The Role of Aldosterone and Aldosterone-Receptor Antagonists in Heart Failure

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Prolonged overactivation of neurohormonal mechanisms in heart failure produces deleterious effects on the cardiovascular system and leads to poor prognosis. Angiotensin-converting enzyme (ACE) inhibitors and ß-blockers have been shown to interrupt this excessive overactivity and improve survival. Activation of the renin-angiotensin system leads to increased synthesis of aldosterone in heart failure. Some aldosterone production is independent of ACEs; therefore, ACE inhibition does not entirely suppress the excessive formation of aldosterone. An excess of aldosterone in heart failure leads to sodium retention and myocardial fibrosis. The use of aldosterone antagonists, combined with standard therapy for heart failure, improves morbidity and mortality.

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Key words: Congestive heart failure • Aldosterone • Aldosterone-receptor antagonist • Spironolactone • Eplerenone

The activation of compensatory mechanisms in heart failure leads to increased levels of production of renin-angiotensin-aldosterone, norepinephrine, endothelin-1, natriuretic peptides, and prostaglandin. Chronic stimulation by these agents is detrimental and results in an increase in afterload and preload, and further worsening of left ventricular function.[1] Various trials have shown that interruption of this cycle with angiotensin-converting enzyme (ACE) inhibitors and ß-blockers improves survival in heart failure.[2,3] These results have led to a considerable interest in the role of aldosterone-receptor antagonists in the management of heart failure.

Table 1
Adverse Effects of Raised Levels of Plasma Aldosterone

- Sodium retention
- Potassium depletion
- Magnesium depletion
- Catecholamine potentiation
- Reduced compliance of aorta and branches
- Baroreceptor dysfunction
- Reduced heart-rate variability
- Higher incidence of arrhythmia
- Higher incidence of cardiac mortality
- Myocardial remodeling/fibrosis
  - Mechanical: Due to fluid retention and ↑ ventricular wall stress
  - Fibroblast activation (secondary to)
    - Mineralocorticoid-based receptor activation of fibroblasts
    - Myocyte necrosis and scarring due to aldosterone
    - ↑ Na+/K+-adenosine triphosphatase (ATPase)
    - ↑ mRNA synthesis for type I and III collagen
    - ↑ in endothelin receptor numbers
    - ↑ in AT-1 receptor density
    - ↑ in macrophage production of transforming growth factor (TGF)-ß$_1$
    - ↑ vascular permeability
      - ❑ Local ↑ in platelet-derived growth factor

Deleterious Effects of Aldosterone

Raised aldosterone levels are associated with sodium retention and increased cardiac mortality.[2] Aldosterone potentiates the pressor effects of norepinephrine by blocking tissue catecholamine uptake.[4] It modulates parasympathetic tone and results in reduced heart-rate variability. Reduced heart-rate variability in heart failure is associated with increased mortality and a higher incidence of sudden death.[5,6]

Aldosterone levels have been shown to inversely relate to compliance of the aorta and its major branches. This has detrimental effects on myocardial function.[7] Aldosterone has also been shown to promote aggregation and activation of platelets, and it produces arteriolar constriction.[8] It stimulates an increase in cardiac angiotensin-1 (AT-1) receptor density and AT-1 mRNA levels.[9]

Aldosterone has arrhythmogenic properties. A chronic increase in aldosterone levels leads to myocyte necrosis and microscopic scarring.[10] Patchy myocardial fibrosis has been shown to lead to a reduced threshold for ventricular arrhythmia. Aldosterone causes a loss of magnesium and potentiates the effects of catecholamines, and, therefore, further predisposes to ventricular arrhythmias.[4,11] See Table 1 for a list of the adverse effects of raised aldosterone levels in plasma.

Aldosterone Escape

Although ACE inhibitors reduce angiotensin-II (AT-II) activity, usual doses of ACE inhibitors do not completely block production of aldosterone. In fact, increased levels of aldosterone may be seen after several months of therapy with ACE inhibitors.[12] This is, in a way, an "escape" production of aldosterone, despite ACE inhibition.

