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Scientific Update™

Survival Benefits of Aldosterone Blockade: Expanding the Standard of Care for Congestive Heart Failure Post-Myocardial Infarction

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Patients who suffer myocardial infarctions (MIs), complicated by left-ventricular (LV) systolic dysfunction and/or heart failure (HF), experience very high 1-year mortality (eg, sudden death) despite contemporary management strategies that include revascularization, angiotensin-converting enzyme (ACE) inhibition, blockade of angiotensin and aldosterone receptors, and β-blockade. As a result, physicians who manage these patients are frequently confronted with urgent treatment decisions that must be made to improve clinical outcomes. Eplerenone, a specific aldosterone-receptor blocker, has been demonstrated to reduce all-cause mortality and morbidity early in this group of patients with MI. This issue of *Cardiology Scientific Update* reviews the role of aldosterone-receptor blockade in the management of high-risk patients with MI complicated by HF.

Urgency to treat patients earlier in the post-MI paradigm

Acute MI remains a significant public health problem worldwide.[1] Despite improved therapies and process of care, LV systolic dysfunction and HF remain common complications of acute MI and are associated with increased mortality and morbidity in these patients.[2-5] In the Global Registry of Acute Coronary Events (GRACE) study,[4] a prospective evaluation of patients hospitalized with acute coronary syndrome (ACS), the development of HF as a complication in ACS was associated with adverse clinical outcomes. The incidence and mortality rate of HF according to the type and timing of ACS are indicated in Figure 1. HF presence on admission was observed in 13% of patients and was associated with a marked increase in mortality during hospitalization and 6 months after discharge. Figure 1 also reveals that HF increased mortality in patients with unstable angina, defined as ACS with normal biochemical markers of necrosis. Admission HF was associated with longer hospital stays and higher readmission rates. The development of HF in hospital (vs on presentation) was associated with an even higher in-hospital mortality rate (17.8% vs 12.0%, $P<0.0001$). A nested registry that was part of the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial[5] analyzed the contemporary incidence, outcomes, and predictors of HF and/or LV systolic dysfunction before discharge in patients with acute MI. Of the 5566 patients analyzed, 42% had HF and/or LV dysfunction during hospitalization; their in-hospital mortality rate was 13.0%, compared with 2.3% for those without HF and/or LV dysfunction. After adjustment for other baseline risk factors, HF and/or LV systolic dysfunction still carried a hazard ratio for in-hospital mortality of 4.12 (95% confidence interval [CI], 3.08-5.56). Furthermore, the mortality also increased with the increasing severity of HF and LV dysfunction and, as well, these patients had disproportionately higher rates of other cardiovascular (CV) events.

Current treatment of patients with HF and/or LV dysfunction complicating an acute MI includes the use of ACE inhibitors, angiotensin-receptor blockers (ARBs), β-blockers, and aldosterone-receptor blockers.[6-9] The use of implantable cardioverter-defibrillators (ICDs) in these high-risk patients with LV dysfunction and impaired cardiac autonomic function following a recent acute MI does not appear to reduce overall mortality.[2] On the other hand, aldosterone is known to mediate a multitude of adverse CV effects that include the following: induction of cardiomyocyte necrosis and apoptosis, and myocardial fibrosis resulting in adverse cardiac remodeling; coronary vasculopathy; tachyarrhythmia; and positive feedback activation of the renin-angiotensin-aldosterone system (RAAS).[10] Plasma aldosterone levels on admission among patients referred for primary percutaneous coronary intervention for ST-segment MI (STEMI) are associated with early and late adverse clinical outcomes; these outcomes include mortality and appear to be independent of age, HF, and reperfusion status.[11] A mortality

