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Scientific Update™

Evidence-based strategies for the cardioprotective role of selective aldosterone blockade: Late-breaking results of the EPHESUS study

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Activation of the renin-angiotensin-aldosterone system (RAAS) induces end-organ damage, which contributes to adverse clinical outcomes in patients with hypertension and congestive heart failure (CHF). Even with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), aldosterone levels frequently remain elevated and constitute an important risk factor for cardiovascular (CV) disease progression. Experimental data from the past few years strongly support the hypothesis that aldosterone exerts important deleterious effects on the CV system, independent of its classical action on the kidney. The new selective aldosterone receptor antagonist eplerenone has been shown to produce significant cardioprotective effects in experimental models of CV disease. In this *Cardiology Scientific Update*, experimental data supporting the pathophysiologic role of aldosterone in CV disease progression and clinical data on the use of eplerenone in hypertension and CHF, including the late-breaking results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), will be reviewed.

The evolving role of aldosterone in CV disease: rationale for selective aldosterone blockade

It has long been appreciated that aldosterone may play an important pathophysiologic role in CHF. Plasma aldosterone level is markedly increased in animal models of CHF and patients with advanced CHF.[1,2] Until recently, aldosterone was thought to play a pathophysiologic role essentially through its mineralocorticoid effects, thereby leading to increased extracellular fluid volume.[3] Research from the past few years has, however, refined the role of aldosterone in the development of CHF. Aldosterone can exert multiple actions that may be deleterious to the heart and vasculature.[4] Some of these effects are summarized in Figure 1. Aldosterone promotes hypertrophy, cardiac remodeling, and fibrosis, independent of BP. The effects appear to involve the transcription factors AP-1, and NF-κB, as well as bFGF.[5] Mineralocorticoid receptor blockade downregulates these effectors and reduces angiotensin II-induced cardiac damage. Spironolactone, added to an ACE inhibitor, normalizes nitric oxide (NO)-mediated relaxation in experimental CHF by modulating the balance of NO and superoxide anion formation, indicating that aldosterone induces oxidative stress.[6] Furthermore, in the rat heart, aldosterone induces a vascular inflammatory phenotype, including increased

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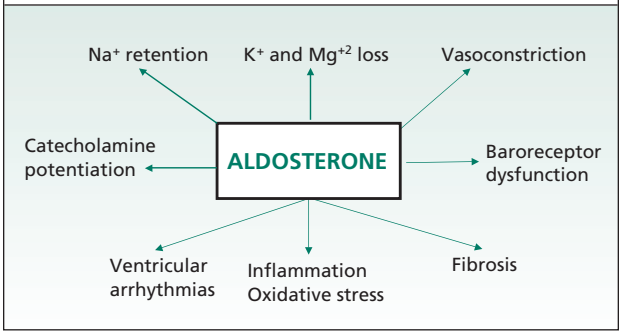
Figure 1: The multiple actions of aldosterone



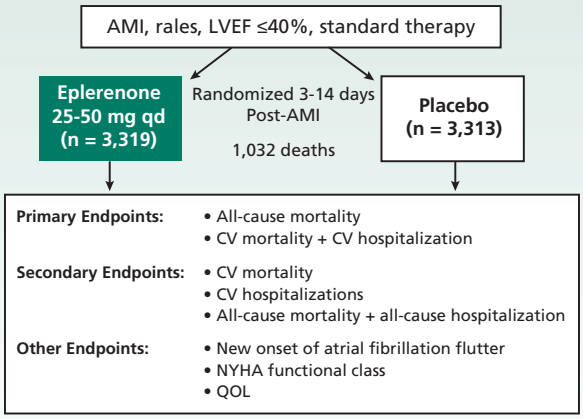
expression of cyclooxygnease-2, macrophage chemoattractant protein-1, and osteopontin.[7] These effects are attenuated by the selective aldosterone receptor eplerenone. Myocardial norepinephrine reuptake is reduced by aldosterone and reversed by spironolactone.[8] In patients with CHF, spironolactone improves heart rate variability and reduces the early morning rise in heart rate.[9] These two observations suggest that aldosterone receptor blockade may potentially reduce sudden death in patients with CHF.

