Aldosterone Receptor Blockade in Patients with Left Ventricular Systolic Dysfunction Following Acute Myocardial Infarction

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Acute myocardial infarction (AMI) is extremely prevalent worldwide, with an estimated 700,000 new cases this year and a total mortality of 221,000 in 2002 in the United States alone [1]. Left ventricular systolic dysfunction (LVSD), as evidenced by the presence of new heart failure (HF) symptoms at the time of AMI or by documented reduction in left ventricular ejection fraction (LVEF), is common, with reported incidences of approximately 30% post-AMI [2–6]. Patients with LVSD following AMI are at high risk of in-hospital and long-term morbidity and mortality. Analysis of the Second National Registry of Myocardial Infarction (NRMI-2) demonstrated a 3-fold increase of in-hospital death (21% versus 7%) in patients hospitalized for AMI with clinical evidence of LVSD compared with those without LVSD [4]. In the Global Registry of Acute Coronary Events (GRACE), patients with clinical evidence of LVSD on admission for acute coronary syndromes (ACS) had a threefold increase in 6-month mortality (9% versus 3%) and a higher rehospitalization rate (24% versus 16%) than other patients with ACS [3].

Patients with LVSD after AMI are at a critical point in time when two different disease processes, coronary artery disease (CAD) and LVSD, are at work. The presence of underlying CAD with recent thrombosis places these patients at high risk for reinfarction, ischemia, and progression of their CAD. In addition, LVSD may progress to the development of HF, worsening pump function, ventricular arrhythmias, and sudden cardiac death (SCD). Targeting the ischemia associated with AMI, the underlying CAD, and the ventricular remodeling associated with LVSD can minimize the deleterious consequences of CAD and LVSD. Failure to attack these targets and to initiate life-saving therapies results in future morbidity and mortality.

Significant progress has been made in the development of acute reperfusion strategies, platelet inhibition, and ischemia reduction that are of critical importance in the acute phase of AMI. Secondary prevention measures for CAD, such as aspirin, clopidogrel, beta blockers, angiotensin converting enzyme (ACE) inhibitors and the use of hydroxymethylglutaryl coenzyme A reductase inhibitors (stains), play a role in reducing ischemic events and mortality after AMI in general. In addition, pharmacological strategies to prevent adverse ventricular remodeling, such as ACE inhibitors and beta blockers, have proven beneficial in patients with post-AMI LVSD in particular. Due to these interventions, there has been a gradual decline in hospital mortality rates among this patient group. However, long-term mortality did not change over the two decades between 1975 and 1995 in one large, community-wide study [7].

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The high mortality rates despite optimal reperfusion and medical therapy observed in patients with post-AMI LVSD may be related to an increased risk for postdischarge SCD. Although there is evidence that ACE inhibitors, beta blockers, and perhaps statins reduce its incidence, SCD remains an important cause of death in patients with post-AMI LVSD. The placement of a prophylactic implantable cardioverter defibrillator (ICD), a proven therapy for primary prevention of SCD in select populations, has not shown benefit if placed too soon after an AMI. Blockade of aldosterone receptors, however, has demonstrated efficacy in this particular patient population, especially in the immediate post-AMI period. This article discusses the epidemiology behind SCD in patients with post-AMI LVSD, the pathophysiology of aldosterone blockade in relation to SCD, the evidence behind aldosterone receptor blockade, safety concerns with the treatment, and, finally, a summary of available therapies for patients with post-AMI LVSD.

Sudden cardiac death

Much of what is known about the timing and risk of SCD after AMI in the presence of contemporary therapy comes from the Valsartan in Acute Myocardial Infarction Trial (VALIANT), published in 2003. This trial randomized 14,703 patients with AMI complicated by clinical or radiological HF, LVSD (LVEF ≤35% by echocardiography, contrast angiography, or ≤40% by radionuclide ventriculography), or both, to treatment with valsartan, captopril, or both within 0.5 to 10 days of AMI. Patients were required to have a systolic blood pressure >100 mm Hg and a serum creatinine (Cr) <2.5 mg/dL. There was 15% use of primary percutaneous coronary intervention (PCI) and 35% use of thrombolytic therapy. Adjunctive medical therapy for AMI included 91% aspirin, 70% beta blockers, but only 34% statins and 9% potassium-sparing diuretics. Mortality at 24 months was 20% and did not differ between groups compared [8]. In a subsequent analysis, the cause of death was reviewed by a central adjudication committee. SCD was defined as death that occurred "suddenly and unexpectedly" in a patient in otherwise stable condition who had not had premonitory HF, AMI, or other clear cause of death. SCD was combined with cardiac arrest with resuscitation to define the event rate in this analysis. A total of 7% of patients in this trial had such an event,

19% of whom had the event in the first 30 days post-AMI. The event rate was 1.4% per month during the first 30 days, and dropped to 0.5% per month during months 1 through 6, and to 0.14% 2 years post-AMI. During the critical first 30 days post-AMI, each reduction in LVEF by 5% was associated with a 21% increase in event rate. VALIANT established that the first 30 days post-AMI is a vulnerable period with the highest SCD and cardiac arrest-with-resuscitation rates, and that low LVEF can increase this risk dramatically [9].

In an attempt to reduce SCD during this vulnerable post-AMI period, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) was published in 2004 [10]. In this trial, 674 post-AMI patients with LVEF ≤35% (assessed by angiography, radionuclide scanning, or echocardiography) and depressed heart-rate variability or elevated heart rate on 24-hour Holter monitoring were randomized to either an ICD or no ICD 6 to 40 days post-AMI. DINAMIT's adjunctive medication use was more aggressive than that of VALIANT, with 92% on antiplatelet agents, 87% on beta blockers, 95% on ACE inhibitors, and 78% on statin. In addition, there were slightly more primary PCIs at 36%, with similar use of thrombolytic therapy at 37%. After a mean follow-up of 30 months, overall mortality was 18% with no significant difference between treatment groups. Prespecified cause-of-death analysis was ascertained by the investigators at each site and derived from witnesses, family members, death certificates, hospital records, and autopsy reports, but not from ICD telemetry. Although there was a significant reduction in death from arrhythmia (hazard ratio [HR] 0.42, 95% CI, 0.22–0.83, $P = .009$), this was offset by an increase in death from nonarrhythmic causes (HR 1.75, 95% CI, 1.11–2.76, $P = .02$), primarily driven by cardiac nonarrhythmic causes (HR 1.72, 95% CI, 0.99–2.99, $P = .05$). There were no deaths related to device implantation; however, in-hospital, device-related complications such as lead dislodgment, pneumothorax, and inappropriate shocks were documented in 25 patients.

