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Effects of mineralocorticoid receptor antagonists on the risk of thrombosis, bleeding and mortality: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Aldosterone seems to influence the haemostatic system by several mechanisms and to increase the risk of thrombosis. The objective of this meta-analysis was to assess the impact of inhibition of the mineralocorticoid receptor due to the use of mineralocorticoid receptor antagonists (MRAs) on venous and arterial thrombosis, bleeding events and mortality.

Materials and methods: We systematically searched PubMed and EMBASE through August 1, 2014, without language restrictions. Randomised controlled trials (RCTs) that tested the effect of MRAs versus active control/no treatment and reported data on thrombotic or bleeding events or mortality in patients with common causes of secondary hyperaldosteronism were included.

Results: 20 published RCTs reported in 19 papers for a total of 17,610 patients met inclusion criteria. Of these, all reported data on mortality, 15 on cardiovascular mortality, 14 on thrombotic events and 12 reported data on bleeding events. No RCTs investigated patients with primary hyperaldosteronism. 19 RCTs were performed in patients with hypertension and heart failure. In general, the heterogeneity was low. No differences were observed in arterial thrombotic and bleeding events. Patients treated with MRAs had 20% lower odds of total mortality and 23% of cardiovascular mortality compared with controls (odds ratio (OR) 0.80, 95% confidence interval (CI) 0.73–0.87 and OR 0.77, 95% CI 0.70–0.85, respectively).

Conclusion: Inhibition of the mineralocorticoid receptor with MRAs in patients with hypertension and heart failure does not change the risk of myocardial infarction, stroke and bleeding events. Our meta-analysis confirms the favourable effects of MRAs on total and cardiovascular mortality. These data suggest that MRAs can be considered as safe regarding their effects on haemostasis in patients with hypertension and heart failure.

Contents

Abbreviations: CV, cardiovascular; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; RCTs, randomised clinical trials; PE, pulmonary embolism; DVT, deep venous thrombosis; OR, odds ratio; CI, confidence interval; PAI-1, plasminogen activator inhibitor-1.

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1. Introduction

Both altered coagulation and fibrinolysis markers and thrombotic disorders have been described in several endocrine diseases. One of the hormones of interest is aldosterone, a steroid hormone produced by the adrenal glands, endothelial cells, vascular smooth muscle cells and, locally, in tissues such as the brain and the heart muscle [1]. It mainly acts to conserve sodium (and with it, water) and to promote potassium excretion. Several mechanisms have been suggested by which aldosterone interacts with the cardiovascular (CV) system increasing the risk of CV disease: it may promote endothelial dysfunction, reduce vascular compliance, impair baroreceptor function and cause myocardial and vascular fibrosis [2]. There are limited and contradictory data of aldosterone on coagulation and fibrinolysis but it is suggested that the net effect of aldosterone promotes a procoagulant state [3–7]. In a retrospective case–control study, compared to patients with essential hypertension, the risk of stroke was 4-fold in primary hyperaldosteronism and the risk of non-fatal myocardial infarction (MI) 6.5-fold [8]. Considering these data, it's possible that the positive effect of mineralocorticoid receptor antagonists (MRAs) may be, partially, mediated by an effect on haemostasis. It is also possible that inhibiting aldosterone with MRAs could lead to a bleeding risk. This was suggested by a population based case–control study that showed an increased risk of gastrointestinal bleeding in patients using spironolactone [9]. Meta-analyses have explored the effect of MRAs on mortality, heart failure including its associated comorbidities and blood pressure. Analyses assessing the effect of inhibition of the mineralocorticoid receptor due to MRA use on thrombotic and bleeding events in patients with primary hyperaldosteronism and/or common causes of secondary hyperaldosteronism have been lacking. Accordingly, we attempted to conduct a meta-analysis of existing randomised controlled trials (RCTs) of MRAs compared to placebo or control used in patients with primary or common causes of secondary hyperaldosteronism with the hypothesis that MRAs could affect the haemostatic system and thereby may decrease the risk of thrombosis and increase the risk of bleeding events. Our secondary objective was to confirm the favourable effects of MRAs on mortality.

2. Materials and methods

We performed a systematic review and meta-analysis of RCTs of MRAs in patients with primary hyperaldosteronism or conditions that are associated with secondary hyperaldosteronism, according to the PRISMA guidelines [10].

2.1. Data sources

We conducted a systematic search of the major scientific databases PubMed (MEDLINE) and EMBASE without language restrictions through August 1, 2014, for RCTs (for keywords please refer to Supplementary data). In addition, we searched references of the included manuscripts.

