HEART FAILURE

Placing an EMPHASIS on the mineralocorticoid receptor—benefit of eplerenone in mild HF

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The EMPHASIS-HF investigators have demonstrated that the addition of the selective mineralocorticoid receptor antagonist (MRA), eplerenone, to standard evidence-based therapy reduces the risk of death and hospitalization in patients with mild systolic heart failure (HF). The benefits were so pronounced that the trial was stopped early, before the target study population of 3,100 patients had been enrolled. The results of the EMPHASIS-HF study were reported at the AHA 2010 Scientific Sessions in Chicago, IL, USA, and published in the *New England Journal of Medicine*.

Earlier studies of MRAs have shown that these agents benefit patients with moderate to severe HF (spironolactone in RALES) and those with HF post-infarction (eplerenone in EPHESUS). "The results [of EMPHASIS-HF] extend the findings of RALES and EPHESUS and the benefits of MRAs to a milder HF population," explains investigator Faiez Zannad.

Eplerenone works by antagonizing the action of aldosterone at the mineralocorticoid receptor. An elevated aldosterone level is associated with adverse outcomes in patients with cardiovascular disease, and mineralocorticoid receptors are overexpressed in the hearts of patients with left ventricular dysfunction. Conventional therapies, such as angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) and β-blockers do not act on the mineralocorticoid receptor and, therefore, do not reduce plasma aldosterone levels. Eplerenone thus fills a therapeutic gap in the treatment of patients with HF.

EMPHASIS-HF was a randomized placebo-controlled trial conducted at 278 treatment centers in 29 countries. Patients were enrolled if they had a left ventricular ejection fraction of ≤30% and NYHA class II symptoms, were already undergoing treatment with an ACE inhibitor and/or an ARB, plus a β-blocker, and had been hospitalized for a cardiovascular cause within the preceding 6 months. Patients with renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m^2), and those with hyperkalemia (serum potassium >5.0 mmol/l) were excluded from the trial.

Study participants were randomly assigned to receive eplerenone ($n = 1,364$) at 25 mg per day, increasing to 50 mg per day after 4 weeks, or to placebo ($n = 1,373$). Patients were monitored every 4 months and the dose of eplerenone was adjusted according to serum potassium level.

When compared with placebo, eplerenone reduced the incidence of the primary composite end point (cardiovascular death or hospitalization for HF) by 47% (25.9% versus 18.3%; $P < 0.001$). The individual components of this end point were also significantly reduced with eplerenone. The incidence of cardiovascular death was 10.8% in the eplerenone group compared with 13.5% in the placebo group ($P = 0.01$). All-cause hospitalization occurred in 29.9% of patients receiving eplerenone versus 35.8% of those taking placebo ($P < 0.001$). Moreover, fewer patients in the eplerenone group were hospitalized for HF than in the placebo group ($P < 0.001$). These findings were consistent when analyzed across 20 predefined subgroups of patients.

On the whole, eplerenone was well-tolerated, with the exception of an increased rate of hyperkalemia that, according to Dr Zannad, was expected. More patients in the eplerenone group than in the placebo group had elevations in serum potassium level >5.5 mmol/l (11.8% versus 7.2%; $P = 0.001$). By contrast, the incidence of hypokalemia (serum potassium <4.0 mmol/l) was higher in the placebo group than in the eplerenone group (48.4% versus 38.8%; $P < 0.001$). However, these adverse effects did not lead to a significant increase in the proportion of patients who discontinued their medication during the study (eplerenone 13.8%, placebo 16.2%; $P = 0.09$).

The EMPHASIS-HF investigators acknowledge that, although clinically important, their findings might not be relevant to the treatment of all patients. For example, individuals with poor renal function at baseline were excluded, so any potential benefit of eplerenone therapy in patients with HF and concurrent chronic kidney disease cannot be determined at present. However, "the implications of EMPHASIS-HF are that symptomatic patients with HF and low ejection fraction should now receive the triple combination of an MRA, in addition to an ACE inhibitor and a β-blocker, if not contraindicated," says Dr Zannad. "Results from other clinical and experimental work suggest that MRAs should be tested in other cardiovascular risk populations." In this respect, the results of TOPCAT and the ALBATROSS trial are eagerly awaited.

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Original article Zannad, F. *et al.* for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* doi:10.1056/NEJMoa1009492