Various mechanisms have been discovered that explain this escape (see Table 2)[13-17]: a) AT-II production that is independent of ACE inhibitor activity; b) ACE production that is not inhibited by ACE inhibitors; and c) AT-II–independent aldosterone production.

Extra-adrenal production of aldosterone has been documented in various tissues, including the myocardium and the blood vessels. The production of aldosterone synthase mRNA in the heart is not related to plasma levels of AT-II.[17] Extra-adrenal expression of this mRNA has also been demonstrated in ventricular fibroblasts, as well as in brain and blood vessels.[15,18,19]

The physiological importance of this locally produced aldosterone is not completely known. Local production of aldosterone is not totally regulated by AT-II. This AT-II–independent production of aldosterone may have increased importance in chronic heart failure.[20]

Local production of aldosterone has been shown to increase as the severity of heart failure worsens.[15] In fact,

Increased levels of aldosterone may be seen after several months of therapy with ACE inhibitors. This is, in a way, an "escape" production of aldosterone, despite ACE inhibition.

Table 2
Pathophysiology of Increased Levels of Aldosterone in Patients With Heart Failure

Increased aldosterone levels in heart failure		
↓	↓	
Angiotensin II-independent	Angiotensin II-dependent	
(Not inhibited by ACEI)	↓	↓
Stimulus for production	Angiotensin II-production	Angiotensin II-production
↓	dependent on ACE	independent of ACE
a: ⇑ Potassium	(Inhibited by ACEI)	(Not inhibited by ACEI)
b: ⇑ Magnesium		- Inadequate suppression of ACE in target tissue
c: ⇓ Sodium		- Local peptidase production with ACE-like activity
d: ⇓ Extracellular volume		
+		
e: ⇓ Metabolic clearance of aldosterone secondary to hepatic congestion		

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor.

local production of aldosterone in heart failure may lead to myocardial levels of aldosterone that are many times higher than those in plasma.[17]

Genetic factors may also play a role in aldosterone escape. Patients with heart failure and aldosterone escape have a higher prevalence of DD genotype than do patients with aldosterone levels within normal limits.[13] Higher ACE levels in tissue have been detected in patients with ACE DD genotype. This can lead to a manifold increase in serum and cardiac ACE levels.[13,21] This inadequate suppression of ACE by ACE inhibitors in target tissue adds to the failure of aldosterone suppression in some patients. The DD genotype has been shown to be associated with higher mortality in patients with heart failure.[21,22]

Extracellular volume depletion, sodium restriction, hypermagnesemia, and hyperkalemia are potent stimulators of angiotensin-independent production of aldosterone. The production of aldosterone stimulated by raised plasma potassium levels is more marked in the presence of excessive sodium restriction, and is especially potent when loop diuretics lead to urinary sodium loss. This effect increases even further when potassium supplements are added to loop diuretics in patients with heart failure. Potassium restriction has been shown to produce a marked dampening of levels of plasma aldosterone.[23] A reduction in aldosterone clearance by the liver, secondary to impaired hepatic blood flow in heart failure, also contributes to increased aldosterone activity.[24]

Aldosterone and Myocardial Fibrosis

Aldosterone has important effects on cardiac structure and mass.[25] Mineralocorticoid receptors are present in the cardiomyocytes, endothelial cells, and fibroblasts of the human heart.[26] Aldosterone binds to and activates these receptors. This leads to fibroblast growth and proliferation and increased production of collagen. This effect is independent of the actions of AT-II as well as ventricular systolic pressure.[24-28]

Aldosterone promotes the entry of sodium into the fibroblasts by activating the preexisting sodium pumps and increasing the expression and activity of Na+/K+-adenosine triphosphatase (ATPase) in the heart. The aldosterone-dependent transcriptional regulation of Na+/K+-ATPase promotes growth of fibroblasts and synthesis of collagen.[29,30]