2.2. Study selection

We included RCTs that met the following criteria: enrolment of patients with primary or common causes of secondary hyperaldosteronism (heart failure or left ventricular dysfunction, hypertension, liver cirrhosis with portal hypertension); randomisation of patients to MRA therapy versus placebo or no active treatment on top of standard therapy (control group); reporting data or corresponding author providing additional data on either one of the following: total and CV mortality, thrombotic or bleeding events and study duration ≥4 weeks. In case of a cross-over design the minimal washout period had to be 2 weeks. Imaging techniques and standardised diagnostic tools for assessment of venous thromboembolic events came into use from 1990 onwards and therefore we solely included RCTs from 1990.

2.3. Data extraction and quality assessment

Two reviewers (L.E. and B.S.) independently screened the abstracts of all the citations obtained by the search in a standardized and unblinded manner. The outcomes of both independent screenings were discussed and discrepancies were resolved by consensus. Full texts of studies that met inclusion criteria were retrieved for secondary data extraction using a standardized form that included baseline patient characteristics, study design, risk of bias, MRAs, primary and secondary outcomes. Primary outcome of our systematic review was the occurrence of thrombotic events including fatal and non-fatal MI, fatal and non-fatal stroke, fatal and non-fatal acute limb ischaemia, fatal and non-fatal pulmonary embolism (PE), deep venous thrombosis (DVT), unusual site venous thrombosis, (i.e. splanchnic vein thrombosis), and other arterial and venous thrombotic events. Secondary outcomes were the occurrence of total and CV mortality and minor and major bleeding events. Criteria for major bleedings were according to the

definition of the International Society of Thrombosis and Haemostasis [11]. All other bleeding events were noted as minor bleedings. The corresponding authors of the included studies were contacted for providing additional data. Risk of bias was assessed according to the Cochrane Collaboration Risk of Bias Tool [12]. Disagreement between the 2 reviewers was resolved by consensus and secondary review from one of the other investigators.

2.4. Statistical analysis

Statistical analysis was performed using Review Manager 5.2 [13] and extracted in accordance with intention to treat-analysis. We calculated the summary odds ratio (OR) and 95% confidence interval (CI) for the outcome variables by using Mantel–Haenszel fixed effects model. Random effects model was used in case of significant heterogeneity. Statistical heterogeneity was measured by the I^2 [2] statistic. A priori, we defined significant heterogeneity between trials as an I^2 [2] value of >30% (>30 and ≤50% as intermediate heterogeneity with >50% as high heterogeneity). Clinical heterogeneity between the trials was explored by using subgroup analysis on the patient population, MRA agent and dosage used.

3. Results

3.1. Study selection

Our search strategy yielded 2514 studies (Fig. 1). The full texts of 61 studies were assessed for eligibility. 13 were excluded for the reasons depicted in Fig. 1 (references available on request). Finally, 20 RCTs reported in 19 papers, for a total of 17,610 patients, met our inclusion criteria [14–32]. The study characteristics of all included RCTs are summarized in Tables 1 and 2.

3.2. Available data

5 RCTs reported ≥1 our outcomes of interest as a primary outcome (Table 2), 19 RCTs described ≥1 outcome of interest in their result section including the description of serious adverse events and, finally, corresponding authors of 7 RCTs provided additional data on outcomes of interest. Data on fatal and non-fatal MI were available in 15 RCTs for a total of 16,956 patients. Data on fatal and non-fatal stroke were available in 14 RCTs for a total of 16,851 patients. Data on our other primary outcomes were available in 11 RCTs for a total of 10,202 patients, except

