Early Aldosterone Blockade in ST-elevation Acute Myocardial Infarction: Further Evidence of Benefit of Mineralocorticoid Receptor Antagonists in Improving Outcomes

Authors: Dr Kieran F. Docherty MBChB(Hons)

Dr Pardeep S. Jhund MBChB, MSc, PhD

Affiliations: BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland, UK

Correspondence: Dr Pardeep S. Jhund

Institute of Cardiovascular and Medical Sciences

BHF Cardiovascular Research Centre,

University of Glasgow,

Glasgow, G12 8TA

United Kingdom

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Despite improvements in the invasive and pharmacological management of myocardial infarction (MI), patients remain at risk of adverse cardiovascular outcomes in the months and years following MI. For those with myocardial damage and residual left ventricular systolic dysfunction (LVSD) there is a high risk of developing heart failure with reduced ejection fraction (HFrEF). Much of the progress in the pharmacological management of patients at high risk of HFrEF has been achieved through inhibition of the renin-angiotensin aldosterone system (RAAS) with angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARB]) and beta-blockers. Meta-analysis of randomised controlled trials (RCTs) of ACE-inhibitors in MI, have demonstrated that the greatest benefit in reducing mortality results from early administration of ACE-inhibitors in the first few days post MI and this benefit is observed in all patients, irrespective of the presence or not of HF.[1]

In addition to RAAS blockade with ACE-inhibitors or ARBs, in large randomised trials, mineralocorticoid receptor antagonists (MRA) have been shown to reduce morbidity and mortality in a spectrum of patients from those with LVSD and HF as a complication of MI to those with established, symptomatic HFrEF irrespective of an ischaemic aetiology.[2,3] The Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated the efficacy of eplerenone compared to placebo when administered 3-14 days post MI in reducing mortality in patients with left ventricular systolic dysfunction and heart failure or diabetes.[2] A post-hoc analysis of the EPHESUS cohort reported that this benefit was greater in those administered eplerenone in the early phase (3-7) days post MI compared to those receiving eplerenone at a later time point.[4] This finding, along with the benefits of early ACE-inhibition (in the first 24 hours) have led

investigators to explore the potential role of MRA administration in the early, acute (<3 days) phase following MI.

Two trials have now examined whether early treatment with MRAs is effective and safe. The REMINDER (Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction) trial compared eplerenone (at target dose 50mg) to placebo administered within 24 hours of acute ST-segment elevation MI (STEMI) in 1012 patients.[5] Patients were excluded if they had clinical evidence of HF or a known left ventricular ejection fraction (LVEF) of <40%. Over a mean follow-up of 10.5 months, eplerenone was associated with a reduction in the risk (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.45–0.75; P<0.0001) of the primary composite endpoint. This was a broad composite of cardiovascular (CV) mortality, re-hospitalisation or extended initial hospital stay due to diagnosis of heart failure or sustained ventricular tachycardia or ventricular fibrillation, an LVEF ≤40% (≥1-month post randomisation), or elevated natriuretic peptide levels (≥1-month post randomisation). The benefit was driven by a significant reduction in natriuretic peptide levels associated with eplerenone treatment with no significant difference in mortality found.

The second trial was the Aldosterone Lethal effects Blocked in Acute MI Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) a randomised, open-label trial comparing an MRA regimen consisting of a bolus of intravenous potassium canrenoate administered within 72 hours of symptom onset followed by oral spironolactone 25mg compared to standard therapy alone.[6] In 1603 patients with acute MI (STEMI and high risk [TIMI score ≥3] non ST-elevation MI [NSTEMI])

patients were followed up for a period of 6 months for the occurrence of the primary composite endpoint. Unlike REMINDER, this was a narrower composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, class IA indication for implantable cardioverter defibrillator, or new or worsening HF during 6-month follow-up. No significant difference in the primary endpoint was reported, however, a significant interaction (p=0.01) was reported between treatment effect and type of MI with benefit observed only in STEMI (77% of patients) and not in NSTEMI (23% of patients).

