Should aldosterone antagonists be considered as primary therapy for prevention of sudden cardiac death?

Added Benefit of Mineralocorticoid Receptor Blockade in the Primary Prevention of Sudden Cardiac Death

Bertram Pitt, MD; Geoffrey S. Pitt, MD, PhD

Sudden cardiac death (SCD) is a major public health issue. In patients with heart failure (HF) of various origins, including ischemia post-myocardial infarction (MI), successful development of pharmacological therapies that target neurohormonal abnormalities and modulate disease progression has changed the major cause of death from progressive pump failure to SCD from cardiac arrhythmias. Conditions such as hypertension, hypertrophic cardiomyopathy, aortic stenosis, diabetes mellitus, and aging are accompanied by hypertrophy and fibrosis, increasing the risk of SCD. Also affected are patients with inherited arrhythmogenic disorders such as long-QT syndrome and Brugada syndrome (BrS). Although the mechanisms responsible for SCD, its epidemiology, and treatment have recently been reviewed,1–4 1 aspect of therapy that deserves further emphasis for the prevention of SCD is the role of aldosterone blockade (AB) or, more precisely, mineralocorticoid receptor blockade (MRB).

The Role of MRB in Reducing SCD in Patients With Severe Chronic HF Associated With SLVD and in Patients With SLVD and HF Post-MI

MRB with spironolactone 12.5 to 50 mg/d was shown to be effective in reducing SCD by 29% \( (P=0.02) \) and total mortality by 30% \( (P<0.001) \) in patients with severe HF due to SLVD associated with either ischemic heart disease or idiopathic dilated cardiomyopathy when added to standard therapy that included an angiotensin-converting enzyme inhibitor (ACEI), \( \beta \)-adrenergic blocking agent (BB), diuretics, and digoxin in the Randomized Aldactone Evaluation Study (RALES).5 Because
this study was initiated before the positive results of trials with BB in severe HF were published, only 10% to 11% of patients randomized in RALES were on BB.

In a subsequent study, the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the more selective MRB eplerenone, at 25 to 50 mg/d, was also associated with a 21% (P = 0.02) reduction in SCD and a 15% (P = 0.008) reduction in total mortality in patients with HF and SLVD post-MI. In EPHESUS, 83% of patients were on an ACEI and/or angiotensin receptor blocker (ARB) and 75% of patients on a BB before hospital discharge. Eplerenone was also effective in reducing SCD in patients on “optimal therapy” that included aspirin, reperfusion, a statin, an ACEI and/or an ARB, and a BB, suggesting that MRB adds to the efficacy of the standard therapy of HF in reducing SCD and total mortality. It should be noted that the definition of SCD in EPHESUS included death occurring within 1 hour of new symptoms, un witnessed death with no new symptoms within the previous 72 hours, or cardiac arrest with death within 28 days thereafter; it is therefore possible that not all the deaths classified as SCD were due to an arrhythmia. Nevertheless, the significant reduction in total mortality in RALES and EPHESUS suggests a beneficial effect of MRB on SCD.

Role of MRB in the First 30 Days After MI
In patients with SLVD and/or HF, the first 30 days has been shown to be the period of highest risk for SCD. In EPHESUS, eplerenone 25 mg/d, equivalent to approximately 12.5 mg/d of spironolactone, was effective in reducing both SCD (by 37%; P = 0.051) and total mortality (by 31%; P = 0.004) during this high-risk period. It is possible that eplerenone may be even more effective in reducing SCD if therapy is initiated earlier. In EPHESUS, eplerenone was administered between 3 to 14 days post-MI (mean = 7 days). Elevated plasma aldosterone levels for patients with ST-segment elevation MI on admission to the hospital predicted an increase risk of death and resuscitated cardiovascular death independent of the patients’ age, reperfusion status, or the presence of HF. Of importance, 83% of the patients in this study did not have evidence of HF on admission, suggesting an important role for the early administration of an AB to patients post-MI regardless of the presence of clinical HF. In another study, Hayashi et al randomized patients with their first anterior ST-segment–elevation MI after primary percutaneous coronary intervention on day 1 post-MI to an AB strategy consisting of intravenous canreonate, an injectable MRB, followed by oral spironolactone for 30 days. They found that the AB strategy was well tolerated and was associated with a significant improvement in ventricular remodeling and collagen formation. The potential benefits of initiating AB therapy on day 1 post-MI will, however, require further testing, especially because of the negative experience with the early administration of intravenous ACEI post-MI.

AB during the first 30 days post-MI should be considered because early ICD implantation may be detrimental. The role of ICDs in reducing SCD in patients with SLVD after 30 days post-MI is not in dispute, as established by the results of the Second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). Yet in MADIT-II, in which the mean time of ICD implantation was 81 months post-MI, no reduction in SCD occurred during the first year post implantation. Moreover, The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), which tested the hypothesis that ICD placement during this early vulnerable period would be protective, found an excess of deaths due to an increase in noncardiovascular deaths during 1 year of follow up. Thus, while further exploration of the role of ICDs in the early post-MI setting continues, current guidelines do not recommend the insertion of an ICD in patients post-MI with SLVD before 30 days. The reason for the apparent failure of an ICD to reduce SCD during this early phase is unclear. On the basis of these observations, it would, however, appear prudent to treat patients with SLVD post-MI who otherwise qualify for implantation of an ICD with optimum pharmacological therapy, including a BB, ACEI and/or ARB, an MRB, and an ICD to provide both early and late protection from SCD.

In patients with chronic HF and SLVD associated with ventricular asynchrony, CRT has also been shown to be effective in reducing SCD. However, as yet no evidence exists for the effectiveness of CRT in reducing SCD early post-MI because such a study has not yet been performed. Given the beneficial effects of MRB on ventricular remodeling post-MI, we believe that the early administration of an MRB to prevent persistent SLVD and thus the need for an ICD and/or CRT in many patients should be evaluated. The development of promising stratification algorithms to determine which patients are most likely to benefit from ICDs, such as microvolt T-wave alternans, presents opportunities to test this hypothesis.

