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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