Chronic heart failure
Part 2: treatment and prevention

The currently available pharmacological therapies and surgical interventions for chronic heart failure can have a major impact on patient survival and quality of life. Despite this, the overall prognosis of patients with this condition remains poor.

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Management options for patients with chronic heart failure (CHF) comprise pharmacological therapy, nonpharmacological measures such as dietary advice and exercise, and, in some patients, the use of pacemaker devices and surgery. These approaches are reviewed in this article, the second of a two-part article on CHF. The pathophysiology of CHF and patient assessment were covered in the first part of this article, published in the June issue of *Medicine Today* .

Pharmacological therapy

Large-scale, prospective, randomised clinical trials have established conclusively that beta blockers and inhibitors of the renin–angiotensin–aldosterone axis are safer and more effective therapies for CHF than those that directly increase contractility or that act as direct vasodilators. It should be noted, however, that most of these trials have been conducted in patients with systolic heart failure (defined somewhat arbitrarily in most trials as a left ventricular ejection fraction [LVEF] of less than 40%).

Systolic heart failure

Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors are now established as the cornerstone of therapy for patients with systolic dysfunction, regardless of symptomatic severity. However, concern about their important side effects, including symptomatic hypotension, worsening renal dysfunction, cough and angioedema, probably accounts for the widespread underprescribing and underdosing of these medications, particularly in the elderly. Clinical trial results indicate that these concerns are largely unfounded. Provided that they are introduced at a low dose and titrated slowly to the target dose shown to be effective in

IN SUMMARY

- **ACE inhibitors are indicated for all patients with systolic heart failure regardless of symptomatic severity.**
- **Beta blockers are approved for use in patients who have stable chronic symptomatic heart failure despite ACE inhibitor and diuretic treatment.**
- **Diuretics should be used in all patients with symptomatic heart failure to control symptoms and signs of congestion.**
- **Nonpharmacological approaches to CHF management include sodium and fluid restriction, exercise for patients with stable CHF and patient support.**
- **A multidisciplinary approach to CHF management markedly improves patient quality of life, reduces the need for hospitalisation and is cost effective.**
- **The most effective therapy available for heart failure is heart transplantation; its use is limited by donor organ availability.**
- **Despite the therapeutic options available, the overall prognosis of patients with CHF remains poor.**

Table 1. Use of ACE inhibitors in patients with CHF

- ACE inhibitors are indicated for all patients with systolic heart failure regardless of symptomatic severity
- Initiate treatment at low dose and titrate to the maximum tolerated dose over three to four weeks
- Advise patients taking ACE inhibitors that they may develop a cough; this occurs in 15 to 20% of patients taking these medications
- Before treatment initiation and during and after titration, check the patient's serum sodium, potassium and creatinine levels
- Warning signs for first dose hypotension are hyponatraemia, high diuretic dosage and hypotension (systolic blood pressure <100 mmHg) before the initiation of ACE inhibitor therapy