The Role of MRB in Reducing SCD in Patients With New York Heart Association Class II HF and SLVD
The role of MRB in reducing SCD in patients with mild HF and SLVD is less certain than in those with severe HF (New York Heart Association class III and IV). The role of the MRB eplerenone in patients with New York Heart Association class II HF and SLVD is currently being evaluated in a large scale, prospective, blinded, multicenter trial, the Effect of Eplerenone versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects With NYHA Class II Chronic Systolic Heart Failure (EMPHASIS-HF).

The Role of MRB in Reducing SCD in Patients With HF and Preserved Left Ventricular Systolic Function
Mounting evidence suggests that the incidence of HF associated with preserved left ventricular systolic function...
(HFPSF) is rising as a result of the aging of the population and the increasing epidemic of obesity and diabetes mellitus. In contrast to patients with chronic HF and SLVD, patients with HFPSF have not been shown to receive a reduction in either total mortality or SCD from pharmacological therapy. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity in Patients with Preserved Systolic Function (CHARM–Preserved Trial) suggested that the ARB candesartan may provide a benefit in reducing hospitalization for HF in these patients, but not in reducing total mortality or SCD. The role of the ARB irbesartan in patients with HFPSF is currently being explored in the Irbesartan in Patients with Heart Failure and Preserved Systolic Function trial (IPRESERVE). Whereas no data currently exist on the effectiveness of an MRB in reducing SCD in patients with HFPSF, spironolactone has been shown to improve diastolic function in patients with HFPSF and is currently being evaluated in a large-scale, prospective randomized multicenter trial sponsored by the National Heart, Lung, and Blood Institute, the Treatment of Preserved Systolic Function in Cardiac Failure with an Aldosterone Antagonist (TOPCAT). The resultant effects on SCD in this patient population will be eagerly awaited.

The Role of MRB in the Prevention of SCD in Patients Without SLVD or HF

The role of MRB in preventing SCD in patients without SLVD, such as those with essential hypertension accompanied by myocardial fibrosis and/or hypertrophy, is also promising but as yet unproven. Both myocardial fibrosis and hypertrophy predispose to SCD. MRB, as noted above, has been shown to be effective in reducing myocardial fibrosis and hypertrophy in experimental animal models as well as in patients with essential hypertension. Myocardial fibrosis increases electrical inhomogeneity of conduction and alters gap junction function. Ventricular hypertrophy as well as myocardial fibrosis is associated with a decrease in coronary flow reserve, which predisposes to myocardial ischemia and therefore SCD. Whereas, as yet, no large scale studies exist that demonstrate a benefit of MRB on SCD in patients with hypertension without SLVD or HF, an analysis of the EPHEUS data has suggested that almost all of the benefit of eplerenone in reducing SCD in patients with SLVD and HF post-MI may have occurred in those patients with a history of hypertension, even though they were not hypertensive at the time of their MI. The explanation for the benefit of MRB in these patients is uncertain but may relate to prevention of detrimental electrical remodeling associated with an increase in MR activity (see Mechanisms by Which MRB Reduces SCD below).

MRB may also play a role in preventing SCD in patients with obstructive coronary artery disease but without structural abnormalities of the ventricle. MRB has been shown to improve endothelial function in an experimental model of hyperlipidemia, and MRB has been shown to be effective in preventing the development of experimental atherosclerosis in the ApoE knockout mouse as well as in a primate model of atherosclerosis. Thus, although not as yet proven, the effectiveness of MRB in the primary prevention of SCD can be postulated both for patients without SLVD but with structural abnormalities of the ventricle (such as fibrosis and hypertrophy) and for patients with obstructive coronary artery disease or ischemia without structural abnormalities of the ventricle.

Mechanisms by Which MRB Reduces SCD

Although MRB affects a number of mechanisms associated with SCD, it is unlikely that any single mechanism explains its benefits in reducing SCD in patients with chronic HF and SLVD, as well as in patients with SLVD and HF post-MI. Under certain circumstances, one or another of the mechanisms reviewed below may be of particular importance.

Aldosterone has been shown to increase tissue ACE expression and to upregulate the AT1 receptor. Thus, in HF or in the post-MI setting, an increase in serum aldosterone levels may lead to an increase in the concentration and effect of angiotensin II on the AT1 receptor, resulting in a vicious cycle, with activation of the renin-angiotensin-aldosterone system and a further production of aldosterone by the adrenal gland. Because angiotensin II is a major stimulus for the production of aldosterone from the adrenal gland, one might conclude that the use of an ACEI and/or ARB would decrease aldosterone levels and eliminate the need for an MRB. Other stimuli, such as the extracellular concentration of potassium, are also of importance. For example, in angiotensinogen knock-out mice, in which no angiotensin II is present, an increase in serum sodium with a consequent decrease in serum potassium significantly raises aldosterone levels. Although an ACEI and/or ARB may transiently suppress the production of aldosterone, over time aldosterone production “escapes” and the serum aldosterone level increases.

Whereas activation of MR is important in regulating renal sodium, potassium, and magnesium concentration in the distal renal tubule, it is also of importance in a number of other tissues that express MR, including the myocardium, vascular wall, glomerulus, and brain. In HF, expression of MR in the myocardium increases. Furthermore, cortisol may also activate the MR in several tissues, such as the renal tubule and vascular wall. These tissues, however, express the enzyme 11β-hydroxysteroid dehydrogenase-2 that regulates the conversion of cortisol to cortisone, which cannot stimulate the MR.

