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Reviews

Aldosterone Blockade in Post-Acute Myocardial Infarction Heart Failure

BERTRAM PITT, M.D., ROBERTO FERRARI, M.D.,* MIHAI GHEORGHIADE, M.D.,† DIRK J. VAN VELDHUISEN, M.D., PH.D.,‡ HENRY KRUM, M.D., PH.D.,§ JOHN MCMURRAY, M.D.,‖ JOSE LOPEZ-SENDON, M.D.#

University of Michigan Medical Center, William Beaumont Hospital, Ann Arbor, Michigan, USA; *University Hospital of Ferrara, Ferrara, Italy; †Northwestern University, Chicago, Illinois, USA; ‡University Hospital Groningen, Groningen, The Netherlands; §Monash University, Melbourne, Australia; ‖University of Glasgow, Glasgow, Scotland; #La Paz University Hospital, Madrid, Spain

Summary: Development of heart failure (HF) or left ventricular systolic dysfunction (LVSD) significantly increases mortality post acute myocardial infarction (AMI). Aldosterone contributes to the development and progression of HF post AMI, and major guidelines now recommend aldosterone blockade in this setting. However, lack of practical experience with aldosterone blockade may make clinicians hesitant to use these therapies. This review is based on a consensus cardiology conference that occurred in May 2005 (New York City) concerning these topics. Potential barriers to the use of aldosterone blockade are discussed and an algorithm for appropriate in-hospital pharmacologic management of AMI with LVSD and/or HF is presented.

Key words: aldosterone, myocardial infarction, heart failure, left ventricular systolic dysfunction, eplerenone, EPHESUS

Introduction

Aldosterone has emerged as an important risk factor in patients with heart failure (HF). This is underscored by two large-scale clinical trials, the Randomized Aldactone Evaluation Study (RALES)[1] and the Eplerenone Post-Acute Myocardial Infarction (AMI) Heart Failure Efficacy and Survival Study (EPHESUS).[2] These trials demonstrated significant improvements in mortality and morbidity with aldosterone blockers added to standard therapy in patients with chronic, severe systolic HF and in patients with left ventricular systolic dysfunction (LVSD; left ventricular ejection fraction [LVEF] ≤40%) and HF following an AMI, respectively.

This review focuses on aldosterone blockade specifically in patients with post-AMI HF and LVSD and proposes a practical treatment algorithm to assist clinicians in providing optimal care to these patients.

The Burden of Post-Acute Myocardial Infarction Heart Failure and the Role of Aldosterone

The development of HF and/or LVSD significantly increases morbidity and mortality post AMI.[3–7] It is estimated that 20 to 40% of patients with AMI will develop HF.[3, 4, 7] Patients post AMI with HF and/or LVSD have a 3- to 4-fold increased risk of in-hospital death, as well as significant increases in 30-day mortality, long-term mortality, and rehospitalization rates compared with patients with AMI and without HF.[3–6] Recently, it has been shown that the first 30 days post infarction is the period of highest risk in patients with LVSD, especially for sudden cardiac death (Fig. 1).[8] This occurs despite routine treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and beta blockers.[8]

Some of the cardiovascular effects of aldosterone that may contribute to the development and progression of post-AMI HF include myocardial and vascular fibrosis, catecholamine potentiation, potassium and magnesium loss, ventricular arrhythmias, cardiomyocyte apoptosis, sodium retention, ischemic injury, and endothelial dysfunction.[9–12] Animal and human models have demonstrated reversal of these harmful pathophysiologic effects with aldosterone blockade post AMI.[12–15] Based on the above, EPHESUS was designed to explore the

The authors have served as consultants to Pfizer Inc, manufacturer of eplerenone and spironolactone.

Address for reprints:

Bertram Pitt, M.D.
University of Michigan Medical Center
William Beaumont Hospital
Cardiovascular Department
1500 East Medical Center Drive
Ann Arbor, MI 48109, USA
e-mail: bpitt@med.umich.edu

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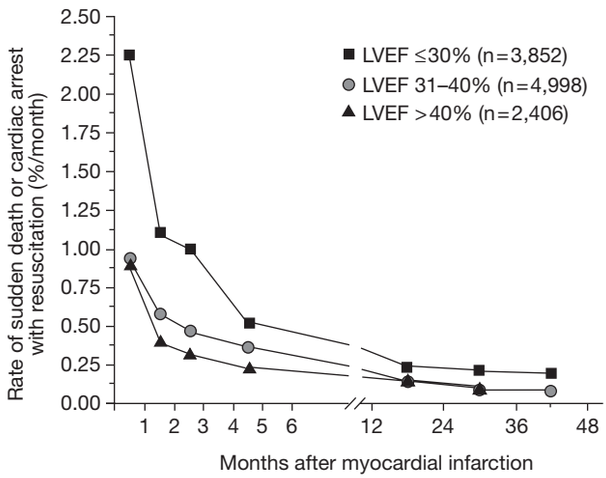


