Aldosterone blockade in heart failure
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Abstract
Aldosterone plays a key role in the pathophysiology of heart failure. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may not suppress aldosterone production in the long term. This allows aldosterone to exert its effects on myocardial fibrosis and cardiac remodelling, endothelial function, electrolytes and baroreceptor response.

The Randomized Aldactone Evaluation Study (RALES) tested spironolactone against placebo in patients with severe heart failure. The study found a 30% reduction in the risk of death among patients treated with spironolactone and a 31% reduction in the risk of death from cardiac causes. Patients in the spironolactone group had significantly lower risks of death from progression of heart failure and sudden cardiac death.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) investigated the effects of eplerenone against placebo in patients with myocardial infarction complicated by left ventricular dysfunction. Compared to placebo, the relative risk of death from any cause was 0.85 in eplerenone-treated patients, and the relative risk of death from cardiovascular causes was 0.87. The reduction in the risk of sudden death from cardiac causes was statistically significant. In conclusion, aldosterone blockade should form part of optimal therapy for patients with heart failure.

Introduction
Aldosterone plays a key role in the pathophysiology of heart failure. It promotes the retention of sodium and the loss of potassium and magnesium. It is implicated in myocardial fibrosis and cardiac remodelling, it contributes to endothelial dysfunction, it has pro-inflammatory effects and it can blunt the baroreceptor response.

Current therapy for heart failure (HF), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers (ARBs), may not suppress aldosterone production in the long term. For example, Staessen and colleagues measured the plasma concentration of aldosterone in seven hypertensive patients before and during treatment with the ACE inhibitor (ACE-I) captopril. Initially, the plasma concentration of aldosterone decreased from 74 to 21 pg/ml. However, after one month the plasma concentration of aldosterone began to rise, and after a year it reached 165 pg/ml.

Partial ‘escape’ of renin-angiotensin-aldosterone (RAAS) blockade was demonstrated by Borghi in patients with acute myocardial infarction (MI). In patients treated with the ACE-I zofenopril, in vitro dose-dependent ACE inhibition was shown. Plasma aldosterone decreased during the first three days of treatment and then returned towards baseline levels, despite a persistent inhibition of ACE.

In one study of patients with symptomatic heart failure, up to 40% of patients had aldosterone concentrations greater than 144 pg/ml despite long-term treatment with an ACE-I. In the RESOLVD trial, patients received both the ACE-I enalapril and the ARB candesartan but even with maximal doses of both agents the mean aldosterone level returned to baseline by 43 weeks.

Aldosterone may be produced by Ang II levels rise over time in patients treated with an ACE-I or by Ang II-independent production through intracellular depletion, potassium ACTH, endothelin and vasopressin. This is clinically significant because the level of plasma aldosterone is an important predictor of survival in patients with heart failure.

The combination of an ACE-I and a mineralocorticoid receptor (MR) blocker is more effective than either alone in causing natriuresis but it is unlikely that their beneficial effects can be explained solely on this basis.

Magnesium
Aldosterone promotes urinary excretion of magnesium, and low blood levels of both magnesium and potassium are the commonest electrolyte disorders in heart failure. Low levels of magnesium may lead to ventricular arrhythmias. A study by Gottlieb of 199 patients with heart failure found a higher one-year survival rate (71%) in patients with normal serum magnesium levels; it was 45% in patients with low magnesium levels.

Endothelial dysfunction
Aldosterone may contribute to endothelial dysfunction. Farquharson and Struthers performed a study on 10 patients with New York Heart Association class II to III chronic heart failure on standard diuretic and ACE-I therapy, comparing spironolactone 50 mg/day with placebo. Forearm vasculature endothelial function was assessed using acetylcholine (ACh) and the nitric oxide synthase inhibitor L-NMMA, and vascular ACE activity was assessed using angiotensin I. Spironolactone significantly increased the forearm...
blood flow response to ACh, with an associated increase in vasoconstriction in response to L-NMMA. There was no effect on blood flow in response to sodium nitroprusside, an endothelium-independent vasodilator. The angiotensin I response was also significantly reduced with spironolactone. Thus, spironolactone was shown to improve endothelial dysfunction, increase NO bioactivity and inhibit angiotensin I/II conversion.