In contrast with the findings in DINAMIT, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) evaluated prophylactic ICD therapy in patients with prior AMI and LVEF ≤30%, and demonstrated that the rate of death due to arrhythmia was markedly reduced and the rate of nonarrhythmic death was not increased at a mean follow-up of 20 months [11]. These

patients differed from DINAMIT patients in that they had a lower LVEF, did not have assessment of autonomic dysfunction, and, most importantly, were randomized a mean of 6.5 years after their most recent AMI. It is unclear why patients in DINAMIT who were assigned to ICD therapy had an increase in nonarrhythmic mortality. The presence of impaired autonomic dysfunction distinguishes DINAMIT patients from other post-AMI LVSD populations and may be a marker of risk for advanced HF. ICD therapy in these patients may therefore convert SCD into eventual death from pump failure. Additionally, inappropriate shocks and placement of an ICD itself may lead to negative remodeling and worsened HF. Whatever the mechanism, placement of an ICD for primary prevention of SCD within the first 40 days of AMI is recommended against by the ACC/AHA guidelines for the management of patients with ST-segment-elevation MI and the ACC/AHA/ESC guidelines for the prevention of SCD [12,13]. With failure of proven therapies to prevent SCD in patients with post-AMI LVSD, there has been a need for newer therapies. Aldosterone receptor blockade has proved to be an effective experimental and clinical strategy in this patient group.

The role of aldosterone in myocardial infarction

Aldosterone is implicated not only in fluid and potassium balance, but also in post-AMI left ventricular (LV) remodeling. Depressed cardiac function after AMI leads to a series of neurohormonal reflexes that activate the sympathetic nervous system and the renin-angiotensin-aldosterone systems. These reflexes are initially adaptive to preserve mean arterial pressure, but prolonged neurohormonal activation eventually becomes maladaptive and leads to increased myocardial oxygen demand, progressive myocardial injury, ventricular dysfunction and ultimately HF [14,15]. Alterations in ventricular architecture result, involving infarcted and noninfarcted areas of the left ventricle, and these alterations lead to contractile dysfunction, fibrosis, progressive dilation, hypertrophy and distortion of the ventricular cavity, known as LV remodeling [16]. LV remodeling and neurohormonal activation are associated with increased risk for ventricular arrhythmias and SCD. Aldosterone has been found to be elevated in patients with LVSD and associated with poor outcomes in the chronic [17] and acute MI settings [18].

Aldosterone blockade, alone or in combination with ACE inhibitors, has been associated with many potentially favorable effects on post-AMI LV remodeling in a wide range of animal models. These include reduced collagen deposition, norepinephrine levels, interstitial fibrosis, hypertrophy, LV dimensions and increased LVEF [19–25]. Table 1 outlines the mechanisms of the deleterious effects of aldosterone in the AMI setting and the efficacy of aldosterone blockade in reversing these effects.

Endothelial dysfunction

In experimental models, aldosterone has been found to inhibit the production of nitrite oxide

Table 1
Potential deleterious mechanisms, anatomical effects, and possible clinical consequences of aldosterone on the cardiovascular system, beyond fluid and potassium balance

Mechanisms	Anatomical effects	Possible clinical consequences
↓ Endothelial-derived nitric oxide [26]	Vasoconstriction	Ischemia
↑ Oxidative stress [31]	Inflammation and fibrosis	LV remodeling, HF
Collagen deposition [32–34]	Fibrosis, stiffness, and distortion of the myocardial structure	LV remodeling, HF
Vascular inflammation [39]	Myocardial fibrosis and necrosis	LV remodeling, HF
Myocardial apoptosis [46]	Myocytes loss	LV remodeling, HF
↓ Baroreceptor sensitivity and Reflex function [40,41]	↑ Heart rate variability, arrhythmias	SCD
↓ Myocardial uptake of norepinephrine [42]	Arrhythmias	SCD
↑ Action potential duration [44]	Arrhythmias	SCD
↓ Fibrinolysis [45]	Thrombophilic state	Ischemia, necrosis
↑ Platelet activation [45]	Thrombophilic state	Ischemia, necrosis

Abbreviations: LV, left ventricular; ↑, increased; ↓, decreased.

(NO) in peripheral vessels [26,27]. This reduction in NO causes vasoconstriction and increased vascular tone that, in turn, leads to reduced myocardial perfusion and, eventually, myocardial injury [28,29]. The nonselective aldosterone blocker spironolactone seems to improve endothelial dysfunction and normalize these deleterious effects in animal and human studies [30].

Aldosterone, in combination with a high-salt environment, seems to promote oxidative stress by increasing the activity of reduced-form nicotinamide adenine dinucleotide phosphate oxidase. This increase leads to the production of superoxide radicals, endothelial damage and vasoconstriction, and, eventually, inflammation and fibrosis in animal models—effects that are attenuated by spironolactone [31].

Collagen synthesis

There is increasing evidence that aldosterone may exert adverse affects on the vascular and myocardial matrix by increasing collagen synthesis. Although collagen has important structural properties, its overproduction (particularly types I and III) is associated with stiffness and distortion of the tissue structure [32–34]. This mechanism explains, at least in part, the role of aldosterone in LV remodeling post-AMI [35–37]. Still, after 8 weeks of spironolactone treatment in patients with chronic HF, reversal of collagen synthesis was demonstrated by a 20% reduction of pro-collagen type III N-terminal amino peptide (PIIINP, a biomarker of vascular collagen turnover) [38].

Inflammation

Vascular inflammation is another potential effect of aldosterone-induced myocardial injury and fibrosis. There is evidence that aldosterone infusion in salt-loaded rats induced severe coronary inflammatory lesions, resulting in fibrosis, focal ischemia, and necrosis [39]. These structural alterations may also be responsible for the decreased arterial compliance in patients with hypertension [32]. These phenomena can be altered after 8 weeks of treatment with eplerenone, a selective aldosterone receptor blocker [39].

Autonomic nervous system

Aldosterone has been shown in animal [40] and human [41] models to decrease baroreceptor sensitivity and reflex function. Furthermore, aldosterone has been shown to block myocardial uptake of norepinephrine in rats by 24%, which may reduce heart-rate variability and, potentially, catecholamine-induced arrhythmias [42]. These findings are consistent with data from patients with chronic, stable HF in whom spironolactone, in addition to standard medical therapy, increased myocardial norepinephrine uptake, reduced ventricular arrhythmias on 24-hour ambulatory electrocardiography, and improved heart-rate variability compared with similar patients given placebo [38,43]. Although its potential pro-arrhythmic effects are not completely understood, growing literature shows that aldosterone may influence electrical properties of cardiac myocytes by increasing action potential duration by altering calcium channel current density [44].