Despite continued treatment with ACE inhibitors or an ACE inhibitor combined with an ARB, aldosterone levels increase over time in patients with CHF.[10,11] Neither ACE inhibitors, nor ARBs, block the actions of aldosterone at its receptor site. In the Randomized Aldactone Evaluation Study (RALES),[12] spironolactone (a non-specific aldosterone receptor blocker), when added to an ACE inhibitor, resulted in a 30% reduction in all-cause mortality, including progressive CHF death and sudden death, as well as CHF hospitalization. Gynecomastia and breast pain, a common side effect of spironolactone, occurred in 10% of the spironolactone group and 1% of the placebo group. It should be noted, however, that the patients in the RALES study had very advanced CHF and <10% of patients were on ß-blockade therapy.

Specific aldosterone receptor blockade in MI and heart failure

Eplerenone is a novel specific aldosterone receptor antagonist that has been shown to have significant cardioprotective effects in experimental models of CV disease.[4] In a dog model of myocardial infarction (MI) and CHF, eplerenone administered at a subpressor dose lowered left ventricular (LV) filling pressure and attenuated LV remodeling; this was accompanied by decreases in myocyte size, interstitial collagen, and matrix metalloproteinases 2 and 9.[13]

Figure 2: EPHESUS study design and endpoints



AMI = acute myocardial infarction
QOL = quality of life
NYHA = New York Heart Association

The EPHESUS Study

Design

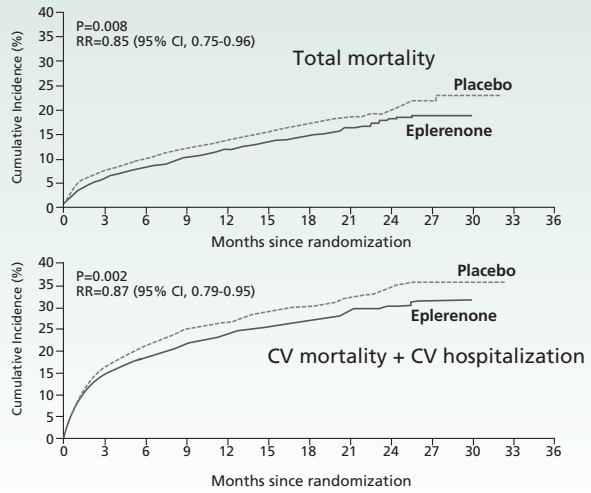
The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) was initiated in December 1999 to further investigate the effects of selective aldosterone receptor blockade in the treatment of CV disease. EPHESUS was designed to assess whether selective aldosterone receptor blockade with eplerenone reduces morbidity and mortality in patients with acute MI complicated by CHF. The rationale and design of EPHESUS has been published previously,[14] and the study design is summarized in Figure 2. Major inclusion criteria included documented acute MI, LV ejection fraction ≤ 40%, and clinical or radiographic signs of CHF such as rales (not required in diabetics). The key exclusion criteria were serum potassium > 5 mmol/L, serum creatinine >220 µmol/L, and the use of potassium-sparing diuretics. Revascularization was allowed if the patient was stable before randomization. The sample size was calculated to detect an 18.5% reduction in mortality compared with placebo with 88.3% power. A total of 6642 patients were randomly assigned at 674 centres in 37 countries to 25 mg of eplerenone or placebo daily. After 4 weeks, the dose of eplerenone was increased to 50 mg daily; 3319 patients were assigned to eplerenone and 3313 to placebo. Five hundred and twenty-eight patients (15.9%) and 493 patients (14.9%) of the eplerenone and placebo groups, respectively, were permanently withdrawn from the study

Table 1: EPHESUS – baseline characteristics[15]

Characteristic	Eplerenone Group (N=3319)	Placebo Group (N=3313)
Age (yr)	64±11	64±12
Race no. (%)		
• White	2995 (90)	2989 (90)
• Black	30 (1)	44 (1)
• Other	294 (9)	280 (8)
Sex no. (%)		
• Male	2380 (72)	2334 (70)
• Female	939 (28)	979 (30)
Blood pressure (mm Hg)		
• Systolic	119±17	119±17
• Diastolic	72±11	72±11
Left ventricular ejection fraction (%)	33±6	33±6
Days from MI to randomization	7.3±3.0	7.3±3.0
Previous hospitalization for heart failure (%)	7	8
Reperfusion therapy revascularization (%)	45	45
Symptoms of heart failure (%)	90	90
Serum potassium concentration (mmol/L)	4.3±0.4	4.3±0.5
Serum creatinine concentration (mg/dl)	1.1±0.3	1.1±0.3
Creatinine clearance (ml/min)	79±60	78±57
Medical history (%)		
• Acute MI	27	27
• Diabetes	32	32
• Heart failure	14	15
• Hypertension	60	61
Medications (%)		
• ACE inhibitor or ARB	86	87
• Beta-blockers	75	75
• Diuretics	60	61
• Aspirin	88	89
• Statins	47	47

medication. Ten (0.3%) and 7 patients (0.2%), respectively, were lost to follow-up. Ten patients were excluded from analysis before unblinding because of the quality of data from one centre. The study ended on August 30 2002, at which point 1032 deaths had occurred.

