

Does eplerenone benefit postinfarction patients with heart failure and left ventricular systolic dysfunction?

Original article Pitt B *et al.* for the EPHEUS Investigators (2005) 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* 46: 425–431

SYNOPSIS

KEYWORDS acute myocardial infarction, aldosterone blocker, eplerenone, heart failure

BACKGROUND

The risk of early in-hospital mortality after an acute myocardial infarction (AMI) is raised significantly if the patient has left ventricular systolic dysfunction (LVSD) and signs of heart failure. This finding suggests that patients could benefit from therapeutic intervention immediately following an AMI.

OBJECTIVE

To evaluate the effect of the aldosterone blocker eplerenone on 30-day mortality and morbidity in patients with LVSD and heart failure following AMI.

DESIGN

In this post hoc study, Pitt *et al.* analyzed the results of the multicenter, international, double-blind, randomized Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHEUS). Inclusion criteria for the original EPHEUS trial were clinical signs of heart failure, even if transient, and a left ventricular ejection fraction of 40% or less. Patients with diabetes mellitus only needed LVSD for inclusion. Exclusion criteria included serum creatinine levels more than 221 μM (>2.5 mg/dl) and serum potassium levels over 5.0 mM.

INTERVENTION

In the 3–14 days after AMI, patients were randomly assigned 25 mg eplerenone daily or placebo. If serum potassium levels were lower than 5 mM after 4 weeks of treatment, eplerenone dose was uptitrated to 50 mg daily.

OUTCOME MEASURES

The two main endpoints were time to all-cause death and the composite of cardiovascular-related hospitalization or time to cardiovascular-related death. Secondary endpoints were sudden cardiac death, cardiovascular-related death and hospitalization for heart failure.

RESULTS

Of the 6,632 patients enrolled in the EPHEUS trial, 3,319 were assigned eplerenone therapy and 3,313 were assigned placebo. Following AMI, the average left ventricular ejection fraction was 33% and most patients were receiving standard treatment for LVSD and heart failure. Eplerenone treatment was initiated 7.3 days after AMI on average. The occurrence of all-cause mortality at 30 days was significantly lower in the eplerenone group than in the placebo group; 107 eplerenone patients died compared with 153 placebo patients (relative risk reduction 31%, 95% CI 0.54–0.89, $P=0.004$). Although not significant, there was a trend towards a reduction in the composite cardiovascular-related mortality and hospitalization endpoint in patients treated with eplerenone compared with patients treated with placebo (287 versus 329; risk reduction 13%, 95% CI 0.74–1.01, $P=0.074$). Furthermore, eplerenone significantly reduced the risk of cardiovascular-related mortality, of which sudden cardiac death was the most common cause (sudden cardiac death risk reduction 37%, $P=0.051$). Although nonsignificant, the occurrence of hospitalization for heart failure was also lower in the eplerenone group than in the placebo group.

CONCLUSION

Eplerenone therapy reduces 30-day mortality in patients who have LVSD and signs of heart failure after AMI. On the basis of the benefits seen in this study, the authors suggest that eplerenone treatment should be initiated immediately after AMI, in conjunction with conventional therapeutic intervention.

COMMENTARY

Aldo Pietro Maggioni

Major advances in the clinical diagnosis and treatment of MI have been made in the past 20 years. The introduction of effective treatments, including reperfusion strategies and the use of antiplatelet agents, β -blockers and angiotensin-converting-enzyme (ACE) inhibitors, was associated with reduced in-hospital mortality. Consequently these treatments are now part of the current guidelines.¹ In 2004, the VALIANT registry² showed that after MI, nearly 40% of patients had LVSD, heart failure or both. Notably, in-hospital mortality for this group of patients was more than five times higher than in patients without LVSD or heart failure, thus accounting for 80% of all in-hospital deaths after MI.²

ACE inhibitors,³ angiotensin-receptor blockers (ARBs)⁴ and now aldosterone blockers, specifically eplerenone,⁵ have been shown to improve the long-term outcome of patients with post-MI LVSD, heart failure or both. As the large majority of fatal events, including sudden cardiac death, occur within the first month after the beginning of symptoms following MI, it was not known whether the interventions listed have a significant impact early after MI. In this context Pitt *et al.* have analyzed the EPHEMUS trial database. They showed that with 25 mg eplerenone daily in addition to conventional therapy—86% of patients received ACE inhibitors or ARBs, and 75% received β -blockers—there was a 31% reduction in all-cause mortality 30 days after MI (absolute risk reduction [ARR] 0.6%), a 32% reduction in cardiovascular-related mortality (ARR 1.4%) and a 37% reduction in sudden cardiac death (ARR 0.5%). Although these findings suggest that eplerenone should be administered early after MI, they also raise a couple of clinical questions.

Since the beneficial effect of eplerenone largely related to the early phase after MI (i.e. 61% of the fatal events prevented by eplerenone over the 16-month trial were prevented within the first 30 days), is it necessary to continue treatment for a long period of time? Even if the majority of events occur early after MI, ventricular remodeling—in conjunction with activation of neurohormonal systems, cytokine

production and collagen formation—continues over time, thereby predisposing patients to heart failure progression and sudden cardiac death. Therefore, eplerenone treatment, together with the other neurohormonal blocking agents—ACE inhibitors or ARBs, and β -blockers—should be continued long term.

This consideration then raises the second question: what is the safety profile of the combined use of these drugs in real clinical practice? The EPHEMUS trial showed a reassuring safety profile, with a nonsignificant excess of hyperkalemia in patients treated with eplerenone, at least in the first 30 days of treatment. The intensive monitoring of patients seen in the trial, however, is not generally maintained in routine clinical practice. This, together with the observation that real-world patients are generally older and have more comorbidities than those enrolled in clinical trials, could induce a relevantly higher rate of adverse reactions.⁶ Given that the 30-day all-cause mortality in the EPHEMUS study, even in the placebo group, is considerably lower than that in clinical practice among patients with LVSD after AMI, the importance of careful monitoring of the patients is reinforced, specifically in terms of renal function.

References

- 1 Antman *et al.* (2004) ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* **44**: 671–719
- 2 Velazquez EJ *et al.* for the VALIANT registry (2004) An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J* **25**: 1911–1919
- 3 Flather MD *et al.* (2000) Long term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* **355**: 1575–1581
- 4 Pfeffer MA *et al.* (2003) Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. *N Engl J Med* **349**: 1843–1906
- 5 Pitt B *et al.* (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* **348**: 1309–1321
- 6 Juurlink DN *et al.* (2004) Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* **351**: 543–551

AP Maggioni is Director of the Research Center of the Italian Association of Hospital Cardiologists (ANMCO), Florence, Italy.

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Competing interests

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Correspondence

Italian Association of Hospital Cardiologists (ANMCO) Research Center Via La Marmora 34 50121 Florence Italy maggioni@anmco.it

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PRACTICE POINT

Eplerenone should be given to patients with LVSD and HF after MI, before hospital discharge, with careful monitoring of renal function and potassium levels