What is the optimal medical management of ischaemic heart failure?

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Ischaemic heart disease is probably the most important cause of heart failure. All patients with heart failure may benefit from treatment designed to retard progressive ventricular dysfunction and arrhythmias. Patients with heart failure due to ischaemic heart disease may also, theoretically, benefit from treatments designed to relieve ischaemia and prevent coronary occlusion and from revascularisation. However, there is little evidence to show that effective treatments, such as angiotensin converting enzyme (ACE) inhibitors and β-blockers, exert different effects in patients with heart failure with or without coronary disease. Moreover, there is no evidence that treatment directed specifically at myocardial ischaemia, whether or not symptomatic, or coronary disease alters outcome in patients with heart failure. Some agents, such as aspirin, designed to reduce the risk of coronary occlusion appear ineffective or harmful in patients with heart failure. There is no evidence, yet, that revascularisation improves prognosis in patients with heart failure, even in patients who are demonstrated to have extensive myocardial hibernation. On current evidence, revascularisation should be reserved for the relief of angina.

Large-scale, randomised controlled trials are currently underway investigating the role of specific treatments targeted at coronary syndromes in patients who have heart failure. The CHRISTMAS study is investigating the effects of carvedilol in a large cohort of patients with and without hibernating myocardium. The WATCH study is comparing the efficacy of aspirin, clopidogrel and warfarin. The HEART-UK study is assessing the effect of revascularisation on mortality in patients with heart failure and myocardial hibernation. Smaller scale studies are currently assessing the safety and efficacy of statin therapy in patients with heart failure.

Only when the results of these and other studies are known will it be possible to come to firm conclusions about whether patients with heart failure and coronary disease should be treated differently from other patients with heart failure due to left ventricular systolic dysfunction.

Ischaemic heart disease is the commonest cause of left ventricular systolic dysfunction leading to heart failure in industrialised societies. The prognosis of newly diagnosed heart failure is poor. More than 30%
of patients will die within 3 months and the subsequent annual mortality is around 10%, although much worse in patients with severe heart failure\textsuperscript{1,2}. Most importantly, clinical trials show that the prognosis of heart failure can be modified substantially by a number of pharmacological therapies\textsuperscript{3–12}. However, many treatments for heart failure subjected to randomised trials failed to show benefit or have shown harm\textsuperscript{13}, despite being based on plausible hypotheses. If we should learn one lesson from the randomised controlled trials, it is that treatments cannot be assumed to be beneficial based on theory alone. Formal scientific evaluation of all treatments is essential.

**Targets for therapy in patients with heart failure**

Three major cardiovascular pathways leading to progression of heart failure or death are obvious (Fig. 1).

1. Left and/or right ventricular function may slowly deteriorate, either due to progressive ventricular remodelling, due to decline in the contractile properties of cardiac myocytes or due to an increased load on the heart due to changes in neuro-endocrine, peripheral vascular and/or renal function

2. Left ventricular function may decline abruptly due to coronary vascular occlusion

3. Cardiac function may decline abruptly due to the onset of an arrhythmia, usually atrial fibrillation when the event is not fatal

This is a simple scenario and is a useful starting point, but reality is likely to be much more complex. Ventricular remodelling does occur after myocardial infarction and may be extensive in the first year\textsuperscript{14}; thereafter, changes are small\textsuperscript{15}. Long-term changes in ventricular volume
in patients with chronic heart failure in response to ACE inhibitors are poorly documented, with studies incorporating few patients\textsuperscript{16} or showing only small changes\textsuperscript{17}. The benefits of β-blockers may develop over a longer period and may be more substantial\textsuperscript{18–20}, but long-term data are still sparse. The mechanisms of ventricular remodelling are poorly understood and likely to reflect a complex array of hypertrophy, cell death and myocardial fibrosis\textsuperscript{21} in response to neuro-endocrine and haemodynamic factors\textsuperscript{22}.

A number of ‘ischaemic’ syndromes could make an important contribution to ventricular remodelling. Transmural infarcts, without a surviving epicardial rim of myocardium, may be subject to high and unprotected wall stress in the infarcted zone and, therefore, may be much more likely to remodel. Partial thickness infarcts may lead to an acute decline in ventricular function, although be less likely to trigger extensive remodelling. Recurrent myocardial ischaemia will alter systolic function, neuro-endocrine activation, wall stress and probably accelerate apoptosis. Non-functioning but viable (i.e. hibernating or stunned) myocardium may also be associated with accelerated apoptosis. Patent infarct related arteries may limit remodelling, by modifying the ‘ischaemic’ substrate, although it is also possible that the reverse is true because the nature of the myocardial injury may also determine arterial patency\textsuperscript{23,24}. Silent occlusion of coronary arteries leading to a progressive decline in ventricular function may manifest as worsening heart failure rather than overt ischaemia\textsuperscript{25}. The extent to which exertional breathlessness in heart failure is predominantly a manifestation of myocardial ischaemia is also unknown. We are just beginning to unravel the prevalence of these ischaemic syndromes. They appear to be common\textsuperscript{22,26–28}, it is likely they are important, but the efficacy and nature of treatment directed at them is uncertain.

