Introduction

Heart failure is a common, debilitating condition with a poor prognosis. It is an enormous public health problem in elderly populations, since the morbidity and mortality associated with it increase considerably with increasing age. Characteristic features comprise left ventricular systolic dysfunction with reduced ejection fraction with or without left ventricular hypertrophy. These changes result in activation of neurohormonal mechanisms, including activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS). However, elderly patients who present with heart failure often have preserved left ventricular systolic function (with almost normal ejection fraction); this used to be referred to as ‘diastolic heart failure’, but is better described as heart failure with preserved ejection fraction (HF-PEF). This being the case, heart failure is a heterogeneous disorder, with around half of elderly patients with the condition having normal left ventricular systolic function. Indeed, the cardiovascular status and overall health of an ageing individual result from a complicated interaction between typical cardiovascular changes associated with ‘normal’ ageing, and the development of cardiovascular disease associated with concurrent comorbidities, lifestyle, and social circumstances.

In the elderly, there is an increased incidence of HF-PEF, with characteristics differing from heart failure with reduced ejection fraction (HF-REF), including:

- A greater prevalence in women.
- A shift from coronary heart disease (CHD; in middle age) to hypertension (in advanced age).
- More comorbidities (i.e. CHD, diabetes, hypertension), and other age-related disorders.
- Reduced ventricular relaxation and compliance.

Standard heart failure treatments such as diuretics, neuroendocrine antagonists (angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRAs], and vasodilators have been less effective in HF-PEF than in HF-REF. New treatments and combination schedules are therefore urgently needed for the specific management of HF-PEF in elderly patients.

Pathophysiology and disease classifications

Heart failure with reduced ejection fraction (HF-REF)

The most frequent causes of HF-REF are hypertension and ischaemic heart disease (IHD). Other, less common causes comprise idiopathic cardiomyopathy, cardiotoxic agents (such as anthracyclines), myocarditis, and valvular heart disease. Irrespective of the cause, the key clinical consequences are systemic underperfusion and pulmonary congestion.

Neurohormonal changes in the RAAS lead to compensatory responses affecting the heart, renal and systemic vasculature. The marked extent and sustained duration of neurohormonal activation often leads to permanent cardiovascular changes. For example, angiotensin and aldosterone promote left ventricular hypertrophy in an attempt to increase stroke volume; this leads to increased myocardial oxygen demand, which may precipitate symptoms related to coronary artery disease (CAD) or trigger an acute event. Neurohormonal activation of the RAAS leads to: myocardial fibrosis and left ventricular remodelling with worsening of systemic hypoperfusion and pulmonary congestion, because of increased sodium and water retention and vasoconstriction; increased sympathetic tone, in an attempt to improve organ perfusion, and increased blood pressure with raised peripheral vascular resistance; and progressive deterioration of left ventricular function.

Natriuretic peptides

Endogenous natriuretic peptides represent another means by which the body tries to counteract the neurohormonal compensatory changes initiated by heart failure. Four natriuretic peptides exist:

1. Atrial natriuretic peptide (ANP) — produced by the atria due to myocardial stretching. Increased levels indicate raised intravascular volume.
2. B-type natriuretic peptide (BNP) — produced by the ventricles due to raised ventricular volume and pressure. ANP and BNP have the same physiological actions: increased sodium and water excretion; vasodilation; sympathetic inhibition (due to reduced catecholamine secretion); and RAAS inhibition (due to reduced renin secretion).
3. C-type natriuretic peptide (CNP) — produced by cardiac, peripheral vascular, pulmonary and renal endothelial cells in response to shear stress. CNP is a marked vasodilator and restricts the growth of vascular cells.
4. D-type natriuretic peptide — although this natriuretic peptide is linked with chronic heart failure, little is known about its pathophysiological function and relevance.
Neprilysin

Neprilysin, or neutral endopeptidase, is a membrane-bound enzyme primarily responsible for natriuretic peptide breakdown in the kidneys. Inhibition of neprilysin, and potentiation of the cardiovascular benefits of natriuretic peptides, is an important pharmacological feature of a novel drug category, angiotensin receptor neprilysin inhibitors (ARNIs), in HF-REF (see Treatment of heart failure in the elderly).

