

Dilemmas in the drug treatment of heart failure

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SYNOPSIS

The clinical outcomes for patients in chronic heart failure can be improved by optimising drug and non-drug treatments. The cornerstones of drug therapies for heart failure are diuretics to achieve and maintain euvolemia, and ACE inhibitors to provide symptomatic benefits and prolong survival. There are many additional options for treatment and these often pose a therapeutic dilemma for the treating physician.

Index words: ACE inhibitors, beta blockers, spironolactone, digoxin.

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Introduction

Chronic heart failure is a syndrome associated with high mortality, frequent hospitalisation and poor quality of life. The increasing prevalence and incidence are creating a major public health problem.

Therapeutic strategies which favourably impact upon clinical outcomes in chronic heart failure include optimisation of non-pharmacological therapy (salt restriction, alcohol restriction, exercise and weight loss). Devices and surgery (primarily revascularisation) have a limited role. Optimising drug therapy for each patient also improves outcomes.

Nearly all patients should be treated with ACE inhibitors to provide symptomatic benefits and prolong survival. Diuretics are often added to achieve and maintain euvolemia. Adding other treatments can create a therapeutic dilemma for the treating physician.

Dilemma 1: Should the dose be increased in a symptomatic patient tolerating low to moderate doses of an ACE inhibitor?

Many physicians view maximising the dose of ACE inhibitors as an important strategy in optimising the management of patients with heart failure. Data in support of this approach come from the ATLAS trial¹, a comparison of high-dose versus low-dose lisinopril (32.5–35 mg versus 2.5–5 mg/day). High doses resulted in a small but beneficial impact on mortality. There was also a significant reduction in the combined end-point of mortality and hospitalisation for heart failure.

A practical approach may be to slowly increase the ACE inhibitor to the maximal dose tolerated by the patient. One of the major limitations to increasing the dose of ACE inhibitor

may be worsening of renal function. Often this is related to hypovolaemia which should be identified and managed appropriately, for example by reduction of diuretic dose. A small increase in serum creatinine is normal and to be expected as part of the mechanism of action of the drug on the kidney. Substantial rises in serum creatinine may necessitate reduction in dose or even cessation of the ACE inhibitor. Monitoring renal function is particularly important in patients who have underlying renovascular disease, or are taking non-steroidal anti-inflammatory drugs.

Dilemma 2: When should beta blockers be introduced?

Beta blocker therapy prolongs survival in patients with mild, moderate and severe symptoms.² It also improves the well-being of patients who are moderately to severely symptomatic. The patients in the studies that showed these benefits were also taking ACE inhibitors, usually in moderate doses. Beta blockers should therefore be added to the standard therapy of ACE inhibitor and diuretics in all symptomatic but stable patients, unless they have an absolute contraindication such as reversible airflow obstruction or atrioventricular block.

Dilemma 3: When should spironolactone be added?

In the RALES study³ spironolactone improved well-being and prolonged survival in patients with severe (Class III-IV) heart failure. This suggests that a patient who remains severely symptomatic after optimising ACE inhibitor and loop diuretic therapy is a candidate for treatment with spironolactone. Interestingly, this drug appears to provide benefit whether or not patients are taking beta blockers.

Physicians should be aware of the potential for clinically significant hyperkalaemia in combining spironolactone with an ACE inhibitor. Major problems with hyperkalaemia were not observed in the RALES study, possibly because of the relatively low doses of spironolactone (25 mg per day) and the frequent monitoring of potassium.

Dilemma 4: Is there still a role for digoxin?

With the recent demonstration of survival benefits for beta blockade and spironolactone, there is less place for digoxin in the treatment of heart failure. This is because the only major trial of digoxin in patients with systolic heart failure and sinus rhythm did not find a survival benefit.⁴ Nevertheless, this

study and others (primarily studies of withdrawal of digoxin) did show a beneficial effect of digoxin on patients' symptoms, with an overall reduction in hospitalisation due to heart failure. Digoxin may therefore still have a limited role, purely for symptom relief, in patients with severe heart failure.

Digoxin remains valuable therapy for patients in systolic heart failure with atrial fibrillation. It has an established role in controlling the ventricular response.

Dilemma 5: What is the best alternative for patients who cannot tolerate ACE inhibitors?

The commonest reason for intolerance of ACE inhibitors in patients with heart failure is cough. However, this problem seems less frequent than it is in patients with hypertension.

Angiotensin (AT₁) receptor antagonists have been suggested as potential alternatives in patients who cannot take ACE inhibitors. Indeed, the ELITE I study suggested that angiotensin receptor antagonists were better at prolonging survival than ACE inhibitors. This finding was, however, unable to be replicated in a much larger study adequately powered for mortality (ELITE II).⁵ Indeed, in the ACE inhibitor group slightly fewer patients died than in the angiotensin receptor antagonist group. This was also observed in the RESOLVD pilot study.⁶

The only other drugs compared in a head-to-head manner with ACE inhibitors have been hydralazine and nitrates, in the Ve-HeFT II study. This study found a short-term symptomatic benefit with the vasodilators, however they were clearly inferior to ACE inhibitors in prolonging survival.

Angiotensin receptor antagonists are probably the drugs of choice for patients who are truly intolerant of ACE inhibitors, providing that the intolerance is not due to factors such as angioedema or bilateral renal artery stenosis that would contraindicate the use of either class of drug. The benefits of blocking the renin angiotensin system are undisputed and drugs that act on this system (albeit via a different approach to ACE inhibitors) would be expected to offer at least some potential benefit. However, angiotensin receptor antagonists are not currently approved by the Therapeutic Goods Administration for the treatment of heart failure, even in patients who cannot tolerate ACE inhibitors.