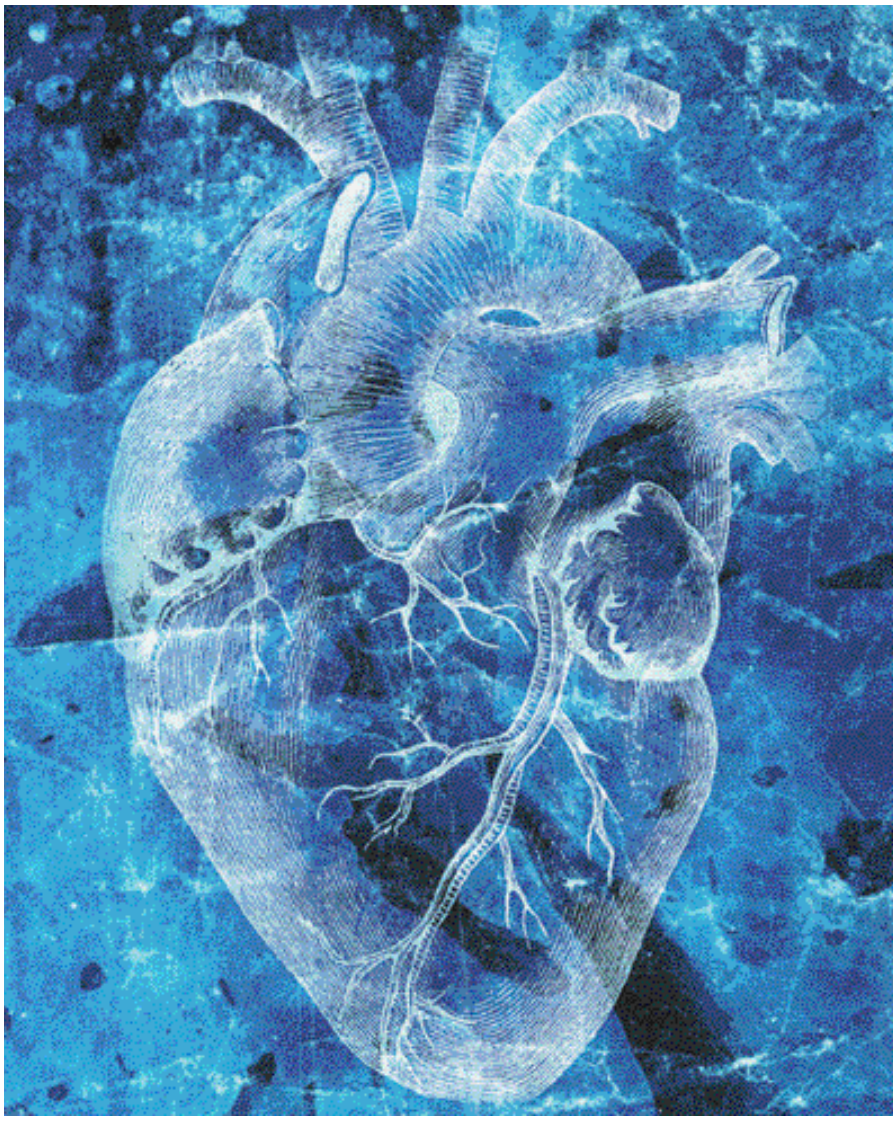
the major trials, ACE inhibitors are generally well tolerated.

Guidelines for the use of ACE inhibitors in heart failure are given in Table 1.

Beta blockers

Almost all 'standard' medications for patients with heart failure have mechanisms of action that result in acute haemodynamic and symptomatic improvement. The acute effects of beta blockers, in contrast, may produce haemodynamic deterioration, sometimes with severe symptomatic worsening, and thus the use of these medications has long been considered contraindicated in patients with CHF. Despite this, evidence has accumulated that chronic administration of beta blockers improves cardiac function and reduces both morbidity and mortality in patients with CHF. Indeed, evidence supporting the use of beta blockers in CHF patients randomised in controlled clinical trials far exceeds that for ACE inhibitors. Furthermore, the beneficial effects of beta blockers in relation to morbidity and mortality are additive to those observed with ACE inhibitors.

Three beta blockers are currently approved for the treatment of heart failure in Australia:



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- bisoprolol (Bicor)
- carvedilol (Dilatrend)
- slow-release metoprolol succinate (Toprol-XL).

Each of these agents has been shown to reduce mortality and hospitalisation due to CHF in large placebo-controlled trials. These benefits are not necessarily seen with other beta blockers. In the Carvedilol or Metoprolol European Trial (COMET), in which carvedilol and standard-release metoprolol tartrate were compared, better survival was observed in patients receiving carvedilol.

Guidelines for the use of beta blockers in heart failure are shown in Table 2.

Table 2. Use of beta blockers in patients with CHF

- Bisoprolol (Bicor), carvedilol (Dilatrend) and slow-release metoprolol succinate (Toprol-XL) are the three beta blockers currently registered and formulated for the treatment of heart failure in Australia
- These medications have been approved for use in patients who have stable chronic symptomatic heart failure (New York Heart Association Classes II to IV) despite ACE inhibitor and diuretic treatment
- Before beta blocker treatment is initiated, patients should have had stable symptoms for at least two weeks while taking their heart failure therapy
- Beta blockers should be started at a low dose and titrated at no less than two-weekly intervals as tolerated up to the target dose; two to three months should be allowed for this titration
- Patients who are about to start taking beta blockers should be warned of the possibility of short term worsening of their heart failure symptoms, symptomatic hypotension and bradycardia

Diuretics

Diuretics have been used in all the clinical trials of ACE inhibitors in heart failure, and they should be used in all patients with symptomatic heart failure to control symptoms and signs of congestion (Table 3). Thiazide or loop diuretics are suitable for use in combination with ACE inhibitors.

Generally, more effective diuresis is achieved by combining low doses of diuretics with different sites of action (so-called 'sequential nephron blockade') rather than using escalating doses of a single agent. Patients treated with combined diuretic therapy need to be closely monitored for electrolyte abnormalities and azotaemia. Both thiazide and loop diuretics can cause hypokalaemia and hypomagnesaemia; ACE inhibitors and potassium-sparing diuretics counteract these actions.

