	stable chronic heart failure patients with reduced influences lung diffusion (DLCO)	spironolactone 25mg/d **versus** placebo	open parallel groups 1 centres,Italy
Farquharson, 2000 [5] n = 10 vs. 10	patients with NYHA class II to III chronic heart failure on standard diuretic/ACE inhibitor therapy	spironolactone 50 mg/d **versus** placebo	double blind Primary endpoint: none
Macdonald, 2004 [6] n = 43 vs. 43	patients with New York Heart Association class I-II congestive heart failure taking optimal treatment (including beta blockers)	spironolactone 12.5-50 mg/d **versus** placebo	double blind cross over Primary endpoint: none
MacFadyen, 1997 [7] n = 21 vs. 16	patients with stable chronic heart failure	spironolactone (50-100 mg/day) **versus** placebo	double blind parallel groups Primary endpoint: none
Mottram, 2004 [8] n= 30	hypertensive patients with diastolic heart failure	spironolactone 25 mg/d **versus** placebo	double blind Primary endpoint: myocardial function
RALES, 1998 [9, 10, 11] n = 822 vs. 841	patients with severeheart failure	spironolactone (25 to 50 mg daily) **versus** placebo	open parallel groups Primary endpoint: death from any cause 195 centres,World

continued...

Trial	Patients	Treatments	Trial design and method
Tsutamoto, 2001 [12] n = 20 vs. 17	patients with mild-to-moderate nonischemic congestive heart failure	spironolactone 25 mg daily **versus** placebo	double blind parallel groups Primary endpoint: neurohumoral factors Japan
Yee, 2001 [13] n = 28 vs. 28	patients with New York Heart Association class II to IV congestive heart failure	spironolactone 50mg/d **versus** placebo	double blind
Spironolactone+captopril			
Spironolactone+captopril versus captopril			
Han, 1994 [1] n = 19 vs. 16	patients with refractory CHF and New York Heart Association functional class IV without renal dysfunction, hypotension and hyperkalemia	captopril plus spironolactone **versus** captopril alone	open Primary endpoint: none China
Spironolactone+furosemide			
Spironolactone+furosemide versus spironolactone+butizide			
Mauersberger, 1985 [1] n= 22	patients with congestive heart failure	spironolactone 50mg + furosemide 20 mg **versus** spironolactone 50mg + butizide 5mg	open Primary endpoint: none

Table 2.2: *Summary of all results for aldactone*

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

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

Table 2.3: *Summary of all results for eplerenone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
eplerenone versus placebo						
hospitalisation for cardiovascular causes	RR=0.93	0.84;1.03	0.1666	1.0000 (0.00)	1	6632
death from cardiovascular causes or hospitalization for cardiovascular causes	RR=0.89	0.82;0.96	0.0028	1.0000 (0.00)	1	6632
serious hyperkalemia	RR=1.74 [1]	1.14;2.65	0.0100	0.0324 (0.78) †	2	9369
sudden death	RR=0.80	0.68;0.95	0.0118	0.9503 (0.00)	2	9369
hospitalisation for heart failure	RR=0.65	0.54;0.78	0.0000	1.0000 (0.00)	1	2737
death from any cause or hospitalization for any reason	RR=0.82	0.74;0.90	0.0000	1.0000 (0.00)	1	2737
death from any cause or hospitalization for heart failure	RR=0.72	0.63;0.83	0.0000	1.0000 (0.00)	1	2737
hospitalization for any reason	RR=0.84	0.75;0.93	0.0000	1.0000 (0.00)	1	2737
cardiovascular death	RR=0.83	0.75;0.92	0.0000	0.6777 (0.00)	2	9369
all cause death	RR=0.85	0.77;0.93	0.0000	0.5670 (0.00)	2	9369
adverse events	RR=0.99	0.97;1.01	0.3374	0.5984 (0.00)	2	9369

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 spironolactone*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
spironolactone versus control						
No data were presented in the trial identified						
spironolactone versus placebo						
hospitalisation for cardiovascular causes	RR=0.79	0.70;0.90	0.0000	1.0000 (0.00)	1	1663
serious hyperkalemia	RR=2.05	0.19;22.52	0.5585	1.0000 (0.00)	1	1663
sudden death	RR=0.76	0.58;1.00	0.0487	1.0000 (0.00)	1	1663
exacerbation of heart failure	RR=0.79	0.71;0.88	0.0000	1.0000 (1.00)	1	1663
NYHA class improvement	RR=1.24	1.09;1.41	0.0000	1.0000 (0.00)	1	1663
cardiovascular death	RR=0.74	0.65;0.85	0.0000	1.0000 (0.00)	1	1663
all cause death	RR=0.75	0.67;0.85	0.0000	1.0000 (0.00)	1	1663
adverse events leading to treatment discontinuation	RR=1.59	1.08;2.33	0.0191	1.0000 (0.00)	1	1663
adverse events	RR=1.03	0.99;1.08	0.1659	1.0000 (0.00)	1	1663

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

[1] with a random model ($\tau^2 = NaN$). The results with a fixed effect model was RRFE=1.64 95% CI 1.36;1.97

Table 2.5: *Summary of all results for spironolactone+captopril*

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

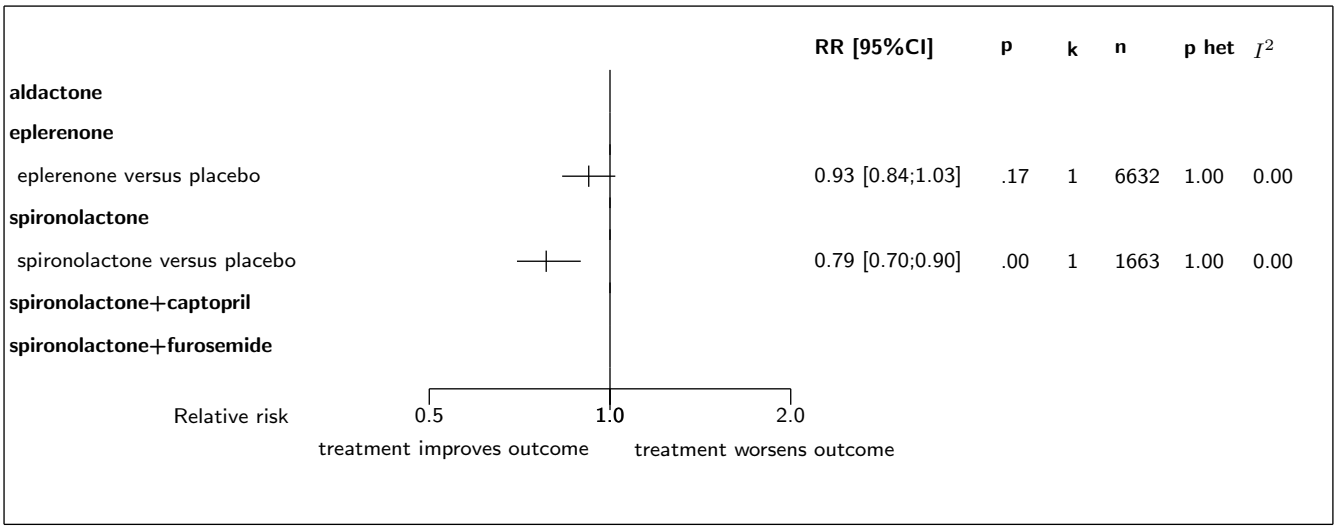
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Table 2.6: *Summary of all results for spironolactone+furosemide*

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

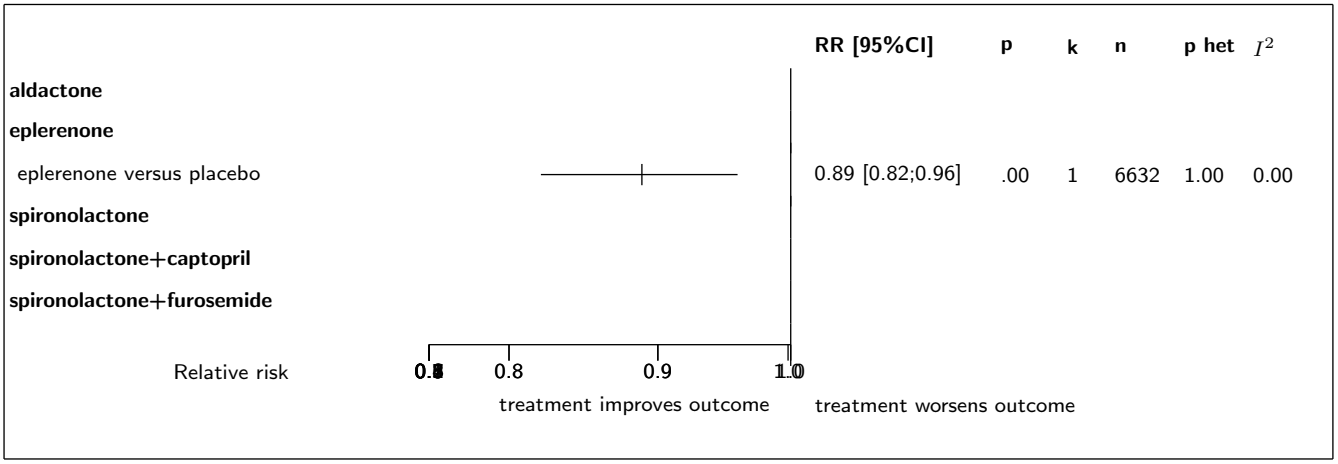
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 2.1: *Forest's plot for hospitalisation for cardiovascular causes*



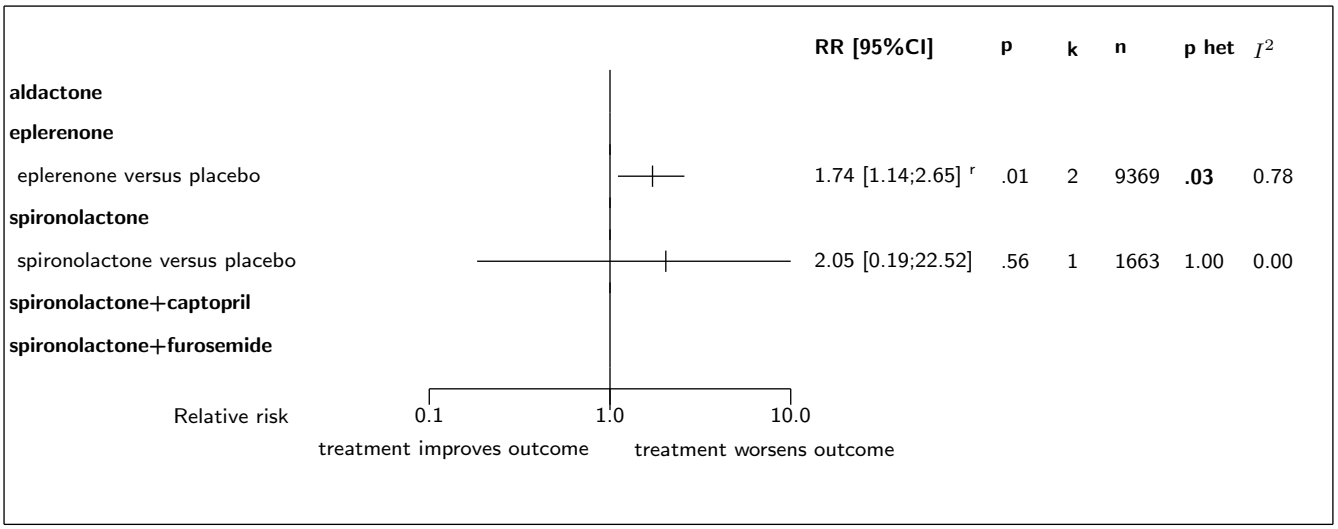
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.2: *Forest's plot for death from cardiovascular causes or hospitalization for cardiovascular causes*



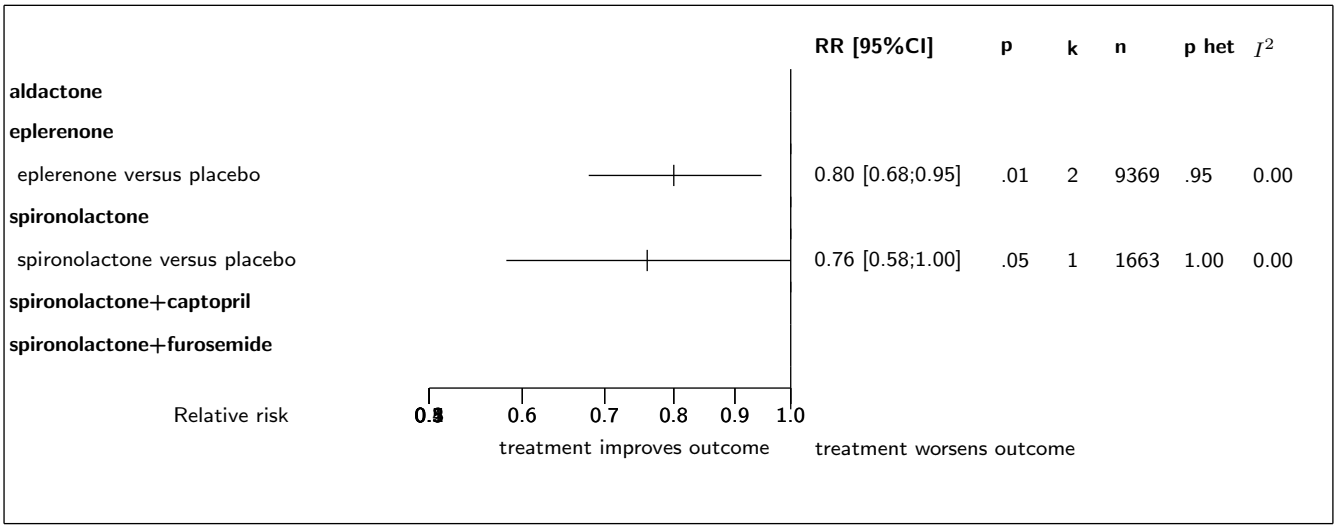
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.3: *Forest's plot for serious hyperkalemia*