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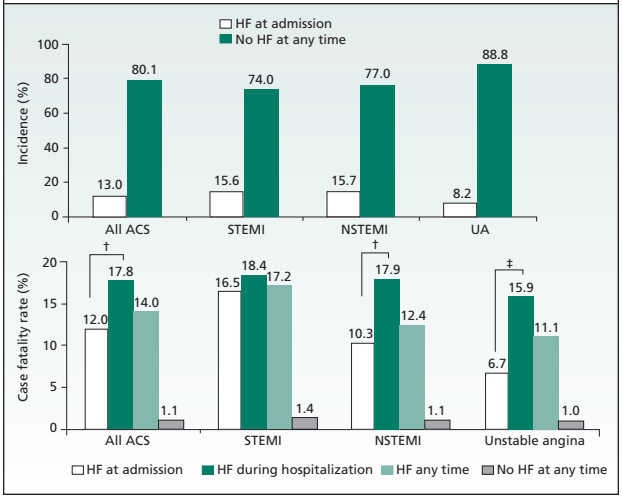
Figure 1: Incidence and mortality rates of heart failure according to type and timing of acute coronary syndrome in the GRACE registry[4]

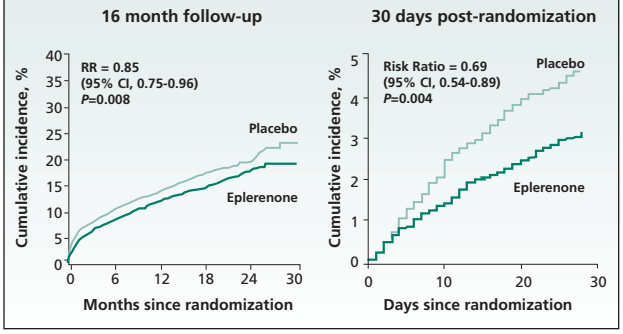


GRACE = Global Registry of Acute Coronary Events; HF = heart failure

benefit of aldosterone blockade was first demonstrated in patients with advanced HF. In the Randomized Aldactone Evaluation Study (RALES),[12] 1663 patients with severe HF and LV ejection fraction (LVEF) ≤35% receiving an ACE inhibitor, a loop diuretic and, in most cases, digoxin were randomly assigned to receive 25 mg of spironolactone daily or placebo. The primary endpoint was death from all causes. The trial was discontinued early after a mean follow-up period of 24 months because an interim analysis determined that spironolactone was significantly more efficacious than placebo. There were 386 deaths in the placebo group (46%) and 284 in the spironolactone group (35%; relative risk [RR] of death, 0.70; 95% CI, 0.60 -0.82; *P*<0.001). This 30% reduction in the risk of death among patients in the spironolactone group was attributed to a lower risk of both sudden death and death from progressive HF.

The Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS) was designed to examine the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality in patients with acute MI complicated by LV dysfunction and HF; these patients were on optimal adjunctive therapy including coronary reperfusion, acetylsalicylic acid (ASA), ACE inhibitors, ARBs and β-blockers.[9] Results of the parent trial have been reviewed in a previous issue of *Cardiology Scientific Update*. Patients were randomly assigned to eplerenone (25 mg/day initially, titrated to a maximum of 50 mg/day; 3313 patients) or placebo (3319 patients). The study continued until 1012 deaths occurred. The primary endpoints were death from any cause and death from CV causes or hospitalization for HF, acute MI, stroke, or ventricular arrhythmia. During a mean follow-up of 16 months, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (RR 0.85; 95% CI, 0.75 - 0.96; *P*=0.008; Figure 2). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to CV causes (RR 0.83; 95% CI, 0.72 - 0.94; *P*=0.005). The rate of the co-primary endpoint (death from

Figure 2: Effect of eplerenone on all-cause mortality long term and at 30 days post-randomization in EPHESUS



EPHESUS = Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study; RR = risk ratio; CI = confidence interval

CV causes or hospitalization for CV events) was reduced by eplerenone (RR 0.87; 95% CI, 0.79 - 0.95; *P*=0.002), as was the secondary endpoint of death from any cause or any hospitalization (RR 0.92; 95% CI, 0.86 - 0.98; *P*=0.02). There was also a reduction in the rate of sudden death from cardiac causes (RR 0.79; 95% CI, 0.64 - 0.97; *P*=0.03).