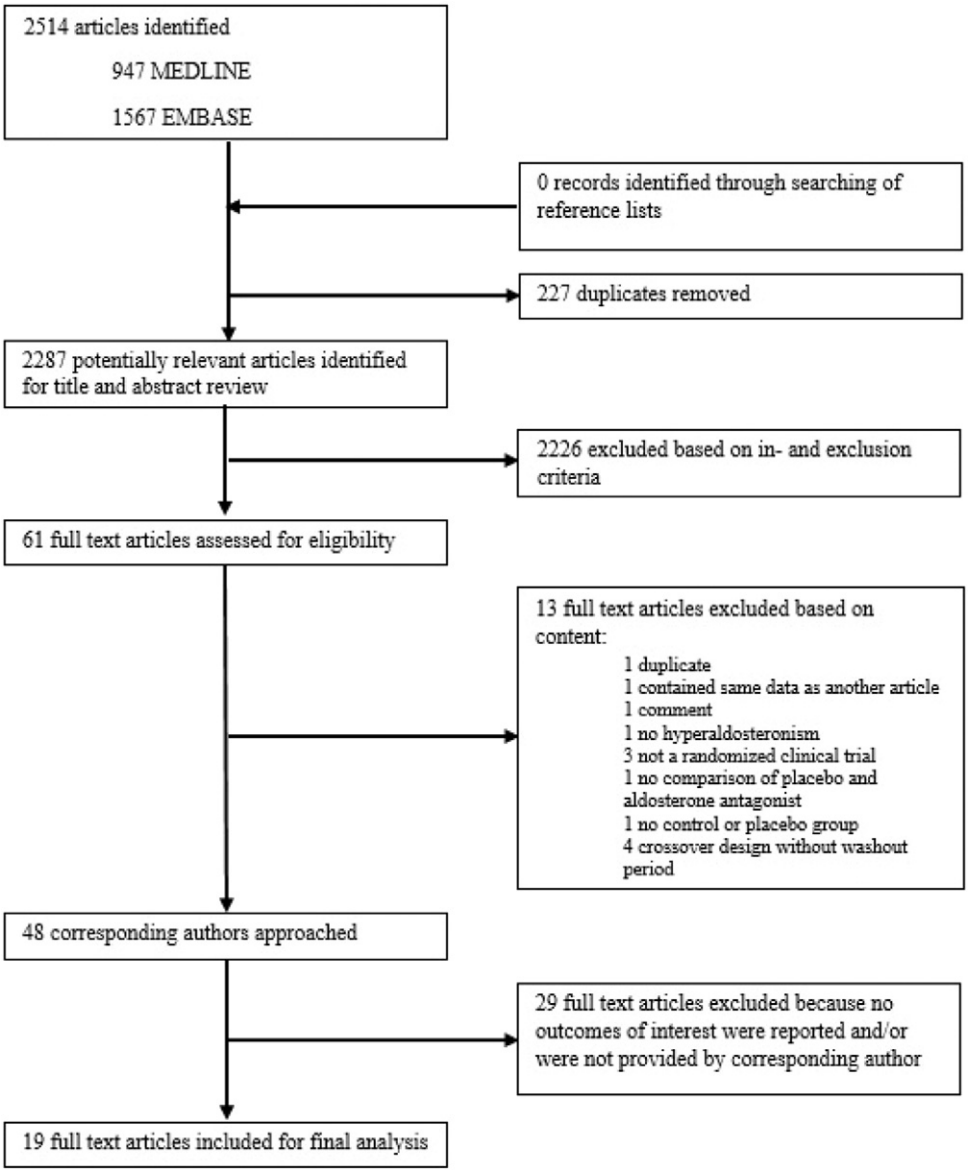

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of included studies.

Source	Patients	MRA (n)	Control (n)	MRA	Drug control	Mean follow-up (months)
Akbulut 2003 [14]	NYHA class III HF	35	35	Spironolactone 25 mg od	Control	12 weeks
Boccanelli 2009 [15]	NYHA class II HF with low EF	231	236	Canrenone 25–50 mg od	Placebo	12
Bolondi 2006 [16]	Child-Pugh A viral pre-ascitic cirrhosis with portal hypertension	66	54	Kcanrenoate 100 mg/day	Placebo	52 weeks
Calhoun 2011 [17]	Primary hypertension	84	77	Eplerenone 50 mg td	Placebo	8 weeks
Cicoira 2002 [18]	NYHA class I–III HF	54	52	Spironolactone 12.5–50 od	Control	12
Deswal 2011 [19]	NYHA class II or III HfpEF	23	23	Eplerenone 25 to 50 mg/day	Placebo	24 weeks
Edelmann 2013 [20]	NYHA class II or III HF, preserved LVEF of ≥50% and diastolic dysfunction	213	209	Spironolactone 25 mg od	Placebo	12
Krum 2002 [21]	Uncontrolled hypertension despite ACEI/ARB	170	171	Eplerenone 50–100 mg od	Placebo	8 weeks
Oxlund 2013 [22]	Type 2 diabetes with BP ≥130/80 mm Hg despite triple therapy	61	58	Spironolactone 25 mg od-td	Placebo	16 weeks
Pitt 2014 [24]	Symptomatic HF and LVEF ≥45%	1722	1723	Spironolactone 15 mg to 45 mg daily	Placebo	3.3 years
Pitt 2013 part A [23]	HFrEF and mild CKD	49	16	BAY 94–8862 2.5–10 mg od	Placebo	4 weeks
Pitt 2013 part B [23]	HFrEF and moderate CKD	328	65	BAY 94–8862 2.5–10 mg od or 5 mg td or spironolactone 25 or 50 mg od	Placebo	4 weeks
Pitt 2003 [25]	AMI complicated by LV dysfunction and HF	3313	3319	Eplerenone 25 to 50 mg/day	Placebo	16
Pitt 1999 [26]	Severe HF with LVEF ≤35%	822	841	Spironolactone 25 mg od	Placebo	24
Taheri 2012 [27]	CAPD patients with NYHA class III or IV HF, EF ≤45%, potassium level ≤5.5 mEg/L	9	9	Spironolactone 25 mg every other day	Placebo	6
Václavík 2011 [28]	Resistant arterial hypertension	59	58	Spironolactone 25 mg od	Placebo	8 weeks
Vizzardi 2014 [30]	NYHA class I–II HF and LVEF <40%	65	65	Spironolactone 25 mg od to 100 mg 4 times a day	Placebo	3.4 years
Vizzardi 2010 [29]	NYHA class I/II HF and LVEF ≤40%	79	79	Spironolactone 25–100 mg od	Placebo	6
White 2003 [31]	Untreated essential hypertension	310	90	Eplerenone 25–200 mg od	Placebo	12 weeks
Zannad 2011 [32]	NYHA class II HF and EF ≤35%	1364	1373	Eplerenone 25–50 mg od	Placebo	Median 21 months