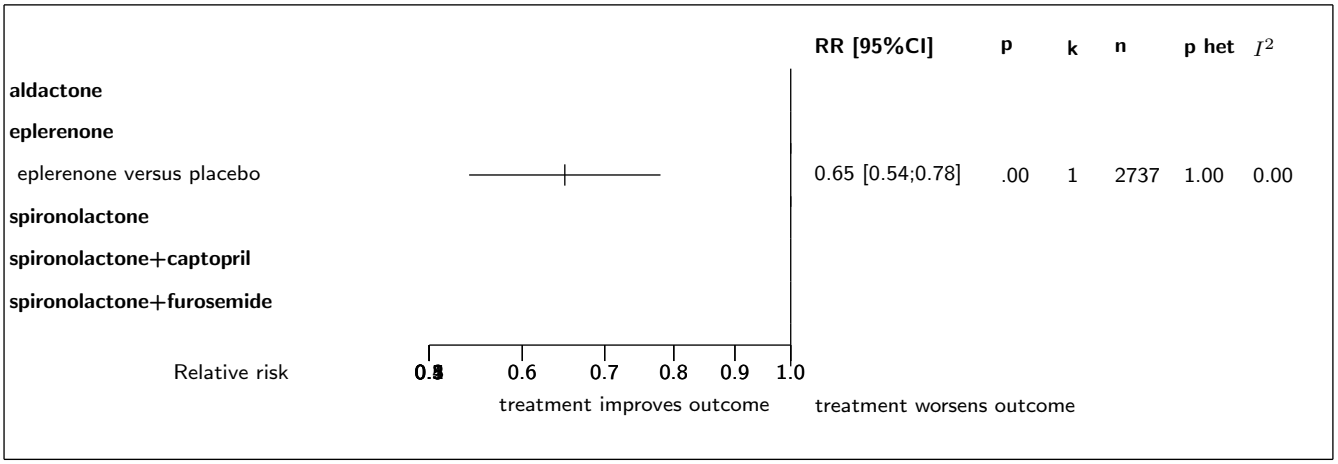
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.4: *Forest's plot for sudden death*



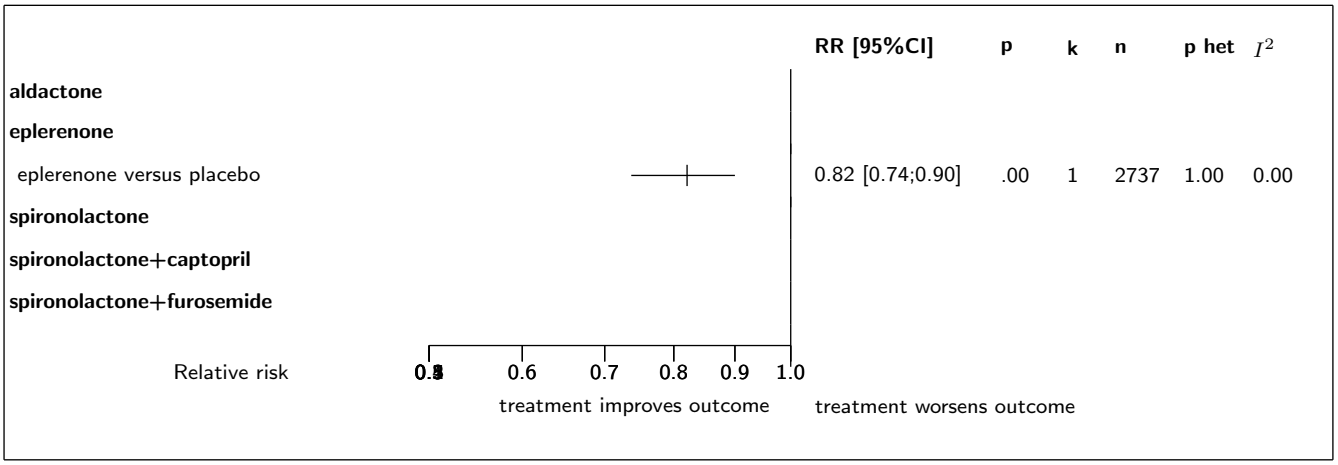
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.5: *Forest's plot for hospitalisation for heart failure*



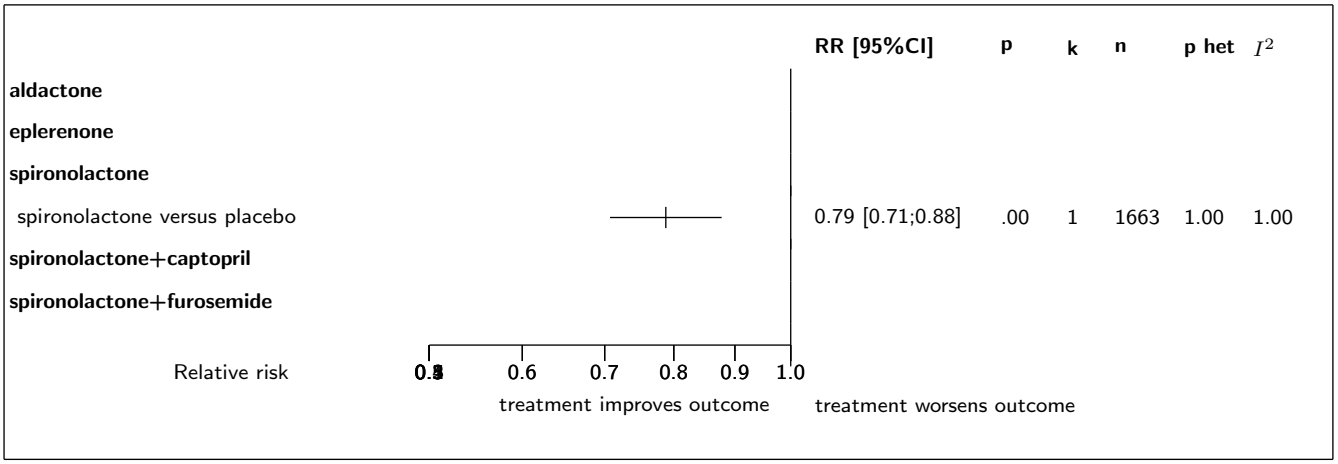
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.6: *Forest's plot for death from any cause or hospitalization for any reason*



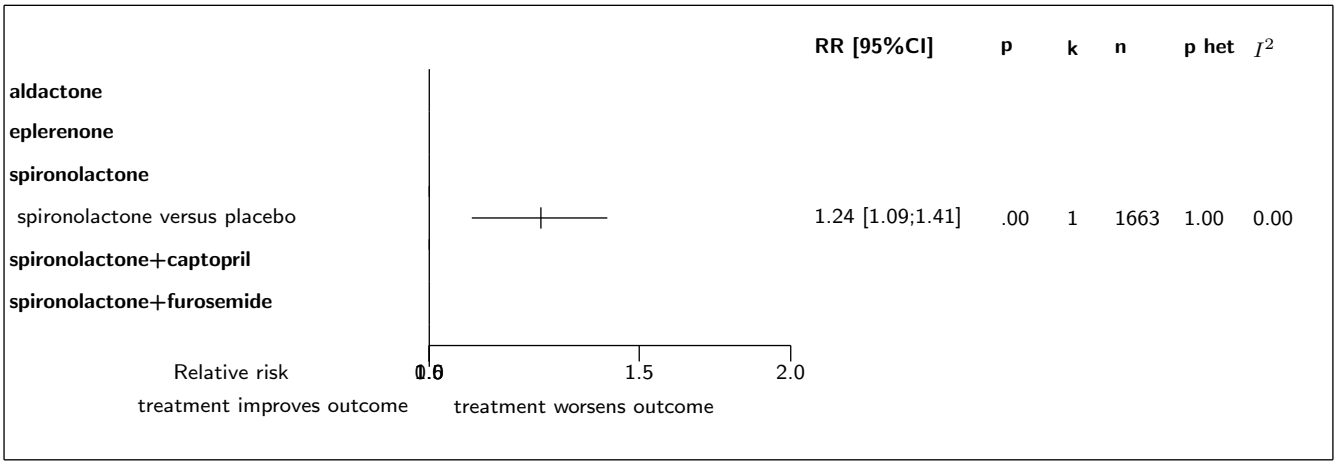
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.7: *Forest's plot for exacerbation of heart failure*



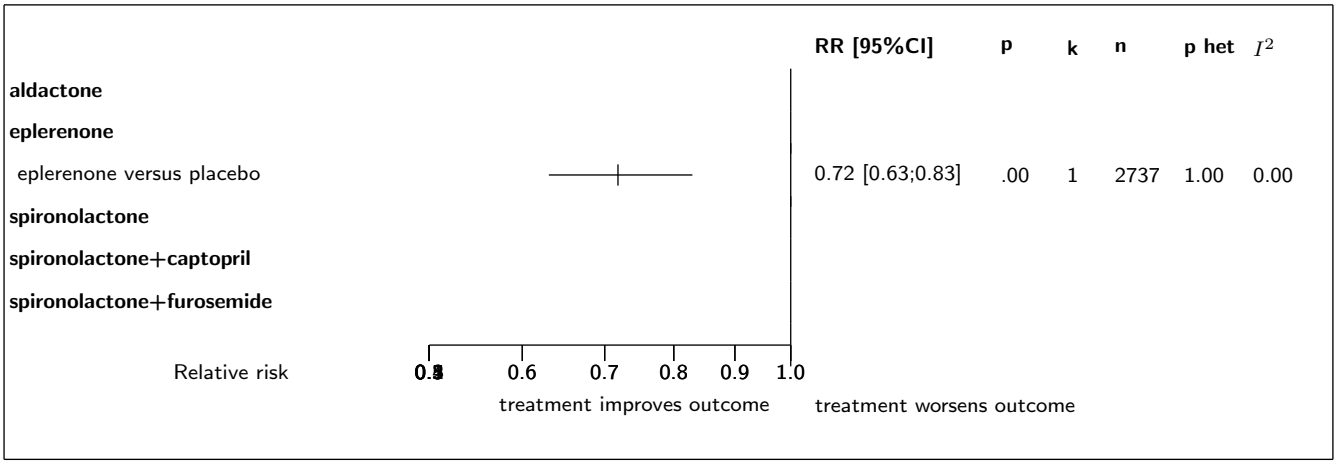
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.8: *Forest's plot for NYHA class improvement*



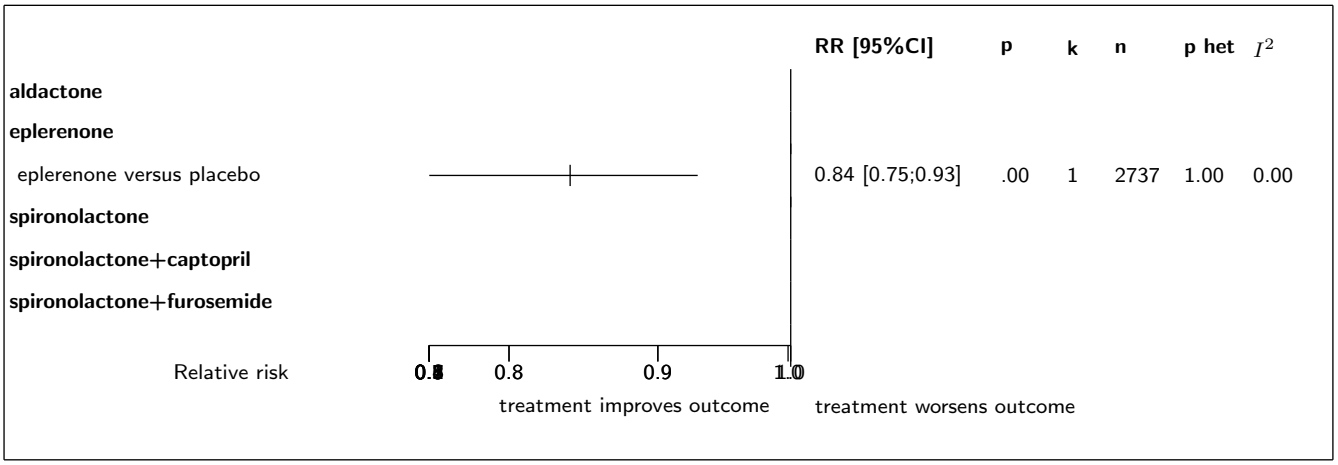
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.9: *Forest's plot for death from any cause or hospitalization for heart failure*



