Evaluating the efficacy of mineralocorticoid receptor antagonism in patients with STEMI without heart failure

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This editorial refers to ‘Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the randomized double-blind REMINDER study’†, by G. Montalescot et al., on page 2295

There are three key elements to any clinical trial: study population, study intervention, and outcome. The REMINDER study† reported by Montalescot et al., is worth considering in detail because of how the investigators ultimately decided these three questions: the choice of ST-segment elevation myocardial infarction (STEMI) patients without heart failure as the population of interest, the selection of the mineralocorticoid receptor antagonist (MRA) eplerenone as the intervention, and the use of natriuretic peptides as the principal measurement of efficacy.

To summarize, the REMINDER study randomized 1012 patients presenting with STEMI but no evidence of heart failure to eplerenone or placebo within 24 h of symptoms, and followed them for ≈10 months. Treatment with eplerenone significantly reduced the risk of a composite endpoint of an elevated natriuretic peptide or an extended list of clinical events by 40% compared with placebo, mostly driven by lower levels of natriuretic peptides at least 1 month after randomization.

ST-segment elevation myocardial infarction without heart failure

Most studies evaluating therapy to improve remodelling focus only on patients with large, anterior STEMI or an ejection fraction <40%, which is logical given that these patients are at the highest risk of subsequent heart failure, arrhythmic events, and death. However, with more rapid reperfusion, they currently account for a small proportion of patients presenting with MI. In >77 000 patients with STEMI enrolled in one contemporary registry, only 12% presented with heart failure and just 3.6% developed heart failure after admission, a substantially lower number than earlier cohorts. Moreover, only 20% of patients with STEMI and no heart failure in this registry had an ejection fraction <40% (Figure 1). Studies restricted to patients with the most severe presentation thus limit generalizability. The REMINDER study is therefore an example of evaluating a broader, more representative cohort, in which a therapeutic agent may have more widespread applicability.

As would be expected based on the entry criteria, patients randomized into the REMINDER study were younger, had better renal function, lower rates of diabetes or prior MI, and a lower rate of anterior MI compared with studies focusing on just patients with heart failure, and a correspondingly lower risk of death or heart failure. The selection of this population is also of interest because the benefit of early initiation of inhibitors of the renin–angiotensin–aldosterone system (RAAS) in post-acute coronary syndrome (ACS) patients without any evidence of heart failure or with normal left ventricular (LV) function remains uncertain. The seminal trials of inhibitors of the RAAS excluded these healthier MI patients (Figure 1). Even in the “all-comer” studies, the benefit of RAAS inhibition was predominately observed in patients with the largest infarcts. Thus early inhibition of the RAAS in patients without heart failure or depressed LV function following ACS has yet to be conclusively demonstrated in patients treated with contemporary strategies. Regardless, most patients in REMINDER were treated with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker as background therapy; thus, the addition of eplerenone in this study most commonly represented ‘dual’ RAAS inhibition.

Mineralocorticoid receptor antagonists

The rationale for choosing a population with smaller infarcts was necessary because of the well-established benefit of MRAs in patients with MI and heart failure or reduced LV function. It is fair to say that...
MRAs have enjoyed one of the most consistent runs of proven efficacy across the cardiovascular spectrum, in particular in patients with established systolic heart failure or heart failure and reduced LV function following MI. In particular, after the EPHESUS study, which demonstrated clear superiority of eplerenone vs. placebo in post-MI patients with heart failure, it would not have been ethical to include patients with heart failure or reduced LV function in a placebo-controlled trial, even for a shorter duration.

The proposed benefits of MRAs following MI are several-fold. First, MRAs preserve serum potassium levels and thereby may prevent arrhythmic triggers in a population vulnerable to lethal arrhythmias. More importantly, MRAs favourably influence a myriad of pathways involved in myocardial remodelling and fibrosis, and improve endothelial dysfunction and peripheral vascular compliance. That MRAs reduced markers of haemodynamic stress in the REMINDER Study, specifically in patients with smaller infarcts, suggests that crude measures of ventricular function such as ejection fraction and symptomatic heart failure fail to reflect the degree of myocardial damage and subsequent maladaptive remodelling in many MI patients.

