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The role of mineralocorticoid receptor antagonists in patients with acute myocardial infarction: Is the evidence reflective of modern clinical practice?

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1. Introduction

Heart failure (HF) and ischaemic heart disease (IHD) are among the leading causes of death globally [1,2]. Despite improvements in the prevention and management of IHD, it remains the commonest cause of HF [2,3]. The prognosis, once a diagnosis of HF is established, is limited with only 50% surviving to 5 years and 10% to 10 years [2]. It is therefore critical that interventional cardiologists not only focus on appropriate revascularisation strategies but also optimal medical therapy to prevent and/or treat HF. Spironolactone, the first available mineralocorticoid receptor antagonist (MRA), has been available for over 50 years when it was used solely in states of hyperaldosteronism [4]. Since then the class has expanded and their role in the medical management and prevention of HF has been firmly established [4]. However, despite the recommendations of both the European Society of Cardiology (ESC) and the American Heart Association (AHA) to initiate eplerenone early after acute myocardial infarction (AMI) associated with left ventricular systolic dysfunction, there are concerns that there is a mismatch between the evidence base behind these recommendations and contemporary management of patients with AMI particularly with regard to revascularisation and speed of discharge [5–7].

2. Mechanism of action

Aldosterone is produced by the zona glomerulosa in the adrenal glands and is a potent mineralocorticoid hormone [8,9]. Its main mechanism of action is via receptors in both the distal convoluted tubule and the collecting duct within the nephron resulting in increased salt and water retention [8,9]. The release of aldosterone is controlled by the renin-angiotensin-aldosterone system. This homeostatic mechanism responds to a reduction in blood pressure by increasing plasma volume and overall vascular tone [10]. Initiation of this pathway occurs when

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hypoperfusion of the kidney is detected by the juxtaglomerular apparatus resulting in the release of renin [9,10]. Renin is a protease that converts angiotensinogen to angiotensin 1 which is then converted by angiotensin converting enzyme (ACE) to angiotensin 2. Angiotensin 2 has a number of effects including stimulation of aldosterone release, vascular constriction, sympathetic stimulation and anti-diuretic hormone release [9,10]. Further, angiotensin 2 signalling via stimulation of angiotensin 1 receptor, causes up regulation and activation of NADPH oxidase in the vessel wall. The resulting oxidative stress is a component of the inflammatory pathway leading to atherogenesis [11–13]. Aldosterone primarily results in increased sodium and water retention at the distal convoluted tubule at the expense of increased urinary loss of both potassium and magnesium [9]. Such a mechanism has clear evolutionary benefits as a response to hypoperfusion secondary to hypovolaemia but in HF the hypoperfusion of the kidneys is not caused by a low volume state but rather by a low cardiac output. This compensatory mechanism therefore has potentially deleterious effects in HF where increased volume can help to precipitate decompensation.

Apart from its effects in the nephron, aldosterone also promotes sympathetic activation, myocardial and vascular fibrosis, and baroreceptor dysregulation which in turn can lead to vascular dysfunction [14]. It is therefore a pathway that can negatively impact on cardiovascular status, especially in HF, and in these circumstances represents an attractive target for therapy.

3. Current roles

In the late 1990s ACE inhibitors (ACEi) became a central part of the standard of care for patients with established HF, but it was noted that their effect on the secretion of aldosterone was only transient [14]. This led to the Randomised Aldactone Evaluation Study (RALES) which enrolled 1663 patients with symptomatic HF (New York Heart Association class III or IV) and systolic dysfunction (left ventricular ejection fraction ≤35%) to receive spironolactone 25 mg/day or placebo in combination with standard of care (ACEi, loop diuretic, and in most cases digoxin) [14]. The primary end point of the study was death from any cause. Secondary end points included death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death from cardiac causes, hospitalization for cardiac causes, and a change in the NYHA class. Key baseline characteristics included mean age of 65 ± 12 years, 55% having ischemic HF whilst 45% had non-ischemic HF, and critically only 11% of the trial population were on a beta-blocker. RALES was discontinued early, after a mean follow-up of 24 months, due an interim analysis demonstrating the efficacy of spironolactone. Spironolactone was associated with a 30% lower risk of death than among patients in the placebo group ($p < 0.001$), as well as a 31% reduction in the risk of death from cardiac causes (RR: 0.69, 95% CI: 0.58–0.82; $p < 0.001$). The reduction in the risk of death in the spironolactone group was attributed to reductions in the risk of death from HF and sudden death from cardiac causes. Spironolactone was also associated with a 30% reduction in the risk of hospitalization for cardiac causes (RR: 0.70, 95% CI: 0.59–0.82; $p < 0.001$), 32% reduction in the risk of death from cardiac causes or hospitalization for cardiac causes (RR: 0.68; 95% CI: 0.59–0.78; $p < 0.001$), and significantly greater improvement in NYHA class. Although the benefits of spironolactone in RALES were very impressive, one needs to bear in mind that the study included both ischaemic and non-ischaemic HF patients, the use of beta blocker therapy was low by current standards and is not reflective of contemporary patients that present with AMI and undergo prompt coronary revascularization.