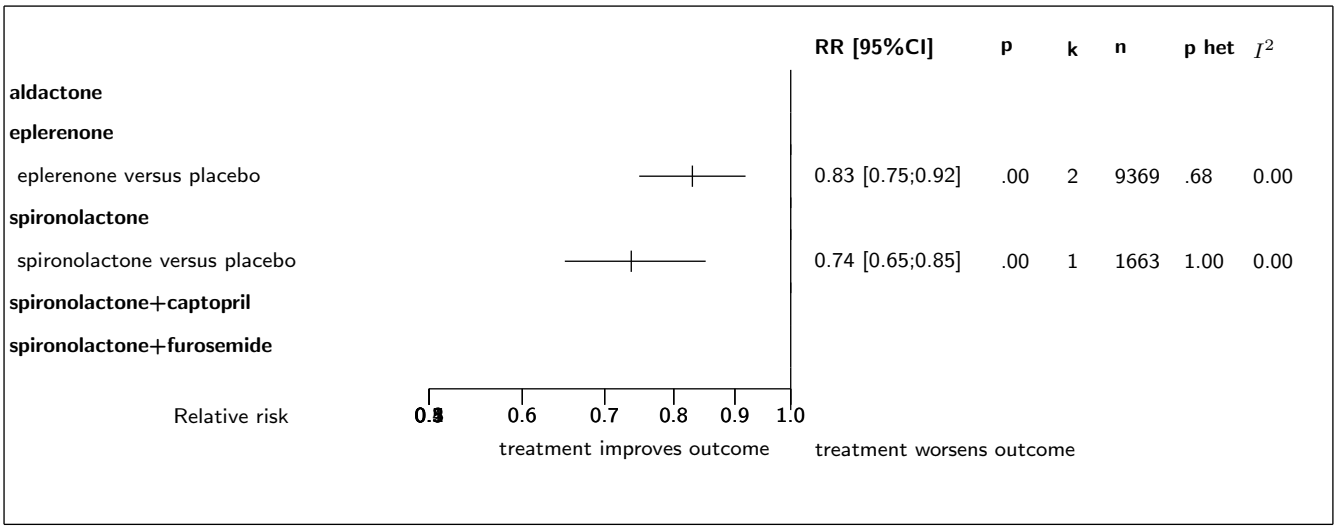
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.10: *Forest's plot for hospitalization for any reason*



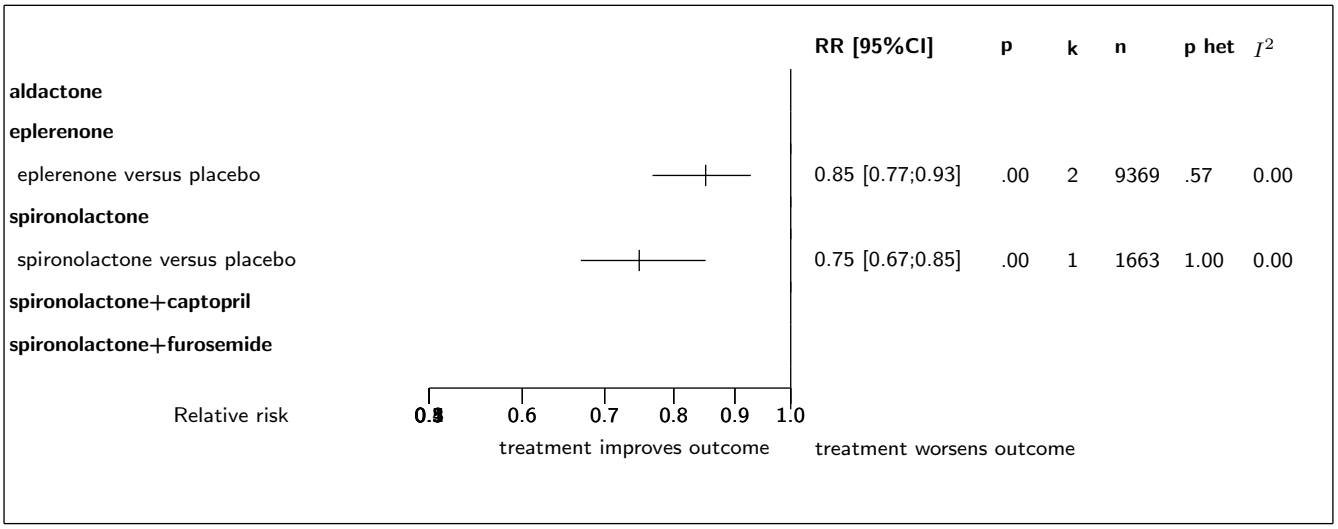
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.11: *Forest's plot for cardiovascular death*



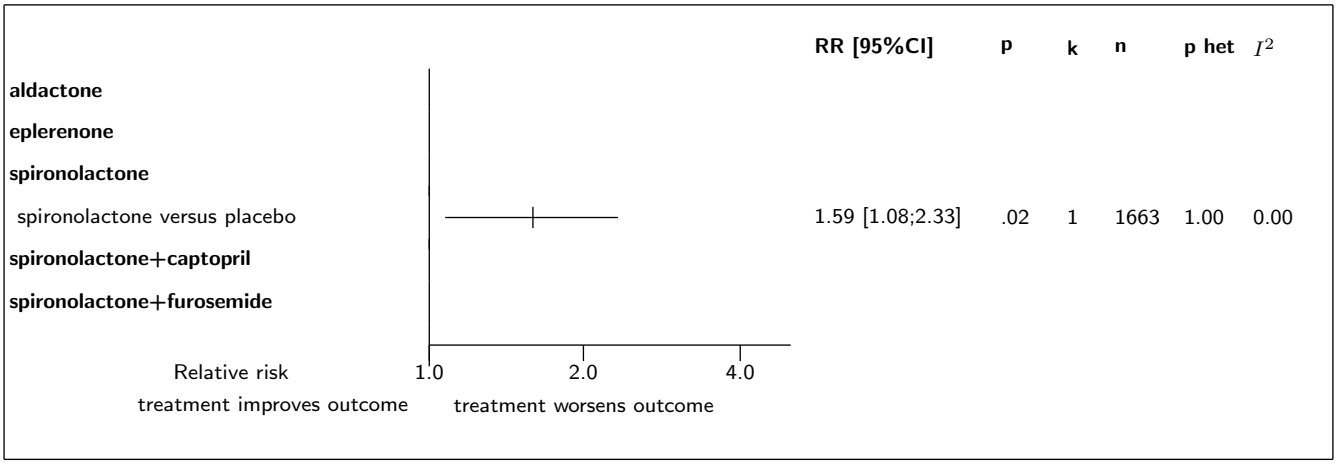
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.12: *Forest's plot for all cause death*



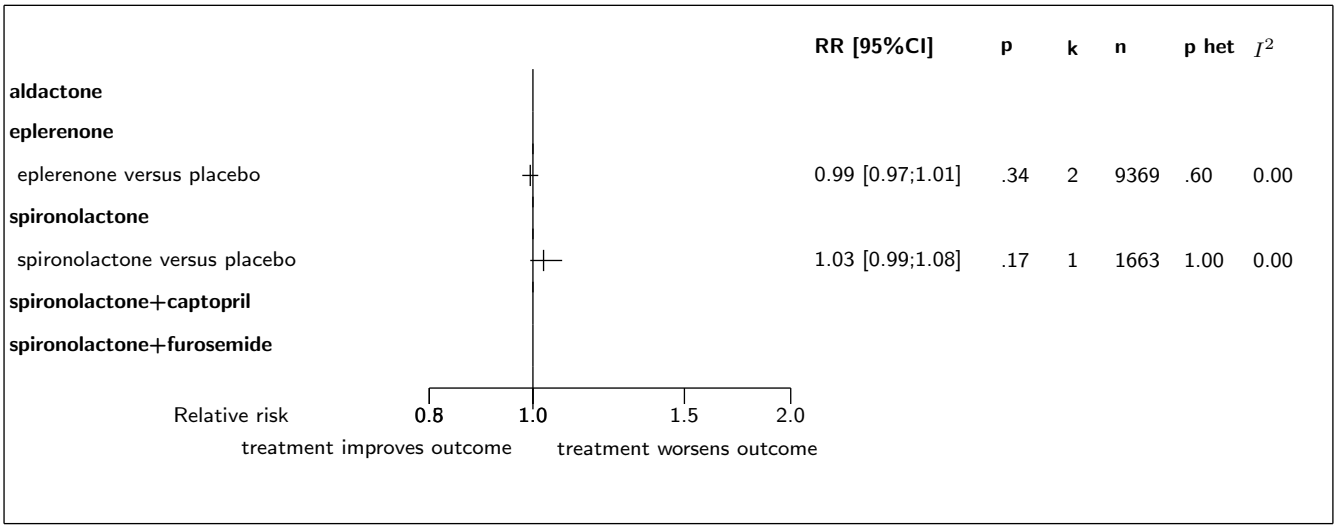
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity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

Figure 2.13: *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

Figure 2.14: *Forest's plot for adverse 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

3 Detailed results for aldactone

3.1 Available trials

Only one trial which randomized 21 patients was identified: it compared aldactone with furosemide.
This trial included 21 patients and was published in 2000.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 4.1 (page 31), 4.2 (page 31), 4.3 (page 31), and 4.4 (page 31) summarized the main characteristics of the trial including in this systematic review of randomized trials of aldactone.

Table 3.1: *Treatment description - aldosterone-receptor blockers - aldactone*

Trial	Studied treatment	Control treatment
Aldactone versus furosemide		
Bednarz (2000) [1, 2]	Aldactone 200 mg i.v	furosemide 20 mg i.v

Table 3.2: *Descriptions of participants - aldosterone-receptor blockers - aldactone*

Trial	Patients
Aldactone versus furosemide	
Bednarz (2000) [1, 2]	Patients with NYHA class III to IV congestive heart failure

Table 3.3: *Main patients characteristics - aldosterone-receptor blockers - aldactone*

Trial	Characteristics
Aldactone versus furosemide	
Bednarz, 2000 [1, 2]	

Table 3.4: *Design and methodological quality of trials - aldosterone-receptor blockers - aldactone*

Trial	Design	Duration	Centre	Primary endpoint
Aldactone versus furosemide				
Bednarz, 2000 [1, 2] n=21	open exploratory trial			

3.2 Meta-analysis results

The results are detailed in table 4.5 (page 32). This table is followed by the Forest's plot corresponding to each endpoint.

Aldactone versus furosemide

No data were presented in the 1 trial identified

Table 3.5: *Results details - aldosterone-receptor blockers - aldactone*

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

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

References

[1] Bednarz B, Cybulski J, Chamiec T,. [Comparison of the therapeutic efficacy of spironolactone and furosemide in patients with severe congestive heart failure]. Pol Merkuriusz Lek 2000;9:519-21. [PMID=11081314]

[2] Bednarz B, Cybulski J, Chamiec T. [Comparison of the therapeutic efficacy of spironolactone and furosemide in patients with severe congestive heart failure]. Pol Merkuriusz Lek 2000 Aug;9:519-21. [PMID=11081314]

4 Detailed results for eplerenone

4.1 Available trials

A total of 2 RCTs which randomized 9369 patients were identified: all compared eplerenone with placebo.
The average study size was 4684 patients (range 2737 to 6632). The first study was published in 2003, and the last study was published in 2010.
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 serious hyperkalemia; 2 trials reported data on cardiovascular death; 2 trials reported data on sudden death; 1 trials reported data on hospitalisation for cardiovascular causes; 1 trials reported data on hospitalisation for heart failure; 1 trials reported data on death from any cause or hospitalization for heart failure; 1 trials reported data on death from cardiovascular causes or hospitalization for cardiovascular causes; 1 trials reported data on death from any cause or hospitalization for any reason; 1 trials reported data on hospitalization for any reason; and 2 trials reported data on adverse events.
Following tables 5.1 (page 33), 5.2 (page 34), 5.3 (page 34), and 5.4 (page 34) summarized the main characteristics of the trials including in this systematic review of randomized trials of eplerenone.