Eplerenone was selected as the MRA in the REMINDER study, though there is little reason to suspect that spironolactone would not have produced similar results. One notable aspect of the study was that the first dose of study drug was initiated early (<24 h of symptom onset), which was earlier than in the EPHESUS study. Moreover, there was a trend in subgroup analyses towards an even greater benefit with very early treatment (<6 h), suggesting that MRAs could play a protective role after the initial reperfusion injury following percutaneous intervention or fibrinolysis. Overall, eplerenone was well tolerated in this relatively healthy population with preserved renal function. There were few episodes of hyperkalaemia, though it occurred 2–4 times more frequently with eplerenone than with placebo. It would be informative to know the timing of hyperkalaemia and whether patients were on other RAAS inhibitors, and at what dose? Additionally, did hyperkalaemia require treatment or lead to study drug discontinuation? Given the concerns of hyperkalaemia when MRAs are used in wider populations, a clearer evaluation of the risk of electrolyte abnormalities and renal dysfunction is necessary to balance any potential benefits in this population.

**Natriuretic peptides as an outcome**

Elevated levels of natriuretic peptides are well-recognized markers of increased risk of heart failure and death following an MI, regardless of whether the levels were measured in the acute phase or during convalescence. However, and in contrast to patients with decompenated heart failure, identifying therapies that actually reduces levels of natriuretic peptides following an ACS has proven more challenging. Several studies have failed to demonstrate any reductions in natriuretic peptides in ACS with specific therapies. The AVANTGARDE-TIMI 43 trial, atrial similar to the REMINDER trial, randomized patients with ACS and elevated levels of natriuretic peptides (but without heart failure and with an LV ejection fraction >40%), and provides additional insight into why treatment with may have significantly reduced natriuretic peptides in the REMINDER Study. In AVANT GARDE-TIMI 43, there were no differences between randomization and 8 weeks in the change in natriuretic peptides between the 1101 patients assigned to valsartan, the renin inhibitor aliskiren, a combination of the two, or placebo. Active inhibition of RAAS did, however, blunt the rise in serum aldosterone levels observed in the placebo group. Thus, even in patients without LV dysfunction, aldosterone levels rose following an infarct, probably reflecting maladaptive remodelling and fibrosis. That even dual inhibition of RAAS with aliskiren and valsartan could just blunt the rise in

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**Figure 1** Summary of cardiovascular studies evaluating inhibition of the renin–angiotensin–aldosterone system in patients presenting with acute coronary syndrome. ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CHF, heart failure; DRI, direct renin inhibitor; EF, ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid antagonist; RAAS, renin–angiotensin–aldosterone system; STEMI, ST-segment elevation myocardial infarction. * - indicates studies with natriuretic peptides as an endpoint.
aldosterone with no actual decline indicates the presence of an 'extra-RAAS' activation of aldosterone, probably at the tissue level that could only be mitigated by direct MRA.

Despite a primary composite endpoint that included several clinical events, the REMINDER study should be considered a ‘proof-of-concept’ trial, driven by the 'surrogate' endpoint of elevated levels of natriuretic peptides, which accounted for 87% of the primary composite endpoint events. The most appropriate clinical composite endpoint of cardiovascular death, heart failure, or sustained ventricular arrhythmia occurred in 9 patients assigned to eplerenone and 16 patients in the placebo group, which is at least reassuring, but insufficient to provide any clinical guidance. A properly powered study, probably 8000–12 000 patients in size with extended follow-up, will be required before a strategy of early MRA administration could be recommended for the broader STEMI population. The ongoing, open-label 1600 patient Aldosterone Lethal effects Blocked in Acute Myocardial Infarction Treated with or without Reperfusion to Improve Outcome and Survival at one Lethal effects Blocked in Acute Myocardial Infarction (ALBATROSS) trial will partially test this hypothesis, but is likely to be underpowered for patients without manifest heart failure and with preserved LV function. Regardless, the REMINDER trial has advanced the field of MRA and natriuretic peptides, and highlighted that direct MRAs may offer an important therapeutic target in the large population of MI patients without heart failure or depressed LV function.

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References


