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Invited Commentary

Mineralocorticoid Receptor Antagonists in ST-Segment Elevation Myocardial Infarction

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Therapy for patients with ST-segment elevation myocardial infarction (STEMI) has been the focus of considerable investigation over the past decade. Our improved understanding of the adequacy, timing, consequences, and extent of early reperfusion and the development of new anticoagulants and antiplatelet drugs have resulted in improved clinical outcomes. Although the incidence of STEMI has decreased relative to the incidence of myocardial infarction without ST-segment elevation, it continues to be associated with substantial morbidity and mortality.[1]

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In this issue of *JAMA Internal Medicine*, Dahal et al[2] focus on the role of mineralocorticoid receptor antagonists (MRAs) in treating patients with STEMI without evidence of heart failure or severe left ventricular dysfunction. Based on the results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial,[3] MRAs are now a class 1 indication in both US and European clinical guidelines for patients with STEMI and low left ventricular ejection fraction complicated by heart failure and/or diabetes. The role of MRAs in the treatment of patients with STEMI but without heart failure is, however, less clear. The Randomized, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Early Treatment with Eplerenone in Patients with Acute Myocardial Infarction (REMINDER) trial (n = 1012), which evaluated the role of eplerenone treatment administered early after STEMI, showed a reduction in brain-type natriuretic peptide levels but was not powered to show a reduction in mortality,[4] in large part because of the relatively low incidence of death among these patients. The Aldosterone Lethal Effects Blocked in Acute Myocardial Infarction Treated With or Without Reperfusion to Improve Outcome and Survival at 6 Months Follow-up (ALBATROSS) trial (n = 1603), which evaluated the role of spironolactone treatment administered early after STEMI and after myocardial infarction without ST-segment elevation, also failed to show a significant reduction in mortality, although subgroup analysis suggested a beneficial effect in patients with STEMI.[5] Thus, because there is insufficient evidence reported in individual studies, current clinical guidelines do not recommend the use of MRAs to treat patients with STEMI without heart failure or severe left ventricular dysfunction. The new study by Dahal et al,[2] a systematic review and meta-analysis of data from 10 randomized placebo-controlled trials including 4147 patients with STEMI but without heart failure and with left ventricular ejection fraction greater than 40%, leads to a different conclusion. The researchers found that the use of MRAs was associated with a significant 38% reduction in mortality but that there was no significant effect on the incidence of subsequent myocardial infarction, heart failure, or ventricular arrhythmias. There was, however, a small but significant increase in left ventricular ejection fraction and an increase in serum potassium level of 0.07 mEq/L but no change in serum creatinine level. It should be pointed out that there were fewer than 10 deaths in 6 of the studies included in the meta-analysis by Dahal et al,[2] and none of the individual studies showed a significant reduction in mortality.

What mechanisms might account for higher mortality associated with an increase in aldosterone level and/or activation of the mineralocorticoid receptor and a reduction in mortality associated with the use of MRAs in patients with

STEMI but without heart failure or severe left ventricular dysfunction? It is known that aldosterone levels may be elevated in patients with acute myocardial infarction but without heart failure as well as in patients with coronary artery disease who are undergoing percutaneous coronary angioplasty. We propose that MRA use may result in a decrease in macrophage accumulation and activation; a reduction in inflammatory cytokines; a decrease in reactive oxygen species; a decrease in myocardial, vascular, and renal fibrosis; an increase in vascular nitric oxide availability; a decrease in vascular stiffness; a decrease in microvascular injury; and an increase in myocardial norepinephrine uptake. All of these changes may contribute to improvement in ventricular remodeling, a decrease in ventricular arrhythmias and atrial fibrillation, and a decrease in sudden cardiac death and the development of heart failure.

Although the results of the meta-analysis by Dahal et al[2] are encouraging and plausible, based on the mechanisms associated with MRAs outlined above as well as on the results of the EPHESUS trial in patients with STEMI and heart failure with reduced ejection fraction (HFrEF) or diabetes and the Randomized Aldactone Evaluation Study (RALES) and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trials in patients with chronic HFrEF and low ejection fraction, one should be cautious in extending the use of MRAs to all patients with STEMI in clinical practice. Additional prospective confirmation in an adequately powered prospective randomized study is indicated. The use of MRAs according to their current class 1 indication, including use in patients after myocardial infarction associated with low ejection fraction complicated by heart failure or diabetes and in patients with chronic HFrEF, is suboptimal. This is especially true among patients with chronic kidney disease and/or diabetes, in large part because of the risk of inducing hyperkalemia and renal failure.[6,7] Once initiated, treatment with MRAs is often discontinued because of an increase in serum creatinine or potassium levels. The availability of new nonsteroidal MRAs, such as finerenone, which in early studies among patients with chronic HFrEF, appears to be as effective as spironolactone in reducing brain-type natriuretic peptide levels but is associated with a lower incidence of hyperkalemia,[8] along with the development of new effective and well-tolerated potassium-lowering drugs, such as patiromer and sodium zirconium cyclosilicate, raises the promise that treatment with MRAs might be more frequently initiated and, if initiated, better tolerated.

Thus, although Dahal et al[2] are to be commended for focusing our attention on the possibility that treatment with MRAs could further reduce mortality among patients with STEMI but without heart failure or severe left ventricular dysfunction, we should await the results of further adequately powered prospective, randomized studies of treatment with MRAs among patients with STEMI, such as Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent Registry (CLEAR-SYNERGY) (NCT03048825). It will also be important to develop additional experience with the newer nonsteroidal MRAs and potassium-lowering agents before routine adoption of this strategy in clinical practice. If we are to change clinical practice among patients with STEMI but without heart failure or severe left ventricular dysfunction, we will need a strategy that is not only safe and effective but also able to be widely adopted, well tolerated, and cost-effective.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Pitt reports having been employed as a consultant by Bayer, Sanofi, AstraZeneca, KBP Pharmaceuticals, Relypsa/Vifor, scPharmaceuticals, Sarfex, Tricida, and Stealth Peptides; having received stock options from KBP Pharmaceuticals, Relypsa/Vifor, scPharmaceuticals, Sarfez, and Tricida; and holding a patent pending for site-specific delivery of eplerenone to the myocardium.

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