In situations in which reactive oxygen species increases, such as in HF and hypertension, 11β-hydroxysteroid dehydrogenase-2 may be downregulated, thereby preventing the conversion of cortisol to cortisone. The consequent increase in cortisol may activate the MR. In the cardiomyocyte, which does not express 11β-hydroxysteroid dehydrogenase-2, the MR may be normally occupied but not activated by cortisol. With increased reactive oxygen species generation, however, the cortisol-MR
complex is activated through unknown mechanisms.\textsuperscript{35} Aldosterone has also been shown to downregulate the enzyme glucose-6-phosphate dehydrogenase, resulting in a decrease in antioxidant reserve and an increase in reactive oxygen species,\textsuperscript{36} which could result in activation of the MR.

Activation of the MR also may directly affect the electrical properties of the ventricle, providing a substrate for arrhythmias and SCD. In a mouse model, conditional cardiac-specific overexpression of the MR led to fatal arrhythmias.\textsuperscript{37} Several factors may contribute. In these mice, the ventricular action potential was prolonged, a harbinger of arrhythmogenesis and an independent risk factor for SCD in HF patients.\textsuperscript{2} In a rat post-MI model, canrenone, the active metabolite of spironolactone, decreased the ventricular fibrillation threshold.\textsuperscript{38} At the tissue level, activation of the MR results in potassium loss, as well as apoptosis, fibrosis, hypertrophy, and central sympathetic nervous system activation.\textsuperscript{39–41} The increase in myocardial fibrosis and resultant ventricular remodeling could promote electrical inhomogeneity and a propensity to ventricular arrhythmias. At the cellular level, aldosterone has been demonstrated to alter the expression of several different ion channels that contribute to the regulation of the cardiac action potential. These resultant changes in the cardiac action potential may also be important contributors to arrhythmogenesis. For example, aldosterone has been shown to cause a dose-dependent increase in the expression of the gap junction protein connexin-43 in cultured rat ventricular myocytes and a concomitant change in conduction velocity.\textsuperscript{42} Aldosterone also affects the levels of several different ionic currents in a manner that consistently results in prolongation of the ventricular action potential. Activation of the MR has been shown to cause an increase in the inward calcium channel current, $I_{\text{Ca}}$.\textsuperscript{43} These changes occur within 1 week of MI, before any morphological changes in the ventricle, and can be prevented by MRB. Aldosterone also decreases $I_{\text{to}}$, the transient outward K$^+$ current.\textsuperscript{43} Interestingly, a decrease in $I_{\text{to}}$ has consistently been found in myocytes from HF patients or in animal models of HF.\textsuperscript{2} Either of these changes, an increase in the calcium current or a decrease in $I_{\text{to}}$—or both together—would prolong the cardiac action potential. Consistent with these findings, MR overexpression in cardiac myocyte causes ion channel remodeling, resulting in prolonged ventricular repolarization that is associated with an upregulation of $I_{\text{Ca}}$ and a downregulation of $I_{\text{to}}$, resulting in severe ventricular arrhythmias.\textsuperscript{37} Administration of aldosterone also increases the expression of cardiac sodium channels.\textsuperscript{44} Whereas the mechanism by which this mode of regulation could contribute to arrhythmogenesis is not clear, it offers a hint of what might underlie the arrhythmogenesis of BrS, an inheritable disorder characterized in many individuals by a haploinsufficiency of SCN5A, the gene for the major cardiac sodium channel.\textsuperscript{45} Interestingly, these patients usually do not experience SCD until adulthood, suggesting the contribution of additional factors to arrhythmogenesis. Thus, the report that SCD in these individuals may be associated with the development of myocardial fibrosis\textsuperscript{46} and an animal model which showed that myocardial fibrosis can be associated with a loss of function of SCN5A\textsuperscript{47} raises the intriguing possibility that sodium channel expression and aldosterone levels may be linked in a feedback loop so that the decrease in sodium channels in BrS patients leads to a compensatory increase in aldosterone production and consequent fibrosis.\textsuperscript{48} Thus, although the effect is not as yet proven, it can be postulated that early administration of an MRB to an individual with BrS will protect against the subsequent development of myocardial fibrosis and thus SCD.

Activation of the MR has also been shown to block norepinephrine uptake into the myocardium, which is associated with an increase in circulating norepinephrine levels and ventricular arrhythmias.\textsuperscript{49} MRB, in contrast, improves the uptake of norepinephrine into the myocardium and decreases ventricular arrhythmias. MRB also improves parasympathetic activity, as indicated by improved heart rate variability, QT dispersion, and baroreceptor function.\textsuperscript{39,50,51} These changes are also associated with an increase in NO availability, which can affect the release of norepinephrine from sympathetic nerve terminals and parasympathetic activity as well as endothelial and platelet function.\textsuperscript{52,53} MRB has also been shown to decrease plasminogen activator inhibitor-1 levels, improve fibrinolysis, and prevent thrombosis.\textsuperscript{54,55} Depending on circumstances, one or another of these mechanisms may be of particular importance in preventing SCD. The benefits of MRB in terms of preventing SCD early post-MI are more likely due to their effects on electrical remodeling of the myocardium, whereas the effects on ventricular remodeling, collagen formation, and hypertrophy may be of equal or greater importance in preventing SCD in patients with HF and SLVD over the long term.