Dilemma 6: Should patients with systolic heart failure be routinely anticoagulated?

There is no doubt that patients with heart failure have an increased risk for thromboembolism with sequelae such as cerebrovascular accident. However, it is not clear from retrospective studies whether routine anticoagulation in all patients reduces this risk sufficiently to offset the risk of serious bleeding.

The WASH study was a small open-label study of patients with heart failure and sinus rhythm, which compared aspirin or warfarin with no anti-thrombotic therapy. Preliminary data suggest that there were no major differences between the three approaches.

A pragmatic approach may be to continue anticoagulation in those patients who are already on it, but not to start anticoagulants in other patients unless there is another overwhelming indication, for example atrial fibrillation, substantial anterior wall akinesis or ventricular thrombus on echocardiography.

Dilemma 7: When should a patient with heart failure be referred to a specialist?

Referral for specialist assessment is warranted for many patients, given the complexities of the disease process, the possible aetiologies that may be contributing and the dilemmas in the management of heart failure. Many heart failure specialists have organised multidisciplinary approaches to the management of these patients. This involves close interaction between the heart failure specialist, the referring general practitioner, and a co-ordinating nurse practitioner, as well as ancillary paramedical staff including dietitians, physiotherapists and psychologists. These multidisciplinary approaches can improve outcomes by reducing the readmission of high-risk patients to hospital.

Dilemma 8: When should heart failure therapy be aimed at palliation rather than survival?

Patients with severe symptoms of heart failure have a quality of life worse than most chronic diseases, and a prognosis worse than most cancers. Many of these patients may benefit from shifting the focus of treatment from improving survival to improving quality of life.

Components of this care include strategies to relieve dyspnoea (diuretics, oxygen, opioids, benzodiazepines), improve uraemia and reduce lower limb oedema. Other components of palliation include the maximisation of comfort and dignity during the terminal stages of the illness, and the potential for receiving this support at home.

Summary

Heart failure is a complex disease requiring a multifaceted approach to management. Fortunately, a number of drugs can be used to optimise treatment of this condition. However, these therapeutic options raise a number of dilemmas and choices. Appropriate use of diuretics and ACE inhibitors is the cornerstone of medical therapy, and now beta blockers appear to offer substantial additional benefit. Patients with severe heart failure may also benefit from spironolactone.

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Self-test questions

The following statements are either true or false (answers on page 139)

1. Digoxin remains the first-line treatment for patients with heart failure who are in sinus rhythm.
2. Beta blockers are contraindicated in heart failure.

Beta blockers in heart failure

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SYNOPSIS

Recent trials have shown the unequivocal benefits of beta blockers in patients with chronic systolic heart failure. These benefits include improved survival (30-35%) and a reduced need for hospitalisation. However, beta blockers may also make a patient with heart failure worse, especially when treatment begins. Complications can generally be avoided by starting with extremely low doses and increasing the dose very slowly. Beta blockers should be added to optimal conventional therapy for heart failure, and started only when the patient is stable.

Index words: carvedilol, digoxin, metoprolol.

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Introduction

Traditional teaching was that beta blockers should be avoided in patients with heart failure. The rationale was that the sympathetic nervous system was overactive and provided a crucial level of compensation for the failing heart. To remove this by using a beta blocker would risk precipitating or exacerbating heart failure.

Recent trials have seriously challenged this conventional wisdom. The risks remain, but now need to be balanced against the major long-term benefits of beta blockade in chronic systolic heart failure (see box).

History

The Scandinavians have been promoting the use of beta blockers in systolic heart failure since the mid-1970s. A number of relatively small trials showed benefits, primarily in patients with non-ischaemic dilated cardiomyopathy. The MDC trial of Metoprolol in Dilated Cardiomyopathy in 1985 failed to show either harm or benefit.

In 1998 there was a meta-analysis of 18 double-blind placebo-controlled trials of beta blockers in chronic systolic heart

failure (see Table 1).¹ The overall reduction of total mortality from chronic beta blockade was 32%, with a 41% reduction in sudden deaths and a 37% reduction in hospitalisation.

Mechanism of action

The benefit of beta blockers almost certainly depends on blockade of beta-1 receptors. This action is consistent with the large body of data documenting high plasma catecholamines in severe heart failure, and more sophisticated studies demonstrating increased cardiac sympathetic activity and catecholamine release. Possible mechanisms for beta receptor blockade improving survival include:

- antiarrhythmic action
- anti-ischaemic action
- attenuation of catecholamine toxicity
- reduced cardiac remodelling.

Metoprolol and bisoprolol are both cardioselective beta blockers acting primarily on beta-1 receptors. By comparison,

Beta blockers in systolic heart failure

In patients with primarily severe systolic heart failure (low ejection fraction) beta blockade has the following long-term benefits which must be balanced against the short-term risks.

| <i>Long-term benefits</i> | <i>Short-term risks</i> |
|---|---|
| <ul style="list-style-type: none"> • improved survival • improved control of heart failure • reduced need for hospitalisation • improved quality of life • improved left ventricular ejection fraction | <ul style="list-style-type: none"> • worsening heart failure • bradyarrhythmias • prolonged intraventricular conduction • hypotension • worsening renal function |