Aldosterone enhances gene expression for fibrillar collagen. It results in increased synthesis of mRNA for type I and type III collagen and synthesis of type I and type III fibrillar collagen.[31] Collagen is synthesized in the fibroblasts as procollagen, which contains polypeptide extensions at its amino- and carboxy-terminal ends. These peptides are removed from the procollagen by procollagen-specific amino- and carboxy-terminal proteinases. The collagen is then integrated into the growing fibrils. Some of these peptides are released into the blood. Circulating levels of some of these peptides can be considered as markers of collagen synthesis.[10]

Aldosterone increases levels of type I and type III procollagen mRNA

in the ventricles[16] and serum levels of peptide markers of collagen synthesis.[10,32] Higher levels of these peptides are associated with poorer outcome.[33]

Aldosterone causes both perivascular and interstitial fibrosis in the myocardium. Progressive myocardial fibrosis begins as an accumulation of fibrillar collagen within the adventitia of the intramyocardial coronary arteries and extends into the intramuscular spaces between bundles of cardiac myocytes.[34] This results in reduced ventricular compliance and impairment of diastolic function.[25,34]

Aldosterone has also been shown to alter intramural coronary permeability to macromolecules. This may contribute to fibroblast proliferation and collagen synthesis because of the appearance of growth factors (eg, platelet-derived growth factor) in the myocardial interstitium.[35] The activation of macrophages and an increase in the macrophage production of transforming growth factor (TGF)-ß$_1$ have also been shown to contribute to increased collagen synthesis. Proliferative changes in the cardiac fibroblasts are controlled by TGF-ß$_1$. TGF-ß$_1$ stimulates fibroblasts to produce collagen. TGF-ß$_1$ also induces the differentiation of fibroblasts to myofibroblasts, which have a higher activity for collagen production than fibroblasts have.[16,34,36-38]

Aldosterone increases AT-1 and endothelin-receptor density, which may also lead to the stimulation of collagen synthesis.[9,39] A prolonged increase of aldosterone levels leads to adverse myocardial remodeling, diastolic and, subsequently, systolic dysfunction, and a worsening of heart failure.

A daily dose of 25 mg of spironolactone has been shown to be effective in blocking the aldosterone receptors.

Effects of Aldosterone Receptor Antagonist Spironolactone

Spironolactone acts as a competitive antagonist to aldosterone. A daily dose of 25 mg of spironolactone has been shown to be effective in blocking the aldosterone receptors.[40] In addition, at high concentrations, spironolactone can inhibit the biosynthesis of aldosterone.[41] Spironolactone has been shown to increase myocardial noradrenaline uptake.[42] Spironolactone also reduces the density of AT-1 receptors induced by aldosterone.[9] It suppresses vascular AT-II conversion, increases nitric oxide bioactivity, attenuates platelet aggregation, and improves endothelial dysfunction induced by aldosterone.[7,43] Spironolactone inhibits aldosterone-induced interstitial and perivascular fibrosis.[44,45]

Spironolactone can markedly prevent not only cardiac but also arterial fibrosis, and therefore arterial stiffness.[46] It inhibits fibrointimal hyperplasia.[47] Long-term treatment with spironolactone results in a reduction in left ventricular mass as well as plasma levels of markers for myocardial fibrosis.[48,49]

Effects of Spironolactone in Heart Failure Shown in Clinical Studies

It is worth noting that in the Cooperative North Scandinavian

Table 3
Characteristics of Patients in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)

			Cause of CHF		Randomized to Receive			
Study	**Patients**	**Age**	**Ischemic**	**Nonischemic**	**Spironolactone**	**Placebo**	**Baseline EF**	**Mean Duration**
RALES[57]	1663	65 ± 12	907	754	822	841	≤ 35%	24 months
					Randomized to Receive			
					Eplerenone	**Placebo**		
EPHESUS[68]	6642	64 ± 12	6642	0	3319	3313	≤ 40%	16 months

EF, ejection fraction; CHF, congestive heart failure.
Data from Pitt et al[57] and Pitt et al.[68]