Progression of heart failure reflects not a vicious cycle, but a matrix (Fig. 1). Myocardial ischaemic events may lead to ventricular remodelling and arrhythmias. Arrhythmias may lead to a decline in ventricular function and myocardial ischaemia. Ventricular remodelling may predispose to arrhythmia. Ventricular remodelling could even predispose to ischaemic events, including vascular occlusion, because coronary arteries have to remodel over the epicardial surface of the heart, because the metabolic demands of the failing myocardium are increased due to hypertrophy and increased wall tension and because of activation of haemostatic factors\textsuperscript{29}.

However, the most common manifestation of a vascular event in patients with heart failure may be sudden death\textsuperscript{25,30,31}. Epidemiological studies suggest that about 30% of all patients in the community who suffer a myocardial infarction will not reach hospital alive\textsuperscript{32,33}. It is likely that patients with heart failure, who have less ventricular reserve and who are more prone to arrhythmias have a much higher rate of sudden
death within the first few minutes of a myocardial infarction. The failure of anti-arrhythmic medication to improve survival in patients with heart failure may have more to do with the inappropriateness of the target than the toxicity of the drugs\textsuperscript{30,34,35}. This may explain why implantable defibrillators have been shown to reduce mortality, so far, only in highly selected groups of patients with heart failure\textsuperscript{10,11,36,37}.

In view of the above, management of coronary disease could be the most important target for therapy in order to improve prognosis in the great majority of patients with heart failure, while the potential of therapy directed at the coronary circulation to improve the symptoms of heart failure should also be recognised.

**Diagnostic steps in patients with heart failure and ischaemic heart disease**

The over-riding reason for carrying out a diagnostic investigation in any patient, including those with heart failure, is to assist in deciding what treatment is most likely to benefit a patient. Until a treatment has been demonstrated to be effective (preferably cost-effective) then investigations to decide whether it should be deployed cannot be considered mandatory and could be considered undesirable.

European guidelines do not recommend routine coronary arteriography or myocardial viability testing in patients with heart failure\textsuperscript{38–41}. This is logical as the only treatments for heart failure secondary to left ventricular systolic dysfunction that are agreed to improve prognosis are ACE inhibitors, β-blockers and, with less certainty, spironolactone\textsuperscript{4–9}. There is no evidence that these treatments exert substantially different benefits in patients with or without ischaemic heart disease (IHD) and, therefore, no need to carry out diagnostic stratification for this purpose\textsuperscript{42,43}. Many patients with heart failure will have clear clinical evidence of IHD heart disease, usually a myocardial infarction and/or a previous revascularisation procedure. These patients do not require angiography to establish the nature of their left ventricular dysfunction although, some would argue, it is important to establish the pattern of their coronary disease. However, in the absence of disabling symptomatic angina uncontrolled by medical therapy, there is no randomised controlled trial to show that revascularisation improves symptoms or prognosis in heart failure or, indeed, in any patient with a left ventricular ejection fraction <35%. Therefore, there is no mandate for coronary arteriography in such patients. In patients who have no definitive history of ischaemic heart disease, a coronary angiogram is required if it is considered desirable to exclude coronary disease. However, again, in the absence of angina, there is no justification for revascularisation and the recommended medical
treatment will be similar whether or not ischaemic heart disease is the cause; therefore, there is no mandate for arteriography. Of course, for prognostic reasons\textsuperscript{44}, for patient information, for research reasons and to satisfy the curiosity of doctors, coronary arteriography will often be carried out. Similar arguments apply to the use of investigations to detect ‘silent’ ischaemia, stunning and hibernation. Merely showing that a test predicts a poor outcome does not prove that an intervention is effective or safe. Until it can be shown that angiography and/or myocardial viability testing are useful in selecting treatments that are shown to alter outcome, they cannot be considered to have a routine place in the management of patients.

In summary, current evidence does not support the need for routine investigations for the presence of the pattern of coronary disease in patients with heart failure. However, investigation is justified when concomitant angina unresponsive to medical therapy is present.

**Standard treatments for heart failure in patients with ischaemic heart disease**

*Diuretics*

Clinical experience and placebo-controlled trials indicate that diuretics improve the symptoms of heart failure, but there are no substantial clinical trials to show whether they alter prognosis. Thiazide diuretics have reduced both the risk of myocardial infarction and left ventricular failure in trials of hypertension\textsuperscript{45-47}.

*Digoxin*

The role of digoxin in the management patients with heart failure in sinus rhythm is uncertain. Studies that helped define a potential role for digoxin were conducted prior to β-blockers entering wide-spread use in heart failure and now need to be repeated (Table 1). Digoxin still

<table>
<thead>
<tr>
<th>Mean follow-up 3 years</th>
<th>Placebo No. with event/total</th>
<th>Digoxin No. with event/total</th>
<th>Change Absolute/relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD (71%)</td>
<td>873/2398 (36.4%)</td>
<td>731/2405 (30.4%)</td>
<td>-6.0%/16%</td>
</tr>
<tr>
<td>Non-IHD (29%)</td>
<td>413/996 (41.5%)</td>
<td>306/983 (31.1%)</td>
<td>-10.4%/25%</td>
</tr>
</tbody>
</table>

Statistical tests for heterogeneity of action between IHD and non-IHD were not significant.
appears to have an important role in the control of atrial fibrillation in heart failure even in the presence of a β-blocker\textsuperscript{48,49}.

