Adjunctive treatment with eplerenone reduced 30-day all-cause mortality in acute myocardial infarction

Pitt B, White H, Nicolau J, et al. **Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure.** J Am Coll Cardiol. 2005;46:425-31.

Clinical impact ratings: Hospitalists ★★★★★★☆ Cardiology ★★★★★★☆

QUESTION

In patients with acute myocardial infarction (MI) complicated by left-ventricular systolic dysfunction (LVSD) and heart failure, does adjunctive treatment with eplerenone reduce morbidity and mortality more than placebo?

METHODS

Design: Randomized placebo-controlled trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS]).

Allocation: {Concealed}†.*

Blinding: Blinded (clinicians, patients, outcome assessors, {data collectors, data analysts, and manuscript writers}†).*

Follow-up period: 30 days.

Setting: 674 centers in 37 countries.

Patients: 6632 patients (mean age 64 y, 70% men) with acute MI complicated by LVSD (ejection fraction ≤ 40%) and heart failure (confirmed by the presence of rales, pulmonary venous congestion on chest radiography, or a third heart sound). Exclusion criteria included serum creatinine ≥ 220 µmol/L (2.5 mg/dL) and serum potassium > 5.0 mmol/L.

Intervention: Eplerenone 25 mg/d (n = 3319) or placebo (n = 3313) started at 3 to 14 days after acute MI. All patients received usual medical care.

Outcomes: Time to death from any cause and time to death from cardiovascular (CV) causes or first hospitalization for a CV event (heart failure, recurrent acute MI, stroke, or ventricular arrhythmia). Secondary outcomes included death from CV causes, sudden cardiac mortality, and hospitalization for heart failure.

Patient follow-up: 100% (intention to treat analysis).

MAIN RESULTS

Rates of all-cause mortality and death from CV causes were lower in the eplerenone group than in the placebo group (Table). The groups did not differ for any other outcomes (Table).

CONCLUSION

In patients with acute myocardial infarction complicated by left-ventricular systolic dysfunction and heart failure, adjunctive treatment with eplerenone reduced 30-day all-cause mortality more than placebo.

Source of funding: Pfizer Inc.

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*See Glossary.

†Information provided by author.

Usual care plus eplerenone vs usual care plus placebo in acute myocardial infarction (MI) complicated by left ventricular systolic dysfunction and heart failure at 30 days‡

Outcomes	Eplerenone	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	3.2%	4.6%	31% (11 to 46)	72 (43 to 216)
Death from CV causes or first hospitalization for CV events§	8.6%	9.9%	13% (–1 to 26)	Not significant
Death from CV causes	3.0%	4.4%	32% (12 to 47)	72 (44 to 207)
Sudden cardiac death	0.9%	1.4%	37% (0 to 60)	Not significant
Hospitalization for heart failure	3.4%	4.2%	18% (–4 to 36)	Not significant

‡CV = cardiovascular. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

§CV events included heart failure, recurrent acute MI, stroke, and ventricular arrhythmia.

COMMENTARY

The EPHESUS trial by Pitt and colleagues clearly showed that eplerenone, an aldosterone inhibitor, reduces mortality in patients with LVSD and heart failure following an acute MI. Based largely on this trial, the U.S. Food and Drug Administration approved eplerenone in October 2003 for use in patients with congestive heart failure after acute MI.

However, if the benefits of eplerenone are to be realized in clinical practice, hyperkalemia ought to be looked for as diligently as it was in the trial. An easy-to-remember algorithm, termed "the rule of ones," was used to survey patients for hyperkalemia as follows: Potassium levels were checked before initiation of therapy (patients with potassium > 5.0 mg/dL were excluded) and at 1 day, 1 week, and 1 month after initiation of therapy and per physician preference thereafter.

Given the large clinical benefit derived within even 30 days, the question arises whether eplerenone might be beneficial if started even earlier than 3 to 14 days after MI, as required in EPHESUS.

Cost is always an issue when new treatments are introduced. A cost-effectiveness analysis from EPHESUS showed that the increased survival of patients treated with eplerenone cost $1391 during the 16-month follow-up (1). Several different models showed that the incremental cost-effectiveness ratio was in the range of $10 400 to $21 876, compared with the generally accepted cost-effectiveness amount of $50 000 per life-year gained.

2 aldosterone inhibitors are currently available: spironolactone and eplerenone. Eplerenone is > 3 times more expensive than spironolactone. It is unknown whether the benefits of eplerenone are a class effect of aldosterone inhibitors or whether they are similar to those of spironolactone. Even if they are, no head-to-head comparisons between eplerenone and spironolactone exist, and it is unknown what the most appropriate dosing strategy with spironolactone would be to match the excellent benefits of eplerenone shown in this study. Based on EPHESUS, physicians should be initiating therapy with eplenerone after MI more than they currently are.

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Reference

1. **Weintraub WS, Zhang Z, Mahoney EM, et al.** Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. Circulation. 2005;111:1106-13.