Table 4
Concurrent Medications Used in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Trials

	RALES Study[57]	
	Spironolactone, %	**Placebo, %**
Loop diuretics	100	100
ACE inhibitors	95	94
Digitalis	75	72
ß-blockers	11	10
	EPHESUS Study[68]	
	Eplerenone, %	**Placebo, %**
Diuretics	60	61
ACE inhibitor or ARB	86	87
ß-blockers	75	75

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Data from Pitt et al[57] and Pitt et al.[68]

Enalapril Survival Study (CONSENSUS) trial, which showed improved survival with ACE inhibitors in heart failure, nearly half of the patients were on spironolactone.[2] Interestingly, the Studies of Left Ventricular Dysfunction (SOLVD) trial also revealed that a reduction in mortality was more pronounced in patients receiving a potassium-sparing diuretic than in those receiving a nonpotassium-sparing diuretic.[50]

Some patients experience hypotension with ACE inhibitor therapy, which precludes increasing the dosage of ACE inhibitors. In this scenario, the addition of spironolactone allows us to use lower doses of ACE inhibitors without influencing natriuresis.[51]

Low-dose spironolactone (25mg/day) produces a significant reduction in diastolic arterial pressure, mean arterial pressure, and systemic vascular resistance. It also significantly diminishes right and left ventricular filling pressures, suggesting that spironolactone improves both venous and arterial compliance. A trend towards greater response with higher doses of 50–75 mg/day has been noted.[52] The addition of spironolactone to ACE inhibitor therapy leads to a reduction in the incidence of life-threatening ventricular arrhythmia, possibly by blunting the urinary magnesium loss,[40] and to reduced myocardial fibrosis.[45]

Aldosterone blockade improves baroreceptor dysfunction, heart rate variability, and QT dispersion in patients with heart failure.[5,6,53,54] Long-term spironolactone use reduces left ventricular volume and mass and improves ejection fraction and exercise tolerance.[54-56] It also results in a decrease in plasma levels of brain natriuretic peptide, which is a marker for worse prognosis in heart failure.[55,56]

The Randomized Aldactone Evaluation Study (RALES) Trial

The most important study to evaluate the effects of spironolactone in patients with heart failure was the Randomized Aldactone Evaluation Study (RALES) (see Table 3).[57] This double-blind, placebo-controlled study enrolled patients who were in severe heart failure and were already on an ACE inhibitor (if tolerated), a loop diuretic, and, in most cases, digoxin (see Table 4). As many as 99% of the patients were in New York Heart Association (NYHA) functional class III–IV heart failure. The exclusion criteria included patients with serum creatinine > 2.5mg/100 mL and serum potassium > 5 mmol/L. Patients were randomized to receive 25 mg daily of either placebo or spironolactone. The dose was increased to 50 mg in 2 weeks if patients had signs or symptoms of worsening heart failure. The dose was reduced back to 25 mg if hyperkalemia developed. The mean daily dose was 31 mg for placebo and 26 mg for spironolactone.

The RALES trial was discontinued after a mean follow-up of 24 months because of a very significant improvement in mortality with spironolactone therapy.

This trial was discontinued after a mean follow-up of 24 months because of a very significant improvement in mortality with spironolactone therapy (Table 5). The study authors found a 30% reduction in the risk of death in the spironolactone group ($P < .001$) (Figure 1). Spironolactone reduced the risk of death from both progres-