Table 4.1: *Treatment description - aldosterone-receptor blockers - eplerenone*

Trial	Studied treatment	Control treatment
Eplerenone versus placebo		
EMPHASIS-HF (2010) [1, 2, 3]	eplerenone started at a dose of 25 mg once daily and increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m2), provided the serum potassium level was no more than 5.0 mmol per liter.Therafter the study dose was decreasesif the serum potassiumlevel was 5.5 to 5.9 mmol per liter and towithhold the study drug if the serum potassiumlevel was 6.0 mmol per liter or more. **Concomittant treatment:** background standard heart failure therapy	placebo
EPHESUS (2003) [4, 5]	eplerenone 25 mg per day initially, titrated to amaximum of 50 mg per day if the serum potassium concentration was higher than 5.5 mmol per liter, the dose of the study drug was reduced or treatment was temporarily discontinued until the serum potassium concentration fell below 5.5 mmol per liter **Concomittant treatment:** optimal medical therapy, which could include ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy	placebo

Table 4.2: *Descriptions of participants - aldosterone-receptor blockers - eplerenone*

Trial	Patients	
Eplerenone versus placebo		
EMPHASIS-HF (2010) [1, 2, 3]	Patients withNew York Heart Association class II heart failure and an ejection fraction of nomore than 35%	
	Inclusion criteria: age of at least 55 years, NYHA functional class II symptoms, an ejection fraction of no more than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography), and treatment with an angiotensin-convertingenzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose	**Exclusion criteria:** acute myocardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol per liter, an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area, a need for a potassiumsparing diuretic, any other clinically significant, coexisting condition
EPHESUS (2003) [4, 5]	Patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure	
	Inclusion criteria: enrollment 3 to 14 days after acute myocardial infarction documented according to standard criteria;criteria; left ventricular dysfunction as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. For patients with diabetes who met the criteria for left ventricular dysfunction after acute myocardial infarction, symptoms of heart failure did not have to be demonstrated	**Exclusion criteria:** use of potassiumsparing diuretics; serum creatinine concentration of more than 2.5 mg per deciliter (220 micromol per liter); serum potassium concentration of more than 5.0 mmol per liter

Table 4.3: *Main patients characteristics - aldosterone-receptor blockers - eplerenone*

Trial	Characteristics
Eplerenone versus placebo	
EMPHASIS-HF, 2010 [1, 2, 3]	
EPHESUS, 2003 [4, 5]	

Table 4.4: *Design and methodological quality of trials - aldosterone-receptor blockers - eplerenone*

Trial	Design	Duration	Centre	Primary endpoint
Eplerenone versus placebo				

continued...

Trial	Design	Duration	Centre	Primary endpoint
EMPHASIS-HF, 2010 [1, 2, 3] n=2737	Parallel groups double blind confirmatory trial at low risk of bias	21 months inclusion period: Mar 2006 - may 2010	29 countries 278 centres	CV death, hospitalization for HF
EPHESUS, 2003 [4, 5] n=6632	Parallel groups Double blind confirmatory trial at low risk of bias	16 mo (mean, range 0 to 33) inclusion period: Dec 1999 - dec 2001	37 countries 674 centres	all cause death AND cardiovascular death or hospitalization for a CV event

4.2 Meta-analysis results

The results are detailed in table 5.5 (page 36). This table is followed by the Forest's plot corresponding to each endpoint.

Eplerenone versus placebo

Only one of the 2 studies eligible for this comparison provided data on **hospitalisation for cardiovascular causes**. There was no statistically significant difference in hospitalisation for cardiovascular causes between eplerenone and placebo, with a RR of 0.93 (95%CI 0.84 to 1.03, p=0.1666) in favour of eplerenone. In other words, hospitalisation for cardiovascular causes was slightly lower in the eplerenone group , but this was not statistically significant.
Only one of the 2 studies eligible for this comparison provided data on **death from cardiovascular causes or hospitalization for cardiovascular causes**. The analysis detected a statistically significant difference in favor of eplerenone in death from cardiovascular causes or hospitalization for cardiovascular causes, with a RR of 0.89 (95% CI 0.82 to 0.96, p=0.0028).
All the 2 studies had extractable data about the number of participants with **serious hyperkalemia**. The analysis detected a statistically significant difference in favor of placebo in serious hyperkalemia, with a RR of 1.74 (95% CI 1.14 to 2.65, p=0.0100). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0324, I^2 = 0.78%).
All the 2 studies had extractable data about the number of participants with **sudden death**. The analysis detected a statistically significant difference in favor of eplerenone in sudden death, with a RR of 0.80 (95% CI 0.68 to 0.95, p=0.0118). No heterogeneity was detected (p = 0.9503, I^2 = 0.00%).
Only one of the 2 studies eligible for this comparison provided data on **hospitalisation for heart failure**. The analysis detected a statistically significant difference in favor of eplerenone in hospitalisation for heart failure, with a RR of 0.65 (95% CI 0.54 to 0.78, p=0.0000).
Only one of the 2 studies eligible for this comparison provided data on **death from any cause or hospitalization for any reason**. The analysis detected a statistically significant difference in favor of eplerenone in death from any cause or hospitalization for any reason, with a RR of 0.82 (95% CI 0.74 to 0.90, p=0.0000).
Only one of the 2 studies eligible for this comparison provided data on **death from any cause or hospitalization for heart failure**. The analysis detected a statistically significant difference in favor of eplerenone in death from any cause or hospitalization for heart failure, with a RR of 0.72 (95% CI 0.63 to 0.83, p=0.0000).
Only one of the 2 studies eligible for this comparison provided data on **hospitalization for any reason**. The analysis detected a statistically significant difference in favor of eplerenone in hospitalization for any reason, with a RR of 0.84 (95% CI 0.75 to 0.93, p=0.0000).

All the 2 studies had extractable data about the number of participants with **cardiovascular death**. The analysis detected a statistically significant difference in favor of eplerenone in cardiovascular death, with a RR of 0.83 (95% CI 0.75 to 0.92, p=0.0000). No heterogeneity was detected (p = 0.6777, I^2 = 0.00%).
All the 2 studies had extractable data about the number of participants with **all cause death**. The analysis detected a statistically significant difference in favor of eplerenone in all cause death, with a RR of 0.85 (95% CI 0.77 to 0.93, p=0.0000). No heterogeneity was detected (p = 0.5670, I^2 = 0.00%).

Table 4.5: *Results details - aldosterone-receptor blockers - eplerenone*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
eplerenone versus placebo						
hospitalisation for cardiovascular causes	RR=0.93	[0.84;1.03]	0.1666	1.0000 (I^2=0.00)	1	6632
death from cardiovascular causes or hospitalization for cardiovascular causes	RR=0.89	[0.82;0.96]	0.0028	1.0000 (I^2=0.00)	1	6632
serious hyperkalemia	RR=1.74	[1.14;2.65]	0.0100	0.0324 (I^2=0.78)	2	9369
sudden death	RR=0.80	[0.68;0.95]	0.0118	0.9503 (I^2=0.00)	2	9369
hospitalisation for heart failure	RR=0.65	[0.54;0.78]	0.0000	1.0000 (I^2=0.00)	1	2737
death from any cause or hospitalization for any reason	RR=0.82	[0.74;0.90]	0.0000	1.0000 (I^2=0.00)	1	2737
death from any cause or hospitalization for heart failure	RR=0.72	[0.63;0.83]	0.0000	1.0000 (I^2=0.00)	1	2737
hospitalization for any reason	RR=0.84	[0.75;0.93]	0.0000	1.0000 (I^2=0.00)	1	2737
cardiovascular death	RR=0.83	[0.75;0.92]	0.0000	0.6777 (I^2=0.00)	2	9369
all cause death	RR=0.85	[0.77;0.93]	0.0000	0.5670 (I^2=0.00)	2	9369
adverse events	RR=0.99	[0.97;1.01]	0.3374	0.5984 (I^2=0.00)	2	9369

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 hospitalisation for cardiovascular causes*

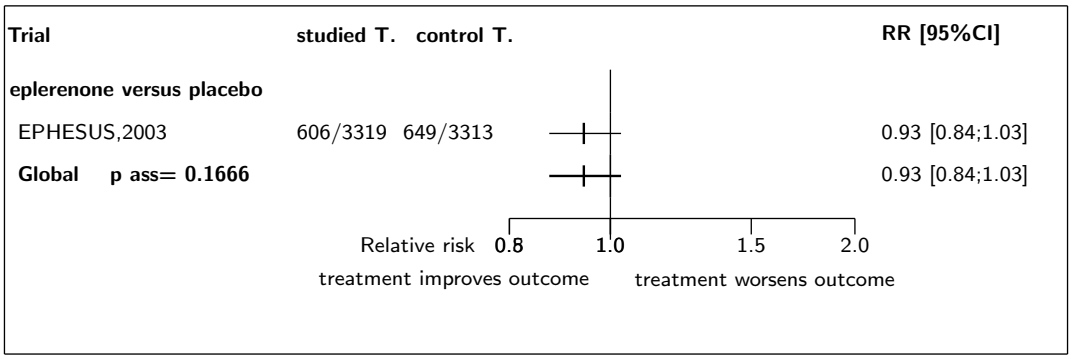


Figure 4.2: *Forest's plot for death from cardiovascular causes or hospitalization for cardiovascular causes*

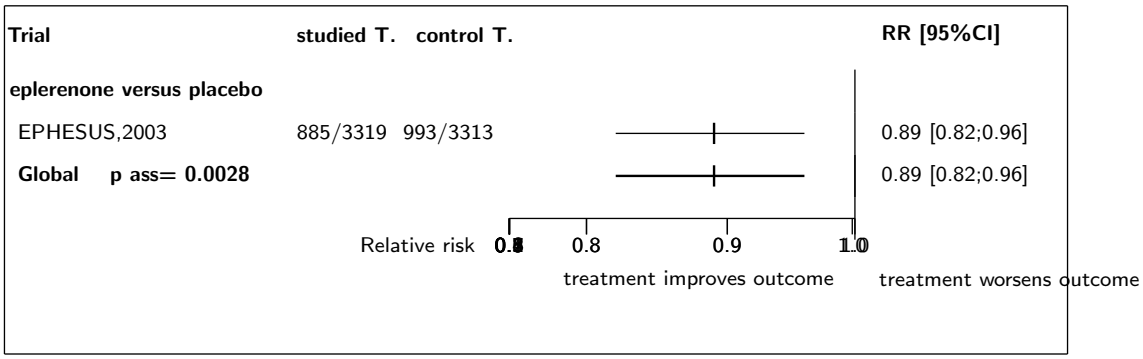


Figure 4.3: *Forest's plot for serious hyperkalemia*

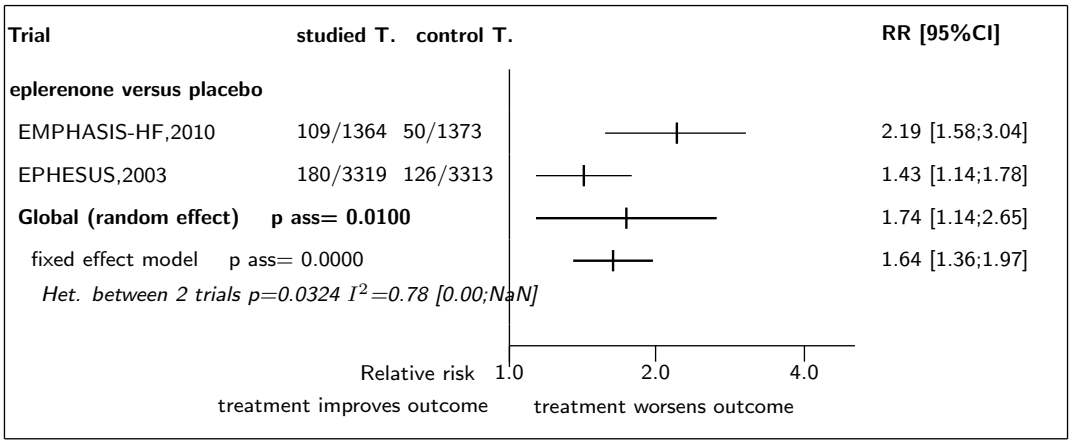


Figure 4.4: *Forest's plot for sudden death*

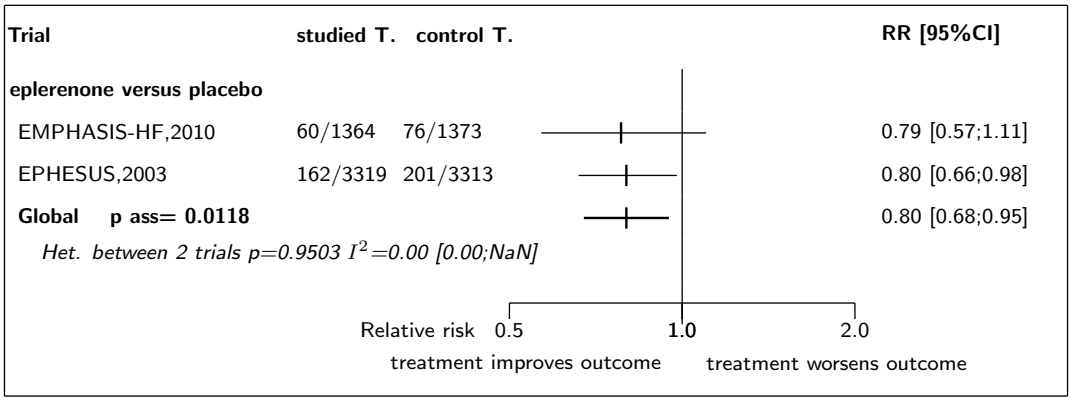


Figure 4.5: *Forest's plot for hospitalisation for heart failure*

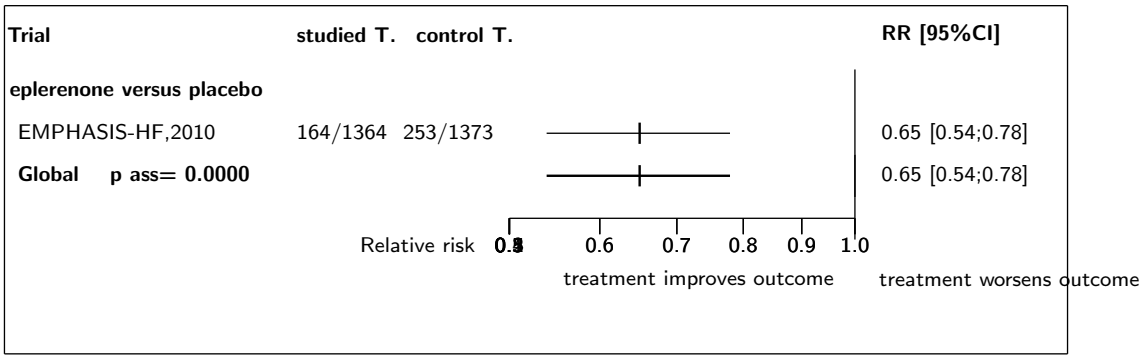


Figure 4.6: *Forest's plot for death from any cause or hospitalization for any reason*