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists such as spironolactone (Aldactone, Spiractin) are usually considered in the class of potassium-sparing diuretics; however, there is accumulating evidence that the beneficial effects of these drugs in heart failure are unrelated to their modest diuretic action.

The Randomised Aldactone Evaluation Study (RALES) examined the use of spironolactone in combination with ACE inhibitors and a loop diuretic in patients with moderate to severe heart failure. It was shown that a low dose of spironolactone (25 to 50 mg/day) resulted in a highly significant improvement in survival and reduced the need for hospitalisation. Recognised side effects such as hyperkalaemia and azotaemia were rare, probably because of the low doses used and the close monitoring of patients enrolled in the trial.

A major drawback with the use of spironolactone in men is the relatively high incidence of gynaecomastia mediated by activation of the progesterone receptor. Eplerenone is a novel mineralocorticoid receptor antagonist that does not activate the progesterone receptor. In the recently reported Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced mortality and hospitalisation in patients with symptomatic heart failure after acute myocardial infarction. As with spironolactone, hyperkalaemia and azotaemia may occur during use of epleronone, but gynaecomastia and impotence are no more common than with placebo. Eplerenone is a promising drug for the management of CHF, but it is not yet approved in Australia.

Digoxin

The safety and efficacy of digoxin (Lanoxin, Sigmaxin), which has been used to treat heart failure for 300 years, have been established only recently. The Digitalis Investigation Group (DIG) study showed that digoxin significantly reduced the need for hospitalisation in patients with CHF who were in sinus rhythm at baseline and who were chronically maintained on an ACE inhibitor and diuretic. Digoxin had a neutral effect on mortality in this study. Thus, the evidence based indication for the use of digoxin in patients with CHF is for the relief of persisting symptoms despite the use of ACE inhibitors and diuretics.

The median daily dose and trough blood levels of digoxin in the DIG Study were 0.25 mg/day and 0.9 ng/mL, respectively. There is evidence that the risk of digoxin toxicity (including death) rises rapidly when the average daily digoxin dose exceeds 0.25 mg/day or when trough serum digoxin levels are above 1.0 ng/mL. The use of lower maintenance doses of digoxin (0.125 to 0.25 mg/day) is particularly important in women and in the elderly because of the age-related decline in renal function. This is likely to be a frequent issue in clinical practice as the elderly constitute the bulk of the heart failure population. Furthermore, digoxin toxicity may be difficult to recognise in the elderly. Concomitant medications (e.g. amiodarone, verapamil) that increase serum digoxin concentrations may also necessitate a reduction in the maintenance dose.

Digoxin can also be used to control atrial fibrillation, which, as mentioned in part 1 of this article (*Medicine Today*, June 2005), is present in up to one-third of

patients with CHF. The need for digoxin to control the heart rate in patients with atrial fibrillation has been questioned with the advent of beta blockers; however, a recent study in patients with CHF and chronic atrial fibrillation demonstrated better outcomes with combined digoxin and carvedilol therapy compared with either treatment alone.

Angiotensin II receptor antagonists

The currently accepted indication for angiotensin II receptor antagonists (ARAs) in CHF is for patients who are intolerant to ACE inhibitors due to cough. The benefit of ARAs in this population was clearly established by the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative study. In this study, the ARA candesartan (Atacand) significantly reduced the combined endpoint of cardiovascular death or hospitalisation in patients with CHF who had previously been found to be intolerant to ACE inhibitors.

Two head-to-head comparisons between an ARA and ACE inhibitor have been conducted in the setting of CHF. The larger of these, the Evaluation of Losartan in the Elderly II (ELITE II), reported no significant differences between losartan (Cozaar) and captopril; however, the survival curves showed a trend towards better survival in the ACE inhibitor-treated patients. A similarly designed study conducted in patients with heart failure following acute myocardial infarction (the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL]) reported a similar outcome.

Another large study conducted in patients with post-AMI heart failure (the Valsartan in Acute Myocardial Infarction Trial [VALIANT]) reported identical survival outcomes between three treatment groups: high dose valsartan (an ARA), high dose captopril and the combination of the two.

Two large studies (the CHARM-Added trial and the Valsartan Heart Failure Trial [Val-Heft]) have examined the impact of adding an ARA to an ACE inhibitor in patients with CHF. Both studies demonstrated that the addition of an ARA significantly reduced the risk of future hospitalisation due to CHF; however, the impact on mortality was less clear-cut.