The Risk of MRB Causing Hyperkalemia

Whereas MRB has been proven to reduce SCD in patients with severe HF and SLVD, as well as in patients post-MI with SLVD and HF, many clinicians have been reluctant to use an MRB because of the fear of inducing serious hyperkalemia. In both the RALES\textsuperscript{5} and EPHESUS\textsuperscript{7} studies, patients randomized to an MRB had a reduction in SCD and total mortality without any deaths attributable to hyperkalemia. However, since publication of RALES,\textsuperscript{5} a number of reports have appeared showing that the use of spironolactone in clinical practice resulted in a marked increase in the incidence of hyperkalemia associated in some circumstances with renal failure and/or death.\textsuperscript{56–59} A review of these reports reveals that many of these episodes of hyperkalemia were due to the use of higher doses of spironolactone than the 12.5 to 50 mg/d used in RALES\textsuperscript{5} and that many deaths occurred in patients with severe renal dysfunction (estimated GFR <30 mL/min) and/or a serum potassium >5.0 mEq/L. A solution to this problem may be to encourage physicians to measure serum potassium either before starting a patient on spironolactone and/or during follow up. In both RALES\textsuperscript{5} and EPHESUS,\textsuperscript{7
serum potassium was measured before considering the use of an MRB, and if serum potassium was $>$5.0 mEq/L the MRB was withheld. Serum potassium was measured during the first week after starting an MRB, at 1 month, and every 3 to 6 months thereafter. In patients with chronic kidney disease, monitoring of serum potassium should be more frequent. Similarly, if a change in serum electrolyte status is suspected, such as after an episode of vomiting or diarrhea or after adding a drug that might affect potassium excretion, serum potassium should be remeasured. If serum potassium is $>$5.5 mEq/L, the dose of the MRB should be halved, and if $>$6.0 mEq/L in a nonhemolyzed sample, the MRB should be withheld until the serum potassium returns to $<$5.0 mEq/L.

It should be pointed out that hyperkalemia (defined as a serum potassium $>$5.5 mEq/L) and especially “serious” hyperkalemia (serum potassium $>$6.0 mEq/L), although a matter of concern, may not necessarily be associated with any serious consequences. Recent data emphasize that serum potassium concentration is not a good indicator of myocardial tissue potassium levels. In patients with HF treated with drugs affecting the transport of potassium into the myocardial tissues such as digoxin, ACEI, ARBs, BBs, or non-steroidal anti-inflammatory agents there may be a defect in transporting potassium into tissues. In some cases, a serum potassium concentration of $>$7.0 mEq/L may not be accompanied by any ECG or clinical manifestations of hyperkalemia if the tissue potassium concentration, as reflected by red blood cell potassium concentration and ionized calcium concentration, are normal. Because the determination of red blood cell potassium concentration is not yet routinely available, it would be prudent to minimize the potential risks of hyperkalemia associated with MRB by eliminating, if possible, any drugs such as potassium supplements or nonsteroidal anti-inflammatory agents that could contribute to hyperkalemia, to prescribe a low-potassium diet, to monitor serum potassium and the ECG serially, and to discontinue the MRB if any ECG and/or clinical manifestations of hyperkalemia appear.

The situation with regard to the use of an MRB to prevent SCD and the risk of hyperkalemia may be analogous to the use of warfarin in a patient to prevent thromboembolism and the risk of serious bleeding. When the international normalized ratio is closely monitored during the initiation of warfarin and the dose adjusted periodically according to this ratio, the risk of serious bleeding can be minimized while preventing thromboembolism. One would consider it malpractice if a patient had a serious bleeding episode while on warfarin and the international normalized ratio had not been measured. Similarly, physicians who elect to prescribe an MRB should be obligated to monitor serum potassium and the ECG.

In conclusion, MRB has been shown to play an important role in the primary prevention of SCD in patients with severe chronic HF and SLVD, as well as in patients with SLVD and HF post-MI. It is likely, but not as yet proven, that MRB will also prevent SCD in patients with mild HF and SLVD or HFPSF, as well as in patients without SLVD or HF, including those with hypertension and myocardial fibrosis and/or hypertrophy and ischemic heart disease, as well as in other conditions associated with myocardial fibrosis and/or hypertrophy, such asortic stenosis, diabetes mellitus, and BrS. Although hyperkalemia is a potential risk, with careful patient selection on the basis of renal function, serial monitoring of serum potassium and the ECG, and appropriate adjustment of the dose of the MRB in response to these factors, it is likely that the benefits of MRB in reducing SCD should far outweigh its potential risks. This hypothesis will, however, require further prospective evaluation in large scale randomized trials.

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References


The 2 MADIT trials that we described in our article unequivocally show that patients with remote myocardial infarctions (>3 to 4 weeks) and reduced left ventricular ejection fraction demonstrated a reduction in total mortality and sudden death with automatic implantable cardioverter-defibrillators. In contrast, in the DINAMIT study patients with recent acute myocardial infarctions (6 to 40 days) and reduced left ventricular function did not demonstrate a reduction in total mortality but did demonstrate a decrease in sudden cardiac death with implantable cardioverter-defibrillator therapy. In the EPHESUS study, eplerenone given early after myocardial infarction (3 to 14 days after myocardial infarction, with an average of ≈7 days) reduced total mortality (but only by ≈15%) and decreased sudden cardiac death in patients with compromised ventricles. We agree with Pitt and Pitt that in the early post–myocardial infarction phase, patients with reduced cardiac function benefited from an aldosterone antagonist. However, existing data do not yet support the administration of this agent specifically to postinfarction patients with left ventricular dysfunction after 2 weeks of infarction with or without concomitant implantable devices. Thus, beyond this time, while it is known that implantable cardioverter-defibrillators reduce total mortality and can be considered first line therapy for preventing sudden death, information on administration of aldosterone antagonists starting during the later phase of myocardial infarction is missing, and therefore these agents cannot be considered primary therapy for preventing sudden cardiac death. It is clear that more research into the interaction (or lack of interaction) between implantable cardioverter-defibrillator and/or cardiac resynchronization devices and pharmacological agents such as aldosterone antagonists is needed, both in the early and late phases after acute infarction. Furthermore, the same type of research on device–drug interaction is needed for patients with congestive heart failure due to any cause, including nonischemic dilated cardiomyopathy.
Uncertainty on the Use of Aldosterone Antagonists for Primary Therapy for Sudden Cardiac Death in the Setting of Implanted Devices

