Adjunctive treatment with eplerenone reduced morbidity and mortality in acute myocardial infarction

Pitt B, Remme W, Zannad F, et al. **Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction.** N Engl J Med. 2003;348:1309-21.

QUESTION

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

DESIGN

Randomized {allocation concealed*}†, blinded (clinicians, patients, outcome assessors, {data collectors, data analysts, and manuscript writers}†),* placebo-controlled trial with mean 16-month follow-up (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS]).

SETTING

674 centers in 37 countries.

PATIENTS

6642 patients (mean age 64 y, 71% men) with acute MI, left ventricular dysfunction (ejection fraction ≤ 40%), and HF (confirmed by the presence of pulmonary rales, pulmonary venous congestion on chest radiography, or a third heart sound). Exclusion criteria included potassium-sparing diuretics, serum creatinine ≥ 220 μmol/L, and serum potassium > 5.0 mmol/L before randomization. 6632 patients (99.8%) were included in the follow-up analysis.

INTERVENTION

Patients were stratified by clinical site and allocated 3 to 14 days after acute MI to eplerenone, 25 mg/d (increased to a maximum of 50 mg/d after 4 wk) (n = 3319), or placebo (n = 3313). All patients received optimal medical therapy (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, β-blockers, and coronary reperfusion therapy).

MAIN OUTCOME MEASURES

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 were death from CV causes, death from any cause, or any hospitalization.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the eplerenone group died from any cause, died from CV causes, or were hospitalized for CV events than did those in the placebo group (Table). Secondary endpoints were also reduced in eplerenone recipients (Table). More patients in the eplerenone group had serious hyperkalemia (serum potassium concentration ≥ 6.0 mmol/L) than did patients in the placebo group (5.5% vs 3.9%, P = 0.002).

CONCLUSION

In patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure, adjunctive treatment with eplerenone reduced morbidity and mortality more than placebo.

Source of funding: Pharmacia.

For correspondence: Dr. B. Pitt, University of Michigan, Ann Arbor, MI, USA. E-mail bpitt@umich.edu.

*See Glossary.

†Information provided by author.

Eplerenone vs placebo for myocardial infarction at mean 16 months‡

Outcomes	Eplerenone	Placebo	RRR (95% CI)	NNT (CI)
Death from any cause	14%	17%	15% (4 to 25)	44 (25 to 174)
Death from CV causes or CV event hospitalization	27%	30%	13% (5 to 21)	31 (19 to 88)
Death from any cause or any hospitalization	52%	55%	8% (2 to 14)	33 (19 to 147)
Death from CV causes	12%	15%	17% (6 to 28)	44 (26 to 148)

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

COMMENTARY

The results of the EPHESUS study by Pitt and colleagues and the previously published Randomized Aldactone Evaluation Study (RALES) (1) provide strong evidence for the addition of an aldosterone antagonist to optimal conventional therapy in patients with CHF and reduced left ventricular systolic function.

EPHESUS establishes the role of selective aldosterone antagonism with eplerenone in patients with an EF ≤ 40% and clinical signs of CHF within 3 to 14 days of an acute MI. Debate will probably focus on whether these results are specific to selective aldosterone antagonists (eplerenone) or whether nonselective agents (spironolactone) could provide similar results (particularly if there is a marked price difference).

Are there strong reasons to believe that the potential mechanisms of benefit are unique to eplerenone rather than spironolactone in the postinfarction subgroup of patients with CHF? Probably not. In addition, the magnitude of benefit with spironolactone in the RALES study (in which 54% of patients had an ischemic basis for CHF) was twice as great in relative terms as, and 4 times greater in absolute terms than, eplerenone in the EPHESUS study. Potential reasons for these differences include the sicker population studied, early termination of the trial, and the scarce use of β-blockers (which were not yet established as CHF therapy) in the RALES study. A head-to-head comparison of the 2 drugs would determine whether true differences exist between them.

Although both drugs were well tolerated, a major difference was that men receiving spironolactone had a 10% risk for gynecomastia or breast pain, which was not seen in men receiving eplerenone.

Overall, the results of the EPHESUS and RALES studies are impressive and warrant the early addition of an aldosterone antagonist (whether eplerenone or spironolactone) for preventing or delaying the considerable mortality and morbidity associated with clinical left ventricular dysfunction caused by MI. These trials also show the need for closer attention to the possibility of hyperkalemia, particularly in patients with impaired renal function.

Manu Prabhakar, MD
David Massel, MD
London Health Sciences Centre
London, Ontario, Canada

Reference

1. **Pitt B, Zannad F, Remme WJ, et al.** N Engl J Med. 1999;341:709-17.