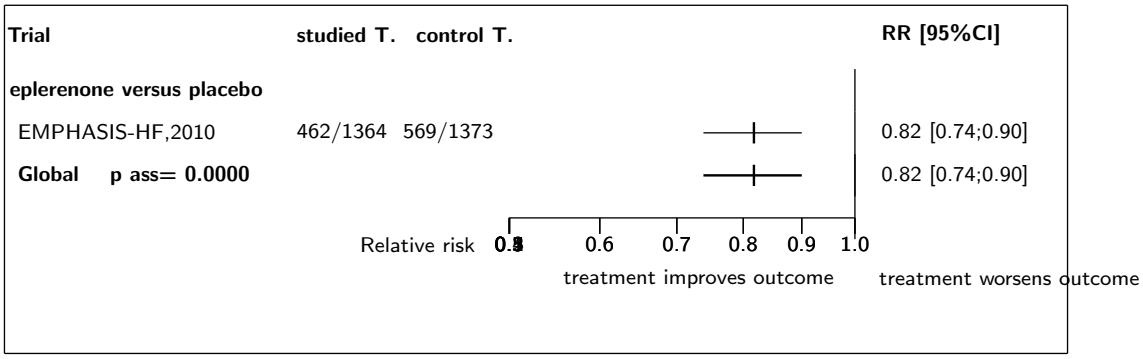


Figure 4.7: *Forest's plot for death from any cause or hospitalization for heart failure*

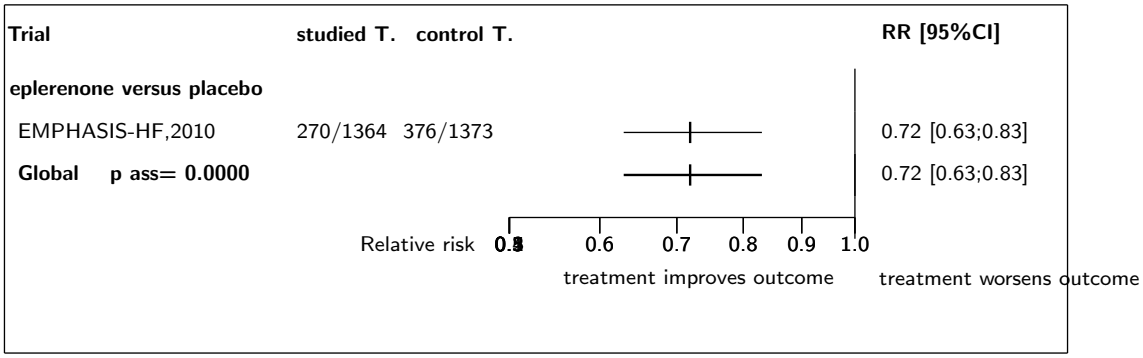


Figure 4.8: *Forest's plot for hospitalization for any reason*

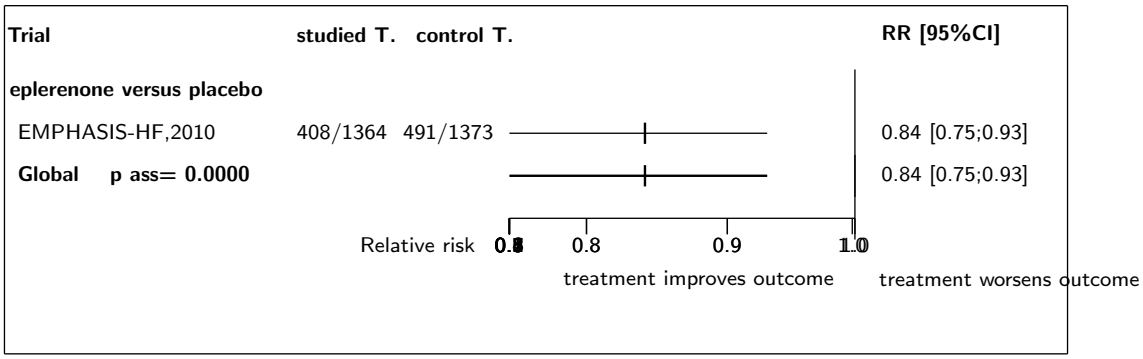


Figure 4.9: *Forest's plot for cardiovascular death*

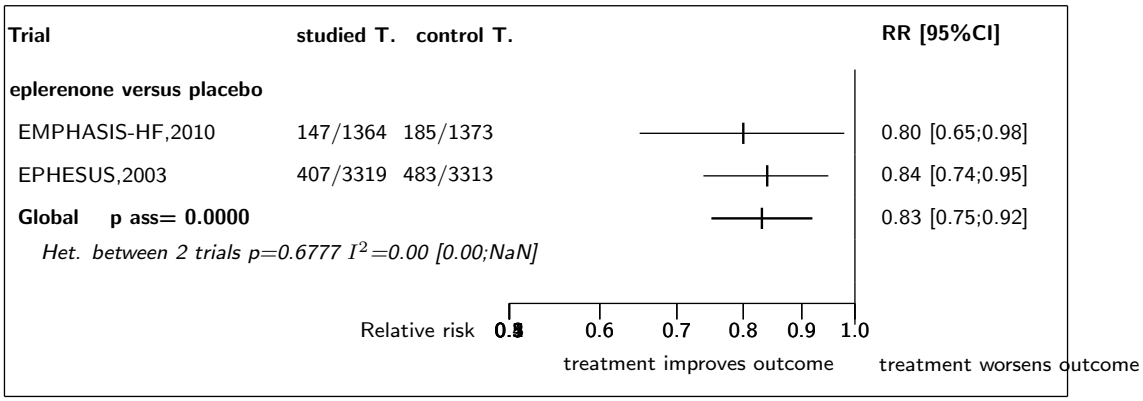


Figure 4.10: *Forest's plot for all cause death*

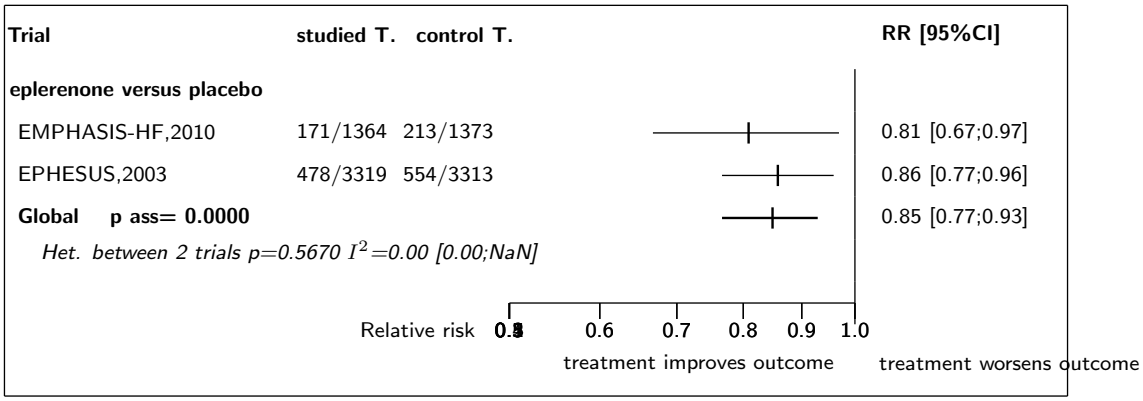
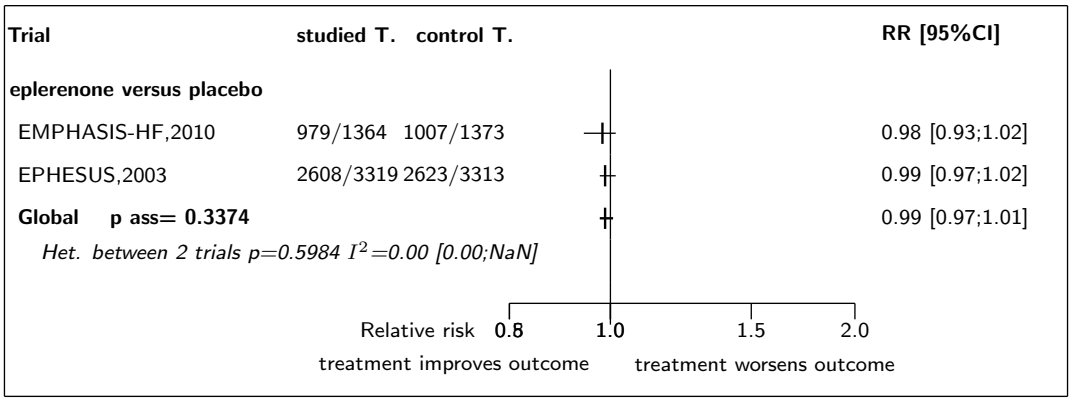


Figure 4.11: *Forest's plot for adverse events*



References

[1] Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2010;12:617-22. [PMID=20388647]

[2] Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2010;12:617-22. [PMID=20388647]

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5 Detailed results for spironolactone

5.1 Available trials

A total of 11 RCTs which randomized 2192 patients were identified: 3 trials compared spironolactone with control and 8 trials compared spironolactone with placebo.
The average study size was 199 patients (range 20 to 1663). The first study was published in 1997, and the last study was published in 2005.
A total of 6 trials were double blind and 5 were open-label in design. All included studies were reported in English language. We did not found any unpublished trial.
Hospitalisation for cardiovascular causes data was reported in 1 trials; 1 trials reported data on all cause death; 1 trials reported data on exacerbation of heart failure; 1 trials reported data on serious hyperkalemia; 1 trials reported data on cardiovascular death; 1 trials reported data on NYHA class improvement; 1 trials reported data on sudden death; 1 trials reported data on adverse events; and 1 trials reported data on adverse events leading to treatment discontinuation.
Following tables 6.1 (page 41), 6.2 (page 42), 6.3 (page 43), and 6.4 (page 43) summarized the main characteristics of the trials including in this systematic review of randomized trials of spironolactone.

Table 5.1: *Treatment description - aldosterone-receptor blockers - spironolactone*

Trial	Studied treatment	Control treatment
Spironolactone versus control		
Cicoira (2002) [1]	spironolactone 12.5 to 50 mg/day	control
Cicoira (2004) [2]	spironolactone	control
Ramires (2000) [3]	spironolactone	standard medical treatment
Spironolactone versus placebo		
Agostoni (2005) [4]	spironolactone 25mg/d	placebo
Farquharson (2000) [5]	spironolactone 50 mg/d	placebo
Macdonald (2004) [6]	spironolactone 12.5-50 mg/d	placebo
MacFadyen (1997) [7]	spironolactone (50-100 mg/day)	placebo
Mottram (2004) [8]	spironolactone 25 mg/d	placebo
RALES (1998) [9, 10, 11]	spironolactone (25 to 50 mg daily) Patients initialy 25 mg of spironolactone. After eight weeks, the dose could be increased to 50 mg once daily if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalemia. If hyperkalemia developed at any time, the dose could be decreased to 25 mg every other day; however, the investigator was encouraged first to adjust the doses of concomitant medications.	placebo

continued...