Robert A. Kloner, MD, PhD; David S. Cannom, MD

In the early development of therapy for acute myocardial infarction, it was thought that once the necrotic process had been completed (usually within 24 hours of coronary artery occlusion), additional therapies could not affect outcome. However, after completion of the necrotic process, the myocardial infarction may thin and stretch (involving lengthwise slippage of myocytes), a phenomenon referred to as myocardial infarct expansion. This process causes local left ventricular cavity dilatation followed by gradual global left ventricular dilatation and lengthwise (eccentric) hypertrophy of the noninfarcted tissue. Apoptosis (programmed cell death) and some attempt of the myocardium to regenerate, especially at the infarct border zone, may also contribute to this remodeling process of the ventricle. If the left ventricle remodels in such a way that it becomes very dilated, then the prognosis is poor, and heart failure is more likely to occur. These later processes of myocardial infarct expansion and left ventricular remodeling became the target of therapies such as angiotensin-converting enzyme (ACE) inhibition that could be initiated after 24 hours of coronary occlusion. ACE inhibition, angiotensin receptor blockade, and long-term β-blockade have become standard pharmacological approaches for postinfarction left ventricular dysfunction and heart failure.

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Ventricular arrhythmias can occur in both the acute and chronic phases of acute myocardial infarction and can lead to sudden cardiac death (SCD). Reentrant arrhythmias may arise at the border zone of infarcts, causing monomorphic ventricular tachycardia that may occur years after the index infarction. Recurrent myocardial ischemia resulting in an unstable substrate may contribute to polymorphic ventricular tachycardia or ventricular fibrillation. Agents such as β-blockers that are anti-ischemic may reduce sudden death by quieting this unstable substrate. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II, implantable defibrillators were shown to reduce mortality in post–myocardial infarction patients with left ventricular dysfunction entirely due to a reduction in SCD. It is likely that these devices did not primarily improve the arrhythmic substrate. However, long-term cardiac resynchronization will encour-
age reverse remodeling that might reduce the substrate for arrhythmia.

**ACE Inhibitors and Angiotensin Receptor Blockers After Myocardial Infarction**

In the now classic study by Pfeffer et al., captopril administered long-term, starting within about the first few weeks of myocardial infarction, decreased total mortality, congestive heart failure, and recurrent myocardial infarction. Echocardiographic analysis demonstrated that captopril reduced diastolic dilatation at 2 years, suggesting a decrease in deleterious left ventricular remodeling. Other studies confirmed that long-term administration of an ACE inhibitor improved cardiac outcome after myocardial infarction. Benefits of long-term therapy with the angiotensin receptor blocker valsartan were also reported to benefit post–myocardial infarction patients with left ventricular dysfunction. Valsartan was shown to result in similar but not superior effects on survival compared with captopril in the Valsartan in Acute Myocardial Infarction (VALIANT) study. Furthermore, treatment with captopril plus valsartan resulted in no advantage over treatment with either agent alone. In a head-to-head comparison of the ACE inhibitor captopril with the angiotensin receptor blocking agent losartan in patients with acute myocardial infarction and evidence of heart failure or left ventricular dysfunction, captopril was associated with a nonsignificantly lower all-cause mortality and a significantly lower cardiovascular mortality compared with losartan, but losartan was better tolerated than captopril. Some of these studies demonstrated less ventricular arrhythmias when an ACE inhibitor was used.

**β-Blockers After Myocardial Infarction**

Another class of drugs that has been shown to reduce mortality after acute myocardial infarction is the β-blockers. The landmark Beta-Blocker Heart Attack Trial (BHAT) tested the effect of long-term propranolol therapy in patients after a myocardial infarction. More than 3800 patients were randomized to either propranolol (180 to 240 mg/d maintenance dose) or placebo starting 5 to 21 days after myocardial infarction and were followed up for ≈2 years. Total mortality was 7.2% in the propranolol group and 9.8% in the placebo group (26% reduction). Sudden cardiac death occurred in 3.3% of the propranolol patients versus 4.6% of the placebo patients (28% reduction). A subset of 826 of these patients also had paired ambulatory ECG monitoring at baseline and after 6 weeks of therapy. An increase in ventricular arrhythmias over the 6-week period was blunted by propranolol. Some but not all studies in which other β-blockers were administered after myocardial infarction showed a reduction in SCD. Hjalmarson postulated that the more lipophilic β-blockers (timolol, metoprolol, propranolol) were more likely to demonstrate this benefit because they could penetrate the brain and maintain high vagal tone during stress, thus reducing ventricular fibrillation. Of course, it is also possible that the β-blockers are primarily reducing postinfarction ischemia, which would explain why they are antiarrhythmic.

Although these findings represented a major advance, as pointed out by Fonarow et al., many of the earlier studies with β-blockers did not include patients with heart failure. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study determined the effects of carvedilol added to standard therapy (including ACE inhibitors) for patients with an acute myocardial infarct who had an ejection fraction <0.40. More than 1900 patients with a mean ejection fraction of 0.33 were randomized to placebo or carvedilol and followed up for 15 months. Total mortality was reduced from 15.3% in the placebo group to 11.9% with carvedilol. SCD was reduced as well (Table 1). In the CAPRICORN study, sudden death occurred in 5% of carvedilol patients versus 7% of placebo patients (P=0.098).

**Aldosterone Antagonists After Myocardial Infarction**

What is known about the use of aldosterone blockers in patients with myocardial infarction and postmyocardial dysfunction? The crucial study is the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) study by Pitt et al. The EPHESUS trial was a double-blind, placebo-controlled study of the selective aldosterone blocker eplerenone, examining morbidity and mortality in post–myocardial infarction patients with heart failure and left ventricular dysfunction (left ventricular ejection fraction of ≤40%). Therapy was started 3 to 14 days after acute myocardial infarction, and patients received placebo (n=3319) or eplerenone (25 mg/d; n=3313) for 4 weeks.