A combined analysis of the PROVED\textsuperscript{50} and RADIANCE\textsuperscript{51} trials suggested that withdrawal of digoxin from patients with dilated cardiomyopathy led to a decline in exercise capacity and ejection fraction and markedly increased the risk of worsening heart failure\textsuperscript{52}. However, there was no increased risk of deterioration on withdrawing digoxin from patients with heart failure due to IHD. The large DIG trial showed a trend to excess mortality with digoxin due to myocardial infarction and sudden death, both potential manifestations of IHD\textsuperscript{53}. Subset analysis according to aetiology suggested a smaller impact of digoxin on the combined end-point of worsening heart failure leading to death or hospitalisation in patients with IHD.

β-Blockers might reduce the efficacy of digoxin, if digoxin’s benefit is primarily related to heart rate reduction. On the other hand, β-blockers might protect against unwanted side-effects of digoxin, while digoxin could limit the possibly unwanted acute negative inotropic effect of β-blockers, producing a beneficial synergy between agents. More research into the current role of digoxin for the management of patients with heart failure and ischaemic heart disease is required.

\textit{ACE inhibitors and angiotensin receptor antagonists}

Clinical trials show that ACE inhibitors improve symptoms and reduce morbidity and mortality in patients with chronic heart failure (Table 2)\textsuperscript{54,55} and after myocardial infarction\textsuperscript{56–58}. The hypothesis that the principal benefit of ACE inhibitors is mediated through a reduction in ventricular remodelling is widely accepted, but there is little evidence to support this belief (see above)\textsuperscript{59}.

There is considerable evidence that ACE inhibitors exert benefit by reducing the risk of recurrent vascular events and this may be their most important effect. Perhaps the clearest evidence for the vascular effects of ACE inhibitors comes from a study from which heart failure patients were excluded, the HOPE study\textsuperscript{60}. In HOPE, ramipril reduced the risk of death, myocardial, stroke and cardiac arrest among patients with or at high risk of vascular disease. A reduction in sudden death, a common presentation of acute vascular occlusion, was also observed. The SOLVD studies, comparing enalapril and placebo in patients with heart failure or major chronic left ventricular systolic dysfunction, also showed a reduction in myocardial infarction (Table 3)\textsuperscript{61}. These data were supported by trends to a reduction in myocardial infarction in all of the landmark studies of ACE inhibitors in patients with post-infarction heart failure or left ventricular systolic dysfunction\textsuperscript{56,58,61,62}. It
is also clear that ACE inhibitors reduce the risk of sudden death in patients with heart failure.\textsuperscript{30,55,56}

The mechanism by which ACE inhibitors reduce arterial occlusive events is uncertain. ACE inhibitors have been reported to improve coronary endothelial function in patients\textsuperscript{63} and the development of fatty streaks in animal models\textsuperscript{64,65}, although the latter requires toxic doses of ACE inhibitors and the relevance of the animal models are open to question\textsuperscript{64}. A recent report indicated no effect of ACE inhibitors on the development of carotid atherosclerosis\textsuperscript{66}, suggesting that the predominant effect of ACE inhibitors may be due to reducing plaque

### Table 2 Trials of ACE inhibitors in chronic heart failure

<table>
<thead>
<tr>
<th>Trial: mean follow-up</th>
<th>Placebo Mortality/total</th>
<th>ACE inhibitor Mortality/total</th>
<th>Change in mortality Absolute/relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus: 0.5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (77%)</td>
<td>49/97 (50.5%)</td>
<td>23/95 (24.2%)</td>
<td>-26.3%/48%</td>
</tr>
<tr>
<td>Non-IHD (23%)</td>
<td>7/29 (24.1%)</td>
<td>9/28 (32.1%)</td>
<td>+8.0%/+33%</td>
</tr>
<tr>
<td>V-HeFT-II: 2.5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (53%)</td>
<td>78/208 (37.5%)</td>
<td>77/219 (35.2%)</td>
<td>-2.5%/7%</td>
</tr>
<tr>
<td>Non-IHD (47%)</td>
<td>75/193 (38.9%)</td>
<td>55/184 (29.9%)</td>
<td>-9.0%/23%</td>
</tr>
<tr>
<td>SOLVD treatment: 3.5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (71%)</td>
<td>362/927* (39.1%)</td>
<td>322/903* (35.7%)</td>
<td>-3.4%/9%</td>
</tr>
<tr>
<td>Non-IHD (29%)</td>
<td>148/352* (42.1%)</td>
<td>130/381* (34.1%)</td>
<td>-8.0%/19%</td>
</tr>
<tr>
<td>Garg &amp; Yusuf meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (64%)</td>
<td>488/1757 (27.8%)</td>
<td>415/1997 (20.8%)</td>
<td>-7.0%/17%</td>
</tr>
<tr>
<td>Non-IHD (36%)</td>
<td>187/1006 (18.6%)</td>
<td>173/1132 (15.3%)</td>
<td>-3.3%/18%</td>
</tr>
<tr>
<td>Mortality or hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>704/1757 (40.1%)</td>
<td>566/1997 (28.3%)</td>
<td>-11.8%/29%</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>292/1006 (29.0%)</td>
<td>263/1132 (23.2%)</td>
<td>-5.8%/20%</td>
</tr>
</tbody>
</table>

Statistical tests for heterogeneity of action between IHD and non-IHD were not significant.