Trial	Studied treatment	Control treatment
	Concomittant treatment: Patient were treated with an ACE inhibitor (if tolerated) and a loop diuretic. Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted. Oral potassium supplements were not recommended unless hypokalemia (d	
Tsutamoto (2001) [12]	spironolactone 25 mg daily	placebo
Yee (2001) [13]	spironolactone 50mg/d	placebo

Table 5.2: *Descriptions of participants - aldosterone-receptor blockers - spironolactone*

Trial	Patients	
Spironolactone versus control		
Cicoira (2002) [1]	Patients with chronic heart failure	
Cicoira (2004) [2]	Chronic heart failure patients	
Ramires (2000) [3]	Patients with systolic dysfunction and NYHA class III CHF secondary to dilated or ischemic cardiomyopathy	
Spironolactone versus placebo		
Agostoni (2005) [4]	Stable chronic heart failure patients with reduced influences lung diffusion (DLCO)	
Farquharson (2000) [5]	Patients with NYHA class II to III chronic heart failure on standard diuretic/ACE inhibitor therapy	
Macdonald (2004) [6]	Patients with New York Heart Association class I-II congestive heart failure taking optimal treatment (including beta blockers)	
MacFadyen (1997) [7]	Patients with stable chronic heart failure	
Mottram (2004) [8]	Hypertensive patients with diastolic heart failure	
RALES (1998) [9, 10, 11]	Patients with severeheart failure **Inclusion criteria:** new York Heart Association (NYHA) class IV heart failure within the sixmonths before enrollment and NYHA class III or IV atthe time of enrollment, diagnosis of heart failureat least six weeks before enrollment, treated with anACE inhibitor (if tolerated) and a loop diuretic, and had a left-ventricular ejection fraction of no more than 35 percent withinthe six months before enrollment (with no clinically significantintercurrent event).	**Exclusion criteria:** primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolicheart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease (other than heart failure), heart transplantation (or awaiting the procedure), serum creatinine concentration of more than 2.5 mg per deciliter (221 micromol per liter), serum potassium concentration of more than 5.0 mmol per liter.
Tsutamoto (2001) [12]	Patients with mild-to-moderate nonischemic congestive heart failure	
Yee (2001) [13]	Patients with New York Heart Association class II to IV congestive heart failure	

Table 5.3: *Main patients characteristics - aldosterone-receptor blockers - spironolactone*

Trial	Characteristics
Spironolactone versus control	
Cicoira, 2002 [1]	
Cicoira, 2004 [2]	
Ramires, 2000 [3]	
Spironolactone versus placebo	
Agostoni, 2005 [4]	
Farquharson, 2000 [5]	
Macdonald, 2004 [6]	
MacFadyen, 1997 [7]	
Mottram, 2004 [8]	
RALES, 1998 [9, 10, 11]	
Tsutamoto, 2001 [12]	
Yee, 2001 [13]	

Table 5.4: *Design and methodological quality of trials - aldosterone-receptor blockers - spironolactone*

Trial	Design	Duration	Centre	Primary endpoint
Spironolactone versus control				
Cicoira, 2002 [1] n=106	Parallel groups open exploratory trial	12 months		Ventricular Function and Exercise tolerance
Cicoira, 2004 [2] n=93	open	12 months		ACE gene insertion/deletion polymorphism
Ramires, 2000 [3] n=35	Parallel groups open exploratory trial	20 weeks		none
Spironolactone versus placebo				
Agostoni, 2005 [4] n=29	Parallel groups open exploratory trial	6 months	Italy 1 centres	
Farquharson, 2000 [5] n=20	double blind exploratory trial	4 weeks		none
Macdonald, 2004 [6] n=86	Cross over double blind exploratory trial	3 months		none

continued...

Trial	Design	Duration	Centre	Primary endpoint
MacFadyen, 1997 [7] n=37	Parallel groups double blind exploratory trial	8 weeks		none
Mottram, 2004 [8] n=30	double blind exploratory trial	6 months		myocardial function
RALES, 1998 [9, 10, 11] n=1663	Parallel groups Open confirmatory trial at risk of bias	24 mo inclusion period: march 1995 - december 1996	World 195 centres	death from any cause
Tsutamoto, 2001 [12] n=37	Parallel groups double blind exploratory trial	12 weeks	Japan	neurohumoral factors
Yee, 2001 [13] n=56	double blind	4 weeks		

5.2 Meta-analysis results

The results are detailed in table 6.5 (page 45). This table is followed by the Forest's plot corresponding to each endpoint.

Spironolactone versus control

No data were presented in the 3 trials identified

Spironolactone versus placebo

Only one of the 8 studies eligible for this comparison provided data on **hospitalisation for cardiovascular causes**. The analysis detected a statistically significant difference in favor of spironolactone in hospitalisation for cardiovascular causes, with a RR of 0.79 (95% CI 0.70 to 0.90, p=0.0000).
Only one of the 8 studies eligible for this comparison provided data on **serious hyperkalemia**. No statistically significant difference between the groups was found in serious hyperkalemia, with a RR of 2.05 (95% CI 0.19 to 22.52, p=0.5585).
Only one of the 8 studies eligible for this comparison provided data on **sudden death**. The analysis detected a statistically significant difference in favor of spironolactone in sudden death, with a RR of 0.76 (95% CI 0.58 to 1.00, p=0.0487).
Only one of the 8 studies eligible for this comparison provided data on **exacerbation of heart failure**. The analysis detected a statistically significant difference in favor of spironolactone in exacerbation of heart failure, with a RR of 0.79 (95% CI 0.71 to 0.88, p=0.0000).
Only one of the 8 studies eligible for this comparison provided data on **NYHA class improvement**. The analysis detected a statistically significant difference in favor of placebo in NYHA class improvement, with a RR of 1.24 (95% CI 1.09 to 1.41, p=0.0000).
Only one of the 8 studies eligible for this comparison provided data on **cardiovascular death**. The analysis detected a statistically significant difference in favor of spironolactone in cardiovascular death, with a RR of 0.74 (95% CI 0.65 to 0.85, p=0.0000).
Only one of the 8 studies eligible for this comparison provided data on **all cause death**. The analysis detected a statistically significant difference in favor of spironolactone in all cause death, with a RR of 0.75 (95% CI 0.67 to 0.85, p=0.0000).

Table 5.5: *Results details - aldosterone-receptor blockers - spironolactone*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
spironolactone versus control						
No data were presented in the trial identified						
spironolactone versus placebo						
hospitalisation for cardiovascular causes	RR=0.79	[0.70;0.90]	0.0000	1.0000 (I^2=0.00)	1	1663
serious hyperkalemia	RR=2.05	[0.19;22.52]	0.5585	1.0000 (I^2=0.00)	1	1663
sudden death	RR=0.76	[0.58;1.00]	0.0487	1.0000 (I^2=0.00)	1	1663
exacerbation of heart failure	RR=0.79	[0.71;0.88]	0.0000	1.0000 (I^2=1.00)	1	1663
NYHA class improvement	RR=1.24	[1.09;1.41]	0.0000	1.0000 (I^2=0.00)	1	1663
cardiovascular death	RR=0.74	[0.65;0.85]	0.0000	1.0000 (I^2=0.00)	1	1663
all cause death	RR=0.75	[0.67;0.85]	0.0000	1.0000 (I^2=0.00)	1	1663
adverse events leading to treatment discontinuation	RR=1.59	[1.08;2.33]	0.0191	1.0000 (I^2=0.00)	1	1663
adverse events	RR=1.03	[0.99;1.08]	0.1659	1.0000 (I^2=0.00)	1	1663

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 hospitalisation for cardiovascular causes*