To explore the potential of eplerenone having an impact on early mortality post-MI, a recent analysis examined the results 30 days after randomization from EPHESUS.[13] At 30 days post-randomization, eplerenone reduced the risk of all-cause mortality by 31% (3.2% vs 4.6% in eplerenone- and placebo-treated patients, respectively; *P* = 0.004) and reduced the risk of CV mortality/CV hospitalization by 13% (8.6% vs 9.9% in eplerenone- and placebo-treated patients, respectively; *P* = 0.074). Eplerenone also reduced the risk of CV mortality by 32% (*P* = 0.003) and the risk of sudden cardiac death by 37% (*P* = 0.051). Eplerenone therefore exerts early survival benefits in patients who experience a high-risk acute MI.

Eplerenone and spironolactone: potentially important differences

Although spironolactone and eplerenone are both aldosterone-receptor blockers, their biochemical profiles are different.[14] The main differences between the 2 drugs are found in their specificity and side-effect profiles. For example, eplerenone has a 20-fold lower affinity for the mineralocorticoid receptor (MR) *in vitro* compared with spironolactone, although the *in vivo* dosage of eplerenone required to inhibit aldosterone binding by 50% was one-half that of spironolactone.[15] There is a greater differential effect between eplerenone and spironolactone in their binding affinities to androgen, glucocorticoid, and progesterone receptors; in fact, spironolactone has a 100- to 1000-fold higher binding affinity (Table 1). There are also differences between eplerenone and spironolactone with respect to metabolism and elimination. Spironolactone undergoes rapid extensive metabolism to 3 active metabolites with prolonged half-lives (14-17 hours).[16] Eplerenone also undergoes extensive metabolism, but its metabolites are inactive and its elimination half-life is short (4-6 hours). Finally, there are suggestions that eplerenone produces more consistent inhibition of several rapid non-genomic

Table 1: Relative binding affinities for spironolactone and eplerenone

Drug	Affinity for the mineralocorticoid receptor (aldosterone=1)	Affinity for the androgen receptor (methyl-trienolone=1)	Affinity for progesterone receptor (progesterone=1)
Spironolactone	1.1×10^{-1}	9.1×10^{-3}	7.0×10^{-3}
Eplerenone	5.1×10^{-3}	7.6×10^{-6}	$<5.0 \times 10^{-5}$

effects of aldosterone, such as the vasoconstrictor actions, compared with spironolactone.[14,17]

Spironolactone is associated with well-known risks of sexual side effects (eg, gynecomastia and impotence in males and menstrual irregularities in females) that are dose and duration dependent.[18] In contrast, eplerenone is associated with none or a very low incidence of sexual side effects.[9,19,20] Sexual side effects of drugs are of particular concern because patients are unwilling to tolerate these effects and sexual dysfunction is an important reason for noncompliance among hypertensive patients.[21]

Both eplerenone and spironolactone are associated with dose-related increases in serum potassium levels.[18,22] Patients with underlying renal dysfunction or HF are at the greatest risk of hyperkalemia.[22] In RALES and EPHESUS, spironolactone and eplerenone were associated with small increases in serum potassium concentrations. In RALES, 1 year of therapy with spironolactone (25 mg/day) was associated with a statistically significant increase in median potassium concentration (0.3 mmol/L vs no change in the placebo group).[12] However, there was no significant difference between the spironolactone and placebo groups in the occurrence of serious hyperkalemia (potassium ≥6 mEq/L; 2% vs 1%; *P*=0.42). Eplerenone was associated with similar changes in EPHESUS. The prevalence of hyperkalemia (>5.5 mEg/L) decreased over time in EPHESUS, and excess hyperkalemia was most prevalent <135 days following randomization. Study treatment discontinuation due to hyperkalemia was <1% in each group. After 1 year of therapy at a mean eplerenone dosage of 43.5 mg/day, potassium levels increased in both the placebo- (0.2 mEq/L) and active-therapy groups (0.3 mEq/L; <0.001).[9] In a new analysis of mortality in patients with potassium ≥6.0 mEq/L, there were no adjudicated deaths due to hyperkalemia (≥6.0 mEq/L) in the eplerenone group, and 1 in the placebo group. Assuming all sudden deaths were due to hyperkalemia, the mortality rate was 4.9% in the eplerenone group and 6.1% in the placebo group.[23]