Considered together, these studies suggest that ARAs and ACE inhibitors, when used in equivalent doses, produce the same outcomes when used as alternative therapies in patients with CHF. The major benefit obtained by combining these treatments in patients with CHF appears to be in reducing the need for hospitalisation.

Other agents

The combination of isosorbide dinitrate (Isordil, Sorbidin) and hydralazine (Alphapress, Apresoline) is another alternative for patients who are intolerant to ACE inhibitors. In patients with moderate heart failure, treatment with this combination was found to be associated with a trend towards improved survival compared with placebo; however, it was less effective than the ACE inhibitor enalapril.

The role of calcium antagonists in patients with systolic heart failure remains controversial. Most studies of older agents (such as verapamil, diltiazem and nifedipine) suggest that these drugs are potentially harmful and best avoided. However, two studies assessing the safety and efficacy of the long acting vascular selective

Table 3. Use of diuretics in patients with congestive heart failure

Class and examples	Advantages	Disadvantages
Thiazides Hydrochlorothiazide (Dithiazide) Indapamide (Dapa-Tabs, Indahexal, Insig, Napamide, Natrilix) Chlorthalidone (Hygroton)	Have an established role in the treatment of hypertension, particularly in the elderly	May be associated with hypomagnesaemia, hyperuricaemia, hyperglycaemia or hyperlipidaemia
Loop diuretics Frusemide (Frusehexal, Frusid, Lasix, Uremide, Urex) Ethacrynic acid (Edecrin) Bumetanide (Burinex)	Have potent, rapid onset and offset of action	May cause hypokalaemia or hypomagnesaemia, and associated with poor compliance
Potassium-sparing diuretics Spironolactone (Aldactone, Spiractin) Amiloride (Kaluril, Midamor) Triamterene (Hydrene 25/50 with hydrochlorothiazide)	A positive survival effect has been shown with spironolactone; counteract potassium and magnesium loss	May cause hyperkalaemia and azotaemia, especially if patients are also taking ACE inhibitors

calcium antagonists felodipine (Felodur, Plendil) and amlodipine (Norvasc) in heart failure suggest that these agents can be used safely in these patients.

Aspirin is indicated in patients with heart failure secondary to ischaemic heart disease.

Warfarin (Coumadin, Marevan) is indicated in patients with atrial fibrillation and heart failure. It is probably beneficial in patients with heart failure who are in sinus rhythm and have evidence of intracardiac thrombus on echocardiography; however, its value in other patients is unproven.

Diastolic heart failure

When diagnosed according to simple clinical criteria, up to 40% of patients with heart failure have predominantly diastolic dysfunction (defined by a LVEF 40 %). Diastolic dysfunction is more likely in the elderly, women, those with a history of hypertension and those with echocardiographic evidence of left ventricular hypertrophy. Therapeutic guidelines are less well defined for patients with diastolic heart failure due to a lack of clinical trial data.

The largest trial to date of any specific drug therapy in diastolic heart failure is the CHARM-Preserved trial. This trial reported a nonsignificant reduction of cardiovascular death or admission for heart failure in patients treated with candesartan compared with placebo, a somewhat disappointing result. Other large clinical studies that are underway include the Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) study and the Hong Kong Diastolic Heart Failure study.

Until further clinical trial results are available, treatment of diastolic heart failure remains largely empirical. Diuretics are indicated for the control of congestive symptoms, and beta blockers have been shown recently to improve diastolic function as judged by Doppler echocardiography. Calcium antagonists may be suitable alternatives for those patients with diastolic dysfunction who are intolerant to beta blockers.

Antihypertensive therapy is appropriate for patients with coexistent hypertension; the agent of choice may depend on comorbidities such as angina, diabetes or hypercholesterolaemia. ACE inhibitors or ARAs are probably the agents of choice for patients with left ventricular hypertrophy. A meta-analysis of 109 trials of different antihypertensive medications concluded that ACE inhibitors were about twice as effective in reversing left ventricular hypertrophy as beta blockers, calcium antagonists and diuretics. In the large Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, antihypertensive treatment initiated with the ARA losartan was compared with that initiated with the beta blocker atenolol in hypertensive patients with left ventricular hypertrophy (but without CHF). Both treatments produced a comparable degree of blood pressure reduction; however, losartan produced significantly greater regression of left ventricular hypertrophy and fewer adverse clinical events.