*Recalculated from percentages at crude annualised.

### Table 3 Effects of enalapril on myocardial infarction and unstable angina in the SOLVD trials

<table>
<thead>
<tr>
<th>Placebo At risk</th>
<th>Placebo Events</th>
<th>Enalapril At risk</th>
<th>Enalapril Events</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>2683</td>
<td>28.1</td>
<td>2667</td>
<td>24.1</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>710</td>
<td>14.1</td>
<td>723</td>
<td>8.9</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2517</td>
<td>28.2</td>
<td>2552</td>
<td>23.7</td>
</tr>
<tr>
<td>No prior MI</td>
<td>880</td>
<td>16.5</td>
<td>835</td>
<td>12.1</td>
</tr>
<tr>
<td>Angina</td>
<td>1216</td>
<td>39.1</td>
<td>1179</td>
<td>30.0</td>
</tr>
<tr>
<td>No angina</td>
<td>2182</td>
<td>17.5</td>
<td>2214</td>
<td>15.9</td>
</tr>
</tbody>
</table>

**Statistical tests for heterogeneity of action between IHD and non-IHD were not significant.**
rupture rather than the development of atherosclerosis. ACE inhibitors also increase endogenous thrombolysis and so could prevent plaque rupture progressing to coronary occlusion.\textsuperscript{67–69}

A meta-analysis of trials of ACE inhibitors in heart failure showed a trend to greater reduction in mortality and the composite end-point of death or hospitalisation for heart failure among patients with IHD than those without.\textsuperscript{70} However, the SOLVD studies showed that ACE inhibitors could reduce the coronary event rate even in patients with heart failure not primarily due to IHD.\textsuperscript{61} As coronary disease was not rigorously excluded in the ‘non-IHD’ population in these studies, it is entirely plausible that most of the benefit observed in patients with heart failure even without overt coronary disease is due to a reduction in coronary occlusion (Table 3).

Recently, the ELITE-II study suggested that angiotensin receptor antagonists were not superior and, indeed, may not be as effective as ACE inhibitors in patients with heart failure.\textsuperscript{71} No subgroup data were presented to indicate whether patients with IHD fared differently. However, there were trends to more vascular deaths in the losartan group and a significant excess of sudden, possibly vascular, death.\textsuperscript{30} Also, among patients treated with β-blockers, a possible therapeutic marker for IHD, there was a significant excess of deaths among those randomised to losartan compared to captopril. These data lend support to the view that increases in vascular wall bradykinin and prostaglandin may be an important mechanism of ACE inhibitor benefit.\textsuperscript{59}

In summary, ACE inhibitors form one of the mainstays of the treatment of heart failure secondary to IHD. Overall, when analysed on an intention to treat basis, studies suggest that ACE inhibitors reduce mortality by about 23% and death or hospitalisation for worsening heart failure by 37% in patients with IHD.\textsuperscript{70} Intention-to-treat studies ignore cross-over effects, which are often substantial, leading to an underestimate of the real magnitude of a treatment’s benefit. The true benefit of ACE inhibitors may be twice as great as the studies suggest. With the exception of a history of angio-oedema, there are no absolute contra-indications. A few patients will not tolerate ACE inhibitors because of renal dysfunction or hypotension.

**Beta-blockers**

Clinical trials show that β-blockers improve symptoms and reduce morbidity and mortality in patients with heart failure (Table 4).\textsuperscript{9,65,72} As with ACE inhibitors the mechanism of benefit is uncertain. Compared to ACE inhibitors, studies have shown much more striking effects of β-blockers on left ventricular systolic function.\textsuperscript{22} This marked reverse
remodelling might be due to prevention of ischaemia and stunning or the resuscitation of myocardial hibernation. At first sight, the fact that most studies show that ventricular function improves to a greater extent and more consistently in patients with heart failure due to dilated cardiomyopathy than in those with IHD appears to confound this hypothesis, but on further consideration perhaps the reverse is true. Subendocardial ischaemia has been documented in patients with dilated cardiomyopathy in the absence of epicardial coronary disease, possibly reflecting microvascular disease and a low arterial-subendocardial pressure gradient during diastole when blood flow occurs. Thus, dilated cardiomyopathy may be a model of chronic myocardial ischaemia without infarction. In contrast, most patients with heart failure and IHD have had a myocardial infarction and, therefore, a myocardial scar that will not respond, at least in the short- or medium-term, to therapy. This could account for the lesser response in patients with IHD. Relief of stunning and or hibernation could account for those cases with IHD who respond, in terms of ventricular function, like a patient with dilated cardiomyopathy. Extensive scar without ischaemia could account for why some patients with IHD do not respond, in terms

