Role of Aldosterone Blockade

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Heart failure (HF) is a major public health problem. It is the only major cardiovascular disorder that is increasing in prevalence in the US. During the past 10 years, the number of hospitalizations per year for HF as a primary and secondary diagnosis rose from 1.7 million to 2.6 million. HF is often a complication of myocardial infarction (MI); within 6 years 22% of men and 46% of women experience HF.

Over the years, a number of agents have become established in the management of HF including diuretics, beta-blockers and ACE inhibitors. More recently, clinical trials have established that aldosterone blockers offer mortality and morbidity benefits above and beyond what has been achieved with more traditional therapies. This *Heartbeat* will focus on evidence supporting the use of aldosterone blockade in chronic HF and in post-MI HF, how to select patients who will most likely benefit from aldosterone blockade and how to use these agents safely and effectively—particularly with regard to hyperkalemia—in the context of HF secondary to left ventricular systolic dysfunction (LVSD).

Mechanism of Action of Aldosterone-blockade

Aldosterone blocking agents are known to increase diuresis and natriuresis and to lower blood pressure in patients with essential hypertension while sparing potassium. Although these "classic" effects of aldosterone blockade may account for its effects in controlling blood pressure, over the past several years, other non-renal neuro-endocrine protective effects of aldosterone blockade have been demonstrated that may in large part be responsible for its beneficial effects in patients with LVSD after acute MI and in chronic HF. These mechanisms include modulating the negative effects of aldosterone on: vascular inflammation, vascular and LV remodeling and compliance, ventricular hypertrophy and fibrosis, endothelial dysfunction, myocardial norepinephrine uptake, heart rate variability, baroreceptor function, fibrinolysis, and platelet activation.

RALES

The **R**andomized **A**ldactone **E**valuation **S**tudy (**RALES**) was designed to check the hypothesis that the aldosterone receptor blocker, spironolactone, would reduce mortality in patients with severe HF secondary to LVSD.[1]

In this study, 1663 patients with severe HF (LVEF <35%), who were being treated with an ACE inhibitor (if tolerated—94%) and a loop diuretic, were randomized to spironolactone 25mg and standard care (822) or a placebo and standard care (841). Digoxin and vasodilators were allowed. Potassium sparing diuretics weren't allowed. *The study was terminated early (24 months) because of a significant 30% risk reduction from progressive HF and sudden cardiac death (SCD) along with improvement in ventricular function and enhanced exercise tolerance, in the spironolactone group—a very impressive result.*

On the basis of this study, spironolactone has been recommended for the treatment of severe HF caused by LVSD in both the United States and European guidelines. The adoption of these recommendations into clinical practice has, however, been variable because the recommendation was based on a single trial, and only 10% to 11% of patients in this study were on a ß-blocker. Additionally, in routine daily practice, hyperkalemia has been bothersome.

In the RALES study the incidence of hyperkalemia was higher in the spironolactone group than in the placebo group, 2% vs 1%. However the incidence of gynecomastia or breast pain in men was 10% in the spironolactone group compared to 1% in the placebo group.

EPHESUS

The **EP**lerenone Post-AMI **H**eart Failure **E**fficacy and **SU**rvival **S**tudy (**EPHESUS**) randomized >6600 patients with evidence of an acute MI, LVEF ≤40%, and evidence of HF (except patients with diabetes

mellitus, who were required to have only evidence of LVSD) to the selective aldosterone blocker eplerenone or placebo 3 to 14 days after infarction.[2] Patients with a serum creatinine ≥ 2.5 mg/dL and those with evidence of serum potassium ≥ 5.0 meq/L were excluded. Study medication was administered a mean of 7.3 days after infarction, beginning at a dose of 25 mg daily for 1 month and then up-titrated to 50 mg daily unless there was evidence of hyperkalemia.

Patients randomized to eplerenone at a mean dose of 43 mg daily over a mean follow-up of 16 months had a 15% reduction in total mortality (co-primary end point), a 17% reduction in cardiovascular mortality, and a 13% reduction in cardiovascular mortality/cardiovascular hospitalizations, including hospitalization for myocardial infarction, stroke, HF, and ventricular arrhythmias (co-primary end point). Epleronone maintained a survival benefit throughout the follow-up period.

