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Editor's Note

Management of Heart Failure and Left Ventricular Systolic Dysfunction Following Acute Myocardial Infarction

Key words: heart failure, systolic dysfunction, myocardial infarction

In an analysis of data from four international fibrinolytic therapy trials, heart failure (HF) occurred in 29.4% of patients with ST-segment elevation acute myocardial infarction (STEMI).[1] These patients are commonly older, female, have a history of comorbidity (such as diabetes or hypertension), and have an anterior MI.[2,3]

Several studies have evaluated outcomes in patients with a clinical diagnosis of mild to moderate HF (Killip class II and III) following an acute MI (AMI). These patients are at a higher risk for in-hospital mortality and adverse outcomes compared with those with no clinical signs of HF.[1–3] This is true whether they present with HF at baseline or develop HF during hospitalization, and when HF symptoms are transient (present at baseline and resolve after admission). In this patient population, in-hospital mortality rates are estimated to be as high as 21%,[2,3] with 1-year mortality rates of 40%.[4] Hasdai *et al.*[1] evaluated the impact of HF on 30-day morbidity and mortality following AMI and found that the incidence of death at 30 days was four times greater in patients with mild to moderate HF than in patients without HF (8 vs. 2%). In addition, the combined incidence of death or recurrent AMI was three times greater in patients with HF (12 vs. 4%). Data from the Global Registry of Acute Coronary Events (GRACE) study indicated that such patterns persist over at least six months.[2] Thus, HF can be detrimental to both short- and long-term outcomes in patients with AMI.

Despite these risks, Wu *et al.*, reported that patients with STEMI in Killip class II or III were less likely to receive aspirin, heparin, oral beta blockers, fibrinolytics, or primary angioplasty than patients with AMI but no HF.[3] Moreover, these same patients were more likely to receive calcium channel blockers. Even when standard-of-care medical therapy is implemented following AMI complicated by HF and left ventricular systolic dysfunction (LVSD), the mortality rate and the rate of hospitalizations for HF or recurrent MI remains high. Although there has been increased use of angiotensin-converting enzyme (ACE) inhibitors and beta blockers in recent years, it seems that there is still a need for additional therapies to further reduce mortality and hospitalizations in these patients.

One recent addition to the agents used in the treatment of patients with HF and LVSD following AMI is eplerenone. Eplerenone, a selective aldosterone blocker, is the only aldosterone blocker that has been studied in this specific group of high-risk patients (Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study [EPHESUS]).[5] The EPHESUS study evaluated the mortality benefits of selective aldosterone blockade in patients with AMI complicated by LVSD (mean ejection fraction 33%) and HF. Eplerenone, initiated at 25 mg/d and titrated in a single step to 50 mg/d, or placebo, was added to standard therapy, which usually included ACE inhibitors, angiotensin receptor blockers, diuretics, beta blockers, statins, and aspirin administered 3 to 14 days following AMI. About half the patients in each treatment group received reperfusion therapy. After a mean follow-up of 16 months, the relative risks of all-cause mortality and cardiovascular mortality/cardiovascular hospitalization were reduced by 15 ($p = 0.008$) and 13% ($p = 0.002$), respectively, with eplerenone. The rate of sudden cardiac death was reduced by 21% ($p = 0.03$). In patients with LVEF < 30%, the relative reductions in total mortality and sudden cardiac death were even greater. The Kaplan-Meier curves for each of these endpoints clearly demonstrate that long-term risk is significantly reduced. It is interesting that in the short-term a clear separation of the placebo and eplerenone curves is evident as early as 30 days post randomization. Although further analyses with preselected time cut-offs need to be conducted in order to understand the onset of benefit relative to the time of randomization, it appears that eplerenone has beneficial effects in the early post-AMI period, when death rates are notably high.

The principal risk associated with eplerenone therapy is hyperkalemia; however, in the EPHESUS trial no deaths were attributed to hyperkalemia in the eplerenone arm and there was a significant reduction of hypokalemia with eplerenone (the risk of which was more than twice that of hyperkalemia). The EPHESUS investigators conclude that with appropriate patient selection, monitoring of potassium and renal function, and dose adjustments, the clinical evidence of mortality benefits of this drug used with standard therapy warrants its use in patients with post-AMI HF and LVSD.

The significance of EPHESUS is far-reaching, as no therapy other than eplerenone has been able to show additional mortality benefits when used with current standard therapy for HF with LVSD after AMI. American College of Cardiology/American Heart Association guidelines for the manage-

ment of STEMI[6] recommend the use of long-term aldosterone blockade for patients with STEMI with LVEF ≤ 40% and symptomatic HF or diabetes who are taking an ACE inhibitor and do not have significant renal dysfunction or hyperkalemia. As a Class IA treatment recommendation, aldosterone blockers are considered with high certainty to be a beneficial, useful, and effective treatment in these patients.[6] Thus, the use of eplerenone may be the next step in achieving reductions in both early and long-term mortality and morbidity in post-AMI patients with LVSD and HF. Given the high risks in this cohort, evidence-based treatment regimens, such as eplerenone, should be more routinely and aggressively used in these patients.

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