ACEI indicates angiotensin-converting-enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BP, blood pressure; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; EF, ejection fraction; HF, heart failure; HfpEF, heart failure with preserved ejection fraction; HfrEF, heart failure and reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA; mineralocorticoid receptor antagonist; n, number; NYHA, New York Heart Association; od, once daily; and td, twice daily.

for unusual site venous thrombosis: because no event was reported it was not possible to analyse this outcome. Data on total mortality and on CV mortality were available in 20 RCTs for a total of 17,610 patients, and in 16 RCTs for a total of 16,861 patients, respectively. Data on major and minor bleeding events were available in 12 RCTs for a total of 10,220 patients, and in 5 RCTs for a total of 8653 patients, respectively.

3.3. MRAs used and follow-up duration

In the RCTs, different types of MRAs were used in different dosages (Table 1). Spironolactone was used in 11 RCTs and Canrenone and Kcanrenoate both in 1 RCT. Eplerenone was used in 6 RCTs and BAY 94-8862 (finerenone) in 2 RCTs. The minimal treatment period was 4 weeks, 14 RCTs had a mean treatment period up to 1 year and the maximal mean treatment period was 3.4 years.

3.4. Risk of bias assessment

In a substantial amount of RCTs, the risk of selection (13 RCTs), performance (12 RCTs) and detection bias (7 RCTs) was unclear due to missing information (Supplementary Figs. 1, 2).

3.5. Patient populations in RCTs

There were no RCTs on primary hyperaldosteronism. The patients in most of the trials were included because of heart failure, and in 5 RCTs, patients with hypertension were included. One study included patients with pre-ascitic cirrhosis with endoscopic and/or ultrasound evidence of portal hypertension. The dropout rate varied from 0 to 13%. The usage of antithrombotic agents was reported inconsistently (Table 2).

3.6. Thrombotic events

Overall, patients treated with MRAs had similar odds of fatal and non-fatal MI compared with controls (OR, 0.98; 95% CI, 0.85–1.12; $P = 0.76$) (Fig. 2, Table 3 for absolute and relative incidences). Patients who were treated with MRAs had similar odds of fatal and non-fatal stroke compared with controls (OR, 1.02; 95% CI, 0.83–1.24; $P = 0.88$) (Fig. 3). No statistical significant differences were found in fatal and non-fatal acute limb ischaemia, fatal and non-fatal PE, DVT and other arterial and venous thrombotic events when comparing patients who were treated with MRAs to controls (Supplementary Figs. 3–7).

3.7. Bleeding events

Patients treated with MRAs had similar odds of major bleeding events compared with controls (OR, 1.03; 95% CI, 0.76–1.41; $P = 0.85$) (Fig. 4). Besides this, patients who were treated with MRAs had similar odds of minor bleeding events compared with controls (OR, 0.91; 95% CI, 0.74–1.11; $P = 0.36$) (Supplementary Fig. 8).

3.8. Total and CV mortality

Patients treated with MRAs had 20% lower odds of death compared with controls (OR, 0.80; 95% CI, 0.73–0.87; $P < 0.00001$) and 23% lower odds of CV death compared with controls (OR, 0.77; 95% CI, 0.70–0.85; $P < 0.00001$) (Fig. 5, Supplementary Fig. 9). The absolute risk reduction for total mortality was 3.8% and for CV mortality it was 3.6% resulting in a number needed to treat of 27 and 28 patients, respectively.

3.9. Subgroup analyses

Subgroup analyses on patient population (heart failure versus hypertension), MRA agent used (spironolactone (±canrenone and Kcanrenoate), eplerenone and finerenone) did not change the results (data not shown). It was not possible to perform subgroup analyses on MRA dosage used since multiple dosages were used in several studies and outcomes were not reported per dosage.

Table 2
Characteristics of patient populations in the trials.