The major cause of cardiovascular death in this study was sudden cardiac death, which was reduced by 21% in patients randomized to eplerenone. The major cause of cardiovascular hospitalizations was HF. Patients randomized to eplerenone had 23% fewer episodes of hospitalization for HF. Of particular interest was the finding that eplerenone was effective in reducing all-cause mortality as well as CV mortality/CV hospitalization in patients already on an ACE inhibitor or an angiotensin receptor-blocking agent (ARB) and a ß-blocker.

It is important to note that the 15% reduction in mortality achieved with eplerenone group was above and beyond that achieved by optimal standard therapy (ASA, statin, Ace inhibitor or ARB and a ß-blocker plus reperfusion). The EPHESUS study had the highest percent of patients on contemporary therapy, with 87% of patients on ACE inhibitors or ARBs and 75% on ß-blockers. This is a striking outcome and now gives us another medication that should be added to our standard treatment program for HF.

In contrast to the experience in RALES, there was no excess of gynecomastia, breast pain, or impotence in males, attesting to the selectivity of eplerenone for the mineralocorticoid receptor in comparison to spironolactone, which also binds to androgen and progesterone receptors.

Sparing a little could save a lot…Importance of aldosterone blockade

The principal risk associated with potassium-sparing eplerenone therapy is hyperkalemia. In the EPHESUS trial no one died from hyperkalemia, and there was a significant reduction of hypokalemia with eplerenone (the risk of which was more than twice that of hyperkalemia). A recent retrospective study—therefore not conclusive but still interesting—from the **S**tudies **O**f **L**eft **V**entricular **D**ysfunction (**SOLVD**) data base concludes that the use of potassium sparing diuretics is associated with reduced risk of death from hospitalization, progressive HF or all-cause or CV death, compared with patients only taking a non-potassium sparing diuretic.[3]

The investigators conclude that with appropriate patient selection, monitoring of potassium and renal function, and dose adjustments, the clinical evidence of mortality benefits of this drug used with standard therapy warrants its use in post-MI patients with LVSD.

Who should receive aldosterone blockade?

ACE inhibition and beta-blockers 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. 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 HF patients. Only 10% to 11% of patients were receiving ß-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. 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. At baseline, 75% of these patients were on beta-blockers and 87% were on ACE inhibitors.

Together, **EPHESUS** plus **RALES** make a "grand slam"—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.

In the post acute MI setting, the preference leans toward using eplerenone as used in EPHESUS—25mg once daily and titrate in a single step to the target dose of 50mg once daily within a month if tolerated. If cost is an issue, there should be no reservation in using spironolactone similarly in the appropriate indicated situations. There is no evidence that eplerenone is more effective than spironolactone and maybe should not have preferential status as first therapy in these patients. Rates of hyperkalemia are similar and cost will be higher, balanced against the improved side effect profile. Until more data is available, it would be prudent to use the drug regimen and indications proven by the pivotal prospective randomized studies.

Presently aldosterone blockade is not recommended in asymptomatic (Class 1 HF) patients with LVSD (risk of hyperkalemia may outweigh the benefit) or for HF secondary to diastolic dysfunction (no supporting data but studies are in progress).

Contraindications

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. Aldosterone blockade is contraindicated in patients with:

- Serum potassium > 5.5meq/L.
- Creatinine clearance $\leq$ 30mL/min which ~ corresponds to a serum creatinine > 2mg/dL (women) or > 2.5mg/dL (men).
- Concomitant use with potent CYP3A4 inhibitors.

Most recommend avoiding aldosterone blockade even with a potassium level of > 5 meq/L.

Monitoring

Measure serum potassium and renal function before beginning therapy, then use the "rule of one": at 1 day, at 1 week, at 1 month and periodically thereafter. Individual patient characteristics and serum potassium or renal function may indicate additional testing.

Patients receiving aldosterone blockade who have renal insufficiency (creatinine clearance $\leq$ 50mL/min; serum creatinine > 2mg/dL [males] or > 1.8mg/dL [females]) 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, cut the dose of aldosterone blockade in half. If the serum potassium increases to 6meq/L, discontinue aldosterone blockade. This being said, ***the benefit (significant mortality reduction) of adding an aldosterone antagonist to usual standard therapy in patients with systolic HF is worth the extra effort of close monitoring of potassium and renal function.***

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