Kelly Bossenbroek, MD; Anne L. Mounsey, MD
Department of Family Medicine, University of North Carolina at Chapel Hill

PURLs EDITOR
Bernard Ewigman, MD, MSPH
Department of Family Medicine, University of Chicago

More help for patients with less severe heart failure

Adding this drug to the medication regimen of patients with Class II heart failure can help to reduce hospitalization and death rates.

PRACTICE CHANGER

Prescribe a mineralocorticoid-receptor antagonist for patients with New York Heart Association (NYHA) Class II systolic heart failure and an ejection fraction (EF) ≤30%. Eplerenone has been found to decrease hospitalizations for heart failure and cardiovascular and all-cause mortality.[1]

STRENGTH OF RECOMMENDATION

A: Based on one high-quality randomized controlled trial (RCT).

Zannad F, McMurray JJ, Krum H, et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.

ILLUSTRATIVE CASE

A 56-year-old man with a history of systolic heart failure and an EF of 30% returns to your clinic for routine follow-up. He reports that he gets mildly short of breath while mowing the lawn, but his condition is stable. He's already taking an angiotensin-converting enzyme inhibitor (ACEI) and a beta-blocker, and his potassium level is 4.8 mmol/L. Should he also be taking eplerenone?

Heart failure has reached epidemic proportions in the United States.[2-4] Each year, heart failure accounts for more than 1 million hospitalizations,[3,5] and millions more are living with the disease.[2] ACEIs and beta-blockers are known to decrease hospitalization and mortality for these patients. Recent evidence suggests that mineralocorticoid-receptor antagonists have additional benefits.[2,4,6]

Benefits for Class III and IV heart failure are well established

The Randomized Aldactone Evaluation Study (RALES) showed that spironolactone decreased all-cause mortality and hospitalization for cardiovascular causes in patients with Class III and IV heart failure.[7] In the Ephesus study, the addition of eplerenone to optimal therapy reduced morbidity and mortality in patients with a myocardial infarction (MI) complicated by systolic heart failure.[8] These studies led to the current guidelines, which recommend using a mineralocorticoid-receptor antagonist for patients with NYHA Class III and IV heart failure, as well as patients with acute MI and either left ventricular dysfunction or heart failure.[2,4,6] Until recently, however, there was no reason to think about using this class of medications for patients with less severe disease.

STUDY SUMMARY

Eplerenone improves outcomes for patients with mild symptoms

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[1] was a randomized, double-blinded trial designed to evaluate the effect of eplerenone on patients with less severe disease. Eligible patients were older than 55 years, with Class II heart failure and an

EF ≤30% (or >30%-35% with a QRS interval >130 ms). Their existing drug regimen had to include an ACEI, angiotensin receptor blocker, or both, as well as a beta-blocker. Patients with a potassium level >5.0 mmol/L, acute MI, or a low glomerular filtration rate (GFR <30 mL/min) were excluded.

Randomization occurred within 6 months of hospitalization for a cardiovascular disorder; study participants without a recent hospitalization were included if they had either a plasma level of B-type natriuretic peptide (BNP) >250 pg/mL or a pro-BNP >500 pg/mL for men or >750 pg/mL for women. A total of 2737 patients were randomized to receive either eplerenone 25 mg/d (the daily dosage was increased to 50 mg after 4 weeks if the potassium level remained <5 mmol/L) or placebo. Patients with an estimated GFR of 30 to 49 mL/min were started on 25 mg eplerenone every other day; if that dose was tolerated, it was increased to 25 mg/d after 4 weeks.

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. Secondary outcomes included any hospitalization for heart failure, all-cause mortality, and cardiovascular death.

Patients were evaluated every 4 months. The dose of the eplerenone was decreased if the potassium level was 5.5 to 5.9 mmol/L, and stopped altogether if potassium was >6 mmol/L. Potassium levels were measured within 72 hours of a dosage change, and the drug restarted if potassium levels returned to <5.0 mmol/L.

After 5 months of data collection, 60% of patients in the eplerenone group were on the higher dosage (50 mg/d), as were 65% of the patients receiving placebo. At the conclusion of the trial, the study drug had been discontinued in 16% of patients in the eplerenone group and 17% of the controls.

The primary outcome (death from a cardiovascular cause or hospitalization for heart failure) occurred in 18% of patients in the eplerenone group vs 26% of those on placebo. The number needed to treat to *prevent* one primary outcome was estimated to be 19 per year of follow-up, and 51 per year of follow-up to *postpone* one death. The study was terminated early (after a median follow-up of 21 months) due to the clear benefits that were evident in the eplerenone group.

WHAT'S NEW?

We have another way to help Class II patients

Previously, mineralocorticoid-receptor antagonists were recommended only for carefully selected patients—those with a history of MI and heart failure, diabetes and heart failure, or more severe (Class III or IV) heart failure.[4,7] This study shows that heart failure patients with milder symptoms can benefit from eplerenone, as well.

CAVEATS

Cost differential means it pays to try spironolactone first

Eplerenone is expensive (approximately $100 for 30 25-mg tablets at Drugstore.com compared with $4 for the same quantity of spironolactone at Walmart.com). Because eplerenone's beneficial effects are likely due to its action as a mineralocorticoid-receptor antagonist, it makes sense to use spironolactone as a first-line agent and reserve eplerenone for patients who cannot tolerate it.

Risk of hyperkalemia

Both spironolactone and eplerenone can cause hyperkalemia and should not be used in patients with a baseline potassium level >5.0 mmol/L. Patients who are started on either of these medications should have their potassium levels checked after 3 days, 7 days, and 1 month, then periodically, whenever the dosage is changed.[4] If the potassium level is >5.0 mmol/L, the dose should be decreased by 50%—and the drug should be stopped if the potassium level is >5.5 mmol/L.[1]

In this study, serum potassium levels were >5.5 mmol/L in 12% of patients in the eplerenone group and 7% of those on placebo—a statistically significant difference. Eplerenone therapy was reduced or discontinued in hyperkalemic patients. No one suffered from the significant, but rare, sequelae associated with hyperkalemia, including arrhythmias and sudden death.

CONTINUED

It makes sense to use spironolactone, another mineralocorticoid-receptor antagonist, as a first-line drug and reserve eplerenone for patients who can't tolerate it.

Only 2.4% of the patients included in this study were African American (the majority were white, but there was a significant number [11.5%] of Asians). We cannot be sure that African Americans with less severe heart failure would reap the same benefits from treatment with a mineralocorticoid-receptor antagonist.

This was a well-done RCT, which found a significant benefit of eplerenone over placebo. It was a relatively small study, however, and it would help if the findings were replicated in larger studies. It is noteworthy, too, that this study was supported by Pfizer, which manufactures eplerenone, and 2 of the authors were employed by the pharmaceutical company.

CHALLENGES TO IMPLEMENTATION

Close follow-up, lab work is crucial

Hyperkalemia can be a significant side effect of both spironolactone and eplerenone. Patients started on either medication will need close follow-up and frequent lab monitoring of potassium levels. Patients who are unable or unwilling to comply with this strict follow-up are not good candidates for either drug.

Overall, this is a straightforward change to implement. In many cases, convincing patients of the benefits of taking yet another pill will be the greatest challenge. For the right patient population, however, both eplerenone and spironolactone appear to be medications we should encourage more often. **JFP**

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