<table>
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<th>Drug</th>
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<td>ACE inhibitor</td>
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<td>Spironolactone</td>
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<td>Eplerenone</td>
<td>EPHESUS: acute MI (3–14 days), LVEF ≤:0.40</td>
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<td>0.79 (0.64–0.97)</td>
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Table 1. Recent Key Randomized Controlled Trials of Nonantiarrhythmic Drugs and Effect on SCD

MI indicates myocardial infarction; HOPE, Heart Outcomes Prevention Evaluation; LVEF, left ventricular ejection fraction; and CHF, congestive heart failure.

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after which the dose was increased to 50 mg/d. If the potassium concentration was $>5.5$ mmol/L, the dose of study drug was reduced or treatment stopped temporarily. Patients were already on standard optimal medical therapy including ACE inhibitors, angiotensin receptor blockers, β-blockers, diuretics, and reperfusion therapy. Follow-up was for 16 months. Fewer patients died in the eplerenone group (478; 14.4%) than in the placebo group (554 patients; 16.7%; relative risk [RR]=0.85; 95% confidence interval [CI], 0.75 to 0.96; $P=0.008$). Death due to cardiovascular causes occurred in 407 patients in the eplerenone group versus 483 patients in the placebo group (RR=0.83; 95% CI, 0.72 to 0.94; $P=0.005$). Sudden death from cardiac causes occurred in 162 of the eplerenone group versus 201 in the placebo group (RR=0.79; 95% CI, 0.64 to 0.97; $P=0.03$). Death from cardiovascular causes or hospitalization for cardiovascular events, death from any cause or any hospitalization, and hospitalization for heart failure were also reduced by eplerenone. At 1 year, potassium levels increased by 0.2 mmol/L in placebo-treated patients versus 0.3 mmol/L in the eplerenone group ($P<0.001$). Serious hypokalemia (potassium $<3.5$ mmol/L) occurred in 8.4% of eplerenone patients versus 13.1% in the placebo group ($P<0.001$). Hyperkalemia, with a serum potassium level $\geq 6.0$ mmol/L, occurred in 5.5% of eplerenone-treated versus 3.9% of placebo-treated patients ($P=0.002$). Twelve patients in the eplerenone group versus 3 in the placebo group were hospitalized for the condition; 1 patient in the placebo group died of the condition.

A number of proposed mechanisms for the reduction in mortality in the eplerenone group were suggested, including effects of eplerenone on plasma volume and electrolyte excretion, reductions in coronary vascular inflammation, improvements in endothelial function, attenuation of platelet aggregation, improvements in ventricular remodeling with a decrease in activation of matrix metalloproteinases, and a decrease in interstitial fibrosis. Besides these direct effects on the vasculature and myocardium, the authors pointed out that aldosterone blockade decreased sympathetic drive in experimental animal studies, improved norepinephrine uptake in heart failure victims, and improved heart rate variability.

One of the simplest explanations for the benefit of eplerenone in reducing sudden death is its prevention of hypokalemia, a known trigger of ventricular arrhythmias, especially in patients also taking digitalis preparations. In a letter to the editor, Coca and Buller raised the issue that the 21% decrease in the rate of sudden death from cardiac causes associated with eplerenone in the EPHESUS trial may have been attributable to the reduction of hypokalemia. However, Pitt responded that “a preliminary analysis of data from EPHESUS reveals a significant reduction in the risk of sudden death from cardiac causes, which is independent of the effects of eplerenone in preventing hypokalemia.” It is still conceivable that some of the benefit of eplerenone in reducing sudden death was related to preventing hypokalemia. Subsequent analyses revealed that eplerenone reduced the risk of sudden death by 33% in patients with baseline left ventricular ejection fraction of $\leq 30\%$ and that eplerenone reduced the early incidence of sudden death by 37% within 30 days of randomization in this trial.

Although the results show that eplerenone reduced sudden death in the post–myocardial infarction patients with left ventricular dysfunction, many questions in this field remain unanswered. Was this benefit primarily due to a reduction in hypokalemia? Would eplerenone provide this benefit to patients with heart failure but not in the post–myocardial infarction setting? Would eplerenone benefit patients with heart failure who had automatic implantable defibrillators and/or patients with biventricular pacing for cardiac resynchronization therapy?

**Aldosterone Antagonists in Patients With Chronic Heart Failure**

The RALES (Randomized Aldactone Evaluation Study) was a double-blind, randomized study of 1663 patients with severe heart failure and a left ventricular ejection fraction $\leq 35\%$ who were already on an ACE inhibitor, a loop diuretic, and in many cases digoxin. Patients were randomized to 25 mg of the aldosterone antagonist spironolactone (n=822) versus placebo (n=841). The study was stopped at 24 months with 386 deaths (46%) in the patients receiving placebo versus 284 deaths (35%) in the spironolactone group (RR of death=0.70; 95% CI, 0.60 to 0.82; $P<0.001$). Spironolactone was associated with a lower risk of death from progressive heart failure as well as a lower rate of sudden death. Sudden death due to cardiac cause occurred in 82 of 822 spironolactone-treated patients versus 110 of 841 placebo-treated patients (RR=0.71; 95% CI, 0.54 to 0.95; $P=0.02$). Spironolactone also reduced all cardiac causes for hospitalization as well as hospitalization for worsening heart failure. The median potassium concentration increased by 0.30 mmol/L in the spironolactone group but did not increase in the placebo group. Serious hyperkalemia was observed in 10 placebo patients (1%) and 14 spironolactone patients (2%; $P=\text{NS}$).

Again, although the exact mechanism by which the aldosterone antagonist reduced SCD in RALES is unknown, prevention of hypokalemia cannot be ruled out entirely, despite the rather small increase in potassium levels in the treated group. In addition, it is unknown whether spironolactone could also reduce sudden death in post–myocardial infarction patients with left ventricular dysfunction with or without clinical congestive heart failure or in patients already receiving automatic implantable cardioverter-defibrillators (ICDs) and/or biventricular pacing for resynchronization therapy.