Other mechanisms

Other potentially deleterious effects of aldosterone have been shown in human and animal models, including inhibition of fibrinolysis and platelet activation, which promotes the hypercoagulable state observed in the post-AMI setting [45], and myocardial apoptosis as an adjunctive mechanism of LV remodeling [46]. Once again, aldosterone receptor blockade attenuated these processes [47].

Experimental evidence in humans

Modena and colleagues [48] studied the effects of aldosterone suppression with potassium canrenoate (50 mg/d) on collagen synthesis and LV dimensions. This small, randomized, placebo-controlled study enrolled 46 patients after recent thrombolysis for anterior AMI who were also given ACE inhibitors at the time of discharge. Serum PIIINP, a marker of collagen synthesis, and LV diameter were significantly lower in the canrenoate group compared with placebo at 3, 6, and 12 months.

The reduction in collagen synthesis and attenuation of remodeling may slow progression of diastolic dysfunction after AMI. Echocardiographic studies demonstrated that in AMI patients not receiving, or unsuitable for, reperfusion therapy, canreoate (25 mg/d) in addition to captopril resulted in lower LV end-systolic volumes (LVESV), higher LVEF, higher E-wave-to-A-wave (E/A) ratios, and lower isovolumetric relaxation (IVRT) times compared with placebo after 6 months in a larger randomized pilot study [49].

In a study by Hayashi and colleagues [50], 134 patients with anterior AMI were assigned to enalapril and spironolactone (25 mg/d) versus

enalapril alone immediately after revascularization. At 30 days, the combination therapy arm had a significantly greater increase in LVEF (+7.2% versus +4.46%, $P < .05$), and decreases in LV end-diastolic (LVEDVI) and end-systolic (LVESDI) volume indices, transcardiac extraction of aldosterone, and PIIINP levels compared with the enalapril-only group, suggesting a greater protective effect of combination therapy against post-AMI LV remodeling. These small clinical trials with promising results for the improvement of LV remodeling and reduction in electrical instability, summarized in Table 2 led to a large, randomized, controlled trial evaluating hard endpoints for aldosterone receptor blockade in high-risk, post-AMI LVSD patients.

Aldosterone blockade with eplerenone

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, published in 2003, was a multicenter, double-blind, placebo-controlled, international trial of 6,632 patients with AMI complicated by LVSD (LVEF ≤40% by echocardiography, radionuclide angiography, or contrast angiography), with symptoms of HF (pulmonary rales, pulmonary edema, or presence of a third heart sound) or diabetes who were randomized to eplerenone, a selective aldosterone receptor blocker, or placebo within 3 to 14 days of AMI [51]. Eplerenone was started at 25 mg/d and increased to a maximum of 50 mg/d after 4 weeks. In patients with diabetes and post-AMI LVSD, symptoms of HF were not required, because outcomes in such patients compared with those in nondiabetic patients with post-AMI LVSD with symptoms of HF were similar [52]. Patients with a serum Cr >2.5 mg/dL and those with evidence of serum potassium >5.0 mEq/L were excluded. Standard therapy included reperfusion (45%), ACE inhibitors or ARBs (86%), beta blockers (75%), aspirin (88%), statins (47%), and diuretics (60%). After a mean follow-up of 16 months, eplerenone significantly reduced the risk of all-cause mortality by 15% (14% versus 17%, $P = .008$) and cardiovascular (CV) mortality/CV hospitalization by 13% (27% versus 30%, $P = .002$), both primary end points in the study. Death from CV causes was reduced by 17% (12% versus 15%, $P = .005$), driven by a 21% reduction in SCD (4.8% versus 6.1%, $P = .03$). There was a nonsignificant reduction in hospitalization for CV events of 9% (18% versus 20%, $P = .09$),

driven by a 15% reduction in HF admissions (10% versus 12%, $P = .03$) (Fig. 1).

The critical period of 30 days after AMI, when the risk of SCD is greatest, was studied in a prespecified analysis of EPHESUS [53]. Analysis of primary endpoints demonstrated that, compared with placebo, eplerenone reduced all-cause mortality by 31% (3.2% versus 4.6%, $P = .004$), and nonsignificantly reduced death from CV causes/CV hospitalization. Using Kaplan-Meyer analysis, a significant treatment effect was seen starting at 10 days into treatment. Death from CV causes was reduced by 32% (3.0% versus 4.4%, $P = .003$), again driven by a 37% reduction in SCD (0.9% versus 1.4%, $P = .03$) (Fig. 2). This 1.4% risk of SCD within 30 days post-AMI in the placebo arm is the same as that in the treatment arms of VALIANT, making the reduction to 0.9% by eplerenone of significant clinical relevance.

In the post-AMI patients with LVEF ≤30%, further reductions in the primary and secondary endpoints were observed with eplerenone in a post hoc analysis of EPHESUS [54]. Of the 6,632 patients in EPHESUS, 2,106 (32%) had an LVEF of ≤30%, and similar baseline characteristics between treatment groups, but more diabetes, HF, and prior AMI history than the overall EPHESUS population. Compared with the overall placebo-treated EPHESUS population, placebo-treated patients with LVEF ≤30% had a higher incidence of all-cause death (24.0% versus 16.7%), CV mortality/CV hospitalization (40.9% versus 30.0%), and SCD (9.7% versus 6.1%). In this high-risk group, compared with placebo, eplerenone administration was associated with a 21% reduction in all-cause mortality (20% versus 24%, $P = .12$) and a 21% reduction of CV mortality/CV hospitalization (34% versus 41%, $P = .001$). At the conclusion of the study, CV mortality was reduced by 23% (17% versus 21%, $P = .008$) and SCD was reduced by 33% (6.8% versus 9.7%, $P = .01$). Nonfatal hospitalization for HF was reduced by 20% (15% versus 17%, $P = .75$) but death due to progressive HF was reduced nonsignificantly (4.7% versus 5.6%, $P = .28$) (Fig. 3). Compared to the overall EPHESUS population, the patients with LVEF ≤30% had a higher event rate but derived the greatest benefit with eplerenone (Fig. 4).