Cardiac remodelling, myocardial fibrosis and electrical stability

Aldosterone promotes perivascular and interstitial myocardial fibrosis, reducing the flexibility of myocardial tissue and increasing the likelihood of diastolic dysfunction. Myocardial fibrosis may also be an arrhythmogenic influence. The first demonstration of these effects in man was given by MacFadyen and colleagues. They examined 31 patients with stable chronic HF who were treated with spironolactone 50-100 mg/day or placebo in addition to diuretics and ACE-I. Spironolactone treatment reduced circulating levels of procollagen type III N-terminal amino peptide, a marker of vascular collagen turnover, and it also increased time-domain parameters of heart rate variability. Spironolactone significantly reduced heart rate, particularly between 6 and 10 a.m., when cardiac death is most prominent. Limitation of excessive extracellular matrix turnover may be one of the extrarenal mechanisms that contributes to the beneficial effects of spironolactone in patients with heart failure, according to the RALES Investigators. Spironolactone has also been shown to improve heart rate variability and QT dispersion in heart failure. MR blockers have been shown to improve ventricular remodelling in patients with chronic heart failure due to ischaemia and non-ischaemic cardiomyopathy. In the rat, aldosterone has been shown to stimulate cytokine production to activate macrophages and stimulate the growth of fibroblasts and the synthesis of collagen.

Baroreceptors

Aldosterone is able to blunt the baroreflex response, another potentially harmful effect. Acute perfusion of aldosterone into the isolated carotid sinus decreased baroreceptor activity. Impaired baroreceptor activity in man is related to mortality.

Trial experience with aldosterone blockade

RALES (Randomized Aldactone Evaluation Study). This trial was designed in the context of emerging evidence that inhibition of the RAAS by an ACE-I only transiently suppressed aldosterone, that there was a significant correlation between aldosterone production and mortality in patients with heart failure, and that aldosterone blockade when added to an ACE-I resulted in potential benefit, as seen in Barr et al. A dose-finding study was first performed to establish whether aldosterone was effective and safe when co-administered with other agents used in heart failure, and in particular to examine its effects on serum potassium levels.

This preliminary study, performed by the RALES investigators, enrolled 214 patients with symptomatic heart failure. Patients continued their previous therapeutic regimes, including ACE-I, loop diuretics and digitalis, and were randomised to placebo or to spironolactone 12.5, 25, 50 or 75 mg once daily for 12 weeks.

At 12 weeks, significant increases in plasma renin and aldosterone excretion, and significant decreases in systolic and diastolic blood pressure and pro-ANF were observed in the spironolactone group. The incidence of hyperkalaemia (defined as serum potassium >5.5 mmol/L) was 5% in the placebo group and in the 12.5 mg spironolactone group; it was 13% in the 25 mg, 20% in the 50 mg and 24% in the 75 mg spironolactone groups, respectively. Predictors of hyperkalaemia included dose of ACE-I and baseline elevation of serum creatinine or potassium.

The RALES investigators concluded that 12.5 mg to 25 mg spironolactone was relatively safe and effective in blocking the effects of aldosterone when co-administered with ACE-I, loop diuretics and digitalis, provided that potassium levels were monitored. Following on from this preliminary study, RALES tested the hypothesis that daily treatment with 25 mg spironolactone would significantly reduce the risk of death from all causes among people who had severe heart failure as a result of systolic left ventricular dysfunction and who were receiving standard therapy (including an ACE-I, if tolerated).

For inclusion, patients had been given a diagnosis of heart failure at least six weeks before enrolment and had New York Heart Association (NYHA) class III or IV heart failure at the time of enrolment (with NYHA class IV heart failure at some point during the six months before enrolment). Patients were taking a loop diuretic, an ACE-I if tolerated, and had a left ventricular ejection fraction (LVEF) <50% within the six months before enrolment. Treatment with potassium-sparing diuretics was not allowed.

Patients with operable valvular heart disease, unstable angina, awaiting or post heart transplantation, with a serum creatinine >221 µmol/L and serum potassium >5.0 mmol/L were excluded.

Patients were randomly assigned to 25 mg spironolactone once daily or to matching placebo. After eight weeks of treatment, the spironolactone dose could be doubled if there was progression of heart failure without hyperkalaemia. Follow-up evaluations and laboratory measurements were conducted every four weeks for the first 12 weeks, then three-monthly up to one year, and thereafter every six months until the end of the study. The primary end point was death from any cause. Secondary end points included death and/or hospitalisation from cardiac causes and a change in the NYHA class.