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mortality/total</th>
<th>Carvedilol Mortality/total</th>
<th>Reduction in mortality Absolute/relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>USCT: 6.7 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD (48%)</td>
<td>17/189 (9.0%)</td>
<td>13/332 (3.9%)</td>
<td>-5.1%/57%</td>
</tr>
<tr>
<td>Non-IHD (52%)</td>
<td>14/208 (6.7%)</td>
<td>9/362 (2.5%)</td>
<td>-4.2%/63%</td>
</tr>
<tr>
<td>CIBIS-II: 1.3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>121/654 (18.5%)</td>
<td>75/662 (11.3%)</td>
<td>-7.2%/39%</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>15/157 (9.6%)</td>
<td>13/160 (8.1%)</td>
<td>-1.5%/16%</td>
</tr>
<tr>
<td>MERIT: 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>161*/1312 (12.3%)</td>
<td>103*/1294 (8.0%)</td>
<td>-4.3%/35%*</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>56*/689 (8.1%)</td>
<td>42*/696 (6.0%)</td>
<td>-2.1%/26%*</td>
</tr>
<tr>
<td>BEST: 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>7/791</td>
<td>7/796</td>
<td>Non-significant 10% reduction in mortality.</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>7/563</td>
<td>7/558</td>
<td>No heterogeneity between IHD/non-IHD</td>
</tr>
<tr>
<td>COPERNICUS: 0.9 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>140/760 (18.4%)</td>
<td>103/778 (13.2%)</td>
<td>-5.2%/31%</td>
</tr>
<tr>
<td>Non-IHD</td>
<td>50/373 (13.4%)</td>
<td>27/378 (7.1%)</td>
<td>-6.3% / 48%</td>
</tr>
</tbody>
</table>

Table 4 Trials of β-blockers in heart failure

Statistical tests for heterogeneity of action between IHD and non-IHD were not significant for all studies. Divide absolute benefit by duration of follow-up to compare absolute benefits across trials. *Recalculated from figure.
of ventricular function, to a β-blocker. β-Blockers may be the best available test for the presence of myocardial stunning or hibernation, it may also be the best therapy\(^{22,79,80}\). These issues are currently being addressed in a substantial (\(n = 400\)) clinical trial, the CHRISTMAS study\(^{22}\), in which patients, stratified by the volume of hibernating myocardium, are randomised to placebo or carvedilol. The study will report in 2001.

Despite a potentially greater and more consistent effect of β-blockers on ventricular function in patients with dilated cardiomyopathy, these agents appear to have similar or greater effects on mortality in patients with IHD\(^{65,81,82}\). This suggests that β-blockers have an additional mechanism of benefit in patients with IHD that compensate for their less consistent effects on ventricular function. The obvious candidate mechanism for this effect is coronary protection. β-Blockers have not been shown to reduce restenosis after atherectomy, a process that may be somewhat related to endogenous atherosclerosis\(^{83}\). β-Blockers may modify vascular wall permeability to lipid particles, while drugs such as carvedilol, that can retard oxidation of LDL, may reduce lipid accumulation in plaque\(^{64}\). β-Blockers may also reduce the risk of plaque rupture or increase endogenous thrombolysis\(^{84}\).

At first sight, the studies of heart failure have generally not shown a reduction in myocardial infarction with β-blockers. This is contrast with previous and recent studies of β-blockers post-infarction, where a substantial effect on recurrent myocardial infarction was observed\(^{12,85,86}\). The reason for the difference probably reflects differences in the presentation of myocardial infarction. It is likely that most recurrent infarctions in studies of heart failure present as sudden death\(^{30}\) and studies of β-blockers show that, numerically, this is their most important effect\(^{3,7,8}\). β-Blockers could not only reduce the rate of infarction, but also reduce the risk of subsequent arrhythmia; therefore it would not be surprising to see an increase in non-fatal myocardial infarction with β-blockers in patients with heart failure.

The evidence that β₁-selective and non-selective agents exert different effects is inconclusive\(^{85,87}\). Only non-selective agents have been shown to reduce mortality, long-term, after myocardial infarction, although meta-analysis failed to show conclusive evidence of heterogeneity\(^{86,88}\). Similarly, there are trends to a greater effect with non-selective agents in heart failure but only in some analyses have these shown a significant effect\(^{89,90}\). Confirmation of the hypothesis that there are differences in the effect of β-blockers in heart failure is being sought in a study (COMET) comparing metoprolol with carvedilol in patients with heart failure\(^{87}\).

In summary, β-blockers are part of the first-line treatment for all patients with heart failure secondary to left ventricular systolic dysfunction regardless of the underlying aetiology and, apart from a few patients with recent severe decompensation, severity. The only absolute contra-indication
is asthma but use may be limited by low arterial pressure (e.g. systolic <90 mmHg) and bradycardia. Initial exacerbation of symptoms is not uncommon but, with persistence, this is usually reversed. More than 85% of patients initiated on a β-blocker can be maintained on them3,7,8.

**Spironolactone**

One substantial randomised controlled study, unsupported by any smaller trials, has shown that the combination of spironolactone and an ACE inhibitor, compared to ACE inhibitor alone, reduced mortality substantially in patients with severe heart failure6. Patients taking β-blockers or digoxin in addition to their ACE inhibitor appeared to obtain even greater benefits from spironolactone. Spironolactone also appeared to improve symptoms. Reductions in both sudden death and death from progressive heart failure were observed. Non-significant reductions in hospitalisation due to myocardial infarction and stroke were also noted on spironolactone despite the improvement in prognosis, which exposed patients to a longer period at risk of non-fatal events. Patients with and without IHD benefited equally.

In summary, spironolactone should be considered in all patients with heart failure secondary to left ventricular systolic dysfunction who remain severely symptomatic despite treatment with ACE inhibitors, β-blockers and a substantial dose of conventional diuretic. Further clinical trials of aldosterone receptor antagonists in post-infarction ventricular dysfunction and in milder degrees of heart failure are expected.