EPHESUS established the mortality benefit of aldosterone receptor blockade with eplerenone in patients with post-AMI LVSD and either symptoms of HF or the presence of diabetes. The CV

Table 2
Overview of clinical trials on aldosterone blockade in patients with left ventricular systolic dysfunction after an acute myocardial infarction

Study	Inclusion criteria	Number of patients studied	Randomized groups	Follow-up	Primary end point(s)	Main finding
Modena et al [48]	Anterior AMI, r-tPA within 6 hours of chest pain, ACE I after randomization	46	Potassium canreonate (50 mg/d) versus placebo on discharge following AMI	Months 3, 6, 12	Measurement of PIIINP and LV volume	Significant reduction in PIIINP in canreonate-treated group at 3, 6, and 12 months, significant reduction in LV volume in canreonate-treated group at 6 and 12 months
Di Pasquale et al [49]	Anterior AMI, without reperfusion	187	Potassium canreonate (25 mg/d) plus captopril versus placebo plus captopril immediately following AMI	Days 10, 90, 180	Measurement of LVESV, LVEF, LVEDD, E/A ratio, E decal time, IVRT	Improvement in LVESV, LVEF, E/A ratio, and IVRT
Hayashi et al [50]	Anterior AMI, successful reperfusion within 24 hours	134	Spironolactone (25 mg/d) plus enalapril versus placebo plus enalapril immediately after revascularization for AMI	1 month	Measurement of PIIINP, LVEF, LVEDVI, LVESVI	Transcardiac aldosterone extraction reduced, PIIINP levels suppressed in treatment group, LVEF increase greater, LVEDVI increase suppressed, LVESVI decrease greater in treatment groups compared with placebo
EPHESUS [51]	AMI, LVEF ≤40% and either HF symptoms or DM	6,632	Eplerenone (25-50 mg/d) versus placebo plus optimal medical therapy 3–14 days following AMI	16 months	Time to death from any cause and time to death from any CV cause or hospitalization for CV event	15% all-cause mortality risk reduction ($P = .008$), 13% CV mortality or CV hospitalization risk reduction ($P = .002$)

Abbreviations: ACE I, angiotensin-converting enzyme inhibitor; DM, diabetes mellitus; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; IVRT, isovolemic relaxation time; LVEDD, left ventricular end diastolic dimension; LVEDVI, left ventricular end diastolic volume index; LVESV, left ventricular end systolic volume; LVESVI, left ventricular end systolic volume index; r-tPA, recombinant tissue plasminogen activator.
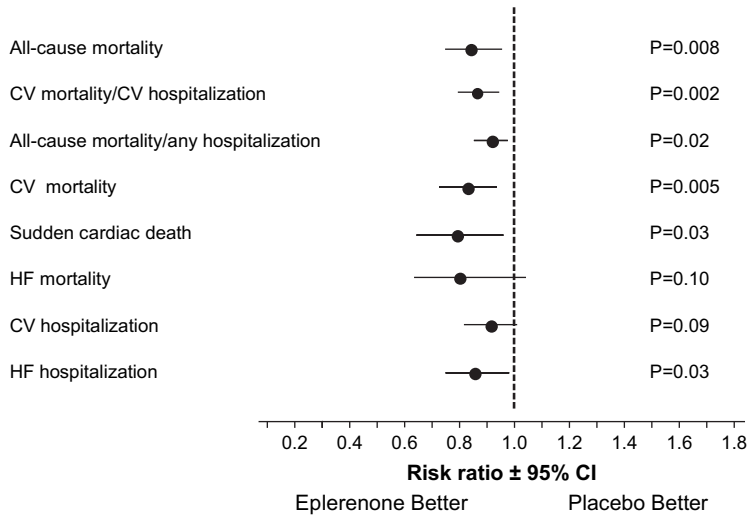
Fig. 1. Relative risks of primary and secondary end points in EPHESUS. (*Adapted from* Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.)

mortality reduction is predominantly driven by reductions in SCD, and this SCD reduction is seen as early as 10 days after therapy. The benefit of eplerenone is greatest in those patients with the worst LVSD. EPHESUS patients were on standard medical therapy, with ACE inhibitors or ARBs (85%), beta blockers (75%), and statins (47%). In addition, 45% of patients had reperfusion therapy to limit the infarct size, and 89% were receiving antiplatelet therapy with aspirin. Accordingly, eplerenone was effective in patients who were already receiving evidence-based therapy for CAD and LVSD, including ACE inhibitors and beta blockers.
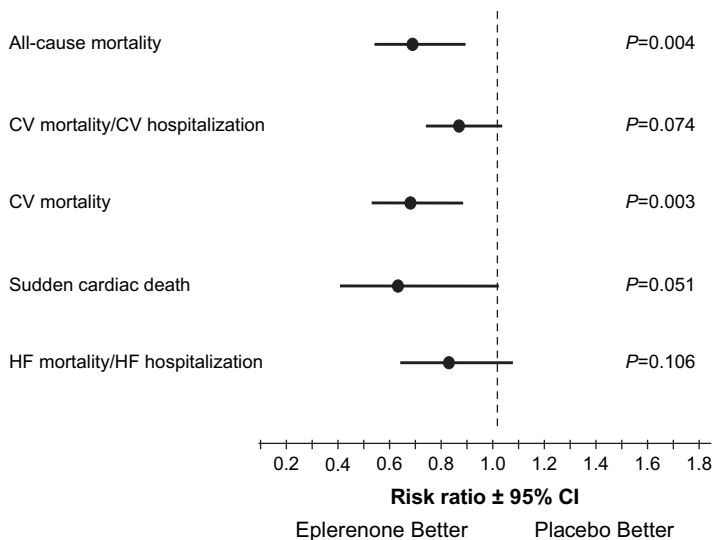

Fig. 2. Relative risks of mortality and morbidity at 30 days in all EPHESUS patients. (*Adapted from* Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005;46:425–31.)
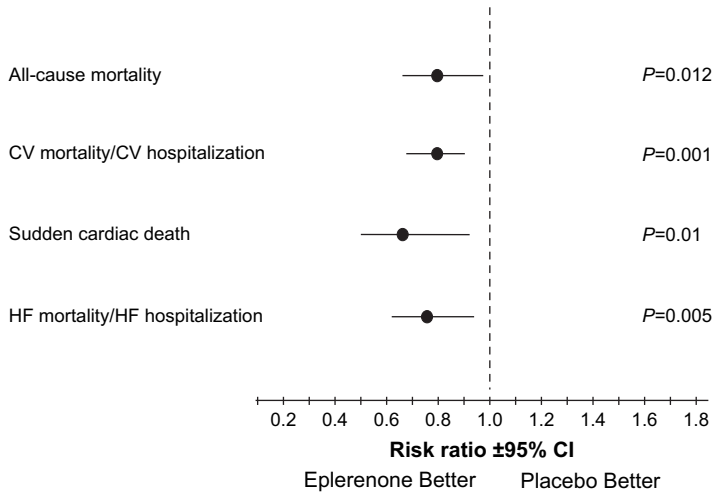
Fig. 3. Relative risks of mortality and morbidity in EPHESUS patients with left ventricular ejection fraction of 30% or less. (*Adapted from* Pitt B, Gheorghiade M, Zannad F, et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction < or = 30%. Eur J Heart Fail 2006;8:295–301.)