It is more difficult to compare the incidence of hyperkalemia between eplerenone and spironolactone in hypertension trials because not all studies provide information on potassium levels and definitions of hyperkalemia may be different across studies. In 2 studies that defined hyperkalemia as ≥5.5 mEq/L, the incidence of hyperkalemia ranged from 3% to 6% at spironolactone doses of 12.5-400 mg/day.[24,25] At this threshold, the incidence of eplerenone-induced hyperkalemia ranged from 1%-3% at doses of 50–200 mg/day.[25–27] For studies using a threshold of ≥6.0 mEq/L, the incidence of hyperkalemia ranged from 0% to 11% at eplerenone doses of 50-200 mg/day.[26,27] Note, however, that although the reported incidence of hyperkalemia in EPHESUS and RALES was low, the use of spironolactone in clinical practice has been associated with a relatively high incidence of serious hyperkalemia resulting in the need for dialysis and leading to death.[28] These higher rates are likely related to the older age of patients in clinical practice; in addition, they may have higher pretreatment creatinine and potassium levels, and less serial monitoring of potassium levels than in the clinical trials.

Given a general lack of direct head-to-head comparative data between spironolactone and eplerenone, caution is required in comparing the rates of hyperkalemia between the 2 agents. Nevertheless, the currently available evidence suggests that sexual side effects, as well as the risk of hyperkalemia are less with eplerenone when the drugs are administered at recommended doses.

Expanding standards of care based on aldosterone blockade guidelines

With the publication of the results of RALES and EPHESUS,[9,12] the American College of Cardiology/American Heart Association (ACC/AHA), the Heart Failure Society of America (HFSA), the Canadian Cardiovascular Society (CCS), and the European Society of Cardiology (ESC) have updated their guidelines to support the use of aldosterone blockade in the management of patients with either HF and LV dysfunction following acute MI, or with advanced chronic HF.[29-32] In addition, the focused update of the ACC/AHA 2004 guidelines for the management of patients with STEMI[33] also recommend the use of aldosterone blockade in post-MI patients without significant renal dysfunction or hyperkalemia, with the patients already receiving therapeutic doses of an ACE inhibitor and a β-blocker, with LVEF ≤40%, and with either diabetes or HF (class I, level A).

Implementation of these guidelines may be difficult, particularly in cases of treatment for high-risk post-MI patients with HF and LV dysfunction in countries where eplerenone is unavailable, including Canada. Physicians in those countries must then consider administering spironolactone, but with an awareness of uncertainty in appropriate dose conversions, and questions as to whether spironolactone will provide the same degree of cardioprotection as eplerenone.

Advancing knowledge of aldosterone blockade: the EMPHASIS trial

The RALES and EPHESUS studies have provided compelling evidence for the use of aldosterone blockade in patients with advanced HF and those with HF and LV systolic dysfunction complicating acute MI, respectively. However, aldosterone blockade has not yet been evaluated by a placebo-controlled outcome trial in patients with mild-to-moderate chronic HF from an ischemic or nonischemic etiology. Accordingly, the ongoing Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) is designed specifically to fill this knowledge gap. The key inclusion criteria for EMPHASIS consist of:

- HF with New York Heart Association class II symptoms
- Age ≥55 years
- LVEF ≤30% (≤35%, if QRS interval ≥130 ms)

• CV hospitalization within 6 months or B-type natriuretic peptide (BNP) ≥250 pg/mL or N-terminal proBNP ≥500 pg/mL

The primary endpoint is CV death and HF hospitalization. The study will be event driven, anticipating 813 primary events, an annual placebo event rate of 18%, and 18% treatment benefit from eplerenone; therefore, the study requires 2584 HF patients to be followed over 48 months. As of August 2008, 1506 patients had been recruited. The baseline characteristics were: median age 70 years (range 47 to 96); median LV ejection fraction 27% (range 6%-40%); 75% were male; 70% had HF from an ischemic etiology; 969 subjects (64%) had an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2; and 507 subjects (34%) had an eGFR 30-60 mL/min/1.73m^2. Another ongoing study, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), is a National Heart, Lung, and Blood Institute-sponsored trial that will examine the effect of spironolactone in patients with HF and with preserved systolic function. When these studies are completed, the role of aldosterone blockade will be better defined across the continuum of patient management from acute MI to moderate and advanced HF.

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