Heart failure with preserved ejection fraction (HF-PEF)

Elderly individuals are more likely to develop HF-PEF than their younger counterparts. Indeed, approximately 50–70% of elderly patients with heart failure have preserved ejection fraction. Characteristic features of HF-PEF comprise:8,10

- Increased end-diastolic pressure due to impaired active relaxation and reduced left ventricular compliance.
- Normal heart-chamber volumes, but reduced chamber compliance.
- Impaired atrial function, particularly during exercise.
- Echocardiographic evidence of:
  - Impaired long-axis function.
  - Systolic twist.
  - Torsional impairment.
  - Reduced systolic reserve.
- Interstitial fibrosis, leading to reduced myocardial compliance and raised resting ventricular pressures.

HF-PEF may develop due to various pathophysiological aspects of normal ageing (Figure 1).11,12 For example, myocyte number and function decrease with age, even in individuals without cardiovascular disease. This is attributed to increased apoptosis and necrosis, together with reduced regeneration of progenitor cells. Compensation for loss of functioning cells leads to hypertrophy of the remaining myocytes. As individuals age, myocytes also develop changes in calcium metabolism and regulation, leading to altered contraction and relaxation. The expression of genes for contractile proteins is also altered, as is the efficiency of adenine triphosphate use due to mitochondrial dysfunction. Telomere shortening has also been associated with cellular and biological ageing, and with heart failure pathogenesis.11,12

The ageing myocardium is also predisposed to altered metabolism within extracellular matrix cells, leading to myocardial collagen deposition and fibrosis; the latter is enhanced by RAAS upregulation, and by increased general inflammatory activity and oxidative stress. Thus, as healthy individuals age, left ventricular hypertrophy and impaired left ventricular relaxation may occur. Additional age-related changes throughout the cardiovascular system lead to arterial wall fibrosis, stiffening, and thickening, consequences of which are extra increases in cardiac afterload and left ventricular hypertrophy. Such changes may lead to clinically noticeable HF-PEF, symptoms of which generally first manifest during exercise. Age-related reductions in myocardial and cardiovascular compliance may ultimately cause raised left ventricular end-diastolic pressure and subsequent pulmonary congestion and/or oedema. With additional time and further injury, left ventricular dilation and dysfunction may manifest as the final stage of HF-PEF.11,12

**Figure 1.** Age-related cardiovascular changes associated with the pathogenesis of HF-PEF (adapted from Lazzarini et al.11).

↑, increase; ↓, decrease; ATP, adenosine triphosphate; Ca²⁺, calcium; CPC, cardiac progenitor cell; CV, cardiovascular; HF-PEF, heart failure with preserved ejection fraction; LV, left ventricular.
Chronic Heart Failure in the Elderly

**NYHA classification**

The most commonly used classification system for chronic heart failure is the New York Heart Association (NYHA) functional classification, which places patients in one of four categories according to the degree of restriction in physical activity (Table 1). Approximately two-thirds of cardiologists use patient self-reported walking distance and/or difficulty climbing stairs as the principal criteria for NYHA categorisation.23

<table>
<thead>
<tr>
<th>Subjective assessment of patient symptoms</th>
<th>Objective assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. No limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitation, dyspnoea.</td>
<td>A. No objective evidence of CVD. No symptoms, and no limitation of ordinary physical activity.</td>
</tr>
<tr>
<td>III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea.</td>
<td>C. Objective evidence of moderately severe CVD. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.</td>
</tr>
<tr>
<td>IV. Unable to continue any physical activity without discomfort. Symptoms of heart failure at rest. If physical activity started, discomfort increases.</td>
<td>D. Objective evidence of severe CVD. Severe limitations. Experience symptoms even while at rest.</td>
</tr>
</tbody>
</table>

