Treatments that improve outcome in the patient with heart failure, left ventricular systolic dysfunction, or both after acute myocardial infarction

R Weir, J J V McMurray

Patients with heart failure, left ventricular systolic dysfunction, or both, after acute myocardial infarction have a poor prognosis. It is important to focus treatment on this high risk group to reduce the persistently high morbidity and mortality after acute myocardial infarction. As in chronic heart failure, there is now good evidence that inhibition of the renin–angiotensin–aldosterone system and sympathetic nervous system, with the appropriate drugs, can reduce morbidity and mortality. In addition to angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and β blockers, the aldosterone blocker eplerenone has now been shown to be effective in reducing adverse outcomes.

Any studies show that patients with clinical evidence of heart failure or imaging evidence of substantial left ventricular systolic dysfunction (LVSD) early after acute myocardial infarction (AMI) have a poor subsequent prognosis. In one of the most recent of these, an international registry collected in conjunction with a clinical trial, the adjusted hazard ratio for death during admission in patients with an AMI complicated by heart failure, LVSD, or both, was 4.12. Remarkably, 80% of inpatient deaths occurred in this subset of high risk individuals who accounted for 42% of all patients with an AMI in the registry. Morbidity, especially the subsequent development of chronic heart failure, is also particularly high in this patient subset. These findings emphasise the importance of focusing treatment on patients with LVSD, heart failure, or both in order to reduce the persistently high morbidity and mortality after AMI.

**ANGIOTENSIN CONVERTING ENZYME INHIBITORS**

Three landmark studies published in the early 1990s demonstrated the effectiveness of long term treatment with an angiotensin converting enzyme (ACE) inhibitor in reducing the risk of death, heart failure and, unexpectedly at the time, the risk of recurrent infarction in patients with LVSD, heart failure, or both after AMI (fig 1). Other studies showed a smaller benefit with short term treatment in a much broader patient population after AMI. However, these studies with broader inclusion criteria demonstrated a greater absolute benefit in higher risk patients. Importantly, they showed that treatment could be started, safely, early after the onset of infarction and that a reduction in death was seen within the first few days of treatment. The findings of these trials are reflected in all major guidelines which advocate early initiation and long term treatment with an ACE inhibitor in patients with LVSD, heart failure, or both after AMI.

**β BLOCKERS**

Despite being the first evidence based treatment for AMI, on the basis of key trials conducted in the 1970s and 1980s, physicians had been reluctant to give β blockers to patients with LVSD, heart failure, or both. In retrospect, it seems that such patients were probably passively excluded by investigators from the early β blocker trials and there was undoubtedly some clinical concern that β blocker treatment might worsen ventricular function or heart failure in these patients. Consequently, for example, only 25% of patients in SAVE, AIRE, and TRACE were treated with a β blocker. As a result of the parallel discovery that β blockers could not only be used safely in patients with chronic heart failure but also substantially reduced morbidity and mortality in those patients, a new β blocker trial in AMI was conducted. In that study, CAPRICORN, patients with LVSD (and with or without heart failure) were randomised to placebo or carvedilol. All patients were treated, according to guidelines, with an ACE inhibitor. In other words, CAPRICORN tested whether a β blocker would give added benefit on top of the best, evidence based, background treatment. Compared with placebo, there was a 23% relative risk reduction...

**Abbreviations:** ACE, angiotensin converting enzyme; AIRE, acute infarction ramipril efficacy; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAPRICORN, carvedilol post infarct survival control in left ventricular dysfunction; CARE, cholesterol and recurrent events; EMPHUS, eplerenone neurohormonal efficacy and survival study; 4S, Scandinavian simvastatin survival study; LIPID, long-term intervention with pravastatin in ischemic disease; LVSD, left ventricular systolic dysfunction; OPTIMAAL, optimal trial in myocardial infarction with the angiotensin II antagonist losartan; SAVE, survival and ventricular enlargement; TRACE, trandolapril cardiac evaluation study; VAULTANT, valsartan in acute myocardial infarction trial.
in mortality with carvedilol and a reduction in re-infarction (but not, curiously, in heart failure).

This finding, taken in conjunction with the “pre-ACE inhibitor era” β blocker trials and the new chronic heart failure β blocker trials, argues persuasively for routine, combined, ACE inhibitor and β blocker treatment for patients with LVSD, heart failure, or both after AMI (fig 2). This evidence is also reflected in guideline recommendations.10–11

ANGIOTENSIN RECEPTOR BLOCKERS

Because it was thought that angiotensin receptor blockers (ARBs) might be more effective than ACE inhibitors in reducing the harmful effects of angiotensin II, two trials, OPTIMAAL and VALIANT, were designed to compare these two types of treatment.17 18 Also, because there were theoretical reasons to believe that both drugs together might be better than either alone, one of these trials, VALIANT, also compared combination ACE inhibitor and ARB treatment to each monotherapy.18 Neither trial showed that the ARB tested was superior to the ACE inhibitor tested (capto-