FIG. 1 The rate of sudden death or cardiac arrest with resuscitation by category of left ventricular ejection fraction (LVEF) in the VALIANT trial.[8] The rate of events was highest in all patients during the first 30 days post infarction and in those with the most compromised LVEF. Adapted from Ref. No. 8 with permission.

impact of the selective aldosterone blocker eplerenone on mortality and morbidity in patients with AMI complicated by LVSD and HF.[2]

Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)

Clinically stable patients with LVEF ≤ 40% and HF or diabetes were randomized 3 to 14 days after AMI to receive eplerenone (25 mg/day increased to 50 mg/day after 4 weeks) or placebo.[2] After a mean follow-up of 16 months, eplerenone significantly reduced the risk of all-cause mortality by 15% (p = 0.008), cardiovascular mortality/cardiovascular hospitalization by 13% (p = 0.002), cardiovascular mortality by 17% (p = 0.005), and sudden cardiac death by 21% (p = 0.03) in patients already receiving standard therapy, including ACE inhibitors (87% of patients) and beta blockers (75% of patients).

The significant beneficial effects of eplerenone were seen as early as 30 days post randomization, although patients were not titrated to the target dose (50 mg) until Month 1.[16] The risk of all-cause mortality was reduced by 31% (p = 0.004) and the risk of sudden cardiac death was reduced by 37% (p = 0.051) during this early period. This is particularly noteworthy given that the risk for sudden death in this population is highest during this time period (Fig. 1)[8] and also considering that other therapies, including implantable cardioverter defibrillators,[17] have failed to demonstrate incremental benefit when used with standard treatment during this high-risk period. This underscores the importance of early initiation of aldosterone blockade in patients with post-AMI LVSD and HF. Figure 2 shows early and long-term mortality benefits in EPHESUS.[2, 16]

Barriers to Implementation of Aldosterone Blockade in Post-Acute Myocardial Infarction Heart Failure

Major therapeutic guidelines for AMI and HF now include specific recommendations for the use of aldosterone blockade in addition to other well-accepted life-saving therapies (Table I).[18–20] However, the lack of practical experience with aldosterone blockers in patients post AMI with LVSD and HF poses barriers to implementation.

How to Manage Patients Who Cannot Be Titrated to the Target Dose

A recent subanalysis of EPHESUS demonstrated that patients unable to achieve the target dose of 50 mg experienced significant reductions in endpoints with a dose of 25 mg/day, or even 25 mg every other day.[21] Significant reductions in all-cause mortality (by 34%, p < 0.001), cardiovascular mortality/cardiovascular hospitalization (by 22%, p = 0.009), cardiovascular mortality (by 36%, p < 0.001), and sudden cardiac death (by 35%, p = 0.03) were achieved.

Risk of Hyperkalemia Secondary to Aldosterone Blockade

In EPHESUS, the incidence of hyperkalemia (serum potassium > 6.0 mmol/l) was greater with eplerenone than with placebo (5.5 vs. 3.9%), but discontinuation due to hyperkalemia was < 1% in both treatment groups, and no deaths in eplerenone-treated patients were attributable to hyperkalemia.[2]

Reports of excess hyperkalemia secondary to spironolactone use appeared after publication of RALES.[22] However, patients in these reports were much older, had higher pretreatment creatinine values, were exposed to higher doses of spironolactone than in RALES, and may not have had serial potassium monitoring with dose adjustment for serum potassium > 5.5 mmol/l or discontinuation for serum potassium > 6.0 mmol/l.[23, 24] As demonstrated in EPHESUS, proper patient se-

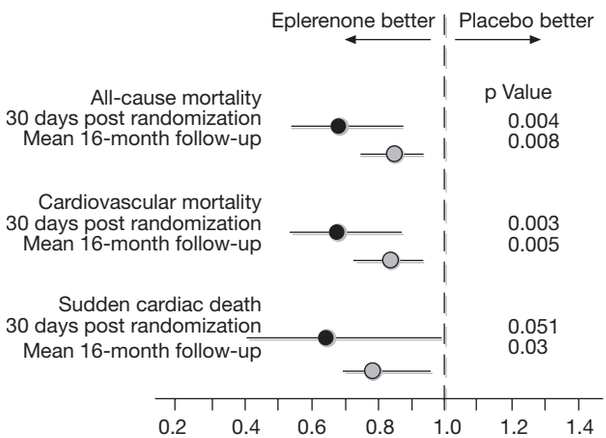


FIG. 2 The reduction in early (30 days post randomization) and long-term (mean 16-month follow-up) mortality with eplerenone used in addition to standard therapy in EPHESUS.[2, 16]