Figure 3: EPHESUS results: primary endpoints[15]



Results

The results of EPHESUS have recently been published.[15] Baseline characteristics of the two groups were similar and are shown in Table 1. The majority was receiving standard therapy for acute MI with systolic LV dysfunction and CHF; 87% of patients were on ACE inhibitors or ARBs, 75% were on ß-blockers, 88% were taking aspirin, and 60% were on diuretics.

Results of the two co-primary endpoints are shown in Figure 3. All-cause mortality was reduced by eplerenone by 15% and combined CV mortality and CV hospitalization was reduced by 17%. Results of secondary endpoints are summarized in Table 2. Of note, sudden cardiac death was reduced by 21%. CHF hospitalization was reduced by 15%, and the number of episodes of CHF hospitalization by 23% (p=0.02). Analyses of the predefined subgroup revealed consistent benefits from eplerenone, regardless of gender, age, LV ejection fraction, diabetes, or revascularization. Those with a serum creatinine ≤96 µmol/L at baseline had a greater benefit in mortality than those with higher serum creatinine. Interestingly, the test for heterogeneity for patients who received neither ACE inhibitors/ARBs, nor ß-blockers, received one or the other, or received both agents, yielded a p value for interaction of 0.04, with patients on none of the therapies experiencing the least benefit.

The incidence of adverse events is shown in Table 3. Gastrointestinal upset was slightly more frequent in the

Table 2: EPHESUS – secondary endpoints

Secondary endpoints	Eplerenone (N=3319)	Placebo (N=3313)	HR (95% CI)	P value
Death from any cause or any hospitalization (no. of patients)	1730	1829	0.92 (0.86-0.98)	0.02
Death from cardiovascular causes (no. of patients)	407	483	0.83 (0.72-0.94)	0.005
• Sudden death from cardiac causes	162	201	0.79 (0.64-0.97)	0.03
• Acute myocardial infarction	78	94	0.82 (0.61-1.10)	0.19
• Heart failure	104	127	0.80 (0.62-1.04)	0.10
• Stroke	26	28	0.91 (0.53-1.55)	0.73
• Other	37	33	1.00 (0.60-1.66)	0.99
Any hospitalization (no. of patients)	1493	1526	0.95 (0.89-1.02)	0.20
Hospitalization for cardiovascular events (no. of patients)	606	649	0.91 (0.81-1.01)	0.09
• Acute MI	224	229	0.97 (0.80-1.16)	0.71
• Heart failure	345	391	0.85 (0.74-0.99)	0.03
• Stroke	70	51	1.34 (0.94-1.93)	0.11
• Ventricular arrhythmia	52	54	0.95 (0.65-1.39)	0.79
Any hospitalization (no. of episodes)	2815	2984	0.94	0.12
Hospitalization for cardiovascular events (no. of episodes)	876	1004	0.87	0.03
• Acute MI	268	269	0.99	0.96
• Heart failure	477	618	0.77	0.002
• Stroke	73	54	1.35	0.11
• Ventricular arrhythmia	58	63	0.92	0.69

eplerenone group. Importantly, gynecomastia, impotence, and menstrual disorders, side effects that are associated with non-specific aldosterone receptor blockade, were no more frequent in eplerenone-treated than in placebo-treated patients. The rate of serious hyperkalemia (potassium >6.0 mEql/L) was 5.5% in the eplerenone group and 3.9% in the placebo group (p=0.002), whereas the rate of hypokalemia (potassium <3.5 mEq/L) was 8.4% in the eplerenone group and 13.1% in the placebo group (p< 0.001).

