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Mineralocorticoid receptor antagonists for therapy of coronary artery disease and related complications

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The perception of aldosterone action to be restricted to regulation of fluid balance via sodium reabsorption and potassium excretion is incomplete; plenty of experimental and clinical studies have shown that aldosterone plays a pivotal role in a variety of (patho-) physiologic conditions within the cardiovascular continuum. Deleterious effects include cardiovascular inflammation, endothelial dysfunction, structural and electrical remodelling. Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, prevent some of these maladaptive effects on the cardiovascular system and have proven to be a highly efficacious pharmacological therapy. In this article we review the current clinical impact of MRAs in the treatment of coronary artery disease (CAD) and its related complications, for example, acute myocardial infarction (MI) and chronic heart failure.

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Introduction

Traditionally, the action of aldosterone was thought to be restricted to sodium reabsorption and potassium excretion via activation of the cytosolic mineralocorticoid receptor (MR) in not only epithelial cells of the distal colon, the renal nephron but also salivary and sweat glands thus regulating fluid balance and blood pressure. In recent years, however, aldosterone was shown to play a pivotal role in many pathogenic processes of coronary artery disease (CAD) and its related complications, for example, acute myocardial infarction (MI), ischaemic heart disease and heart failure. MRs could not only be identified in vascular endothelial and smooth muscle cells but also in cardiomyocytes, endothelial cells, fibroblasts and macrophages in the heart [1] (Figure 1).

Aldosterone and glucocorticoids bind with similar affinity to MR. In the normal physiologic state, plasma glucocorticoid levels are more than 100 times higher than aldosterone levels and the majority of MRs in the heart may be occupied by glucocorticoids, however, to which extent glucocorticoids indeed activate the MR in (pathological) physiological conditions is still unclear. In patients with acute MI and chronic heart failure, not only circulating aldosterone levels but also aldosterone biosynthesis are enhanced. Moreover, the aldosterone–MR complex is more stable than the glucocorticoid–MR complex [2–4]. On the basis of these findings, aldosterone is nowadays considered as a main regulator in the progression of cardiovascular disease. Indeed, MR activation by aldosterone mediates or at least aggravates pathophysiological processes that remain current targets for therapeutic interventions in patients with CAD, acute MI or chronic heart failure, including endothelial dysfunction, collagen deposition, vascular inflammation, increased oxidant stress, disruption of fibrinolysis and activation of the sympathetic nervous system. Given these broad effects of aldosterone on the cardiovascular system, MR blockade is thought to be beneficial for a broad spectrum of patients with cardiovascular disease. Today we know that MR antagonists (MRAs), such as spironolactone and eplerenone, are able to prevent maladaptive effects of aldosterone on the cardiovascular system. In this article we review the current clinical impact of MRAs in the treatment of CAD and its related complications, for example, acute MI and chronic heart failure (Table 1).

MRAs in coronary artery disease

While a plethora of experimental studies indicate that aldosterone is an important stimulus for vascular disease in many animal models, fewer clinical data exist supporting the deleterious aspects of aldosterone or the positive influence of MRAs on chronic CAD; particularly there are no large randomized treatment trials.

Two clinical studies have evaluated the relationship between the aldosterone levels and the risk of death or the occurrence of an acute ischaemic event in patients with chronic CAD. During a median observation time of 7.7 years in 3153 patients with CAD referred for catherization, Tomaschitz *et al.* observed that plasma aldosterone levels, even within normal values, are independently associated with cardiovascular death and all-cause mortality. Analyses of specific causes for cardiovascular death showed that elevated levels of aldosterone are specifically related to a higher risk of sudden cardiac death and fatal stroke [5]. Accordingly, Ivanes *et al.* described in a setting of 799 patients with chronic CAD without heart failure that the