Safety concerns with eplerenone

Hemodynamics

At the time EPHESUS was planned, there was little experience with the use of aldosterone receptor blockade during the early hours after AMI and hypotension seemed to be one of the major concerns, given the high-risk post-AMI population. Thus, it was decided to delay the administration of eplerenone until patients were hemodynamically stable between 3 to 14 days after myocardial infarction. At 30 days after randomization, placebo-treated patients experienced significantly greater systolic and diastolic blood
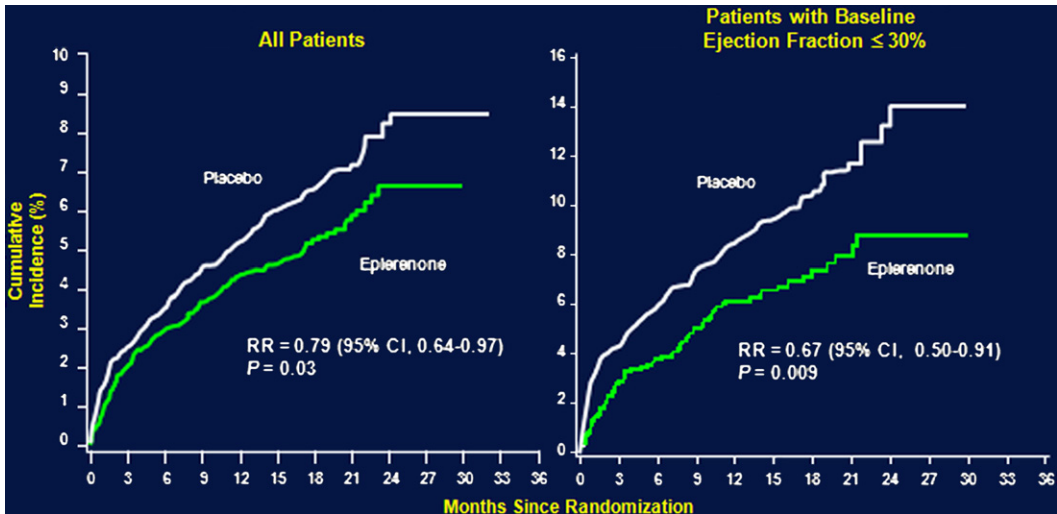

Fig. 4. Relative risk (RR) of sudden cardiac death in the eplerenone and in the placebo group in the main EPHESUS trial compared with the subgroup analysis of patients with left ventricular ejection fraction ≤30%. (*Adapted from* Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21 and Pitt B, Gheorghiade M, Zannad F, et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction < or = 30%. Eur J Heart Fail 2006;8:295–301.)

pressure elevation than patients treated with eplerenone (4.0/2.9 versus 2.4/1.7 mm Hg, $P < .01$), a magnitude that may not be clinically significant. This effect was sustained at 1 year (8/4 versus 5/3 mm Hg, $P < .01$). No significant change in body weight was observed at 1 year. These data, summarized in Fig. 5, suggest that the antihypertensive effect of eplerenone is minimal even with background therapy of ACE inhibitors and beta blockers and may be used early post-AMI. Now that it is known that administration within 3 to 14 days of AMI does not adversely lower blood pressure, it is unclear if earlier administration of eplerenone will give greater benefit, by preventing SCD and worsening pump failure. Although Hayashi and colleagues [50] demonstrated benefits in LV function and remodeling with aldosterone receptor blockade as early as 1 hour after revascularization, the translation to clinical endpoints requires prospective evaluation in larger trials.

Renal function

In EPHESUS, serum Cr increased by 0.02 mg/dL in the placebo group and 0.06 mg/dL in the eplerenone group ($P < .001$) at 1 year. EPHESUS excluded patients with serum Cr >2.5 mg/dL. With a mean age of enrollment of 64, a serum Cr > 2.5 mg/dL translates to an estimated glomerular filtration rate (eGFR) of ≤ 29 mL/min/1.73 m^2 for men and ≤ 22 mL/min/1.73 m^2 for women, using the modification of diet in renal disease (MDRD) formula. Calculation and close monitoring of the eGFR rather than serum Cr may be a more reliable way of predicting CV outcome, especially in the elderly and in women: eGFR is significantly worse with age and female gender for any given Cr level [55]. In fact, analysis of VALIANT demonstrated that, for eGFR <81 mL/min/1.73 m^2, there was a hazard ratio for death or nonfatal CV outcomes of 1.1 for every 10-unit reduction in eGFR, independent of treatment assignment [56]. Eplerenone should be discontinued when the eGFR approaches 30 mL/min/1.73 m^2, and use of other nephrotoxins such as nonsteroidal anti-inflammatory drugs should be avoided.