TABLE I Major therapeutic guidelines including a recommendation for aldosterone blockade in patients with post-AMI LVSD and HF

Guideline	Class of recommendation/ level of evidence [a]	Comments
American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines for treatment of patients with ST-segment elevation myocardial infarction (STEMI)[18]	Class I/Level A	Aldosterone blockade should be used in patients post STEMI without significant renal dysfunction or hyperkalemia who are already receiving an ACE inhibitor, have LVEF ≤ 40%, and have either symptomatic HF or diabetes
ACC/AHA guidelines for management of chronic HF[19]	Class I/Level B	Aldosterone blockade should be used in patients with moderate to severe HF and reduced LVEF who can be monitored for preserved renal function and normal potassium concentration
European Society of Cardiology guidelines for management of chronic HF[20]	Class I/Level B	Aldosterone blockade should be used in addition to ACE inhibitors and beta blockers in patients post AMI with LVSD and signs of HF or diabetes

[a] Class I: Conclusive evidence and/or general agreement that a given treatment is useful, beneficial, and effective. Level of evidence A: Data are derived from multiple randomized clinical trials or meta-analyses; level of evidence B: Data are derived from a single randomized trial, or non-randomized studies.
Abbreviations: ACE = angiotensin-converting enzyme, AMI = acute myocardial infarction, HF = heart failure, LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction.

lection, monitoring, and dose adjustments can minimize the risk of hyperkalemia associated with aldosterone blockade (Table II).[24]

Fear that Adding Eplerenone to Standard Therapy Post Acute Myocardial Infarction May Result in Hypotension

Retrospective analysis of EPHESUS data has revealed that adding eplerenone to ACE inhibitors/ARBs and beta blockers did not result in hypotension compared with placebo either early (1-week) or late (mean 16-month follow-up) post AMI (data on file). Patients in the lowest baseline systolic blood pressure (SBP) quartile showed no mean decrease in SBP, whereas patients in the highest quartile had a mean SBP decrease into the normal range.

Uncertainty of Benefit in Patients Who Are Reperfused and thus May Have Only Transient Heart Failure or Left Ventricular Systolic Dysfunction

In EPHESUS, the evidence of LVSD and/or HF could have been transient, occurring any time from onset of the in-

TABLE II Administration and dosing considerations for aldosterone blockers[19, 20]

1. Serum potassium should be < 5.0 mmol/l and serum creatinine should be < 2.5 mg/dl prior to initiation
2. Impaired renal function is a risk factor for hyperkalemia; the risk of hyperkalemia increases when serum creatinine > 1.6 mg/dl. In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate (GFR), determination that GFR or creatinine clearance > 30 ml/min is recommended
3. Potassium supplements should be discontinued or reduced
4. An initial dose of eplerenone 25 mg/day or spironolactone 12.5–25 mg/day is recommended
5. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and 1 week after initiation of therapy and dosage changes, and at least monthly for the first 3 months
6. If at any time serum potassium ≥ 5.5 mmol/l, reduce dose by 50% (or dose on alternate days if patient is already on lowest dose). Withhold dose if serum potassium ≥ 6.0 mmol/l and restart once potassium < 6.0 mmol/l
7. If normokalemia exists after 1 month, increase dosage to 50 mg/day
8. Nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided. If initiated, potassium and renal function should be checked within 1 week
9. If diarrhea or vomiting occurs, the aldosterone blocker should be stopped until resolution. Caution is also necessary when there are other potential causes of dehydration, including increase in diuretic dose

dex AMI, and did not need to be present at randomization.[2] It is possible that LVEF had improved by randomization due to recovery from myocardial stunning, hibernation, improved myocardial compliance, reperfusion, and pharmacologic treatment with ACE inhibitors, nitrates, beta blockers, and diuretics. Thus, while physicians should require evidence of LVSD and HF on admission post AMI, neither LVSD nor HF needs to persist to initiate eplerenone.

The Cost of Eplerenone

Cost can be an important barrier to the use of evidence-based therapies in the clinical setting. A recent analysis determined that eplerenone, compared with placebo in the treatment of LVSD and HF post AMI, is cost effective in increasing years of life, with an overall incremental cost of approximately $13,700 per quality-adjusted life-year gained[25]; this is below the $50,000 threshold commonly used to determine whether a medication is a good value and is comparable with that of many other well-accepted cardiovascular medications, including ACE inhibitors and beta blockers.