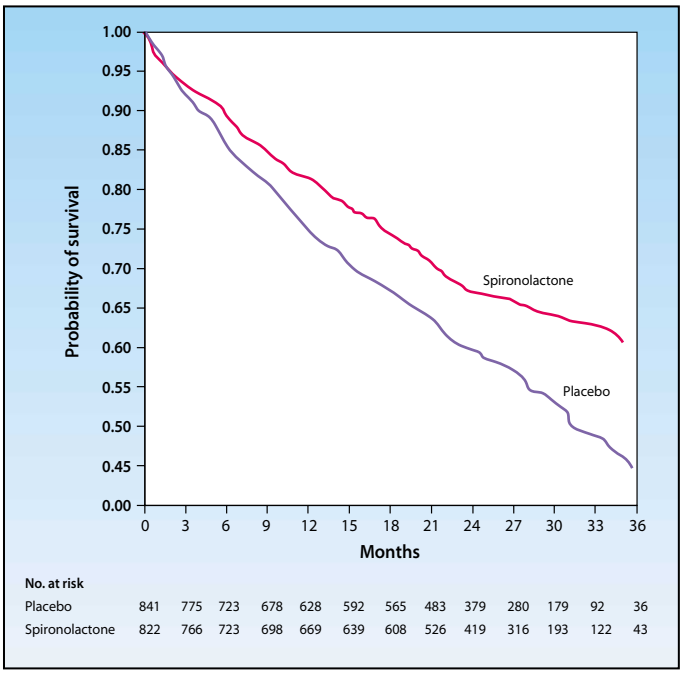

Figure 1. *Kaplan-Meier analysis of the probability of survival among patients in the placebo and spironolactone groups in the Randomized Aldactone Evaluation Study (RALES) trial. The risk of death was 30% lower among patients in the spironolactone group than among patients in the placebo group (P < .001; relative risk = .70 [95% CI, 0.60-0.82]). Reproduced, with permission, from Pitt et al.*[57]

sive heart failure and sudden cardiac death. It also reduced the incidence of hospitalization for worsening of heart failure by 35% lower than that in the placebo group ($P < .001$) (Table 6). Reductions in the risks of death and hospitalization were observed after 2 to 3 months of treatment. Significant improvements in NYHA functional class were also noted ($P < .001$).

One of the criticisms of the RALES study was that approximately only 10% of the patients were on ß-blocker therapy. Some beneficial effects of ß-blockers and spironolactone are produced by similar mechanisms. It is not very clear if the beneficial effects of spironolactone would still be seen if the majority of patients were on ß-blocker therapy. ß-blockers blunt the effects of the activated sympathetic nervous system on the heart. They also reduce secretion of renin, and therefore help reduce aldosterone production.[58] An increase in the effectiveness of ß-blocker therapy has been shown in patients in heart failure with ACE deletion polymorphism,[59] the same group of patients who would theoretically benefit more from an aldosterone receptor antagonist.

Another criticism of the RALES study was that the doses of ACE inhibitors should have been maximized aggressively. The mean doses of ACE inhibitors in the placebo and spironolactone groups, respectively, were 62.1 and 63.4 mg of captopril, 16.5 and 13.5 mg of enalapril, and 13.1 and 15.5 mg of lisinopril.[57] The beneficial effects of enalapril, however, have been shown with the mean dose of 11.2 mg in the SOLVD study.[50]

Adverse Effects of Spironolactone

The risk of hyperkalemia is especially higher in patients who are elderly, diabetic, receiving a dose of spironolactone ≥ 50 mg/day, or taking other medications that could cause an increase in serum potassium levels.[60,61] In the RALES study, however, 9% of the patients were over the age of 80, and approximately 25% had diabetes at baseline. None of these patients had any fatal incidence of hyperkalemia, and they had a similar benefit in mortality from spironolactone as did the other patients in general who participated in the study.[62] There was no significant difference in the incidence of hyperkalemia in patients treated with placebo or spironolactone in the RALES study (Table 7).[57]

Spironolactone has some sexual endocrine effects because of its affinity for the androgen and progesterone receptors.[63] Gynecomastia and breast pain were the main adverse effects of spironolactone therapy in the RALES study.[57]

Eplerenone

Eplerenone is a new, competitive antagonist of aldosterone at the mineralocorticoid receptor level in which the 17α-thioacetyl group of spironolactone has been replaced with a carboxy group that confers a much higher degree of selectivity for the aldosterone receptor and a low binding affinity for progesterone, androgen, and glucocorticoid receptors.[64] Eplerenone has been shown to significantly reduce cardiac hypertrophy and cardiac hydroxyproline content in experimental models.[65] It has also been shown to improve left ventricular remodeling in heart failure.[66] It reduces serum b-type natriuretic peptide (BNP) levels comparable to spironolactone.[67] Eplerenone also prevents aldos-

Eplerenone has been shown to improve left ventricular remodeling in heart failure.