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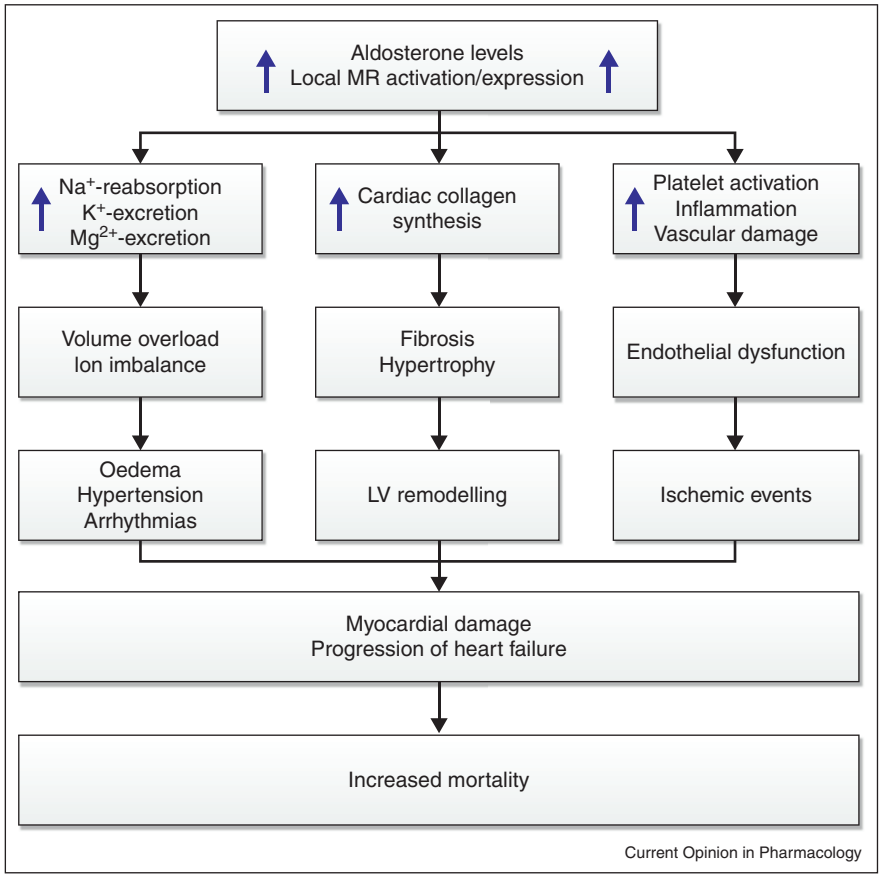
Figure 1



Effects of aldosterone/mineralocorticoid receptor (MR) activation on the cardiovascular system.

level of aldosterone was strongly and independently associated with mortality as well as the occurrence of an acute ischaemic event. In the median follow-up period of 14.9 months, patients with higher aldosterone levels were more likely to die due to cardiovascular causes or to sustain an acute ischaemic event, defined as MI or ischaemic stroke [6•]. Additionally, Amano *et al.* prospectively enrolled 156 patients with stable CAD who underwent successful coronary angioplasty with bare-metal stenting. Their findings indicate that the plasma aldosterone levels independently predict in-stent restenosis since patients with restenosis after six months were found to have significantly higher plasma aldosterone levels at the time of stenting than patients without subsequent restenosis [7]. Rita *et al.* studied the progression of carotic total plaque area in 848 patients with symptomatic vascular disease, family history or risk factors for vascular disease who presented at their local stroke prevention clinic. Variables like plasma aldosterone levels, age, sex, total cholesterol, systolic blood pressure, diabetes and smoking were evaluated. Strikingly, plasma aldosterone was the only independent predictor of plaque progression [8]. Although clear evidence exists that there is a strong relationship between aldosterone and the progression of chronic CAD, up to now no clinical study has specifically evaluated the effect of MRAs on amelioration of plaque formation in coronary arteries. Noteworthy, Vukusich *et al.* designed a randomized, double-blind, placebo-controlled trial to assess the effectiveness of spironolactone in preventing progression of carotid intima–media thickness (CIMT) in nondiabetic haemodialysis patients. 53 patients received either 50 mg spironolactone or placebo thrice weekly after dialyses for 24 months. CIMT measurements via ultrasound revealed a progression in the placebo-group whereas in the spironolactone group a significant decrease in CIMT could be observed [9]. These findings are concordant with various experimental data, showing the selective MRA eplerenone to inhibit atherosclerosis progression in different animal models [10–12]. However, further clinical studies are needed to prove that MRA might also be useful in CAD patients in the absence of an acute MI or heart failure.

MRAs after acute myocardial infarction

Preclinical animal studies have provided substantial evidence that activation of the MR plays a pivotal role in cardiac healing and remodelling after myocardial

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