To further explore this subgroup finding, Beygui and colleagues now report the results of a pooled analysis of individual patient-level data of STEMI patients (n=2241) from the REMINDER and ALBATROSS trials.[7] Treatment with an MRA within 72 hours of STEMI was associated with a 70% reduction in risk of all-cause mortality (HR 0.30; 95% CI 0.11-0.81; p=0.01) with 5 (0.4%) and 17 (1.5%) deaths in the MRA and control groups, respectively. There was a significant reduction in the risk of the secondary outcome of death or resuscitated sudden death in favour of MRA (HR 0.27; 95% CI 0.11-0.67; p=0.002) with numerical trends towards reduced risk of CV death and ventricular fibrillation which did not reach statistical significance (p= 0.06 and p=0.08, respectively). Hyperkalaemia (>5.5mmol/L) was more common with MRA treatment (odds ratio [OR] 1.89; 95% CI 1.09-3.29; p=0.03), however no significant differences in the rates of acute renal failure or severe hyperkalaemia (>6mmol/L) were reported. No significant inter-study heterogeneity was reported, and results were consistent across the sub-groups examined. Beygui and colleagues conclude that these findings, accepting the limitations of a subgroup analysis, are suggestive of a consistent beneficial treatment effect of early use of MRAs and that this treatment approach appears to be safe in this population.

Before accepting the results of this analysis and using MRAs early in clinical practice we must ask ourselves a number of questions. The first of these is ”Is such a mortality benefit biologically plausible?” In patients with a STEMI there is activation of the mineralocorticoid receptor which induces myocardial fibrosis, increasing the risk of adverse ventricular remodelling, ventricular dysrhythmias, sudden cardiac death and development of HFrEF. As prior studies have reported a beneficial effect of early mineralocorticoid receptor blockade with MRAs in attenuating adverse ventricular remodelling, reducing levels of biomarkers of fibrosis and the risk of ventricular dysrhythmias, it should follow that any benefit on outcomes from early use of MRAs would result in a reduction in sudden cardiac death or the development of heart failure. In the analysis presented, the occurrence of sudden death was the same in the MRA and control arm of the pooled analysis (3 [0.3%] in both arms) and heart failure was numerically less common in the MRA arm, but this did not reach statistical significance (45 [4%] vs. 51 [4.5%]; HR 1.03; 95% CI 0.69-1.55; p=0.9). While this does not seem to support the hypothesis, it highlights another question that we may ask about the analysis by Beygui et al; “Is the sample and number of events sufficiently large to draw conclusions and change practice?”

The event rates in these trials were low, reflecting the relatively low-risk population enrolled and the high uptake of evidence-based revascularisation and pharmacological therapies. However, the lack of any evidence of between-trial heterogeneity, despite the differences in the populations enrolled in the two trials, are suggestive of a consistent treatment effect of early MRA administration. Furthermore, the results of this analysis are given further backing by a recently published meta-analysis of summary estimates from 11 RCTs evaluating the use of MRA following MI.[8] Although not an individual level meta-

analysis, as with the study by Beygui et al., and coupled with the broad range of included studies (those with and without HF and early and late administration of MRA) the authors reported a significant reduction in all-cause mortality (OR 0.82; 95% CI 0.73-0.93; p=0.002) and CV mortality (OR 0.82; 95% CI 0.71-0.93; p=0.003) with no significant interaction between treatment effect and the presence or not of HF (p for interaction=0.43). Therefore, despite the small number of events, there appears to be consistency across trials, the spectrum of disease from NSTEMI to STEMI, from low to higher ejection fractions and in those with and without heart failure.

What do these results mean for clinical practice and guidelines? As noted above, the results of Beygui et al. are not enough alone to change clinical practice but they further support the role of MRAs in addition to therapy with ACE-inhibitors or ARB and beta-blockers through the spectrum of patients in the continuum from the Coronary Care Unit to chronic HFrEF following MI. This is crucially important as the use of MRAs remains low even in populations where there is little doubt to their benefit such as HFrEF and is even lower in those with LVSD post MI.

The potential benefit of early MRA administration in patients with STEMI and the safety of this approach reported by Beygui and colleagues, ideally requires further confirmation in a large randomised trial adequately powered to assess mortality and morbidity and confirm safety. In the absence of such a trial, these data support the already undoubted benefits of MRAs post MI in those with HF or LVSD and should serve as a reminder to clinicians to consider these life-saving drugs sooner rather than later.

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