Table 5
Number and Cause of Deaths From Spironolactone Therapy in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Trials

	RALES Study[57]			
	Placebo	**Spironolactone**	**RR (95% CI)**	***P* value**
	No. of deaths/ no. in group (%)	No. of deaths/ no. in group (%)		
Total deaths	386/841 (46)	284/822 (35)	0.70(0.60-0.82)	< .001
Death due to progression of heart failure	189/841 (22)	127/822 (15)	0.64(0.51-0.80)	< .001
Sudden death	110/841 (13)	82/822 (10)	0.71(0.54-0.95)	.02
	EPHESUS Study[68]			
	Placebo	**Eplerenone**	**RR (95% CI)**	***P* value**
	No. of deaths/ no. in group (%)	No. of deaths/ no. in group (%)		
Total deaths	554/3313 (18)	478/3319 (14)	0.85(0.75-0.96)	.008
Death due to progression of heart failure	127/3313 (4)	104/3319 (3)	0.80(0.62-1.04)	.10
Sudden death	201/3313 (6)	162/3319 (4.88)	0.79(0.64-0.97)	.03

RR, relative risk; CI, confidence interval.
Data from Pitt et al[57] and Pitt et al.[68]

terone-induced fibronectin accumulation in large arteries. This leads to improvement in vascular stiffness.[32]

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

Eplerenone is well tolerated and has a good safety profile (Table 7).[64] However, the incidence of hyperkalemia has been reported in up to 12% of treated patients at a dose of ≥ 100 mg/day.[67] Lower doses of 25 and 50 mg may have much lower incidences of hyperkalemia. These lower doses were evaluated in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial.[68]

Aldosterone receptor blockade has shown beneficial effects in patients with heart failure,[57] but the effect on patients with acute myocardial infarction complicated

Table 6
Effects of Aldosterone Receptor Antagonists on the Number of Hospitalizations in Patients With Heart Failure in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Trials

		RALES Study[57]	
Reason for Hospitalization	**Placebo**	**Spironolactone**	***P* value**
		No. of episodes/ no. in group	No. of episodes/ no. in group
Cardiovascular events	753/841	515/822	< .001
Heart failure	663/841	413/822	< .001

		EPHESUS Study[68]	
Reason for Hospitalization	**Placebo**	**Eplerenone**	***P* value**
		No. of episodes/ no. in group	No. of episodes/ no. in group
Cardiovascular events	1004/3313	876/3319	.03
Heart failure	618/3133	477/3319	.002

Data from Pitt et al[57] and Pitt et al.[68]