Hyperkalemia

The incidence of serious hyperkalemia (serum potassium ≥ 6.0 mEq/dL) in EPHESUS was greater in patients treated with eplerenone than with placebo (5.5 versus 3.9%, $P = .002$) at 1 year. Among patients with a baseline eGFR <50 mL/min, calculated using the Cockcroft-Gault formula, incidence of serious hyperkalemia was 10.1% in the eplerenone group and 5.9% in the placebo group ($P = .006$). Corresponding rates for eGFR ≥ 50 mL/min were 4.6% and 3.5%, respectively ($P = .04$). Within the first 30 days of treatment, serum potassium increased by 0.24 mmol/L in the eplerenone group and 0.17 mmol/L in the placebo group ($P < .001$). However, in this trial after adjudication, no deaths were attributed
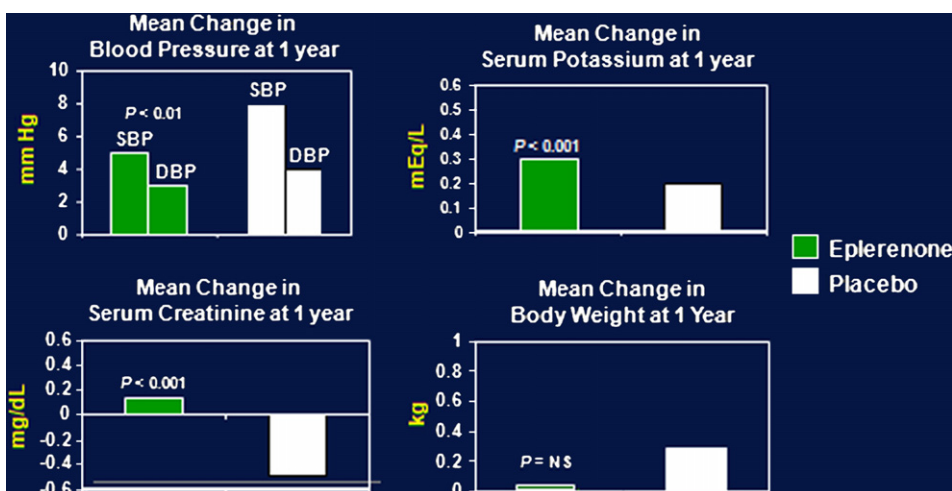

Fig. 5. Effects of eplerenone on blood pressure, serum potassium, serum Cr, and body weight in EPHESUS patients at 1 year. (*Adapted from* Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.)

to hyperkalemia. Hypokalemia (serum potassium ≤ 3.5 mEq/L) may be as great if not a greater risk than hyperkalemia in patients with HF [57] and occurred less frequently in eplerenone-treated patients than in placebo-treated patients (8.4% versus 13.1%, $P < .001$).

In real-world practice, care must be taken with aldosterone receptor blockade in patients with post-AMI LVSD. The Randomized Aldactone Evaluation Study (RALES) trial was a pivotal study published in 1999 that showed a mortality benefit of spironalactone in patients with an LVEF $\leq 35\%$, with severe (NYHA Class III-IV), chronic HF being treated with ACE inhibitors, if tolerated, and a loop diuretic [58]. Publication of this trial led to a more widespread use of aldosterone receptor blockade in patients with LVSD. A population-based, time-series analysis was performed using health care databases and hospitalization records obtained from the Canadian Institute of Health Information Discharge Abstract Database and the Ontario Drug Benefits Program of all patients 65 years of age or older in Ontario, Canada. The accuracy of the hospitalization records had not been previously established for hyperkalemia. This study analyzed the rates of spironolactone use and hyperkalemia in patients with HF treated with ACE inhibitors before and after publication of RALES [59]. There was an increase in prescription of spironolactone by a factor of about 5 from 1999 compared with late 2001. The rate of hospital admissions involving a diagnosis of hyperkalemia increased from 4.0/1000 patients to 11.0/1000 patients from 1999 to late 2001. During the same period, the mortality in patients admitted with hyperkalemia increased from 0.7/1000 patients to 2.0/1000 patients.

Since the authors had no knowledge of the serum potassium during hospitalization and did not adjust for comorbidities, it is far from clear whether this substantial increase in mortality was related to hyperkalemia caused by spironolactone use. In fact, hyperkalemia has been reported as a major marker for severity of HF, independent of spironolactone use [60]. RALES excluded patients with a serum Cr of > 2.5 mg/dL or a serum potassium of > 5.0 mEq/L. RALES followed laboratory measurements, including serum potassium every 4 weeks for the first 12 weeks, then every 3 months for up to 1 year, and every 6 months thereafter. EPHESUS had the same serum Cr and potassium exclusion criteria, and monitored potassium and Cr levels 48 hours after initiation,

at 1, 4, and 5 weeks, at all scheduled study visits, and within 1 week after any change in dose. Accordingly, when simple monitoring criteria are followed, the rate of hyperkalemia in patients already receiving ACE inhibitors and beta blockers, as was the case in EPHESUS, is low. The rates of serious hyperkalemia in the treatment arms compared with placebo in RALES and EPHESUS were 2% versus 1%, and 5.5% versus 3.9%, respectively.

Recommendations for prevention of SCD in patients with post-AMI LVSD

Patients with post-AMI LVSD present at a critical juncture between acute coronary event and HF. The failure to recognize this syndrome as a distinct entity that needs therapeutic interventions tailored accordingly may, at least in part, explain the questionable results of the recent DINAMIT trial that, as previously discussed, failed to demonstrate any benefit with early ICD implantation in patients with post-AMI LVSD. The available data and ACC/AHA guidelines suggest that several treatment strategies should be implemented in an effort to improve outcomes in this patient population. These treatment strategies are briefly discussed below. The guidelines for ST-segment-elevation MI (STEMI) [12], unstable angina, non-ST-segment-elevation MI (UA/NSTEMI) [61], and prevention of SCD [13] are cited and summarized in Table 3.

With LVSD being such a poor prognostic factor in post-AMI patients, assessment of LVEF is critical in all patients with AMI. This can be done using many modalities, including contrast angiography if coronary angiography is performed, radionuclide angiography, or echocardiography. The ACC/AHA guidelines for the management of STEMI give LVEF assessment a class I indication for all post-AMI patients. A similar recommendation is given in the guidelines for the management of UA/NSTEMI.

Aldosterone receptor blockade is beneficial in patients with post-MI LVSD who are receiving other therapies such as reperfusion therapy, antiplatelet therapy, beta blockers [62,63], ACE inhibitors [64–66], and ARBs [8,67]. The importance of adrenergic blockade, including beta blockers, ACE inhibitors, and ARBs, in this setting is reviewed elsewhere in this issue of the *Cardiology Clinics*.