The role of aldosterone antagonists in reducing mortality and the rate of hospitalization in patients with AMI complicated by left ventricular systolic dysfunction was assessed in the Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [15]. EPHESUS randomised 6642 patients to either eplerenone or placebo in addition to optimal medical therapy. Inclusion criteria included AMI in the preceding 3–14 days, left ventricular ejection fraction ≤40%, and HF as documented by the presence of pulmonary rales, chest radiography, showing pulmonary venous congestion, or the presence of a third heart sound. Eplerenone was initiated at 25 mg/day for four weeks, after which the dose was increased to a maximum of 50 mg/day. If the serum potassium concentration exceeded 5.5 mmol/L, the dose of the drug was either reduced or discontinued until the serum potassium concentration fell below 5.5 mml/L. The two primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including HF, recurrent MI, stroke, or ventricular arrhythmias. Secondary end points included death from cardiovascular causes, and death from any cause or any hospitalization. Important baseline characteristics included mean age 64 years, 45% patients receiving reperfusion therapy or revascularization, and 87% receiving ACEi, 75% beta blockers, 60% diuretics, and 47% statins. Eplerenone was associated with a significant reduction in the end point of death from cardiovascular causes or hospitalization from cardiovascular events as compared to placebo (26.7% vs. 30%; RR: 0.87; $p = 0.002$). The reduction in cardiovascular mortality was similar for the most common causes: sudden death, AMI, and HF. There was a relative reduction of 15% in the risk of hospitalization for HF with eplerenone (RR: 0.85; $p = 0.03$). The rate of death from any cause or any hospitalization was 8% lower in the eplerenone group than in the placebo group (RR: 0.92; $p = 0.02$).

RALES and EPHESUS formed the basis of the AHA and ESC guidelines for the use of spironolactone and eplerenone in AMI patients with left ventricular systolic dysfunction [5–7]. It is noteworthy that the management of patients presenting with AMI has dramatically altered since the publication of these trials and recommendations such that it could be argued that RALES and EPHESUS are no longer representative of modern AMI care. Evidence from both Europe and the US indicate that increasing number of AMI patients undergo prompt angiography and revascularization, in contrast to the 45% of patients in EPHESUS, and the majority of patients are commenced on state of the art medical therapy particularly beta blockers and ACEi that is significantly greater than both RALES and EPHESUS [17–19].

The Myocardial Ischaemia National Audit Project (MINAP) is one of six national cardiac clinical audits that are managed by the National Institute for Cardiovascular Outcomes Research (NICOR) and provides audit data to the United Kingdom's Department of Health and other regulatory bodies to enable them to make decisions on funding and provision of cardiovascular health services. The MINAP 2016 report has shown that 89% of patients with ST-elevation myocardial infarction (STEMI) were treated with PCI within 90 min of arrival (the equivalent figure for 2005 was 52%). Median door-to-balloon time for England was 40 min, with Wales and Northern Ireland achieving 41 min and 33 min respectively [17]. In patients with non-STEMI (NSTEMI), 96% were seen by a cardiologist and 86% received an angiogram compared to 68% in 2011. For patients admitted to hospitals with on-site angiography capacity, 17% received an angiogram within 24 h, 53% within 72 h, and 66% within 96 h. Median length of stay for STEMI and NSTEMI patients were 3 and 5 days respectively. In terms of medical therapy, 94.7% of patients were discharged on an ACEi/Angiotensin receptor blocker, 98.4% on aspirin, 96.6% on a beta blocker, 97.4% on a statin, and 97.2% on a thienopyridine.

In the US, professional societies have developed programs such as the American College of Cardiology Door-to-Balloon time initiative and the American Heart Association Mission: Lifeline to mitigate the morbidity and mortality associated with STEMI. Data from the Nationwide Inpatient Sample, a discharge database representative of all short-term, non-federal hospitals in the US has shown that the rate of PCI increased from 53.6% in 2003 to 80% in 2011 whilst the odds ratio of death decreased over the same time period (OR: 0.79, 95% CI: 0.74–0.84) [18]. Data from the National Cardiovascular Data Registry ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry database has examined contemporary patterns of

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