Source	Age (years mean ± SD) MRA/control	% male MRA/control	Study centre type	Primary outcome	Type of blinding/randomization	Use of antithrombotic therapy (%) MRA/control
Akbulut 2003 [14]	58.9 ± 6.1/59.2 ± 5.3	57.1/53.3	Single	QT dispersion	−/−	ASA (≤325 mg) if needed
Boccanelli 2009 [15]	62.3 ± 9.5/62.7 ± 9.5	81.8/85.2	Multi	Change in echocardiographic LVEDV	Double-blind/−	Antiplatelets: 57.0/57.1 Other: 23.7/24.8
Bolondi 2006 [16]	60.4 ± 9.5/61.0 ± 8.3	65.2/74.1	Multi	Progression of variceal status or appearance of ascites	Double-blind/computer random number generator	–
Calhoun 2011 [17]	55.3 ± 9.1/53.9 ± 8.7	66.7/59.7	Multi	Mean DBP	Double-blind with matching placebo/IVRS provider	–
Cicoira 2002 [18]	62.5 ± 7.9/61.7 ± 9.8	85.2/88.5	Single	LV function and exercise tolerance	Response variables evaluated by physicians blind to treatment group/−	–
Deswal 2011 [19]	72.2 ± 9.8/68.7 ± 9.1	95.2/91.3	Single	Change in 6MWD	Double-blind with matching placebo/−	–
Edelmann 2013 [20]	67 ± 8/67 ± 8	48/47	Multi	Diastolic function and maximal exercise capacity	Double-blind with matching placebo/Pocock minimization algorithm	If needed
Krum 2002 [21]	55.0/54.9	48.2/46.2	Multi	Mean diastolic and systolic BP	Double-blind/computer generated schedule	–
Oxlund 2013 [22]	62.9 ± 7.1/63.9 ± 6.9	75/78	Multi	Mean ABPM	Double-blind/scheme generated by Randomization.com	–
Pitt 2014 [24]	Median (IQR) 68.7 (61.0–76.4)/ 68.7 (60.7–75.5)	48.4/48.5	Multi	Death from CV causes, aborted cardiac arrest, or hospitalization for HF	Double-blind with matching placebo/permuted blocks	Aspirin: 65.2/65.6 Warfarin: 23.4/22.3
Pitt 2013 part A [23]	Mean (range): 67.0 (42–85)/63.9 (50–75)	77.6/87.5	Multi	Potassium concentration, eGFR and albuminuria	Double-blind with placebo/validated automated system	–
Pitt 2013 part B [23]	Mean (range): 72.1 (40–89)/72.4 (51–85)	80.1/76.9	Multi	Potassium concentration	Double-blind placebo and open-label spironolactone comparator arms/validated automated system	–
Pitt 2003 [25]	64 ± 11/64 ± 12	72/70	Multi	Death from any cause and CV causes or hospitalization for HF, AMI, stroke or ventricular arrhythmia	Double-blind with matching placebo/permuted blocks	Aspirin: 88/89
Pitt 1999 [26]	65 ± 12/65 ± 12	73/73	Multi	Death from any cause	Double-blind with matching placebo/−	Aspirin: 36/37
Taheri 2012 [27]	50.7 ± 17.4/57.2 ± 13.1	55.6/55.6	Single	Potassium levels and EF	Double-blind with matching placebo/−	–
Václavík 2011 [28]	61.4 ± 9.6/60.1 ± 9.4	67.3/57.1	Multi	Fall of systolic and diastolic pressure on ABPM	Double-blind with matching placebo/simple randomization	–
Vizzardi 2014 [30]	61 ± 14.7/65 ± 17.4	–	Single	CV death or hospitalization	Single-blind with matching placebo/−	–
Vizzardi 2010 [29]	61 ± 13/58 ± 13	84/82	Single	LV systolic and diastolic functions and functional capacity	Single-blind/−	–
White 2003 [31]	51–54 ± 9–11/54 ± 11	45.2/40	Multi	Mean diastolic BP	Double-blind/−	–
Zannad 2011 [32]	68.7 ± 7.7/68.6 ± 7.6	77.3/78.1	Multi	CV death or hospitalization for HF	Double-blind with matching placebo/computerized system	Antiplatelet or oral anticoagulant: 88.3/88.4

ABPM indicates blood pressure by ambulatory monitoring; AMI, acute myocardial infarction; ASA, acetyl salicylic acid; CV, cardiovascular; DPB, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; IVRS, interactive voice response system; LV, left ventricular; LVEDV, LV end-diastolic volume; MRA, mineralocorticoid receptor antagonist; SD, standard deviation; and 6MWD, 6-minute walk distance.

3.10. Heterogeneity

In general, the heterogeneity among the trials was low ($I^2 = 0–18\%$), except for the outcomes fatal and non-fatal acute limb ischaemia, which had high heterogeneity ($I^2 = 70\%$), and fatal and non-fatal PE, with intermediate heterogeneity ($I^2 = 31\%$).

3.11. Publication bias

In general there is a low risk of publication bias (Supplementary Figs. 11–20).