A total of 1,663 patients underwent randomisation; 822 received spironolactone and 841
received placebo. The baseline characteristics of the two groups were similar, with a mean age of 65 years, 75% male patients and a mean blood pressure at randomisation of 122/75 mmHg. Approximately 70% of patients were in NYHA class III and the LVEF was 25%. All patients were taking loop diuretics, 95% were taking ACE-Is but only 10% were taking β-blockers.

A brief summary of the results is shown in Table 1. The trial was in fact discontinued early, after a mean follow-up of 24 months, because data analysis showed that spironolactone treatment was more efficacious than placebo in reducing the number of deaths.

Table 1 Risks of death and hospitalisation in RALES

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Spironolactone</th>
<th>RR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac deaths</td>
<td>314</td>
<td>226</td>
<td>0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression HF</td>
<td>189</td>
<td>127</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>110</td>
<td>82</td>
<td>0.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths</td>
<td>386</td>
<td>284</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalisations for cardiac causes</td>
<td>753</td>
<td>515</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalisations for worsening HF</td>
<td>663</td>
<td>413</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The table shows a 30% reduction in the risk of death among patients treated with spironolactone and a 51% reduction in the risk of death from cardiac causes (p<0.001 for both). Patients in the spironolactone group had significantly lower risks of death from progression of heart failure and sudden cardiac death. The reduction in risk of death was similar in all pre-specified subgroups.

There were significant differences between the groups in heart failure symptoms between baseline and the end of the study, as assessed by NYHA class. In the spironolactone group, 41% of patients improved, in 21% symptom class remained unchanged and in 38% symptoms worsened. The equivalent figures for the placebo group were 34%, 18% and 48%.

In this selected group of patients who were closely monitored in a clinical trial, treatment tolerability and safety were encouraging, with no differences between the two groups in serum sodium, blood pressure or heart rate during the study. The median creatinine concentration in the spironolactone group increased by 4–9 µmol/L and the median potassium concentration by 0.30 mmol/L in the spironolactone group, though they remained unchanged in the placebo group. These differences were not thought to be clinically important. Serious hyperkalaemia occurred in 1% of the placebo group and in 2% of the spironolactone group (p=0.42). Nevertheless, close and careful monitoring of renal function is absolutely mandatory when using spironolactone in patients with heart failure, especially if they are taking full-dose ACE-I treatment and a β-blocker.

Aldosterone affects a number of pathophysiological mechanisms that are thought to be important in the prognosis of patients with acute myocardial infarction (MI). The role of aldosterone blockade in reducing mortality and hospitalisation among patients with MI complicated by left ventricular dysfunction and heart failure (or diabetes) was investigated in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study).

Patients were eligible for randomisation 3–14 days after documented MI, with a LVEF of 40% or...
lower documented on echocardiography or radionuclide angiography, and heart failure evidenced by pulmonary rales, pulmonary venous congestion or a third heart sound. Patients with a LVEF of 40% or lower who were diabetic also qualified for RALES. Patients received optimal medical therapy (including anti-platelet treatment, ACE-Is, diuretics and β-blockers) and coronary reperfusion therapy.

Patients were excluded if they were taking potassium-sparing diuretics, if their serum creatinine was >220 µmol/L and if their serum potassium was >5.0 mmol/L before randomisation. Follow-up visits were held at one week and four weeks, at three months and every three months until the end of the study.

The primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalisation for a cardiovascular event such as heart failure, acute MI, stroke or ventricular arrhythmia. The trial was designed to enrol 6,200 patients and to continue until 1,012 deaths occurred.

A total of 6,642 patients underwent randomisation between December 1999 and December 2001. Of these patients, 3,319 were assigned to eplerenone 25 mg/day and 3,313 to placebo for four weeks. At that point, the eplerenone dose was increased to a maximum of 50 mg/day. There were no significant differences between the two groups at baseline in medical history, medications or serum creatinine or potassium concentrations. Their mean age was 64 years, approximately 70% were male and their mean LVEF was 33%; 27% had a history of MI, 32% had diabetes, 15% a history of heart failure and 61% hypertension. At baseline, 87% were taking ACE-Is or angiotensin receptor blockers, 75% were taking β-blockers, 61% diuretics, 88% aspirin and 47% were taking statins.

