Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure – EMPHASIS-HF

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Description:

Based on earlier trials, current guidelines indicate that the use of mineralocorticoid receptor antagonists such as spironolactone and eplerenone in addition to standard therapy in patients with left ventricular (LV) systolic dysfunction post-myocardial infarction (MI) and New York Heart Association (NYHA) class III or IV symptoms is a class I indication. The current trial sought to study the utility of eplerenone in patients with LV systolic failure and mild (NYHA class II) symptoms.

Contribution to the Literature: In the EMPHASIS-HF trial, eplerenone when added to optimal medical therapy results in significant improvements in cardiovascular outcomes compared with placebo in patients with mildly symptomatic LV systolic dysfunction.

Study Design

- Placebo Controlled
- Randomized
- Blinded
- Parallel

Patient Populations:

- Patients with NYHA class II HF of at least 4 weeks' duration on optimal HF medications
- Age at least 55 years
- EF ≤30% (if QRS complex width >130 msec, then EF 30-35% were included)
- Treatment with ACEI/ARB or both, and a beta-blocker in the absence of contraindications at the recommended or maximal tolerated dose

Number of enrollees: 2,737
Duration of follow-up: 3 years
Mean patient age: 68.7 years
Percentage female: 22%
Ejection fraction: 22.6%

NYHA class: II (100%)

Exclusions:

- Acute MI
- NYHA class III/IV symptoms
- Serum K >5 mmol/L
- GFR <30 ml/min/1.73 m2
- Need for potassium-sparing diuretic
- Significant coexisting condition

Primary Endpoints:

- Death from CV causes or first CHF hospitalization

Secondary Endpoints:

- Hospitalization for CHF or all-cause mortality
- CV mortality
- Any hospitalization
- CHF hospitalization

Drug/Procedures Used:

Eplerenone was started at a dose of 25 mg daily, and then increased after 4 weeks to 50 mg daily (or if glomerular filtration rate [GFR] was between 30 and 45 ml/min/1.73 m2), then started at 25 mg every other day, and increased to 25 mg daily, as long as the serum K was <5.0 mmol/L. The K was monitored every 4 months. If levels were >5.5 mmol/L, the dose was decreased, and if >6 mmol/L, the drug was stopped. The K was rechecked after 72 hours, and the drug was resumed only if K was <5 mmol/L.

Concomitant Medications:

Angiotensin-converting enzyme inhibitor (ACEI) (78%), angiotensin-receptor blocker (ARB) (19%), beta-blocker (87%), lipid-lowering agent (62%), digitalis (27%), and diuretic (85%)

Principal Findings:

A total of 2,737 patients were randomized, 1,364 to eplerenone and 1,373 to placebo. Baseline characteristics were fairly similar between the two arms. About 32% had diabetes mellitus, and 69% had ischemic cardiomyopathy. The mean left ventricular ejection fraction (LVEF) was 26.2%. The mean duration of chronic heart failure (CHF) was 4.7 years, and 52% had a history of CHF hospitalization. About 22% had undergone prior percutaneous coronary intervention and 19% prior coronary artery bypass grafting. Mean systolic blood pressure and diastolic blood pressure at baseline were 124 and 75 mm Hg, respectively.

The trial was stopped early after an interim analysis suggested an overwhelming benefit of eplerenone over placebo. The primary endpoint of cardiovascular (CV) death or hospitalization for CHF was significantly lower in the eplerenone arm, as compared with the placebo arm (18.3% vs. 25.9%, hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54-0.74, $p < 0.001$). The secondary endpoint of all-

cause mortality or CHF hospitalization was also significantly lower in the eplerenone arm (19.8% vs. 27.4%, HR 0.65, 95% CI 0.55-0.76, p < 0.001). All-cause mortality was also lower (12.5% vs. 15.5%, HR 0.76, 95% CI 0.62-0.93, p = 0.008), as was CV mortality (10.8% vs. 13.5%, HR 0.76, 95% CI 0.61-0.94, p = 0.01). Other outcomes, including all-cause hospitalization (29.9% vs. 35.8%, p < 0.001) and CHF hospitalization (12% vs. 18.4%, p < 0.001), were similarly reduced in the eplerenone arm. Effects were similar whether enrollment took place shortly after (within 42 days) or beyond a cardiovascular hospitalization event (p = NS for all interactions).

Drug discontinuation due to side effects was similar (13.8% vs. 16.2%, p = 0.09). Hyperkalemia was significantly higher in the eplerenone arm (8.0% vs. 3.7%, p < 0.001). Renal failure (1.9% vs. 2.3%, p = 0.51) and hypotension (3.4% vs. 2.7%, p = 0.32) were similar between the two arms.

Subgroup analysis in high-risk subsets (≥age 75 years, with diabetes mellitus, with chronic kidney disease [CKD] [estimated GFR 30-59], and with systolic blood pressure <median of 123 mm Hg at baseline): Drug discontinuation rates were highest in patients with CKD (16.1% vs. 22.3%). A higher risk of hyperkalemia (K >5.5) was noted, especially in CKD patients (16.6% vs. 9.3%, p = 0.002), but there was no increase in severe hyperkalemia (K >6) and hospitalization or mortality due to hyperkalemia in any of these subgroups. The benefit of eplerenone over placebo for the primary endpoint was maintained in all four high-risk subgroups.

Interpretation:

The results of the EMPHASIS-HF trial indicate that eplerenone when added to optimal medical therapy results in significant improvements in all-cause mortality, CV mortality, all-cause hospitalization, and CHF hospitalization, as compared with placebo in patients with mildly symptomatic LV systolic dysfunction (EF ≤30%). The most common side effect was hyperkalemia, which was noted in 8% of treated patients (patients with serum K >5 mmol/L at baseline were not enrolled).

This trial thus extends the results of earlier trials with mineralocorticoid receptor antagonists. The RALES trial demonstrated superiority of spironolactone over placebo in patients with severely symptomatic LV dysfunction (mean LVEF 25%). The EPHESUS trial demonstrated superiority of eplerenone over placebo in post-MI patients with NYHA class III/IV symptoms and significant LV dysfunction (mean LVEF 33%). This trial thus expands the indication to patients with mildly symptomatic LV dysfunction, and is likely to be featured in future CHF guidelines.

One consideration is the relatively high incidence of hyperkalemia with this class of medications. This needs to be carefully monitored, especially in high-risk subsets such as CKD patients, and is likely to be even higher in routine practice than what was noted in this trial, where patients were carefully followed and evaluated every 4 months after study drug initiation. Further studies are necessary to outline the biological mechanisms responsible for these improvements in outcomes, since they seem to extend beyond improvements in diuresis.

A consistent benefit in high-risk subgroups, especially in diabetics, is reassuring. Earlier studies have reported worsening of glycemic control and upregulation of inflammatory cytokines in diabetic patients receiving spironolactone. It is unclear whether eplerenone has different effects as compared with spironolactone in diabetic patients, and deserves further study.

References:

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Clinical Topics: Cardiac Surgery, Heart Failure and Cardiomyopathies, Invasive Cardiovascular Angiography and Intervention, Aortic Surgery, Cardiac Surgery and Heart Failure, Acute Heart Failure

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