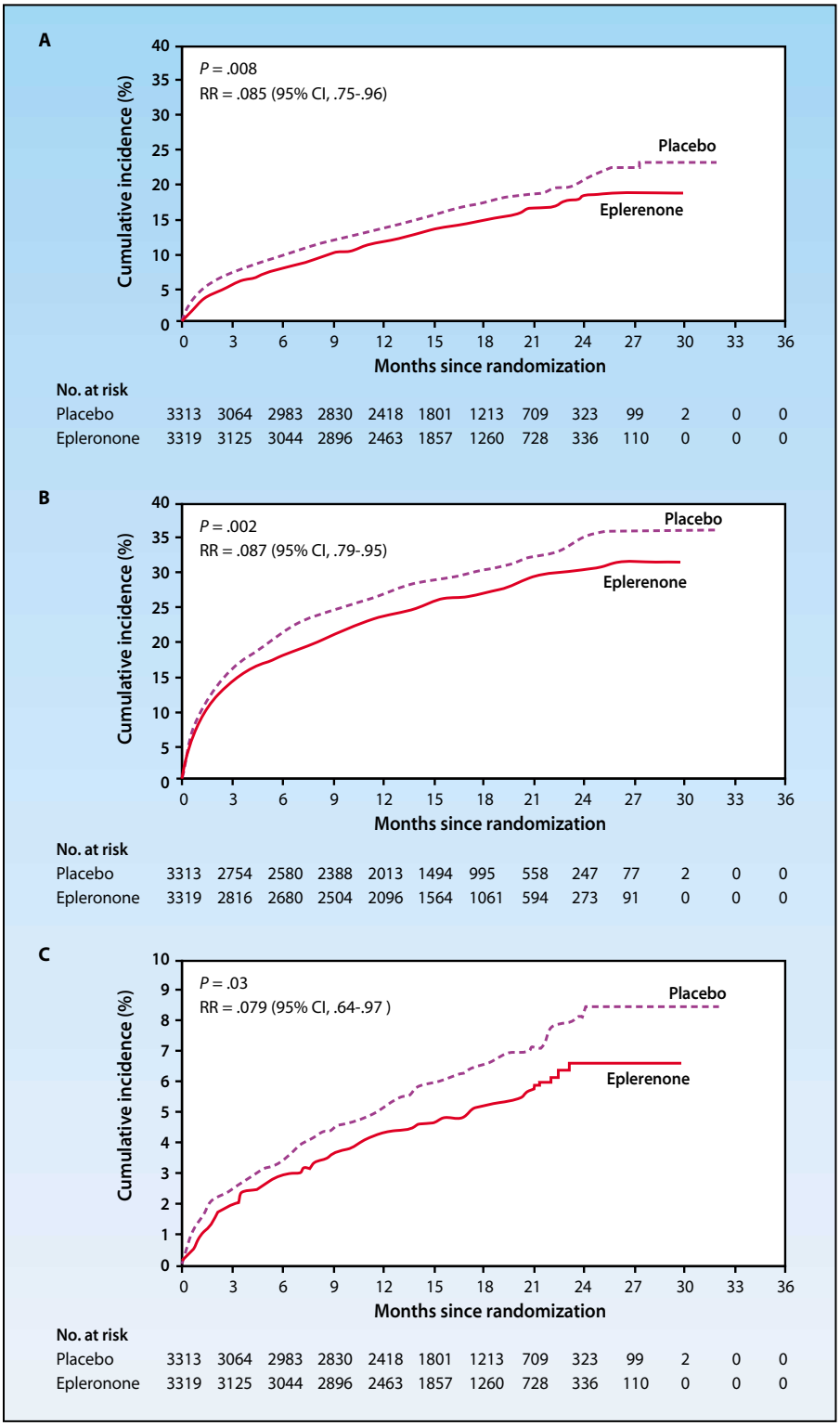

Figure 2. *Kaplan-Meier analysis of the estimates of* ***(A)*** *the rate of death from any cause,* ***(B)*** *the rate of death from cardiovascular causes or hospitalization for cardiovascular events, and* ***(C)*** *the rate of death from cardiac causes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial. RR, relative risk; CI, confidence interval. Reproduced, with permission, from Pitt et al.*[68] www.medreviews.com

by heart failure was not known. The EPHESUS trial evaluated the impact of the aldosterone antagonist eplerenone on morbidity and mortality in patients with recent myocardial infarction complicated by an ejection fraction ≤ 40%, and either diabetes or clinical evidence of left ventricular dysfunction (eg, pulmonary rales, pulmonary venous congestion on chest X-ray, or heart sound S3). This was a multicenter, randomized, double-blind, placebo-controlled study that randomized 6642 patients (see Table 3) to receive either placebo or eplerenone within 3 to 14 days of a myocardial infarction. Patients who required spironolactone were excluded. A total of 90% of patients had symptoms of heart failure. The primary end points were death from any cause, death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia.