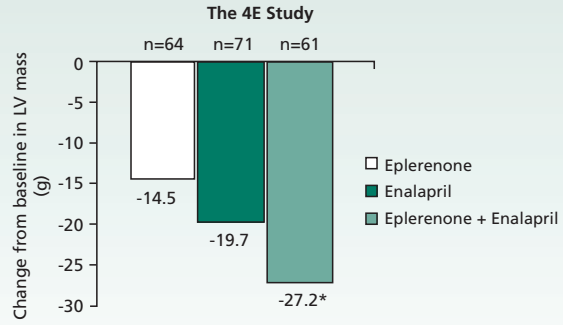
Table 3: Adverse events

	Eplerenone (n=3319)	Placebo (n=3313)	P-value
Gastrointestinal upset	659 (19.9%)	583 (17.7%)	0.02
Gynecomastia	12 (0.5%)	14 (0.6%)	0.7
Impotence	21 (0.9%)	20 (0.9%)	1.0
Menstrual disorder	13 (0.4%)	13 (0.4%)	1.0
Metabolic disorder	568 (17.2%)	635 (19.2%)	0.03

Summary

The results of EPHESUS indicate that specific aldosterone receptor blockade reduces the time to all-cause mortality, combined CV mortality and hospitalization, CV death including sudden cardiac death, and hospitalization for CHF in patients following acute MI complicated by LV dysfunction and CHF. These benefits are accrued in patients who have received contemporary management of acute MI and CHF, including ACE inhibition, ß-blockade and reperfusion therapy. Furthermore, patients in EPHESUS were a high-risk population as evidenced by the relatively high placebo one-year mortality of 13.6%, as compared to another recently reported study of patients with CHF post-MI.[16] In terms of absolute benefit, one life is saved for 50 patients treated and 1 episode of CV mortality and hospitalization is avoided for every 33 patients treated. The results of EPHESUS extend the role of aldosterone receptor blockade from patients with advanced CHF[12] to patients with CHF following the acute event that leads to CHF,

Figure 4: Effect of eplerenone, enalapril and combination on LV mass



* p = 0.007 versus eplerenone only.
p = <0.05 versus baseline in all 3 groups.

and will likely impact future guidelines on the management of CHF.

From hypertension to heart failure: The emerging role of selective aldosterone blockade

Uncontrolled hypertension can be associated with increased LV mass, LV systolic and diastolic dysfunction, and MI.[17] As reviewed earlier, aldosterone plays an important pathophysiologic role in the progression along the continuum of CV disease, from hypertension, atherosclerosis, MI, to CHF.[2,18,19] Eplerenone represents a novel class of agents with a unique mechanism of action, including high selectivity for the mineralocorticoid receptor.

Many pre-clinical studies have reported the beneficial effects of eplerenone in experimental models of hypertension and atherosclerosis.[18] To date, there are 14 completed trials examining the use of eplerenone in over 3000 patients with hypertension and different risk factors.[2] The majority of these trials has been reported only in abstract form.[20-25] Treatment durations have ranged from 8 weeks to 12 months, with over 600 patients exposed to the agent for >6 months. In studies that involved the assessment of monotherapy, eplerenone was either equivalent or superior to calcium channel blockers (CCBs), ACE inhibitors, or ARBs.[20,24,25] In elderly patients with systolic hypertension, eplerenone reduced BP by a magnitude that was similar to the CCB amlodipine; however, only eplerenone reduced urinary albumin/creatinine ratio (UACR).[25] In black hypertensives, eplerenone was superior to losartan in lowering BP when compared to placebo, whereas the response to eplerenone and losartan was similar in white hypertensives.[26]

In studies that evaluated combination therapies in patients who were poorly controlled on ACE inhibitors and ARBs, the addition of eplerenone significantly lowered systolic BP in both arms, and diastolic BP in the ARB patients.[27] In diabetic hypertensives with microalbuminuria, the combination of eplerenone and enalapril reduced albuminuria by a greater magnitude than eplerenone or enalapril alone.[21] The 4E study (Eplerenone, Enalapril, and Eplerenone/ Enalapril combination in patients with left ventricular hypertrophy) compared the effect of eplerenone, enalapril, and combination on LV mass in patients with LV hypertrophy.[28] After 9 months of therapy, the BP decline was similar in the three groups. The change in LV mass as determined by magnetic resonance imaging is shown in Figure 4. Combination therapy produced a more pronounced reduction in LV mass compared to monotherapy with eplerenone (p= 0.001) or with enalapril (p=0.038). The UACR was reduced by a greater magnitude with combination therapy compared to either eplerenone or enalapril. Data from the 4E study therefore indicates that aldosterone receptor blockade provides additional organ protection beyond that provided by ACE inhibition.

Conclusion

In summary, the totality of data indicates that aldosterone receptor blockade represents the most promising approach to neurohormonal modulation beyond ACE inhibition and ß-blockade in patients with CHF. Equally promising is the use of specific aldosterone receptor blockade in other conditions and at earlier stages along the CV continuum. Further data are likely forthcoming that will further define the therapeutic role of this new class of agents.

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