4. Discussion

In this meta-analysis we systematically reviewed the impact of inhibition of the mineralocorticoid receptor due to the use of MRAs on venous and arterial thrombosis, bleeding events and mortality in patients with common causes of secondary hyperaldosteronism (mainly hypertension and heart failure). We may conclude that in patients with hypertension and heart failure, inhibition of the mineralocorticoid receptor with MRAs did not materially alter the risk of thrombotic events and bleeding events. The favourable effects of MRAs on both total and CV mortality were confirmed. Our attempt was to also include RCTs with mainly patients with primary hyperaldosteronism but there were no such RCTs.

We hypothesized that MRAs could affect the haemostatic system and thereby may decrease the risk of thrombosis and increase the risk of bleeding events. This was based on studies which suggested that aldosterone influences the haemostatic system with a net procoagulant effect [2,5–7]. Experimental studies in rats showed that aldosterone infusion results in a shorter bleeding time, more platelet adhesion, higher expression of Plasminogen activator inhibitor-1 (PAI-1), more thrombus formation [3] and high thrombin activatable fibrinolysis inhibitor levels implying enlarged thrombin generation [4]. In humans, aldosterone and PAI-1 seem to be correlated [5,6] and treatment with spironolactone abolished this correlation. Finally, in healthy persons and in hypertensive patients, spironolactone reduced PAI-1 concentrations compared with triamterene [7]. Besides this, clinical endpoint studies showed that patients with primary hyperaldosteronism experienced more arterial thrombotic events [8] and that the use of spironolactone leaded to more gastrointestinal bleeding events [9]. With this meta-analysis we have shown that in patients with hypertension and heart failure, inhibition of the mineralocorticoid receptor with

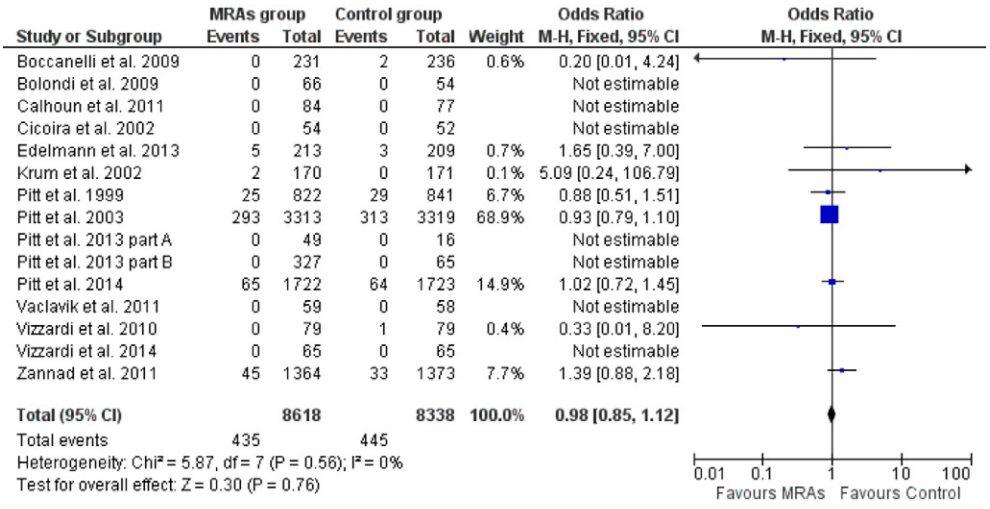

Fig. 2. Forest plot comparing fatal and non-fatal myocardial infarction in patients treated with and without mineralocorticoid receptor antagonists. CI indicates confidence interval; M-H, Mantel-Haenszel; and MRAs, mineralocorticoid receptor antagonists.

MRAs did not materially alter the risk of fatal and non-fatal MI, fatal and non-fatal stroke or minor and major bleeding events. Other thrombotic primary outcomes of interest were not reported enough to draw any conclusions. The under-reporting of relevant clinical outcomes is well-known problem and a recent meta-analysis of therapeutic RCTs published in major clinical journals concluded that the incidence of venous and arterial thrombosis is highly under-reported [33]. Based on our funnel plots per outcome, there is a suspicion of selective data outcome reporting, in particular for minor bleeding events and for CV mortality, but this could also be explained by the low number of RCTs reporting most of our outcomes of interest.