Nonpharmacological treatment and multidisciplinary management

Many patients with CHF will be taking a complex combination of drugs, not only for the treatment of heart failure but also for other illnesses. Not surprisingly, noncompliance with medical therapy is common, often leading to acute decompensation and rehospitalisation. Optimal treatment of patients with heart failure is probably best achieved by a multidisciplinary approach, using specialist nursing, pharmacy, physiotherapy, occupational therapy and social work personnel.

Multidisciplinary CHF clinics and programs have been established in most Australian States and Territories. The number and variety of the personnel within these clinics vary considerably, according to available funding. In addition, there is variability in the location of these clinics, some being based in hospitals and others in community care centres. In addition, telephone-based CHF programs are currently being evaluated as a support for rural and isolated patients.

Irrespective of their structure and location, all chronic care programs share the common goal of keeping the patient with CHF well and minimising the need for acute care. Specific approaches used to achieve this goal, and which involve the use of important nonpharmacological treatments (see Table 4), include:

- providing patient education and self-empowerment through techniques such as daily weighing and the use of a flexible diuretic regimen to deal with major weight variations
- providing patients with an action plan for dealing with possible emergencies
- optimising patient compliance with prescribed medication and lifestyle measures, such as salt restriction, daily exercise and smoking cessation
- ensuring that patients are receiving evidence based treatments and provided with appropriate dose titration schedules
- ensuring that patients are up to date with influenza and pneumococcal vaccinations.

There is now substantial evidence that this multidisciplinary approach to CHF management markedly improves patient quality of life, reduces the need for rehospitalisation and is cost effective.

Devices and surgery

Cardiac resynchronisation (biventricular pacing)

About one-third of patients with CHF have marked intraventricular conduction delay manifested as QRS widening on the surface ECG (usually left bundle branch block [LBBB]). LBBB produces several haemodynamic abnormalities that impair both systolic and diastolic function of the left ventricle, and its presence on the ECG

is associated with an increased risk of death in patients with CHF.

The rationale of cardiac resynchronisation therapy is that it corrects the haemodynamic abnormalities caused by intraventricular conduction delay and, thereby, improves patient outcomes. Initial clinical trials of cardiac resynchronisation therapy showed that it could be performed safely with a procedural success rate of over 90% and that it produced acute haemodynamic improvements.

Single-blind crossover and more recent double-blind controlled trials have been conducted in patients with advanced symptomatic heart failure (New York Heart Association [NYHA] Class III to IV despite optimal medical therapy) with low LVEF (<35%) and QRS widening (QRS duration >130 msec). These studies have shown consistent improvements in patients' quality of life, symptomatic status and exercise capacity for periods up to 12 months. In addition, echocardiographic substudies have shown significant reversal of left ventricular remodelling and improved ejection fraction.

Post-hoc analyses have not revealed any significant differences between the responses of patients with ischaemic heart disease versus nonischaemic causes of heart failure, nor between patients with LBBB versus other forms of QRS widening. Separate studies suggest that patients with atrial fibrillation, permanent right ventricle pacing or implanted cardioverter/defibrillator in association with systolic heart failure also improve with cardiac resynchronisation therapy.

Recently published large-scale clinical trials (the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION] trial and the Cardiac Resynchronization in Heart Failure [CARE-HF] study), as well as meta-analyses of earlier clinical trials of cardiac resynchronisation therapy, demonstrate significant reductions in CHF-related hospitalisations and in mortality. Cardiac resynchronisation therapy appears to be a promising new treatment for patients with advanced symptomatic CHF and intraventricular conduction delay.

Table 4. Nonpharmacological measures for CHF[1]

- Exercise and rehabilitation
  - regular physical exercise for clinically stable patients
  - bed rest for acute exacerbations or clinically unstable CHF
- Lifestyle modification
  - weight reduction for overweight or obese patients
  - salt restriction (less than 2000 mg/day)
  - fluid restriction (generally limited to 1.5 L/day for mild to moderate CHF and 1 L/day for severe CHF)
  - alcohol abstinence (for patients with cardiomyopathy) or limitation
  - discouragement of smoking
- Patient education on self-management
  - daily weight measurement to detect sudden weight gain
  - identification of warning signs of dyspnoea, oedema or abdominal bloating
- Patient support
- Vaccination against influenza and pneumococcal disease
- Avoidance of high altitude locations, and travel to very hot or humid climates undertaken with caution

Implantable defibrillators

The major indication for implantation of an automatic implanted cardioverter/defibrillator (AICD) is documented sustained ventricular tachyarrhythmia causing cardiac arrest or haemodynamic compromise. Most patients with this indication also have advanced left ventricular dysfunction (usually on the basis of ischaemic heart disease). Generally, the presence of symptomatic heart failure does not represent a contraindication to insertion of an AICD with the possible exception of patients with intractable NYHA Class IV symptoms. In all other patient groups, AICDs have been shown to improve survival when compared with optimal medical therapy alone.