A small study by Ramires et al randomized 35 patients with class III congestive heart failure due to dilated or ischemic cardiomyopathy and mean ejection fraction of 33% to spironolactone in addition to standard medical therapy for
benefit: failure (as well as hypertension) have demonstrated this is most likely.

Antagonists to date do not clarify which of these mechanisms in ventricular remodeling). The studies with the aldosterone substrate (for example, an anti-ischemic effect or a reduction venting hypokalemia), or due to a change in the cardiac antiarrhythmic, indirectly antiarrhythmic (for example, pre- lation). A possible explanation for the reduced frequency of ventricular arrhythmia could be related to electrolyte regulation promoted by spironolactone in combination with ACE inhibitors.” They described the concern that hypokale-mia could have contributed to increased arrhythmias in the setting of digoxin, which was then corrected by the aldoste-rome antagonist.

Clinical trials are currently lacking of patients with chronic heart failure (not related to the postinfarct setting) who received eplerenone. Table 1 summarizes some recent key randomized trials of nonantiarrhythmic drugs and their effect on SCD.26 Several agents used for the treatment of heart failure (as well as hypertension) have demonstrated this benefit: β-blockers, ACE inhibitors, and aldosterone antagonists. Again, a host of mechanisms have been postulated, including improvements in ventricular remodeling and endothelial function, a reduction in sympathetic tone, and improved electrolyte balance, including less hypokalemia with ACE inhibitors and aldosterone antagonists.

For all the aforementioned studies, the assessment of whether the precise cause of death is arrhythmic or due to heart failure, recurrent infarction, or other causes is very difficult. The ICD randomized trials have used total mortality as the end point precisely because retrospective analysis of an individual death is so difficult. Therefore, studies with β-blockers, ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists that claim to demonstrate a reduction in sudden death need to be interpreted cautiously and with the realization that all deaths, in a sense, are sudden. It is feasible that the mechanisms of benefit of agents including eplerenone and spironolactone may be directly antiarrhythmic, indirectly antiarrhythmic (for example, preventing hypokalemia), or due to a change in the cardiac substrate (for example, an anti-ischemic effect or a reduction in ventricular remodeling). The studies with the aldosterone antagonists to date do not clarify which of these mechanisms is most likely.

Aldosterone Antagonists in ICD and Cardiac Resynchronization Trials
The primary prophylactic ICD trials were initiated in the early 1990s at the same time that new data were emerging on the importance of β-blockers and ACE inhibitors in the prevention of SCD in patients with low ejection fraction.27–31 As is noted in Table 2, use of β-blockers and ACE inhibitors increased over time but was quite low in both the MADIT I and Multicenter Unsustained Tachycardia Trial (MUSTT) when these therapies had not reached wide acceptance.32–39 The use of spironolactone antagonists was very sparing in the ICD trials except for the Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION) trial, which was conducted by heart failure specialists. It is of interest that, as the medical therapy in these trials improved, the degree of superiority of the ICD over conventional therapy declined (from MADIT I32 to Sudden Cardiac Death in Heart Failure [SCD-HeFT]),38 suggesting that survival in both arms in these trials improves as a result of contemporary background medical therapy. In all the trials except 2 (Cor- onary Artery Bypass Graft [CABG] Patch33 and the Defibril-lator in Acute Myocardial Infarction Trial [DINAMIT]), the ICD demonstrated a survival advantage over best medical therapy. In the Defibrillators in Non-Ischemic Cardiomyop athy Treatment Evaluation (DEFINITE) trial,39 implantation of ICDs into patients with nonischemic dilated cardiomyop athy and already on ACE inhibitors and β-blockers resulted

**TABLE 2. Therapies According to Treatment Assignment in the Primary Prophylactic ICD Trials**

<table>
<thead>
<tr>
<th>Study and Groups</th>
<th>ACE Inhibitor</th>
<th>Digoxin</th>
<th>β-Blocker</th>
<th>Spironolactone</th>
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<td>42</td>
<td>84</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are percentage of patients. NA indicates not applicable. *Spironolactone/potassium-sparing diuretics.
in a nonsignificant trend toward a reduction in death from any cause and a significant decrease in sudden death.

To conclusively determine whether aldosterone antagonists confer additional benefit on reducing SCDs in patients with ICDs, one would need to design a study in which patients with ICDs (and preferably a group without ICDs as well) were randomized to aldosterone antagonists versus placebo in addition to the usual heart failure medicines. Unfortunately, and to the best of our knowledge, such a study has not been performed. We have been able to obtain some observational retrospective data from MADIT II and the COMPANION trial that address this issue to some extent. We briefly present our findings, realizing that limitations exist that must be kept in mind when these data are viewed. The limitations of this analysis include the following: a lack of randomization for the use of spironolactone; a relatively small number of patients who were assigned to spironolactone, which resulted in the studies not being powered to definitely answer the question about a benefit of aldosterone antagonists in patients already treated with ICD, cardiac resynchronization therapy [CRT], or both; the possible presence of a type II or β error; and the possibility of confounding biases. For example, patients assigned to spironolactone may have been sicker. The analyses below are retrospective and must be considered exploratory and hypothesis generating, not definitive. However, when we were assigned the topic of presenting the “con” side of the aldosterone antagonist argument by Circulation, we tried to find all available data on this concept. Therefore, we briefly present our findings below, and we are not aware of more definitive data at the time of this writing.

Although there has been little use of spironolactone in the ICD trials, the MADIT II Investigators have kindly provided new data on the issue of the possible effects of spironolactone in this trial (S. McNit, MS, and J. Hall, PhD, written communication, 2006). MADIT II was a study of 1232 patients assigned to spironolactone may have been sicker. The analyses below are retrospective and must be considered exploratory and hypothesis generating, not definitive. However, when we were assigned the topic of presenting the “con” side of the aldosterone antagonist argument by Circulation, we tried to find all available data on this concept. Therefore, we briefly present our findings below, and we are not aware of more definitive data at the time of this writing.