While spironolactone offers a less expensive alternative to eplerenone for aldosterone blockade, caution should be exercised in applying the dosing strategy of spironolactone used in RALES to patients with post-AMI LVSD and HF, as long-term outcomes have not been evaluated in this setting. Because spironolactone is a more potent, although less specific, inhibitor of the mineralocorticoid receptor than eplerenone, it is possible that use of spironolactone beginning with 25 mg/day could result in hypotension or excess hyperkalemia in these patients.

Recommendations for the appropriate use of aldosterone blockade, adapted from the American College of Cardiology/American Heart Association (ACC/AHA)[19] and European Society of Cardiology (ESC)[20] guidelines for chronic HF, are given in Table II.

A Treatment Algorithm to Improve Outcomes in Post-Acute Myocardial Infarction Heart Failure

The algorithm in Figure 3 outlines appropriate in-hospital pharmacologic management of AMI with LVSD and/or HF based on current clinical evidence and available guidelines. This includes the addition of aldosterone blockade as essential adjunctive treatment for eligible patients in this setting.

Despite serious risks of mortality and hospitalizations associated with development of HF and/or LVSD in patients with AMI,[3–6] these patients are less likely to be treated with life-saving, guideline-recommended therapies than those with AMI and without HF.[3,4] Wu *et al.*[4] demonstrated that 75% of patients with AMI and HF were not treated with ACE inhibitors or beta blockers, and 25% did not receive aspirin, although these treatments provided the strongest protection against in-hospital death in patients with HF (odds ratio 0.51, 0.42, and 0.42 for ACE inhibitor, beta blocker, and aspirin, respectively). Treatment rates for patients with AMI without HF were significantly better ($p < 0.001$) (Fig. 4).

New approaches to increasing early initiation and consistent use of guideline-recommended, life-prolonging therapies in eligible patients (Fig. 3) are fundamental to reducing excessive mortality and morbidity in this high-risk population. These new approaches include HF disease management programs and clinical pathways, which have been shown to improve the routine in-hospital initiation of treatments, long-term compliance, and patient outcomes.[26]

Conclusion

Aldosterone blockade offers significant incremental benefit for reducing mortality and morbidity above and beyond other

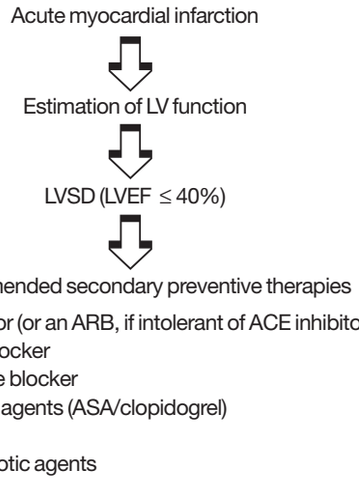
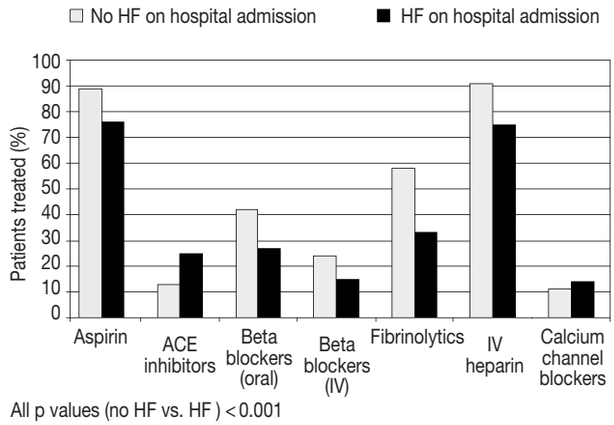


FIG. 3 Pharmacologic treatment algorithm for patients post myocardial infarction with left ventricular systolic dysfunction (LVSD). LVEF = left ventricular ejection fraction, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ASA = aspirin.



All p values (no HF vs. HF) < 0.001

FIG. 4 Utilization of evidence-based therapies in patients with acute myocardial infarction with/without heart failure (HF), on hospital admission.[4] ACE = angiotensin-converting enzyme, IV = intravenous.

proven therapies for post-AMI HF and should be prescribed for all eligible patients. In view of the high early mortality in this population, it is important to start an aldosterone blocker in these patients as soon as they are hemodynamically stable. The widespread use of an aldosterone blocker in eligible patients with HF post AMI will have important implications for improved mortality and morbidity as well as important reductions in health care costs.

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