Because the first episode of sustained ventricular tachyarrhythmia is often fatal or results in catastrophic brain injury, there has been considerable interest in the insertion of AICDs into patients known to be at high risk of such an event. Two recently published 'primary prevention' trials (the Multicenter Automatic Defibrillator Implantation Trial-II [MADIT II] and Sudden Cardiac Death/Heart Failure Trial [SCDHeft]) showed that implantation of AICDs into patients with severe left ventricular dysfunction with or without symptomatic heart failure improved their survival, although patients with advanced symptomatic (NYHA Class IV) CHF were excluded from both trials. The cost implications of translating these results into clinical practice are formidable.

Surgical treatment

Some patients with heart failure that is secondary to coronary artery disease will benefit from coronary revascularisation.

In addition, there is renewed interest in surgical remodelling of the left ventricle in patients who have suffered previous myocardial infarction. The role of surgical coronary revascularisation with or without left ventricular remodelling in the current era is being investigated in a large international multicentre trial (the Surgical Treatment for Ischemic Heart Failure [STICH] study). There is also interest in surgical correction of severe functional mitral regurgitation due to mitral annular dilatation; however, this approach should still be considered experimental. Other surgical approaches such as cardiomyoplasty (heart muscle wrapping procedure) and ventricular reduction (Batista procedure) have been abandoned.

Heart transplantation remains the most effective therapy currently available for the treatment of heart failure; however, it is limited by donor organ availability. Since 1984, about 1600 heart transplants have been performed in Australia. Two-thirds of recipients are still alive and well at 10 years post-transplant and about one-third at 20 years post-transplant.

Xenotransplantation (e.g. transplantation from pig to man) and mechanical heart replacement remain areas of intense research; both approaches could potentially solve the problem of donor organ shortage. A worldwide embargo remains in place on clinical trials of xenotransplantation; however, multiple clinical trials of various types of mechanical circulatory pumps are currently underway, including a multicentre trial of an Australian designed continuous flow pump (VentrAssist). As with pacing and defibrillator devices, the high cost of mechanical pumps is likely to restrict their clinical application.

Prevention of heart failure

As noted in the first part of this article (*Medicine Today*, June 2005), hypertension and ischaemic heart disease account for between 80 and 90% of cases of heart failure in our community. In addition, diabetes mellitus is emerging as a third major antecedent cause of cardiovascular disease and heart failure. Effective therapies are available for all three diseases, thus there is an enormous potential for the prevention of heart failure.

Combined analysis of large placebo-controlled trials of antihypertensive therapies shows that active treatment of hypertension reduces the risk of developing heart failure by about 50%. This risk reduction appears to be independent of the class of blood pressure lowering drug, with the exception of alpha-receptor blockers. In the large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), hypertensive patients treated with the thiazide diuretic, chlorthalidone (Hygroton), had a 50% reduction in the risk of heart failure compared with those treated with the alpha blocker doxazosin.

There is also evidence that for patients with established ischaemic heart disease (but without heart failure), treatment with statins, beta blockers or ACE inhibitors significantly reduces the risk of developing symptomatic heart failure.

Regarding diabetes mellitus (particularly in association with hypertension or diabetic nephropathy), several trials have shown that treatment of such affected patients with ACE inhibitors or ARAs reduces their risk of heart failure as well as other morbid cardiovascular events.

Conclusion

Although the currently available pharmacological and surgical therapies for CHF can prolong survival and improve quality of life, the overall prognosis of patients with CHF remains poor. With the proportion of elderly patients in our community expected to increase steadily over the next two decades, CHF is set to become a major epidemic. Thus, for patients with established CHF there is an urgent need to develop new therapeutic approaches that are applicable to all individuals, that optimise patients' quality of life and that minimise the economic burden on the community. Effective treatment of the main antecedents of CHF – namely, hypertension, ischaemic heart disease and diabetes – is probably the key to preventing the future development of this condition. MT

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Further reading

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DECLARATION OF INTEREST. Dr Swaraj: none. Associate Professor Macdonald has served on industry-sponsored advisory boards for the following heart failure medications: carvedilol, bisoprolol and eplerenone.