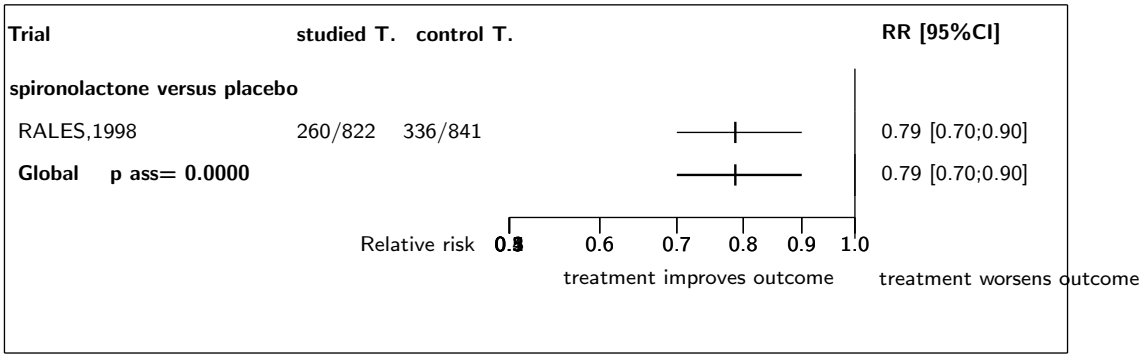


Figure 5.2: *Forest's plot for serious hyperkalemia*

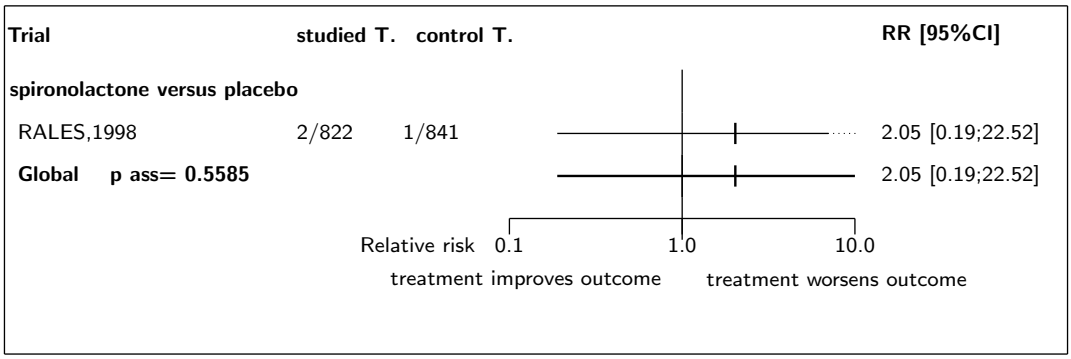


Figure 5.3: *Forest's plot for sudden death*

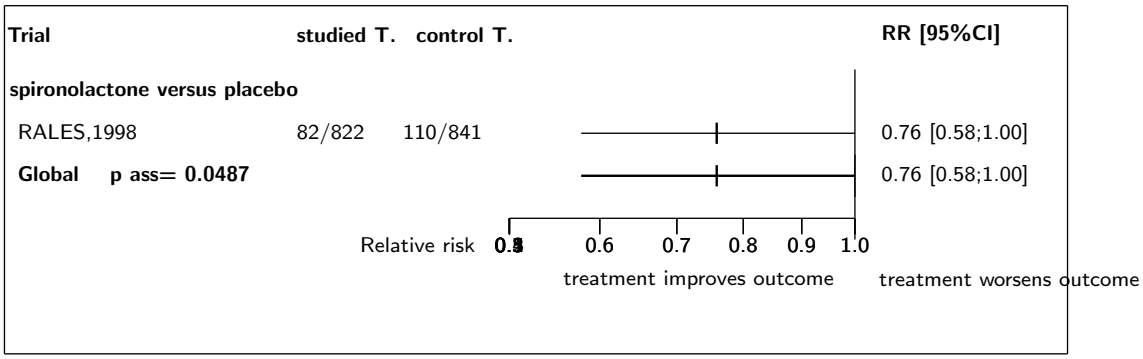


Figure 5.4: *Forest's plot for exacerbation of heart failure*

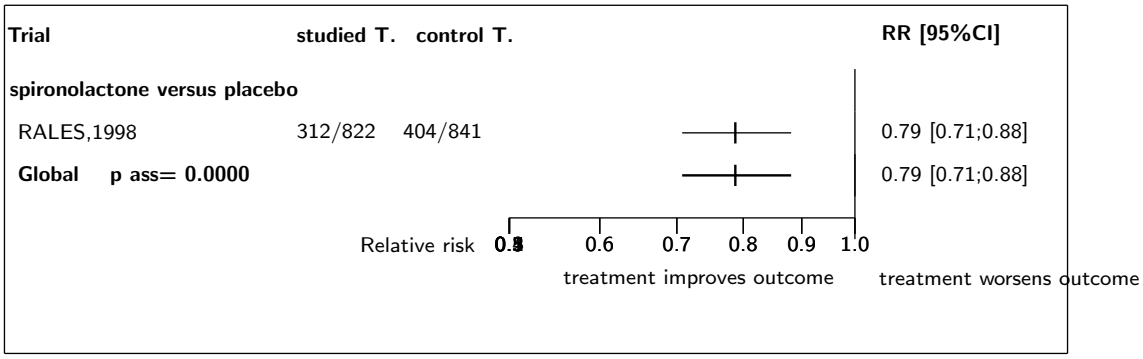


Figure 5.5: *Forest's plot for NYHA class improvement*

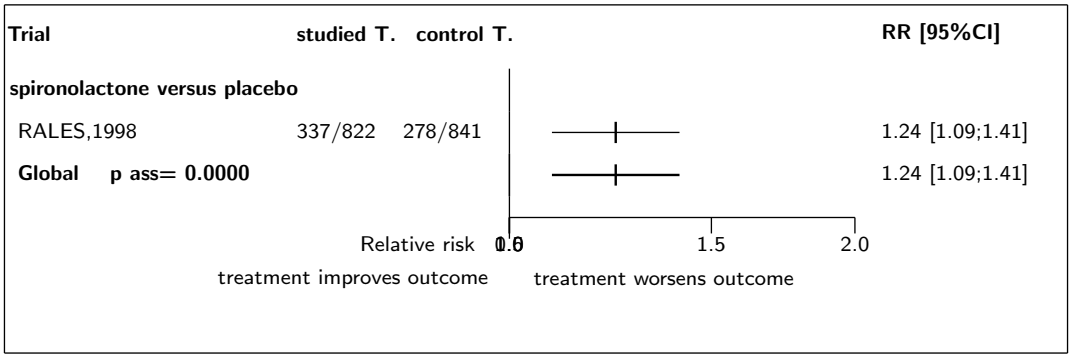


Figure 5.6: *Forest's plot for cardiovascular death*

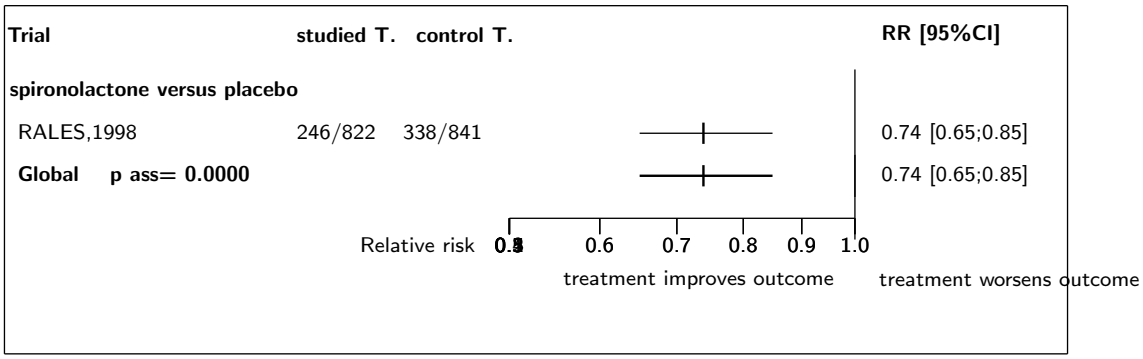


Figure 5.7: *Forest's plot for all cause death*

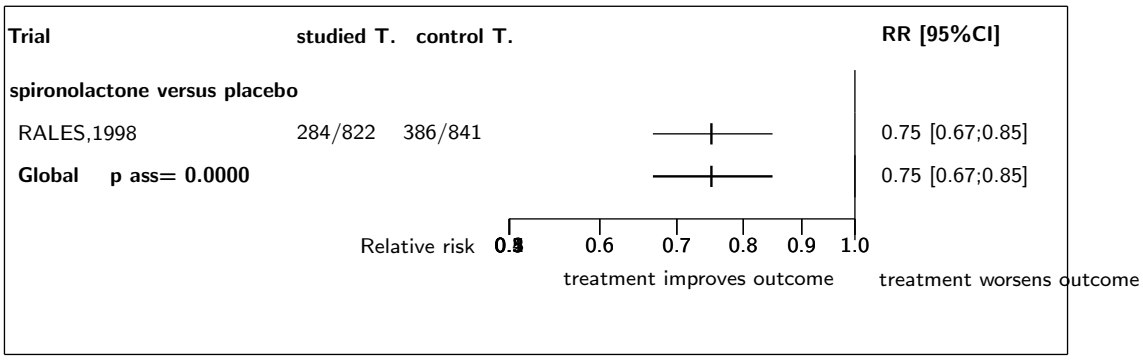


Figure 5.8: *Forest's plot for adverse events leading to treatment discontinuation*

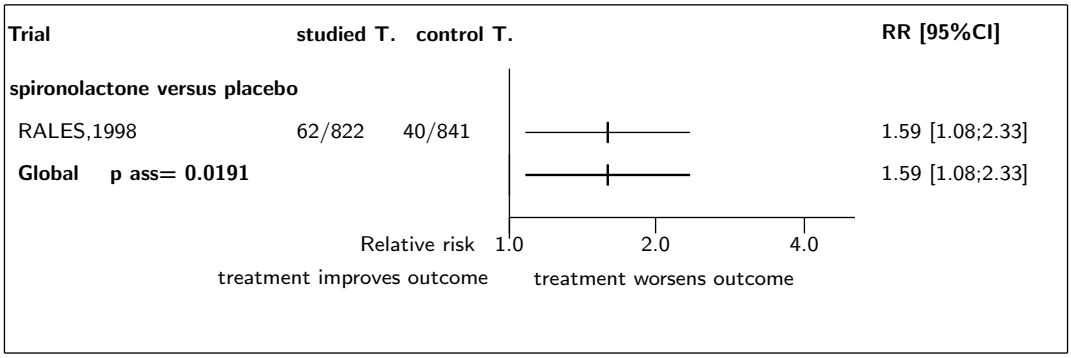
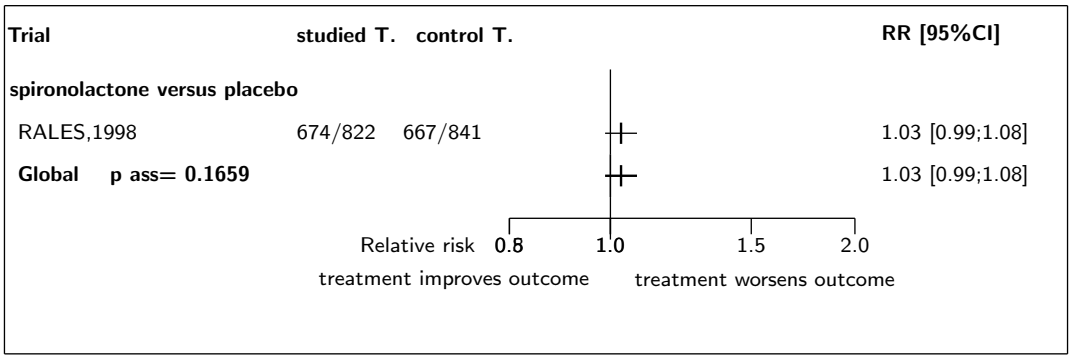


Figure 5.9: *Forest's plot for adverse events*



References

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[2] Cicoira M, Rossi A, Bonapace S, Zanolla L, Perrot A, Francis DP, Golia G, Franceschini L, Osterziel KJ, Zardini P,. Effects of ACE gene insertion/deletion polymorphism on response to spironolactone in patients with chronic heart failure. Am J Med 2004;116:657-61. [PMID=15121491]

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[5] Farquharson CA, Struthers AD,. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation 2000;101:594-7. [PMID=10673249]

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[13] Yee KM, Pringle SD, Struthers AD,. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001;37:1800-7. [PMID=11401114]

6 Detailed results for spironolactone+captopril

6.1 Available trials

Only one trial which randomized 35 patients was identified: it compared spironolactone+captopril with captopril.
This trial included 35 patients and was published in 1994.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 7.1 (page 50), 7.2 (page 50), 7.3 (page 50), and 7.4 (page 51) summarized the main characteristics of the trial including in this systematic review of randomized trials of spironolactone+captopril.

Table 6.1: *Treatment description - aldosterone-receptor blockers - spironolactone+captopril*

Trial	Studied treatment	Control treatment
Spironolactone+captopril versus captopril		
Han (1994) [1]	captopril plus spironolactone	captopril alone

Table 6.2: *Descriptions of participants - aldosterone-receptor blockers - spironolactone+captopril*

Trial	Patients
Spironolactone+captopril versus captopril	
Han (1994) [1]	Patients with refractory CHF and New York Heart Association functional class IV without renal dysfunction, hypotension and hyperkalemia

Table 6.3: *Main patients characteristics - aldosterone-receptor blockers - spironolactone+captopril*

Trial	Characteristics
Spironolactone+captopril versus captopril	
Han, 1994 [1]	

Table 6.4: *Design and methodological quality of trials - aldosterone-receptor blockers - spironolactone+captopril*

Trial	Design	Duration	Centre	Primary endpoint
Spironolactone+captopril versus captopril				
Han, 1994 [1] n=35	open exploratory trial	4 weeks	China	none

6.2 Meta-analysis results

The results are detailed in table 7.5 (page 51). This table is followed by the Forest's plot corresponding to each endpoint.

Spironolactone+captopril versus captopril

No data were presented in the 1 trial identified

Table 6.5: *Results details - aldosterone-receptor blockers - spironolactone+captopril*

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

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

References

[1] Han YL, Tong M, Jing QM, Hu XL, Liu JQ,. Combined therapy of captopril and spironolactone for refractory congestive heart failure. Chin Med J (Engl) 1994;107:688-92. [PMID=7805462]

7 Detailed results for spironolactone+furosemide

7.1 Available trials

Only one trial which randomized 22 patients was identified: it compared spironolactone+furosemide with spironolactone+butizide.
This trial included 22 patients and was published in 1985.
This trial was open-label in design.
It was reported in English language.
data was reported in trials;
Following tables 8.1 (page 52), 8.2 (page 52), 8.3 (page 52), and 8.4 (page 53) summarized the main characteristics of the trial including in this systematic review of randomized trials of spironolactone+furosemide.

Table 7.1: *Treatment description - aldosterone-receptor blockers - spironolactone+furosemide*

Trial	Studied treatment	Control treatment
Spironolactone+furosemide versus spironolactone+butizide		
Mauersberger (1985) [1]	spironolactone 50mg + furosemide 20 mg	spironolactone 50mg + butizide 5mg

Table 7.2: *Descriptions of participants - aldosterone-receptor blockers - spironolactone+furosemide*

Trial	Patients
Spironolactone+furosemide versus spironolactone+butizide	
Mauersberger (1985) [1]	Patients with congestive heart failure

Table 7.3: *Main patients characteristics - aldosterone-receptor blockers - spironolactone+furosemide*

Trial	Characteristics
Spironolactone+furosemide versus spironolactone+butizide	
Mauersberger, 1985 [1]	

Table 7.4: *Design and methodological quality of trials - aldosterone-receptor blockers - spironolactone+furosemide*

Trial	Design	Duration	Centre	Primary endpoint
Spironolactone+furosemide versus spironolactone+butizide				
Mauersberger, 1985 [1] n=22	open exploratory trial			none

7.2 Meta-analysis results

The results are detailed in table 8.5 (page 53). This table is followed by the Forest's plot corresponding to each endpoint.

Spironolactone+furosemide versus spironolactone+butizide

No data were presented in the 1 trial identified

Table 7.5: *Results details - aldosterone-receptor blockers - spironolactone+furosemide*

Comparison	Endpoint	Effect	95% CI	p ass	p het	k	n
spironolactone+furosemide versus spironolactone+butizide							
No data were presented in the trial identified							

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

References

[1] Mauersberger H, Rangoonwala B, Ehrlich E,. [Comparative study of 2 diuretic-containing combination preparations in patients with edematous heart failure]. Wien Med Wochenschr 1985;135:205-13. [PMID=4013351]

8 Global meta-analysis: all aldosterone-receptor blockers

8.1 Global meta-analysis: all aldosterone-receptor blockers versus captopril

Table 8.1: *All aldosterone-receptor blockersversus captopril*

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

legend B

8.2 Global meta-analysis: all aldosterone-receptor blockers versus control

Table 8.2: *All aldosterone-receptor blockersversus control*

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

legend B

8.3 Global meta-analysis: all aldosterone-receptor blockers versus furosemide

Table 8.3: *All aldosterone-receptor blockersversus furosemide*

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

legend B

8.4 Global meta-analysis: all aldosterone-receptor blockers versus placebo

Table 8.4: *All aldosterone-receptor blockersversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n	Plot
hospitalisation for cardiovascular causes	RR=0.86	0.74;1.01	0.0722	0.0512 (0.74)	2	8295	

continued...

Endpoint	Effect	95% CI	p ass	p het	k	n	Plot
death from cardiovascular causes or hospitalization for cardiovascular causes	RR=0.89	0.82;0.96	0.0028	1.0000 (0.00)	1	6632	
serious hyperkalemia	RR=1.74	1.20;2.50	0.0031	0.0998 (0.57)	3	11032	
sudden death	RR=0.79	0.68;0.91	0.0000	0.9521 (0.00)	3	11032	
hospitalisation for heart failure	RR=0.65	0.54;0.78	0.0000	1.0000 (0.00)	1	2737	
death from any cause or hospitalization for any reason	RR=0.82	0.74;0.90	0.0000	1.0000 (0.00)	1	2737	
exacerbation of heart failure	RR=0.79	0.71;0.88	0.0000	1.0000 (1.00)	1	1663	
NYHA class improvement	RR=1.24	1.09;1.41	0.0000	1.0000 (0.00)	1	1663	
death from any cause or hospitalization for heart failure	RR=0.72	0.63;0.83	0.0000	1.0000 (0.00)	1	2737	
hospitalization for any reason	RR=0.84	0.75;0.93	0.0000	1.0000 (0.00)	1	2737	
cardiovascular death	RR=0.80	0.73;0.86	0.0000	0.4188 (0.00)	3	11032	
all cause death	RR=0.81	0.74;0.88	0.0000	0.2739 (0.23)	3	11032	

legend B

8.5 Global meta-analysis: all aldosterone-receptor blockers versus spironolactone+butizide

Table 8.5: *All aldosterone-receptor blockersversus spironolactone+butizide*

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

legend B

9 Ongoing studies

A total of 5 ongoing studies were still ongoing at the date of this report. A list of these ongoing studies with a brief description is given table 10.1.