Figure 1 Effect of angiotensin converting enzyme (ACE) inhibitors on fatal and non-fatal cardiovascular events in survivors of acute myocardial infarction with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction. Adapted from Flather et al.10

Table 1 Absolute benefit of evidence based pharmacological treatments of patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction

| Trials, AIRE, TRACE meta-analysis | ACE inhibitor | 2.6 | 57 | 23 | 36 |
| CAPRICORN | β blocker | 1.3 | 34 | 23 | – |
| EPHEUS | Aldosterone blocker | 1.3 | 23 | – | 14 |

*Events avoided relates to the number of patients avoiding event; more episodes than this were avoided—for example, there were 43 fewer hospital admissions for heart failure per 1000 patients treated with eplerenone (as opposed to 14 fewer patients hospitalised for heart failure). Note: (1) Different duration of follow up; deaths avoided per 1000 patient years would be: 22 with an ACE inhibitor, 26 with a β blocker, 18 with an aldosterone blocker. (2) Events are not mutually exclusive; for the composite of death or acute MI, 66 fewer patients per 1000 treated experienced this composite with an ACE inhibitor and 53 fewer with a β blocker; for death, MI, or heart failure the number was 69 with an ACE inhibitor.

ALDOSTERONE BLOCKADE

The other effector hormone in the renin–angiotensin system is aldosterone; aldosterone blockade is known to reduce substantially mortality in severe chronic heart failure.19 Consequently, this therapeutic approach was also tested in AMI.20 In the EPHEUS trial, patients with LVSD and heart failure (or diabetes mellitus) were randomised to receive placebo or eplerenone added to full conventional background treatment (including an ACE inhibitor/ARB in 86% of cases and β blocker in 75% of cases).21 Eplerenone treatment led to a 15% relative risk reduction in all cause mortality as well as to a reduction in hospital admission for cardiovascular reasons, especially heart failure (fig 4, table 1). The benefit of eplerenone was seen across all subgroups of patients, including those treated with all of an ACE inhibitor (or ARB), a β blocker, aspirin, a statin, and coronary reperfusion therapy—that is, the benefit was clearly obtained over and above that of the best available background treatment (fig 4).

OTHER PHARMACOLOGICAL TREATMENTS

Though the high risk subset of patients discussed in this overview have, to some extent, been excluded from prior statin trials, there is no good reason to believe that this treatment should be ineffective in patients with LVSD, heart failure, or both. The ongoing CORONA trial in chronic heart
failure will, however, provide more evidence which may help answer this question. Similarly, antiplatelet treatment has not been specifically studied in patients with LVSD, heart failure, or both. Furthermore, there has been considerable debate about whether aspirin might attenuate the benefits of ACE inhibitors and this argument remains unresolved. Agents which do not inhibit cyclo-oxygenase—for example, clopidogrel—should not have this theoretical disadvantage of aspirin.

CONCLUSION
Patients with LVSD, heart failure, and especially both remain at remarkably high risk and account for the majority of both short and long term fatal and non-fatal outcomes in patients with AMI. Effective treatments—capable of substantially reducing these adverse outcomes—exist, the latest of which is eplerenone (fig 3). The challenge to physicians is to ensure that this wealth of evidence is applied in practice so that the individual patient and society benefits.

Figure 3 An evidence based algorithm for the early treatment of acute myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both.

<table>
<thead>
<tr>
<th>All patients</th>
<th>LVSD or acute HF</th>
<th>LVSD and acute HF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td><strong>Proven ACE inhibitor</strong> or valsartan 160 mg twice daily</td>
<td><strong>Eplerenone</strong> 25–50 mg every day</td>
</tr>
</tbody>
</table>

CAPRICORN 4S/CARE/LIPID

Figure 4 Incremental benefit of adding an aldosterone blocker to an ACE inhibitor in survivors of acute myocardial infarction with left ventricular systolic dysfunction and acute heart failure. EPHEBUS is compared to the subset of CAPRICORN patients in Killip class I or greater at baseline.

Learning points
- Patients with heart failure, left ventricular systolic dysfunction, or both, after acute myocardial infarction (AMI) have a poor prognosis and it is important to focus treatment on this high risk group to reduce the persistently high morbidity and mortality after AMI.
- As in chronic heart failure, there is now good evidence that pharmacological inhibition of the renin–angiotensin–aldosterone system and sympathetic nervous system can reduce morbidity and mortality.
- In addition to angiotensin converting enzyme inhibitors, angiotensin receptor blockers and β blockers, the selective aldosterone blocker eplerenone has now been shown to be effective in reducing adverse outcomes.
- The wealth of evidence from clinical trials now needs to be applied in practice.

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