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Sparing a Little Could Save a Lot... Importance of Aldosterone Blockade

Which HF patients should receive potassium sparing aldosterone blockade?

The answer is – almost everyone. This *Heartbeat* will discuss findings and clinical implications of the **EMPHASIS-HF** trial, in which the aldosterone antagonist **eplerenone** (Inspra, Pfizer) produced large reductions in both the risk of death and the risk of hospitalization compared with placebo in patients with systolic heart failure (LVEF < 35 %) and mild symptoms.

β -blockers and ACE inhibitors are the therapy of choice in patients with LV systolic dysfunction and HF, but mortality and morbidity still remain high. Aldosterone is either not blocked at all or escapes blockade with traditional therapy, so alternative therapies are needed. In 1999, results of **RALES** showed that aldosterone blockade with spironolactone (Aldactone) added to ACE inhibitor therapy could reduce mortality by 30% in severe Class III-IV HF patients.ⁱ *Only 10% to 11% of patients were receiving β -blockers.*

Eplerenone (Inspra) is a selective aldosterone blocker that is a “cleaner, safer” version of spironolactone. It blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors, resulting in less impotence and

painful gynecomastia in men and less decreased libido in women. The two drugs are similar in their risks of hyperkalemia. Findings from **EPHESUS** showed that treatment with eplerenone early after MI in patients with LV dysfunction and mild HF reduced overall mortality by 15% on top of usual optimal therapy.ⁱⁱ *At baseline, 75% of these patients were on beta-blockers and 87% were on ACE inhibitors.*

Huge Expansion of Eligible Patients

Remarkably, the recently released results of **EMPHASIS-HF** showed a 37% reduction in the primary end point of the composite of death from cardiovascular (CV) causes or hospitalization for HF, a 24% reduction in CV death, and a 42% reduction in hospitalization for HF—in patients with mild Class II HF.ⁱⁱⁱ *These results are especially impressive as eplerenone was given on top of really good contemporary therapy—same as EPHESUS above.* Aldosterone blockade—with either **spironolactone** or the newer more selective **eplerenone**—has already shown benefits in class III-IV HF and in post-MI patients with HF. The current results now extend the benefit to patients with mild HF, a much broader population. The assumption is that new HF guidelines will extend this therapy to Stage B HF and in time even Stage A HF for prevention in addition to Stages C & D.^{iv}

Real Value

In an accompanying editorial,^v **Dr Paul Armstrong** (University of Alberta, Edmonton) says: "The EMPHASIS-HF investigators have added real value to the management of HF. It is now time to overcome under-treatment by ensuring that this form of therapy is incorporated into all heart-failure regimens."

He adds that the effect of death from CV causes or hospitalization for HF translates into an impressively low number needed to treat to prevent one event: just 19 patients. And the number needed to treat to prevent one death is 51, which he says positions this therapy *"in the front rank of therapeutic choices."*

The trial involved 2737 patients with NYHA Class II HF and an ejection fraction of no more than 35%. They were randomized to eplerenone (up to 50 mg daily) or placebo in addition to recommended therapy. After a median follow-up of 21 months, the trial was stopped early because of a significant benefit in the eplerenone group.

EMPHASIS-HF: Major Results

Outcome	Eplerenone (%)	Placebo (%)	Adjusted hazard ratio (95% CI)	p
Cardiovascular death/heart-failure hospitalization	18.3	25.9	0.63 (0.54–0.74)	<0.001
Cardiovascular death	10.8	13.5	0.76 (0.61–0.94)	0.01
Heart-failure hospitalization	12.0	18.4	0.58 (0.47–0.70)	<0.001
Hospitalization for hyperkalemia	0.3	0.2	1.15 (0.25–5.31)	0.85

Death from any cause and hospitalization for any cause were also significantly reduced.

Together, **EPHESUS** plus **RALES** and now **EMPHASIS-HF** make a very strong case — documenting that **aldosterone blockade**

improves outcomes and should be a standard part of the treatment program for all patients with HF secondary to LVSD (mild to severe) associated with both ischemic and non-ischemic cardiomyopathy. Aldosterone blockade is also indicated to improve survival of stable patients with LVSD (LVEF < 40 %) and clinical evidence of HF post-MI.

Beware Hyperkalemia

The main issue that will limit use of eplerenone or spironolactone is the increased risk of hyperkalemia, which can be fatal. Therefore, we need to learn how to use them without causing life-threatening hyperkalemia. This risk is particularly high in patients with reduced renal function, diabetes, and advanced age. The risk/benefit ratio should be specifically assessed for patients who do not require loop diuretic therapy, in whom the risk for HF events may be particularly low but the risk for hyperkalemia may be high. **The tremendous benefits on outcomes completely justify the extra work required to use these drugs.**

Monitoring:

Caution is urged in prescribing aldosterone blockade for patients with elevated potassium or creatinine, and careful close monitoring for hyperkalemia in all patients is recommended. Measure serum potassium and renal function before beginning therapy, then use the *"rule of one"*: at 1 day, 1 week, at 1 month and periodically (3 months) thereafter. Individual patient characteristics and serum potassium or renal function may indicate additional testing.

Patients receiving aldosterone blockade, who have renal insufficiency (creatinine clearance < 50mL/min) or have diabetes including those with proteinuria, should be treated with caution and be monitored even more closely because of the increased risk of

hyperkalemia. This is complicated by the ACE inhibitor or ARB treatment which these patients are already receiving, making treatment quite a challenge. If the serum potassium increases to 5.5meq/L, decrease to every other day or ½ (12.5mg) daily dose of aldosterone blockade. If the serum potassium increases to 6meq/L, discontinue aldosterone blockade.

Contraindications: Aldosterone blockade is contraindicated in patients with:

- Serum potassium > 5.5meq/L
- Creatinine clearance < 30mL/min
- Concomitant use with potent CYP3A4 inhibitors.

*Most experts recommend starting with a 12.5mg dosage with a potassium level of > 5 meq/L and checking the serum potassium in 24 to 48 hours.

Conclusions:

- This data from **EMPHASIS-HF**, in conjunction with the consistent findings from **RALES** in severe HF and **EPHESUS** in post-MI patients with LV dysfunction, provides compelling evidence for a change in clinical practice. *All patients with systolic dysfunction should be treated with an aldosterone antagonist, except for those with contraindications.* The contraindications are patients with severe renal dysfunction and/or potassium levels above 5.5. The caveat here is that you must be willing to check potassium levels and renal function. *“While it is right to be concerned about the hyperkalemia, the tremendous benefits on outcomes completely justify the extra work required to use these drugs.”*

- All experts agree that the benefits are a class effect and that spironolactone is still the best *buy for the money* but with some side effects. Eplerenone is now available in the US as a generic and is not that expensive.

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ⁱ Pitt B et al, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. (**RALES**) *N Engl J Med* 1999; 341: 709-917.

ⁱⁱ Pitt B et al, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. (**EPHESUS**) *N Engl J Med*. 2003; 348: 1309–1321.

ⁱⁱⁱ Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. (**EMPHASIS-HF**) *N Engl J Med* 2011. DOI: 10.1056/NEJMoa1009492. This article (10.1056/NEJMoa1009492) was published on November 14, 2010, at NEJM.org.

^{iv} Tomaschitz A, Pilz S, Meinitzer A, Boehm BO, Marz W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Eur Heart J* 2010;31:1237-47.

^v Armstrong P W. Aldosterone antagonists--Last man standing? *New Eng J Med* 2011. DOI: 10.1056/NEJMe1012547. This article (10.1056/NEJMe1012547) was published on November 14, 2010, at NEJM.org.