Table 9.1: *Ongoing studies for aldosterone-receptor blockers*

Study	Description
Nouvel essai NCT00125437	spironolactone larger dose **vs.** spironolactone standard dose severe congestive heart failure in patients with nonischemic cardiomyopathy
PIE II NCT00123955	Spironolactone 25mg tablet daily for 9 months **vs.** placebo elderly patients with isolated diastolic heart failure
REMODEL NCT00082589	Eplerenone **vs.** placebo Patients with left ventricular systolic dysfunction (EF Less Than or Equal to 35%) and mild to moderate heart failure

continued...

Study	Description
TOPCAT NCT00094302	spironolactone titrated up to 45 mg daily **vs.** placebo adults with heart failure and left ventricular ejection fraction of at least 45%
Weir NCT00132093	eplerenone **vs.** placebo patients with acute myocardial infarction

10 Excluded studies

No trial was excluded.

Part I

Trial's summary - Evidence table

Table 10.1: *Bednarz, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=21 (11 vs. 10) **Follow-up duration:** **Study design:** Randomized controlled trial Open Exploratory trial	Patients with NYHA class III to IV congestive heart failure	**Studied treatment:** Aldactone 200 mg i.v **Control treatment:** furosemide 20 mg i.v	

References

Bednarz B, Cybulski J, Chamiec T,. [Comparison of the therapeutic efficacy of spironolactone and furosemide in patients with severe congestive heart failure]. Pol Merkuriusz Lek 2000;9:519-21 [PMID=11081314]
Bednarz B, Cybulski J, Chamiec T. [Comparison of the therapeutic efficacy of spironolactone and furosemide in patients with severe congestive heart failure]. Pol Merkuriusz Lek 2000 Aug;9:519-21 [PMID=11081314]

Table 10.2: *EMPHASIS-HF, 2010 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=2737 (1364 vs. 1373) **Follow-up duration:** 21 months **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 29 countries, 278 centres **Inclusion period:** Mar 2006 - may 2010	Patients withNew York Heart Association class II heart failure and an ejection fraction of nomore than 35% **Inclusion criteria:** age of at least 55 years, NYHA functional class II symptoms, an ejection fraction of no more than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography), and treatment with an angiotensin-convertingenzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose **Exclusion criteria:** acute myocardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol per liter, an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area, a need for a potassiumsparing diuretic, any other clinically significant, coexisting condition	**Studied treatment:** eplerenone started at a dose of 25 mg once daily and increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m2), provided the serum potassium level was no more than 5.0 mmol per liter.Therafter the study dose was decreasesif the serum potassiumlevel was 5.5 to 5.9 mmol per liter and towithhold the study drug if the serum potassiumlevel was 6.0 mmol per liter or more. **Control treatment:** placebo **Concomittant treat.:**background standard heart failure therapy	Serious hyperkalemia RR=2.19 [1.58;3.04] (Hyperkalemia) Sudden death RR=0.79 [0.57;1.11] (Sudden cardiac death) Hospitalisation for heart failure RR=0.65 [0.54;0.78] (Hospitalization for heart failure) Death from any cause or hospitalization for any reason RR=0.82 [0.74;0.90] (Death from any cause or hospitalization for any reason)

References

Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2010;12:617-22 [PMID=20388647]
Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail 2010;12:617-22 [PMID=20388647]
Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med 2010 Nov 14;: [PMID=21073363]

Table 10.3: *EPHESUS, 2003 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=6632 (3319 vs. 3313) **Follow-up duration:** 16 mo (mean, range 0 to 33) **Study design:** Randomized controlled trial Parallel groups Double blind Confirmatory trial at low risk of bias 37 countries, 674 centres **Inclusion period:** Dec 1999 - dec 2001	Patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure **Inclusion criteria:** enrollment 3 to 14 days after acute myocardial infarction documented according to standard criteria;criteria; left ventricular dysfunction as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the **Exclusion criteria:** use of potassium-sparing diuretics; serum creatinine concentration of more than 2.5 mg per deciliter (220 micromol per liter); serum potassium concentration of more than 5.0 mmol per liter	**Studied treatment:** eplerenone 25 mg per day initially, titrated to amaximum of 50 mg per day if the serum potassium concentration was higher than 5.5 mmol per liter, the dose of the study drug was reduced or treatment was temporarily discontinued until the serum potassium concentration fell below 5.5 mmol per liter **Control treatment:** placebo **Concomittant treat.:**optimal medical therapy, which could include ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy	Hospitalisation for cardiovascular causes RR=0.93 [0.84;1.03] Death from cardiovascular causes or hospitalization for cardiovascular causes RR=0.89 [0.82;0.96] Serious hyperkalemia RR=1.43 [1.14;1.78] Sudden death RR=0.80 [0.66;0.98]

References

Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M, van Veldhuisen DJ, Zannad F, Krum H, Mukherjee R, Vincent J. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005 Aug 2;46:425-31 [PMID=16053953]

Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003 Apr 3;348:1309-21 [PMID=12668699]

Table 10.4: *Cicoira, 2002 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=106 (54 vs. 52) **Follow-up duration:** 12 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Patients with chronic heart failure	**Studied treatment:** spironolactone 12.5 to 50 mg/day **Control treatment:** control	

Reference

Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, Marino P, Zardini P,. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2002;40:304-10 [PMID=12106936]

Table 10.5: *Cicoira, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=93 (47 vs. 46) **Follow-up duration:** 12 months **Study design:** Randomized controlled trial Open	Chronic heart failure patients	**Studied treatment:** spironolactone **Control treatment:** control	

Reference

Cicoira M, Rossi A, Bonapace S, Zanolla L, Perrot A, Francis DP, Golia G, Franceschini L, Osterziel KJ, Zardini P,. Effects of ACE gene insertion/deletion polymorphism on response to spironolactone in patients with chronic heart failure. Am J Med 2004;116:657-61 [PMID=15121491]

Table 10.6: *Ramires, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=35 (19 vs. 16) **Follow-up duration:** 20 weeks **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial	Patients with systolic dysfunction and NYHA class III CHF secondary to dilated or ischemic cardiomyopathy	**Studied treatment:** spironolactone **Control treatment:** standard medical treatment	

Reference

Ramires FJ, Mansur A, Coelho O, Maranho M, Gruppi CJ, Mady C, Ramires JA,. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol 2000;85:1207-11 [PMID=10802002]

Table 10.7: *Agostoni, 2005 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=29 (14 vs. 15) **Follow-up duration:** 6 months **Study design:** Randomized controlled trial Parallel groups Open Exploratory trial Italy, 1 centres	Stable chronic heart failure patients with reduced influences lung diffusion (DLCO)	**Studied treatment:** spironolactone 25mg/d **Control treatment:** placebo	

Reference

Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, Cattadori G, Palermo P,. Spironolactone improves lung diffusion in chronic heart failure. Eur Heart J 2005;26:159-64 [PMID=15618072]

Table 10.8: *Farquharson, 2000 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=20 (10 vs. 10) **Follow-up duration:** 4 weeks **Study design:** Randomized controlled trial Double blind Exploratory trial	Patients with NYHA class II to III chronic heart failure on standard diuretic/ACE inhibitor therapy	**Studied treatment:** spironolactone 50 mg/d **Control treatment:** placebo	

Reference

Farquharson CA, Struthers AD,. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation 2000;101:594-7 [PMID=10673249]

Table 10.9: *Macdonald, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=86 (43 vs. 43) **Follow-up duration:** 3 months **Study design:** Randomized controlled trial Cross over Double blind Exploratory trial	Patients with New York Heart Association class I-II congestive heart failure taking optimal treatment (including beta blockers)	**Studied treatment:** spironolactone 12.5-50 mg/d **Control treatment:** placebo	

Reference

Macdonald JE, Kennedy N, Struthers AD,. Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. Heart 2004;90:765-70 [PMID=15201246]

Table 10.10: *MacFadyen, 1997 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=37 (21 vs. 16) **Follow-up duration:** 8 weeks **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial	Patients with stable chronic heart failure	**Studied treatment:** spironolactone (50-100 mg/day) **Control treatment:** placebo	

Reference

MacFadyen RJ, Barr CS, Struthers AD,. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997;35:30-4 [PMID=9302344]

Table 10.11: *Mottram, 2004 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (30 vs. 0) **Follow-up duration:** 6 months **Study design:** Randomized controlled trial Double blind Exploratory trial	Hypertensive patients with diastolic heart failure	**Studied treatment:** spironolactone 25 mg/d **Control treatment:** placebo	

Reference

Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH,. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation 2004;110:558-65 [PMID=15277317]

Table 10.12: *RALES, 1998 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=1663 (822 vs. 841) **Follow-up duration:** 24 mo **Study design:** Randomized controlled trial Parallel groups Open Confirmatory trial at risk of bias World, 195 centres **Inclusion period:** march 1995 - december 1996	Patients with severeheart failure **Inclusion criteria:** New York Heart Association (NYHA) class IV heart failure within the sixmonths before enrollment and NYHA class III or IV atthe time of enrollment, diagnosis of heart failureat least six weeks before enrollment, treated with anACE inhibitor (if tolerated) and a loop diuretic, and had a leftventricular ejection fraction of no more than 35 percent withinthe six months before enrollment (with no clinically significantintercurrent event). **Exclusion criteria:** primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolicheart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease (other than heart failure), heart transplantation (or awaiting the procedure), serum creatinine concentration of more than 2.5 mg per deciliter (221 micromol per liter), serum potassium concentration of more than 5.0 mmol per li	**Studied treatment:** spironolactone (25 to 50 mg daily) Patients initialy 25 mg of spironolactone. After eight weeks, the dose could be increased to 50 mg once daily if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalemia. If hyperkalemia developed at any time, the dose could be decreased to 25 mg every other day; however, the investigator was encouraged first to adjust the doses of concomitant medications. **Control treatment:** placebo **Concomittant treat.:**Patient were treated with an ACE inhibitor (if tolerated) and a loop diuretic. Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted. Oral potassium supplements were not recommended unless hypokalemia (d	Hospitalisation for cardiovascular causes RR=0.79 [0.70;0.90] (hospitalization for CARDIAC causes) Serious hyperkalemia RR=2.05 [0.19;22.52] Sudden death RR=0.76 [0.58;1.00] Exacerbation of heart failure RR=0.79 [0.71;0.88]

References

. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). Am J Cardiol 1996;78:902-7 [PMID=8888663]
Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17 [PMID=10471456]
Pitt D,. ACE inhibitor co-therapy in patients with heart failure: rationale for the Randomized Aldactone Evaluation Study (RALES). Eur Heart J 1995;16 Suppl N:107-10 [PMID=8682055]

Table 10.13: *Tsutamoto, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=37 (20 vs. 17) **Follow-up duration:** 12 weeks **Study design:** Randomized controlled trial Parallel groups Double blind Exploratory trial Japan	Patients with mild-to-moderate nonischemic congestive heart failure	**Studied treatment:** spironolactone 25 mg daily **Control treatment:** placebo	

Reference

Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Matsui T, Kinoshita M,. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1228-33 [PMID=11300427]

Table 10.14: *Yee, 2001 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=56 (28 vs. 28) **Follow-up duration:** 4 weeks **Study design:** Randomized controlled trial Double blind	Patients with New York Heart Association class II to IV congestive heart failure	**Studied treatment:** spironolactone 50mg/d **Control treatment:** placebo	

Reference

Yee KM, Pringle SD, Struthers AD,. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001;37:1800-7 [PMID=11401114]

Table 10.15: *Han, 1994 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=35 (19 vs. 16) **Follow-up duration:** 4 weeks **Study design:** Randomized controlled trial Open Exploratory trial China	Patients with refractory CHF and New York Heart Association functional class IV without renal dysfunction, hypotension and hyperkalemia	**Studied treatment:** captopril plus spironolactone **Control treatment:** captopril alone	

Reference

Han YL, Tong M, Jing QM, Hu XL, Liu JQ,. Combined therapy of captopril and spironolactone for refractory congestive heart failure. Chin Med J (Engl) 1994;107:688-92 [PMID=7805462]

Table 10.16: *Mauersberger, 1985 - Trial synopsis*

Trial details	Patients	Treatments	Outcomes
n=0 (22 vs. 0) **Follow-up duration:** **Study design:** Randomized controlled trial Open Exploratory trial	Patients with congestive heart failure	**Studied treatment:** spironolactone 50mg + furosemide 20 mg **Control treatment:** spironolactone 50mg + butizide 5mg	

Reference

Mauersberger H, Rangoonwala B, Ehrlich E,. [Comparative study of 2 diuretic-containing combination preparations in patients with edematous heart failure]. Wien Med Wochenschr 1985;135:205-13 [PMID=4013351]