Aldosterone blockade after myocardial infarction

Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348: 1309-21.

Background: Patients presenting with acute myocardial infarction complicated by congestive heart failure are at particularly high risk of death and recurrent cardiovascular events.[1] The use of spironolactone, a nonselective aldosterone inhibitor, led to impressive reductions in morbidity and mortality in a randomized trial involving patients with severe chronic heart failure.[2] The effects of aldosterone blockade on morbidity and mortality after myocardial infarction are largely unknown.

Question: Does eplerenone, a novel selective aldosterone inhibitor, reduce rates of hospital admission and death from cardiovascular events among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure, who are receiving optimal medical therapy?

Design: In this randomized, double-blind trial, patients received either eplerenone (25 mg/d) or matching placebo for 4 weeks, after which the eplerenone dose was increased to a maximum of 50 mg/d. Aside from fulfilling standard criteria for acute myocardial infarction, patients were included if they had a left ventricular ejection fraction of 40% or lower and signs of congestive heart failure. Exclusion criteria were the use of potassium-sparing diuretics, a serum creatinine level of more than 220 μmol/L or a serum potassium concentration of more than 5.0 μmol/L at baseline.

The 2 primary end points were time to death from any cause, and time to death from cardiovascular causes or first hospital admission because of a cardiovascular event. Analyses were conducted according to the intention-to-treat principle.

Results: A total of 6642 patients were randomly assigned to receive eplerenone or placebo, with a mean follow-up of 16 months. The mean age at baseline was 64 years; 71% were men. The mean left ventricular ejection fraction was 33%. At baseline, most patients were receiving optimal medical therapy for acute myocardial infarction. The average dose of eplerenone in the treatment group was 43 mg. Loss to follow-up was less than 1%.

All-cause mortality was lower in the eplerenone group than in the placebo group (14.4% v. 16.7%; relative risk [RR] 0.85, 95% confidence interval [CI] 0.75–0.96). The rate of death from cardiovascular causes or hospital admissions because of cardiovascular events was also lower in the treatment group (26.7% v. 30.0%; RR 0.87, 95% CI 0.79–0.95). Broken down by cause, there was a statistically significant reduction in the rate of sudden cardiac death (RR 0.79, 95% CI 0.64–0.97); there were also reductions in the rates of death from acute myocardial infarction (RR 0.82, 95% CI 0.61–1.10) and death from heart failure (RR 0.80, 95% CI 0.62–1.04), although they did not reach statistical significance.

Serious hyperkalemia (defined as a serum potassium level ≥ 6.0 μmol/L) occurred in 5.5% of patients in the eplerenone group, as compared with 3.9% of patients in the placebo group (p = 0.002). However, the incidence of hypokalemia was significantly less common in the eplerenone group than in the placebo group (8.4% v. 13.1%; p < 0.001).

Commentary: This large, well-designed study shows that the addition of eplerenone to optimal medical therapy reduces the risk of death and readmission to hospital because of heart failure among patients with left ventricular dysfunction following myocardial infarction. It therefore confirms the importance of neurohumoral antagonism at the level of the aldosterone receptor first postulated by the RALES trial.[2] Aldosterone, in addition to causing plasma volume expansion and impaired sodium excretion, is also a potent mediator of adverse vascular remodelling and myocardial interstitial fibrosis. Eplerenone has been shown to reduce vascular inflammation and myocardial fibrosis in animal models of cardiac disease, and to improve vascular compliance and endothelial dysfunction in older hypertensive patients.[3,4]

Practice implications: Patients with myocardial infarction should be treated optimally with an antiplatelet agent, statin, angiotensin-converting-enzyme inhibitor and β-blocker, with the addition of eplerenone for those who have congestive heart failure or left ventricular dysfunction, or both. The expected number needed to treat to save 1 life with 1 year of therapy is 50, with a number needed to treat of 33 to prevent 1 death from cardiovascular causes or 1 hospital admission because of a cardiovascular event in 1 year.

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