In this meta-analysis, treatment with MRAs led to significant reductions in total and CV mortality comparable to those reported in other meta-analyses [34]. Since treatment with MRAs did not reduce the risk of myocardial and infarction and stroke, it is likely that this reduction in mortality is mainly due to the effect of MRAs on death from progressive heart failure and sudden death from cardiac causes. One explanation for the absence of an observed effect of MRAs on thrombotic events could be that ACE-inhibitors lower levels of PAI-1 [35,36]. Given that the vast majority of the RCTs in this meta-analysis included patients with left ventricular dysfunction and resistance hypertension, ACE inhibitor use would have been widespread and this could have hampered the possibility to detect an effect of MRAs on thrombotic events. There doesn't seem to be an important effect of MRAs on haemostasis in patients with heart failure and hypertension, although no evidence of established secondary hyperaldosteronism was provided in the patients in the RCTs that we included. Still, the question remains whether this effect is also absent in patients with primary hyperaldosteronism. Besides this, if aldosterone truly influences haemostasis, despite the results of our meta-analysis, this might be important for patients that are already at risk for bleeding due to other reasons such as liver dysfunction or the use of ulcerogenic drugs [9]. We were not able to perform a subgroup analysis in patients with a higher bleeding risk. We were able to perform subgroup analyses based on patient population (heart failure versus hypertension) and MRA agent used (spironolactone (± canrenone and Kcanrenoate), eplerenone and finerenone) and this did not change our conclusions. One explanation for the absence of an effect of MRAs on bleeding risk in our meta-analysis could be that MRAs don't suppress aldosterone enough to detect limited effects of aldosterone on haemostasis. Although debated due to its design [37], our hypothesis that the use of MRAs could lead to a higher bleeding risk was partly based on a population based case–control study which observed that the use of spironolactone increases the risk of upper gastrointestinal bleeding [9]. The association increased proportionally with dosage and was most pronounced when combined with ulcerogenic drugs. Most of the included RCTs in our meta-analysis were performed in patients with hypertension and heart failure, which require relatively low dosages of MRAs when compared to patients with portal hypertension due to liver cirrhosis. Unfortunately, in our meta-analysis, it was not possible to perform subgroup analyses on MRA dosage used since multiple dosages were used in several studies and outcomes were not reported per dosage.

Table 3
Incidences of primary and secondary outcomes in MRA users.

Outcome	Absolute incidence (n)	Relative incidence (%)
Fatal and non-fatal MI	435	5.0
Fatal and non-fatal stroke	196	2.3
Fatal and non-fatal acute limb ischemia	15	0.3
Other arterial thrombotic events	10	0.2
Fatal and non-fatal PE	13	0.2
DVT	2	0.04
Other venous thrombotic events	18	0.3
Unusual site venous thrombosis	0	0
Major bleeding events	82	1.6
Minor bleeding events	185	4.3
Total mortality	1213	13.4
CV mortality	976	11.3

CV indicates cardiovascular; DVT, deep venous thrombosis; MI; myocardial infarction; N indicates number; and PE, pulmonary embolism.

Another limitation of this meta-analysis is that the use of antithrombotic agents was scarcely reported in the RCTs. However, since this meta-analysis solely consists of RCTs, any possible bias and confounder, including the use of antithrombotic agents, should be evenly distributed between the patients. One could also debate that the RCTs included in this meta-analysis were not designed to study the effect of MRAs on thrombosis and bleeding events and therefore the reporting is inconsistent. However, this should also be the same for both groups due to the design of the included studies and therefore will not influence the conclusion of this meta-analysis. Besides, most of the data on this outcome were achieved from the reporting of serious adverse events as part of performing a RCT with a medical drug.

In conclusion, we observed that inhibition of the mineralocorticoid receptor with MRAs in patients with hypertension and heart failure did not change the risk of MI, stroke and bleeding events. This is relevant for both patients and health care providers considering the high incidence of hypertension and heart failure. Moreover, our meta-analysis confirms the favourable effects of MRAs on both total and CV mortality.

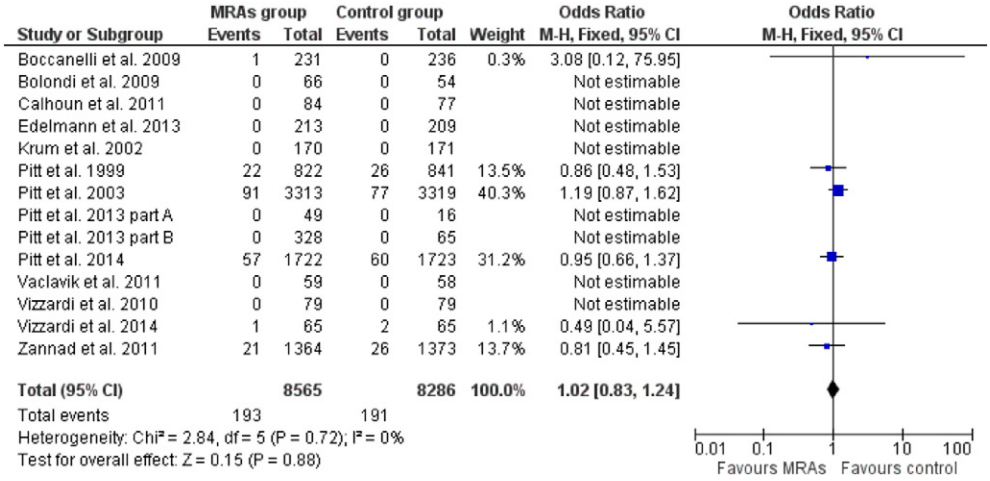

Fig. 3. Forest plot comparing fatal and non-fatal stroke in patients treated with and without mineralocorticoid receptor antagonists. CI indicates confidence interval; M-H, Mantel-Haenszel; and MRAs, mineralocorticoid receptor antagonists.