**Hydralazine and nitrates**

Compared to other available treatments, the efficacy of this combination is not well established and it is often poorly tolerated91,92. Only 186 patients were randomised to this combination in V-HEFT-I study and up to 50% failed to tolerate one or other component92. Its use, even as an alternative to ACE inhibitors where they are not tolerated, is open to doubt. There is little evidence that adding either of these agents to a standard regimen of diuretics, ACE inhibitors and β-blockers confers any benefit on symptoms or prognosis93,94. However, nitrates may be useful in the management of angina. Whether short- or long-acting nitrates are preferred is open to question.

**Amiodarone**

Trials of amiodarone after myocardial infarction have shown no major impact on mortality. Two randomised trials have been conducted in patients with heart failure; one open-label95, the other double-blind96,97. The open-label, GESSICA study suggested a substantial reduction in mortality. 30% of patients had dilated cardiomyopathy or Chaga's
disease and a substantial number had a history of alcoholism. Only 39% of patients had had a myocardial infarction. However, there was a trend to greater benefit in those with IHD\(^98\). In CHF-STAT, over 70% of patients had IHD as the cause for heart failure. This double-blind trial showed no overall effect on mortality, but patients without IHD did have a substantial prognostic benefit and a reduced need for hospitalisation\(^96,97\).

A meta-analysis of trials of amiodarone suggested an overall mortality benefit\(^99\), but the validity of the analysis must be questioned as there was clear heterogeneity between the effect observed in GESSICA and the other trials, in which case meta-analysis is an inappropriate way to assess effect.

Calcium antagonists

Substantial trials of amlodipine\(^100,101\), felodipine\(^102,103\) and diltiazem\(^104\) have been reported none of which showed an overall effect on mortality. The PRAISE trial showed a 60% reduction in mortality in patients without IHD but no effect in those with IHD\(^100\). However, it is possible that control of hypertension in those with hypertensive heart disease was largely responsible for the result. A second trial with much more stringent diagnostic entry criteria for dilated cardiomyopathy has been conducted to test the validity of the results of the first PRAISE trial\(^101\). This showed no mortality benefit. The neutral effect of amlodipine on mortality suggests that this agent is safe for use in patients with heart failure.

The DiDi trial\(^104\), conducted exclusively in patients with dilated cardiomyopathy, suggested that diltiazem improved symptoms and exercise capacity but had no effect on prognosis. In view of the propensity of diltiazem to precipitate heart failure after myocardial infarction, it would seem wise to avoid this agent whenever possible in patients with heart failure\(^105\). Post-infarction trials with verapamil have suggested either no benefit or harm in patients with heart failure\(^106,107\).

In summary, amlodipine has been established as a safe agent for use in patients with heart failure and may be used to manage angina in this setting. Whether it is of benefit to add amlodipine to diuretics, spironolactone, ACE inhibitors and β-blockers in patients who have persistent hypertension is untested.

Standard treatments for coronary disease in patients with heart failure

β-Blockers, calcium antagonists and nitrates have been dealt with above. Detailed discussion about the merits and risks of treatments directed at coronary vascular disease are dealt with in this section.
Smoking cessation

There is no substantial study investigating the effects of smoking cessation in heart failure. Smoking causes sympathetic activation, increases carboxyhaemoglobin thereby reducing oxygen transport in the circulation and has been implicated as a risk factor for atherosclerotic plaque rupture. For these reasons, it would seem wise to support cessation.

Antithrombotic measures

Heart failure is a prothrombotic state and patients with heart failure are at high risk of fatal and non-fatal vascular events. However, the evidence that antithrombotic treatment is beneficial, or indeed safe, in patients with heart failure is limited and controversial.

Warfarin has been shown, in randomised controlled trials, to reduce the long-term risk of re-infarction and death after myocardial infarction and observational data suggest that patients with heart failure treated with warfarin fare better, after adjustment for baseline variables: At least 20% of patients with heart failure have atrial fibrillation and these patients should certainly receive warfarin. However, whether warfarin is required in patients in sinus rhythm, regardless of the severity of ventricular dysfunction, remains in doubt.

Treatment guidelines in Europe and the US do not currently recommend routine prophylaxis with warfarin unless atrial fibrillation is present or even discourage its use.

Aspirin is widely considered to be part of the routine treatment of patients with coronary disease although the quality of the data on which this advice is based is increasingly open to question, as is the safety of aspirin in patients with heart failure. Individual long-term post-infarction trials have uniformly failed to show a reduction in mortality with aspirin (Fig. 2) and the validity of the meta-analysis of the aspirin trials is now seriously in doubt. It is only within the first 6 weeks after myocardial infarction that a reduction in mortality with aspirin has been proven. In contrast to the lack of effect on mortality, several studies suggest that aspirin might reduce the risk of myocardial infarction, which is a paradox given the high mortality of myocardial infarction. Aspirin has consistently been associated with increases in sudden death in secondary prevention studies, leading to the suggestion that chronic aspirin therapy may modify the presentation of vascular events rather than prevent them.