There is increasing evidence that statins, through the improvement they effect in endothelial

Table 3
Class I indications for assessment and treatment of myocardial infarction and concomitant left ventricular dysfunction (adapted from [12,13,60])

Intervention	Class I indication
LVEF assessment	
STEMI	LVEF should be measured in all STEMI patients (*Level of Evidence: B*)
UA/NSTEMI	A noninvasive test (echocardiogram or radionuclide angiogram) is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography (*Level of Evidence: B*)
Beta blockers	
STEMI	Patients with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme (*Level of Evidence: B*)
UA/NSTEMI	Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme (*Level of Evidence: B*)
ACE inhibitors	
STEMI	An ACE inhibitor should be prescribed at discharge for all patients without contraindications after STEMI (*Level of Evidence: A*)
UA/NSTEMI	ACE inhibitors should be given and continued indefinitely for patients recovering from UA/NSTEMI with HF, LV dysfunction (LVEF <0.40), hypertension, or diabetes mellitus, unless contraindicated (*Level of Evidence: A*)
ARBs	
STEMI	An ARB should be administered or prescribed at discharge to STEMI patients who are intolerant of an ACE inhibitor and have either clinical or radiological signs of HF and LVEF <0.40. Valsartan and candesartan have established efficacy for this recommendation (*Level of Evidence: B*)
UA/NSTEMI	An ARB should be administered or prescribed at discharge to UA/NSTEMI patients who are intolerant to ACE inhibitors and have either clinical or radiological signs of HF and LVEF <0.40 (*Level of Evidence: A*)
Aldosterone receptor blockers	
STEMI	Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (Cr should be ≤2.5 mg/dL in men and ≤2.0 mg/dL in women) or hyperkalemia (potassium should be ≤5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF of ≤0.40, and have either symptomatic HF or diabetes (*Level of Evidence: A*)
UA/NSTEMI	Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated Cr clearance should be > 30 mL/min) or hyperkalemia (potassium should be ≤5 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF ≤0.40, and have either symptomatic HF or diabetes mellitus (*Level of Evidence: A*)
ICDs	ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction because of prior MI who are at least 40 days post-MI, have an LVEF ≤30%–40%, are NYHA-functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year (*Level of Evidence: A*)

function, plaque stabilization, and lipid profile, may contribute to the reduction in SCD in patients with CAD [68,69]. Although most of the data are retrospective in nature, it appears that, irrespective of their exact mechanism of action, statins have shown a significant reduction in ventricular arrhythmias [70–73]. Although no specific ACC/AHA recommendation exists regarding statins in post-AMI LVSD, statins are recommended in all post-MI patients irrespective of their LV function.

Table 3 summarizes the ACC/AHA recommendations for care of patients with post-AMI LVSD.

ICD implantation, although found to improve mortality long-term, does not seem to be beneficial in the early phase post-AMI, as suggested by the MADIT-II and DINAMIT trials. Accordingly, the ACC/AHA/ESC gives a class I recommendation for the prophylactic implantation of an ICD in these patients, but only beyond 40 days post-AMI [13].

The ACC/AHA guidelines for the management of STEMI and UA/NSTEMI give aldosterone receptor blockers, such as eplerenone, a class I indication for hospital management and secondary prevention in patients with post-AMI LVSD. Despite this recommendation, the use of aldosterone receptor blockade is sparse in post-AMI LVSD in clinical practice. Recent analysis of the 48,612 patients in the Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry of patients hospitalized for acute heart failure demonstrated that, in patients with LVSD, defined as LVEF ≤40% and CAD with prior revascularization procedures, only 11% were taking an aldosterone receptor blocker of some kind, while 65% were taking a beta blocker, 59% an ACE inhibitor or ARB, and 49% a statin (unpublished data). Efforts need to be placed to initiate this life-saving medication during the critical period after AMI and before discharge.

Summary

AMI is commonly associated with LVSD and HF, and confers substantial mortality and morbidity. Several adjunctive therapies have proved to reduce mortality and morbidity, including antiplatelet agents, statins, beta blockers, ACE inhibitors, ARBs for patients intolerant of ACE inhibitors, and ICD implantation at least 40 days after AMI. Aldosterone has many deleterious effects and is elevated in patients with post-AMI LVSD. Eplerenone, by blocking the aldosterone receptor, is a new therapy for these high-risk patients that has proved to reduce mortality and morbidity when used in conjunction with beta-blocker and ACE-inhibitor therapy. Eplerenone reduces SCD in the early post-AMI period (<30 days), particularly in patients with a LVEF ≤30%. These patients with severe LVSD are at very high risk of SCD despite receiving beta-blocker and ACE-inhibitor/ARB therapy.

Although ICD therapy is known to reduce the rate of SCD in patients with HF and post-AMI LVSD, it does not seem to be effective within the first 40 days post-AMI. Aldosterone receptor-blocking agents are beneficial with proper patient selection (serum Cr <2.5 mg/dL, potassium <5.0 mEq/L) and close monitoring of renal function and serum potassium concentration, particularly in patients who are receiving ACE inhibitors or ARBs and have diabetes.

References

[1] Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–171.

[2] Hasdai D, Topol EJ, Kilaru R, et al. Frequency, patient characteristics, and outcomes of mild-to-moderate heart failure complicating ST-segment elevation acute myocardial infarction: lessons from 4 international fibrinolytic therapy trials. Am Heart J 2003;145:73–9.

[3] Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109:494–9.

[4] Wu AH, Parsons L, Every NR, et al. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 2002;40:1389–94.

[5] Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. Eur Heart J 2004;25:1911–9.

[6] Spencer FA, Meyer TE, Gore JM, et al. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure: the National Registry of Myocardial Infarction. Circulation 2002;105:2605–10.

[7] Spencer FA, Meyer TE, Goldberg RJ, et al. Twenty year trends (1975–1995) in the incidence, in-hospital and long-term death rates associated with heart failure complicating acute myocardial infarction: a community-wide perspective. J Am Coll Cardiol 1999; 34:1378–87.

[8] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349: 1893–906.

[9] Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005;352:2581–8.

[10] Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481–8.

[11] Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

[12] Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588–636.

[13] Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006;48:e247–346.

[14] Udelson JE, Patten RD, Konstam MA. New concepts in post-infarction ventricular remodeling. Rev Cardiovasc Med 2003;4(Suppl 3):S3–12.

[15] Harrison TR, Kasper DL. Harrison's principles of internal medicine. 16th edn. New York: McGraw-Hill Medical Pub. Division; 2005.

[16] Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1161–72.

[17] Swedberg K, Eneroth P, Kjekshus J, et al. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730–6.

[18] Beygui F, Collet JP, Benoliel JJ, et al. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. Circulation 2006;114:2604–10.

[19] Delyani JA, Robinson EL, Rudolph AE. Effect of a selective aldosterone receptor antagonist in myocardial infarction. Am J Physiol Heart Circ Physiol 2001;281:H647–54.

[20] Suzuki G, Morita H, Mishima T, et al. Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodeling in dogs with heart failure. Circulation 2002;106:2967–72.

[21] Fraccarollo D, Galuppo P, Hildemann S, et al. Additive improvement of left ventricular remodeling and neurohormonal activation by aldosterone receptor blockade with eplerenone and ACE inhibition in rats with myocardial infarction. J Am Coll Cardiol 2003;42:1666–73.