Results
A brief summary of the end points in the EPHESUS trial is given in Table 2. During a mean follow-up of 16 months, 14.4% of the eplerenone group died and 16.7% of the placebo group died: this gives Kaplan-Meier estimates of mortality at one year of 11.8% and 13.0%, respectively. The other death/hospitalisation primary end point was reached by 26.7% in the eplerenone group and 30.0% in the placebo group.

New, unpublished data show that the reduction in mortality from any cause with eplerenone was apparent within 30 days of randomisation. The reduction in cardiovascular mortality was similar for the most common causes—sudden death from cardiac causes, acute MI and heart failure—with relative risks varying from 0.79 to 0.82. The reduction in the risk of sudden death from cardiac causes was statistically significant. The rate of death from any cause or any hospitalisation was 8% lower in the eplerenone group (p=0.02).

At one year, the serum creatinine concentration increased by 1.8 µmol/L in the placebo group and by 5.3 µmol/L in the eplerenone group (p<0.001). Potassium levels rose by 0.2 mmol/L in the placebo group and by 0.3 mmol/L in the eplerenone group (p<0.001): serum potassium >6.0 mmol/L, so-called serious hyperkalaemia, occurred in 3.9% of the placebo group and 5.5% of the eplerenone group (p<0.002), with one death in the placebo group. The incidence of hyperkalaemia was higher among patients with a lower baseline creatinine clearance. Using a cutoff value of 50 ml per minute, serious hyperkalaemia was seen in 5.9% of the placebo group and 10.1% of the eplerenone group (p=0.006).

Mortality in the placebo group was lower and the magnitude of the effect of aldosterone blockade was smaller in EPHESUS compared to RALES. These differences in mortality may have been caused by the greater use of β-blockers in EPHESUS and the higher baseline LVEF values in these patients. The most significant reduction in cardiovascular mortality in EPHESUS was the reduction in sudden death from cardiac causes. This may be to do with the effects of eplerenone on norepinephrine uptake and heart rate variability.

The rise in potassium levels found in the study

Table 2 End points in the EPHESUS trial

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>Relative risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause (1°)</td>
<td>478</td>
<td>554</td>
<td>0.85</td>
<td>0.008</td>
</tr>
<tr>
<td>Death/hospitalisation for cardiovascular events (1°)</td>
<td>885</td>
<td>993</td>
<td>0.87</td>
<td>0.002</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>407</td>
<td>483</td>
<td>0.83</td>
<td>0.005</td>
</tr>
<tr>
<td>Sudden death from cardiovascular causes</td>
<td>162</td>
<td>201</td>
<td>0.79</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure</td>
<td>104</td>
<td>127</td>
<td>0.80</td>
<td>0.10</td>
</tr>
<tr>
<td>Any hospitalisation</td>
<td>1,493</td>
<td>1,526</td>
<td>0.85</td>
<td>0.20</td>
</tr>
<tr>
<td>Hospitalisation for cv events (no. episodes)</td>
<td>876</td>
<td>1,004</td>
<td>0.87</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalisation for heart failure (no.episodes)</td>
<td>477</td>
<td>618</td>
<td>0.77</td>
<td>0.002</td>
</tr>
</tbody>
</table>
(despite the exclusion from the study of patients with a high serum creatinine or potassium at baseline) stresses the importance of monitoring serum potassium and of adjusting the dosage of aldosterone blocker if necessary. In elderly patients, those with a low body mass index and those with diabetes, the serum creatinine level may not reflect renal function accurately.

The incidence of gynaecomastia and erectile dysfunction was no greater in the eplerenone group than in the placebo group (in contrast to the RALES findings). This can be attributed to the greater selectivity of eplerenone for the mineralocorticoid receptor (spironolactone also binds to androgen and progesterone receptors).

Thus, in this study addition of eplerenone to optimal medical therapy gave an estimated number needed to treat (NNT) of 50 to save one life at one year and of 33 to prevent one death from cardiovascular causes or one hospitalisation for a cardiovascular event in one year.

References
19. Effectiveness of spironolactone added to an angiotensin converting enzyme inhibitor and a loop diuretic for chronic congestive heart failure (the Randomized Aldactone Evaluation Study (RALES)). Am J Cardiol 1996;78(8):902-07.