Trends to an adverse effect of aspirin on mortality amongst patients with heart failure were noted in subset analyses of two large long-term, postinfarction aspirin trials (Table 5). The circumstantial evidence
supporting the use of aspirin in patients with heart failure due to IHD is contradictory and inconclusive. Extensive summaries of the clinical evidence have been published recently. There are sound theoretical reasons for being concerned about an adverse effect of aspirin in patients with heart failure. Compared to healthy subjects, patients with heart failure have heightened activation of both vasoconstrictor and counter-regulatory vasodilator systems. There is plenty of opportunity for aspirin to have a negative impact on this delicate balance. Aspirin, in doses as low as 75 mg/day, has been shown both to impair vascular wall prostacyclin production for long periods and enhance the vasoconstrictor response to endothelin. High-dose aspirin can also provoke salt and water retention.

**Table 5** Effects of aspirin on total mortality in patients with and without evidence of heart failure after myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total mortality</strong></td>
<td>114/1565 (7.3%)</td>
<td>111/1565 (7.1%)</td>
<td>219/2267 (9.7%)</td>
<td>246/2267 (10.9%)</td>
</tr>
<tr>
<td>HF absent</td>
<td>NA</td>
<td>NA</td>
<td>6.9%</td>
<td>8.3%</td>
</tr>
<tr>
<td>HF present</td>
<td>NA</td>
<td>NA</td>
<td>21.2%</td>
<td>23.7%</td>
</tr>
<tr>
<td>NYHA I</td>
<td>5.8%</td>
<td>4.9%</td>
<td>7.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>NYHA II</td>
<td>8.9%</td>
<td>9.4%</td>
<td>14.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>First infarct</td>
<td>6.2%</td>
<td>5.9%</td>
<td>8.1%</td>
<td>9.2%</td>
</tr>
<tr>
<td>&gt;1 infarct</td>
<td>13.5%</td>
<td>13.5%</td>
<td>19.6%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Digoxin – no</td>
<td>6.3%</td>
<td>5.5%</td>
<td>7.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Digoxin – yes</td>
<td>13.7%</td>
<td>15.6%</td>
<td>21.0%</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

NYHA I was attributed to all patients after myocardial infarction who did not exhibit features of heart failure.
although it is unclear whether doses that are currently employed for cardiovascular prophylaxis do so\textsuperscript{116}.

The controversy surrounding aspirin in heart failure has been further fuelled by an apparent deleterious interaction between aspirin and ACE inhibitors (Fig. 3)\textsuperscript{29,111}. The theoretical basis for this interaction is that ACE inhibitors enhance vasodilator/anti-aggregatory prostaglandin production by enhancing bradykinin production and that this is an important mechanism of ACE inhibitor benefit\textsuperscript{29,59}. Aspirin may block this mechanism of benefit. Several small randomised controlled trials have shown that the central haemodynamic effects of ACE inhibitors are grossly attenuated by aspirin\textsuperscript{117,118}. The evidence of an interaction in the peripheral forearm or renal beds is less conclusive\textsuperscript{29}. The SOLVD studies\textsuperscript{29} and the HOPE study\textsuperscript{5} showed striking evidence of an aspirin/ACE inhibitor interaction. Worryingly, the SOLVD-treatment study suggested a higher mortality on enalapril compared to placebo amongst patients taking aspirin (Fig. 3). The postinfarction studies did not show a consistent interaction between aspirin and ACE inhibitors, perhaps reflecting the instability of baseline treatment in these studies\textsuperscript{29,119}. There is clear evidence that many patients cease to take their aspirin within a few months of infarction while many patients who developed heart failure were placed on open-label ACE inhibitors confounding any chance of observing an interaction\textsuperscript{120}. A recent meta-analysis blurred these differences between different sets of trials, and failed to support an interaction\textsuperscript{119}. However, randomised controlled trials on over 15,000 stable patients in SOLVD and HOPE suggests a highly significant interaction between aspirin and ACE inhibitors.

A recent, substantial randomised-controlled pilot study showed a trend to an excess of deaths and vascular events in patients with heart failure taking aspirin compared to no antithrombotic treatment or
warfarin\textsuperscript{5,121}. Aspirin was associated with a significant excess in hospitalisation, largely due to an increase in worsening heart failure. Warfarin appeared to reduce markedly the frequency of non-fatal vascular events but, compared to no antithrombotic treatment did not exert a beneficial trend in mortality. Patients randomised to warfarin had the least days in hospital and lowest risk of adverse events among the three groups. A large ($n = 4500$), randomised controlled trial comparing warfarin, aspirin and clopidogrel in patients with heart failure is currently being conducted\textsuperscript{5,121}.

In summary, it is not clear that aspirin or warfarin should be used routinely in patients with heart failure and coronary disease. Treatment guidelines in Europe and the US generally do not recommend routine use of aspirin in patients with heart failure\textsuperscript{39–41} or even discourage its use\textsuperscript{110}. Clopidogrel, an antiplatelet agent that does not interfere with prostaglandin production may prove the agent of choice in the majority of patients.

**Lipid lowering therapy**

Patients with heart failure have been uniformly excluded from studies of lipid lowering therapy. This may be appropriate, as there is evidence that patients with heart failure who have a low cholesterol may have a worse prognosis\textsuperscript{12,122,123}. Low cholesterol may only be a marker of more severe disease but the possibility that, in patients with heart failure, that it is intrinsically undesirable should also be considered.