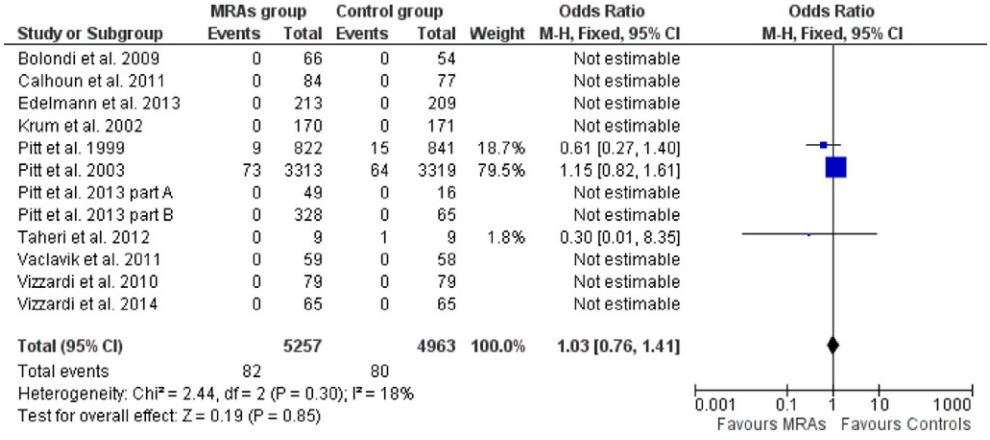

Fig. 4. Forest plot comparing major bleeding in patients treated with and without mineralocorticoid receptor antagonists. CI indicates confidence interval; M-H, Mantel-Haenszel; and MRAs, mineralocorticoid receptor antagonists.

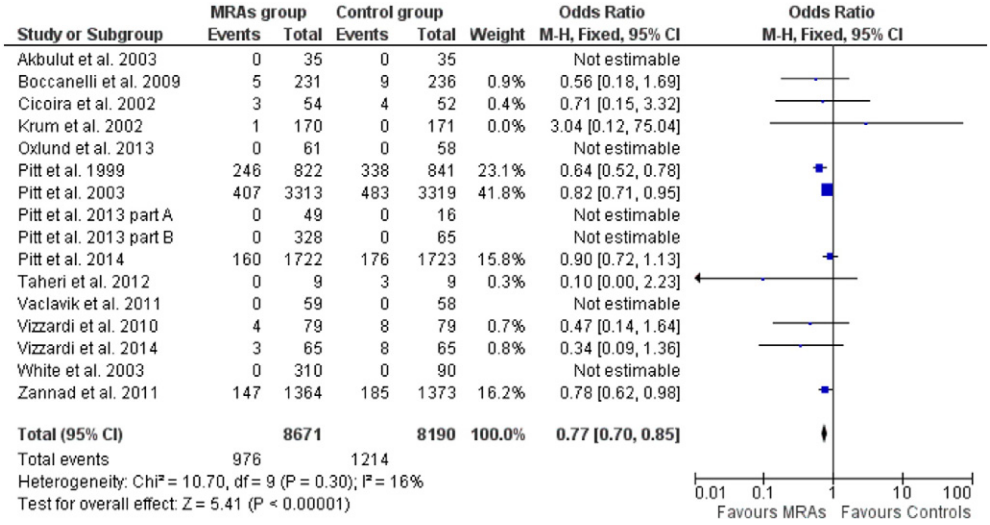

Fig. 5. Forest plot comparing cardiovascular mortality in patients treated with and without mineralocorticoid receptor antagonists. CI indicates confidence interval; M-H, Mantel-Haenszel; and MRAs, mineralocorticoid receptor antagonists.

Besides, this meta-analysis again underlines the under-reporting of both venous and arterial thrombosis in RCTs and the need for uniform registration of adverse events, even when unlikely beforehand to be related to the intervention.

Disclosures

Prof. dr. Zannad reports personal fees from Pfizer during the conduct of the study and personal fees from Janssen, Bayer, Takeda, Novartis, Boston Scientific, Resmed, Stealth peptide, Amgen, CVRx, Mistusbishi, Quantum Genomics, AstraZeneca EliLilly, Relypsa, ZSPharma and Merck outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2016.04.027.

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