Patients were started on 25 mg of placebo or eplerenone daily for 4 weeks and then the dose was increased to a maximum of 50 mg. The reduction in mortality was mainly attributable to a 21% reduction in the incidence of sudden death compared to placebo (Table 5, Figure 2). The reductions in death from progressive heart failure and acute myocardial infarction were statistically not significant. There was, however, a 23% reduction in the number of episodes of hospitalization for heart failure compared to placebo (Table 6).

The placebo group in the EPHESUS trial had a lower mortality rate than that in the RALES trial (Table 5). The reduction in mortality secondary to eplerenone was also smaller than in the RALES trial. The authors postulated that this was secondary to a relatively higher ejection fraction (mean ejection fraction, 33% in

Table 7
Incidence of Hyperkalemia and Gynecomastia in the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Trials

	RALES Study[57]		
	Placebo, %	Spironolactone, %	*P* value
Hyperkalemia	1.0 %	2.0 %	< .42 NS
Gynecomastia	1.0 %	10.0 %	< .001
Breast Pain	0.1%	2.0%	.006
	EPHESUS Study[68]		
	Placebo, %	Eplerenone, %	*P* value
Hyperkalemia	3.9%	5.5%	.002
Gynecomastia	0.6%	0.5%	.70 NS
Breast Pain	0.3%	0.1%	.63 NS

NS, not significant.
Data from Pitt et al[57] and Pitt et al.[68]

EPHESUS versus 25% in RALES) and greater use of ß-blockers in the EPHESUS trial (Table 4).[68] Eplerenone may prove to be a promising aldosterone-blocking agent with better tolerability for treatment of heart failure (Table 7).

Conclusion

Increased aldosterone levels have detrimental effects in heart failure and are associated with increased mortality.[2] The use of loop diuretics leads to further increases in aldosterone levels.[23] These may increase mortality, especially the risk of arrhythmic death.[69]

The usual doses of ACE inhibitors may not completely suppress the production of aldosterone.[12,51] This aldosterone escape from ACE inhibition has pathological consequences for the cardiovascular system.

The combination of ACE inhibitors and spironolactone achieves a more complete inhibition of aldosterone.[40] Recent data from controlled clinical trials have led to the inclusion of ß-adrenergic receptor blockers as part of standard therapy for heart failure.[3] The addition of spironolactone to standard therapy produces further clinical benefits as well as improvement in survival.[57]

Spironolactone treatment is recommended in patients already receiving maximal therapy with ACE inhibitors, ß-blockers, digoxin, and loop diuretics, who remain symptomatic, and/or require a large dose of a loop diuretic (especially with low levels of plasma potassium).

The addition of eplerenone to optimal medical management in patients with left ventricular dysfunction and heart failure precipitated by myocardial infarction has also shown improvement in survival, with fewer androgenic and progestogenic adverse effects compared to spironolactone.[68] ■

Main Points

- An increase in aldosterone levels has detrimental effects in heart failure and is associated with increased mortality.
- Activation of the renin-angiotensin system leads to increased synthesis of aldosterone in heart failure. An excess of aldosterone in heart failure leads to sodium retention and myocardial fibrosis.
- Angiotensin-converting enzyme (ACE) inhibitors and ß-blockers have been shown to interrupt the excessive neurohormonal overactivity and improve survival.
- Some aldosterone production is independent of angiotensin-converting enzymes; therefore, ACE inhibition does not entirely suppress the excessive formation of aldosterone.
- The combination of ACE inhibitors and spironolactone achieves a more complete inhibition of aldosterone.
- Spironolactone treatment is recommended in patients already receiving maximal therapy with ACE inhibitors, ß-blockers, digoxin, and loop diuretics. The addition of spironolactone to standard therapy produces further clinical benefits as well as improvement in survival.
- Adding eplerenone to optimal medical management in patients with left ventricular dysfunction and heart failure precipitated by myocardial infarction has also shown improvement in survival, and eplerenone has fewer androgenic and progestogenic adverse effects than spironolactone has.

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