The 4S study provided some evidence that in patients with ventricular dysfunction simvastatin can retard progression to heart failure\textsuperscript{124}. However, conclusive evidence that cholesterol-lowering therapy is appropriate in heart failure awaits appropriate trial evidence. There are theoretical concerns about the use of statins in heart failure. Statins reduce the naturally occurring antioxidant ubiquinone, an effect both on the metabolic pathway for ubiquinone production and due to a reduction in plasma LDL, a ubiquinone-rich particle\textsuperscript{125}. Patients with heart failure are under increased oxidant stress\textsuperscript{126} and ubiquinone supplements have been shown in some well controlled studies to improve symptoms, cardiac function and quality of life in patients with heart failure\textsuperscript{127,128} as well as reduce the risk of hospitalisation\textsuperscript{129}. Uncontrolled studies have also suggested favourable effects on ventricular function and prognosis\textsuperscript{130}. The exclusion of patients with heart failure from trials and the above theoretical concerns means that statins cannot yet be assumed to be safe or effective for routine use in patients with heart failure, coronary disease and hyperlipidaemia. Randomised clinical trials are underway.
Coronary revascularisation

Randomised controlled trials comparing revascularisation with medical therapy have effectively excluded patients with heart failure and patients with an ejection fraction less than 35% (Tables 6–8). Subgroup analyses of patients with mild left ventricular dysfunction have included only small numbers of patients and these have suggested only trends to overall benefit. Indeed, the CASS study only observed a significant benefit in a subgroup of patients with 3-vessel disease within the subgroup with left ventricular dysfunction (ejection fraction 35–50%). Although the relative benefit in this sub-subgroup appeared large, it represented a total of only 18 deaths. There are no randomised controlled trials of angioplasty in heart failure, but studies comparing

Table 6 Exclusion criteria for randomised controlled trials of coronary artery bypass grafting

<table>
<thead>
<tr>
<th>VA</th>
<th>LV aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>‘Serious cardiac disease’</td>
</tr>
<tr>
<td>CASS</td>
<td>EF &lt; 35%</td>
</tr>
<tr>
<td>ECSS*</td>
<td>EF &lt; 50%</td>
</tr>
</tbody>
</table>

*The only study to reach its primary end-point.

Table 7 CASS randomised study – summary of results

<table>
<thead>
<tr>
<th>EF 34–50% in 160 of 780 (21%) randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>6% of the 160 had heart failure</td>
</tr>
<tr>
<td>60% had angina</td>
</tr>
<tr>
<td>78 had 3 vessel disease of whom 7% had CHF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 vessel disease</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Mortality at 7 years</td>
<td>Overall</td>
<td>25 (30%)</td>
</tr>
<tr>
<td></td>
<td>3 vessel disease</td>
<td>13 (36%)</td>
</tr>
</tbody>
</table>

Table 8 VA randomised study – summary of results

<table>
<thead>
<tr>
<th>EF 34–50% in 325 of 686 (21%) randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low prevalence of CHF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 175</td>
<td></td>
<td>n = 150</td>
</tr>
<tr>
<td>5 years</td>
<td>47 (27%)</td>
<td>30 (20%)</td>
</tr>
<tr>
<td>7 years</td>
<td>65 (37%)</td>
<td>39 (26%)</td>
</tr>
<tr>
<td>11 years</td>
<td>89 (51%)</td>
<td>71 (47%)</td>
</tr>
</tbody>
</table>
medical treatment and angioplasty in patients with chronic stable angina have suggested that a medical strategy may be superior\textsuperscript{136,137} and may lead to better outcomes, reserving intervention only for when medical therapy has failed to control angina.

The combined effect of ACE inhibitors, $\beta$-blockers and spironolactone is probably to reduce mortality by $>50\%$ which matches or exceeds the expectations of benefit with revascularisation. National databases and observational reports are consistent with a 30-day operative mortality from coronary artery bypass surgery of about 7\%\textsuperscript{138}. Only observational studies and anecdote exist to support the selection of patients with heart failure for revascularisation using myocardial ‘viability’ testing. Considering the paucity of evidence to support revascularisation for heart failure, the relatively high postoperative morbidity and mortality and the costs generated by revascularisation, it is difficult to justify investigating patients with heart failure with a view to revascularisation.

A study comparing a strategy of whether or not to proceed to coronary investigation leading to revascularisation among patients with heart failure and evidence of a substantial volume of myocardium affected by reversible ischaemia or myocardial stunning/hibernation has been initiated in the UK\textsuperscript{138}. All patients will receive optimal medical therapy for heart failure. The study intends to recruit 800 patients to determine whether this strategy of management can reduce all-cause mortality by 25\%. A high rate of cross-over between treatment arms has been allowed for.

**Conclusions**

There is evidence that ACE inhibitors and $\beta$-blockers improve prognosis in patients with heart failure and ischaemic heart disease by enhancing ventricular function and by reducing coronary events. It is also likely that $\beta$-blockers, and possibly ACE inhibitors, have favourable effects on other ischaemic syndromes. In contrast, treatments directed primarily against coronary disease, including aspirin, statins and revascularisation, have not yet been shown to be effective or safe in patients with heart failure. There is little clinical imperative to investigate patients with heart failure for the presence and pattern of IHD until such time as these tests are shown to improve therapy for patients.

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