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At study commencement (in which patients were randomized in a 3:2 ratio to ICD versus conventional therapy), 101 patients (13.6%) randomized to ICD treatment were receiving spironolactone, and 57 (11.6%) in the conventional arm were receiving this drug. Spironolactone use was analyzed as a time-varying risk factor in proportional hazards regression analysis of the various end points in MADIT II. Because of the clinical suspicion that spironolactone may have been used as a result of a hospitalization for heart failure, the first occurrence of heart failure was also used as a time-dependent factor.40 The HR for all-cause mortality for patients while on spironolactone compared with patients and periods not on spironolactone was 1.13 (P = 0.53). Thus, no overall effect of spironolactone use on all-cause mortality was found in MADIT II. The HR for spironolactone for all-cause mortality in the conventional medical arm was 1.43 versus 0.90 in the ICD arm (P = 0.23 for difference).

The HR for spironolactone for sudden death in the conventional arm was 1.13 (P = 0.76). The HR for spironolactone for first appropriate shock in the ICD arm was 1.51 (P = 0.07). The HR for spironolactone for either first appropriate shock or death in the ICD arm was 1.20 (P = 0.34). Most of the HRs for spironolactone exceeded unity, suggesting a trend toward an increased risk of the end point occurring when the patients were on the drug relative to being off the drug. However, drug usage could be a proxy for heart failure risk or severity of heart failure. In summary, on the basis of a retrospective analysis, the MADIT II trial produces no evidence that spironolactone provides a benefit.

Supporting evidence is provided by the COMPANION trial along similar lines. The COMPANION trial randomized >1500 New York Heart Association class III/IV heart failure patients with a prolonged QRS and ejection fraction ≥35% to optimal medical therapy, optimal medical therapy plus CRT, or optimal medical therapy plus CRT plus an ICD. Both CRT and CRT plus an ICD reduced combined all-cause mortality and hospitalization in heart failure patients. CRT plus an ICD reduced all-cause mortality; CRT alone had a trend toward reduced mortality.

In the COMPANION trial, 55% of patients were treated with spironolactone, and this was not associated with risk of death in any treatment group and did not protect against appropriate shocks in the patients with CRT plus an ICD. However, β-blockers and ACE inhibitors did afford such protection (L. Saxon, MD, written communication, 2006, and Saxon et al41).

**Summary**

In summary, recent studies have shown the usefulness of eplerenone for post–myocardial infarction patients with heart failure and spironolactone for patients with chronic congestive heart failure. In these 2 studies (which lacked use of ICDs), the aldosterone antagonists reduced SCD. There are a number of potential explanations for the mechanism of this benefit, including protection against hypokalemia. In recent retrospective analyses of MADIT II and COMPANION trials of patients with left ventricular dysfunction/heart failure in which ICDs were used, no evidence was provided that spironolactone afforded a survival benefit or reduced the need for appropriate ICD shocks. Aldosterone antagonists may still benefit heart failure patients who have ICDs independently of...
reduction of arrhythmias, for example, by reducing heart failure symptoms and/or hospitalizations. Thus, if patients with heart failure on spironolactone receive an ICD, we do not suggest that the spironolactone be stopped. Should an aldosterone antagonist be added for patients with severe heart failure who already have a defibrillator? In this case, spironolactone may reduce heart failure symptoms, but whether spironolactone will further reduce total mortality or sudden death is uncertain. Prospective, adequately powered, randomized, blinded trials are needed to examine the interaction or possibly the lack of interaction between ICD, CRT, and both with the aldosterone antagonists. Specifically, a study is needed in which patients who are already on standard medical therapy plus ICD, CRT, or both are randomized to an aldosterone antagonist versus placebo to determine whether this class of drugs further reduces mortality, SCD, and hospitalizations for heart failure. Unfortunately, we think it is unlikely that any agency or industry would fund such a study, and therefore it is possible that a definite answer to whether aldosterone antagonists confer benefits in addition to those of implantable devices alone may never be known.

Disclosures

Dr Kloner is a consultant and speaker for Pfizer. Dr Cannom is a consultant and speaker for Medtronic and Boston Scientific.

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Response to Kloner and Cannom

Bertram Pitt, MD, and Geoffrey S. Pitt, MD, PhD

Drs Kloner and Cannom suggest that reduction of sudden cardiac death (SCD) with mineralocorticoid receptor blockade is attributable to prevention of hypokalemia. Review of EPHEUSUS, however, does not show any relationship between reduction in total mortality or SCD and serum K⁺. Rather, as we noted, the reduction in SCD could be attributed to a mineralocorticoid receptor blockade (MRB)–induced increase in tissue K⁺, which may not be reflected by serum K⁺. We agree that the mechanisms by which MRB reduced SCD in RALES and EPHEUSUS have not been elucidated. As for β-blockers and angiotensin-converting enzyme inhibitors, these protective mechanisms are speculative. While Drs Kloner and Cannom note that retrospective analyses of COMPANION and MADIT II did not show a benefit of MRB in reducing SCD or inappropriate shocks, we must point out that these trials were not powered to examine these effects. Furthermore, we propose that the major benefit of MRB is the primary prevention of SCD. But for MRB, which reduced total mortality within 30 days after myocardial infarction in EPHEUSUS, it is likely that many patients who would qualify for an implantable cardioverter-defibrillator would not have survived to receive it because implantable cardioverter-defibrillators do not reduce mortality when implanted <30 days after a myocardial infarction, nor for ≈1 year when they are implanted >30 days after a myocardial infarction. We agree that definitive demonstration of a role for MRB in reducing SCD in patients with implantable cardioverter-defibrillators can only be provided by a randomized clinical trial.
Uncertainty on the Use of Aldosterone Antagonists for Primary Therapy for Sudden Cardiac Death in the Setting of Implanted Devices
Robert A. Kloner and David S. Cannom

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