[22] Wang D, Liu YH, Yang XP, et al. Role of a selective aldosterone blocker in mice with chronic heart failure. J Card Fail 2004;10:67–73.

[23] Masson S, Staszewsky L, Annoni G, et al. Eplerenone, a selective aldosterone blocker, improves diastolic function in aged rats with small-to-moderate myocardial infarction. J Card Fail 2004;10:433–41.

[24] Silvestre JS, Heymes C, Oubenaissa A, et al. Activation of cardiac aldosterone production in rat myocardial infarction: effect of angiotensin II receptor blockade and role in cardiac fibrosis. Circulation 1999;99:2694–701.

[25] Perrier E, Kerfant BG, Lalevee N, et al. Mineralocorticoid receptor antagonism prevents the electrical remodeling that precedes cellular hypertrophy after myocardial infarction. Circulation 2004;110:776–83.

[26] Ikeda U, Kanbe T, Nakayama I, et al. Aldosterone inhibits nitric oxide synthesis in rat vascular smooth muscle cells induced by interleukin-1 beta. Eur J Pharmacol 1995;290:69–73.

[27] Fleming I, Busse R. NO: the primary EDRF. J Mol Cell Cardiol 1999;31:5–14.

[28] Wang J, Seyedi N, Xu XB, et al. Defective endothelium-mediated control of coronary circulation in conscious dogs after heart failure. Am J Physiol 1994;266:H670–80.

[29] Qi XL, Stewart DJ, Gosselin H, et al. Improvement of endocardial and vascular endothelial function on myocardial performance by captopril treatment in postinfarct rat hearts. Circulation 1999;100:1338–45.

[30] Bauersachs J, Heck M, Fraccarollo D, et al. Addition of spironolactone to angiotensin-converting enzyme inhibition in heart failure improves endothelial vasomotor dysfunction: role of vascular superoxide anion formation and endothelial nitric oxide synthase expression. J Am Coll Cardiol 2002;39:351–8.

[31] Sun Y, Zhang J, Lu L, et al. Aldosterone-induced inflammation in the rat heart: role of oxidative stress. Am J Pathol 2002;161:1773–81.

[32] Duprez D, De Buyzere M, Rietzschel ER, et al. Aldosterone and vascular damage. Curr Hypertens Rep 2000;2:327–34.

[33] Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101:2981–8.

[34] Brilla CG, Zhou G, Matsubara L, et al. Collagen metabolism in cultured adult rat cardiac fibroblasts:

response to angiotensin II and aldosterone. J Mol Cell Cardiol 1994;26:809–20.

[35] Kostuk WJ, Kazamias TM, Gander MP, et al. Left ventricular size after acute myocardial infarction. Serial changes and their prognostic significance. Circulation 1973;47:1174–9.

[36] Eaton LW, Weiss JL, Bulkley BH, et al. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. N Engl J Med 1979;300:57–62.

[37] Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331–6.

[38] MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997;35:30–4.

[39] Rocha R, Rudolph AE, Frierdich GE, et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol 2002;283:H1802–10.

[40] Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. Hypertension 1994;24:571–5.

[41] Yee KM, Struthers AD. Aldosterone blunts the baroreflex response in man. Clin Sci (Lond) 1998;95: 687–92.

[42] Barr CS, Lang CC, Hanson J, et al. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995; 76:1259–65.

[43] Yee KM, Pringle SD, Struthers AD. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001;37: 1800–7.

[44] Perrier R, Richard S, Sainte-Marie Y, et al. A direct relationship between plasma aldosterone and cardiac L-type Ca2+ current in mice. J Physiol 2005; 569:153–62.

[45] Schafer A, Fraccarollo D, Hildemann SK, et al. Addition of the selective aldosterone receptor antagonist eplerenone to ACE inhibition in heart failure: effect on endothelial dysfunction. Cardiovasc Res 2003;58:655–62.

[46] De Angelis N, Fiordaliso F, Latini R, et al. Appraisal of the role of angiotensin II and aldosterone in ventricular myocyte apoptosis in adult normotensive rat. J Mol Cell Cardiol 2002;34:1655–65.

[47] Biondi-Zoccai GG, Abbate A, Baldi A. Potential antiapoptotic activity of aldosterone antagonists in postinfarction remodeling. Circulation 2003;108: e26.

[48] Modena MG, Aveta P, Menozzi A, et al. Aldosterone inhibition limits collagen synthesis and progressive left ventricular enlargement after anterior myocardial infarction. Am Heart J 2001;141: 41–6.

[49] Di Pasquale P, Cannizzaro S, Giubilato A, et al. Additional beneficial effects of canrenoate in patients with anterior myocardial infarction on ACE-inhibitor treatment. A pilot study. Ital Heart J 2001;2: 121–9.

[50] Hayashi M, Tsutamoto T, Wada A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation 2003;107:2559–65.

[51] Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.

[52] Aronson D, Rayfield EJ, Chesebro JH. Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. Ann Intern Med 1997;126:296–306.

[53] Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005;46:425–31.

[54] Pitt B, Gheorghiade M, Zannad F, et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction <or= 30%. Eur J Heart Fail 2006;8:295–301.

[55] Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351: 1296–305.

[56] Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–95.

[57] Ahmed A, Zannad F, Love TE, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. Eur Heart J 2007;28:1334–43.

[58] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

[59] Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351:543–51.

[60] Chakko SC, Frutchey J, Gheorghiade M. Life-threatening hyperkalemia in severe heart failure. Am Heart J 1989;117(5):1083–91.

[61] Anderson JL, Adams CD, Antman EM, et al. ACC/ AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing

Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). Circulation 2007;116:e148–304.

[62] Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730–7.

[63] Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998;339:489–97.

[64] Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670–6.

[65] Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.

[66] Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821–8.

[67] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360:752–60.

[68] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.

[69] Sacks FM, Pfeffer MA, Moye LA, et al. CARE: the effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.

[70] Arntz HR, Agrawal R, Wunderlich W, et al. L-CAD: beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). Am J Cardiol 2000;86:1293–8.

[71] Schwartz GG, Olsson AG, Ezekowitz MD, et al. MIRACL: effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711–8.

[72] Stenestrand U, Wallentin L. RIKS-HIA: early statin treatment following acute myocardial infarction and 1-year survival. JAMA 2001;285:430–6.

[73] Cannon CP, Braunwald E, McCabe CH, et al. PROVE IT-TIMI 22: intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.