Table 1. NYHA classification system for chronic heart failure

**Risk factors and comorbidities**

Key risk factors for the development of heart failure and cardiomyopathy comprise CHD and hypertension. Other risk factors include myocardial injury due to alcohol abuse or infection, valvular heart disease (e.g. rheumatic heart disease), diabetes, and obesity.24 The presence of at least two of the following indicates an increased risk of early morbidity and mortality, or hospital readmission: age ≥65 years; severe symptoms restricting activities of daily living (NYHA IV); left ventricular ejection fraction <30%; living alone or isolated from specialist cardiologist services; depression; marked renal impairment; increased frailty and debilitation; language problems; and lower socioeconomic status.25 From the specific standpoint of HF-PEF, European Society of Cardiology (ESC) guidelines outline that elderly, female, and overweight individuals are at increased risk.25 Such individuals are also more likely to have concomitant atrial fibrillation, diabetes and hypertension, but a lower rate of CAD. Indeed, in epidemiological and clinical trials, and in registry databases, hypertension with chronic pressure overload is the principal predictor of HF-PEF.25,26 Reduced renal function is widely recognised as an independent risk factor for deleterious cardiovascular outcomes and death in patients with HF-REF. Indeed, impaired renal function can restrict the initiation, titration, and efficacy of heart failure therapy, particularly in elderly patients.27 Other risk factors and comorbidities may also markedly influence the management and prognosis of heart failure. For example, atrial fibrillation is present in approximately 50% of patients with NYHA class IV heart failure;28 anaemia is present in up to 60% of patients with heart failure, and has been confirmed as an independent predictor of mortality;29,30 and diabetes is evident in about 40% of patients hospitalised with heart failure.31 Patients with, rather than those without, heart failure are about three times more likely to develop diabetes; and patients with diabetes have an increased risk of developing heart failure. For each 1% increase in glycosylated haemoglobin level in a diabetic patient, the risk of developing heart failure is increased by approximately 10–15%. Furthermore, patients hospitalised with heart failure who have diabetes have increased risks of rehospitalisation due to heart failure and cardiovascular mortality relative to patients without diabetes.32

Frailty, cardiovascular disease, and comorbidities frequently occur together in elderly patients with heart failure.33 Appropriate management of comorbidities is important, but may be complicated by dementia, frailty, and treatment AEs; such factors may lead to increased functional disability, reduced quality of life (QoL), and increased rates of hospitalisation. Overall, more than one-third of elderly patients with heart failure also have anaemia, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, and/or renal failure. These patients may also have cognitive dysfunction, incontinence, psychological disturbances, and restriction of normal activities of daily living. Such a complex list of comorbidities means that evidence-based heart failure treatments (e.g. ACE inhibitors, β-blockers, MRAs) may often be under-utilised in elderly patients,34 because of specific contraindications, or the potential for AEs and drug interactions due to polypharmacy. Indeed, it has been suggested that 20% of patients aged ≥70 years with heart failure receive at least ten medications; if the risk of an AE increases 10% for each additional medication, then the risk of an AE will be 100%.35 Due to the possibility that these multiple comorbidities may confound results, elderly patients with heart failure are often under-represented in randomised clinical trials. Definitive evidence of the therapeutic benefit and safety of pharmacotherapies and nonpharmacological interventions in elderly patients with heart failure has traditionally been lacking.36 Enhanced healthcare for elderly patients with heart disease should therefore involve coordinated collaboration between primary care physicians, cardiologists and geriatricians so that the heterogeneity of ageing and cardiac disease, and patients' disease-management preferences, are fully addressed; the principal disease-management goals are to reduce functional disability and improve QoL.37

Figure 2. Heart failure hospitalisation rates according to age and sex (adapted from AIHW 2011).
Prevalence and prognosis

In Australia, it is estimated that heart failure affects approximately 300,000 people (~1.5–2.0% of the population); the estimated annual number of newly diagnosed heart failure cases is 30,000. Heart failure prevalence increases with age: it is approximately 10% in individuals aged ≥65 years, and 50% in individuals aged ≥85 years. However, many individuals with heart failure remain undiagnosed, so these figures are likely to be an underestimate.

Women are more frequently affected by heart failure than men, particularly in the ≥85-year age group, and the hospitalisation rate for heart failure rises rapidly with age. In men, about 80% of hospitalisations due to heart failure are in individuals aged ≥65 years; the corresponding proportion in women is about 90%; overall, the rate of heart failure hospitalisations is approximately fourfold greater in the 85+ age group than in the 65–74-year age group (Figure 2). Heart failure hospitalisations continue to increase: for example, from 2002–2003 to 2011–2012, the rate increased by 24%.

With ageing of the general population, and enhanced survival of patients due to improved disease-management strategies for acute coronary syndromes and heart failure, the overall prevalence of heart failure is expected to rise markedly in the near- to mid-term. Some authors predict a threefold rise in the number of patients with heart failure over the next two decades. Currently, the lifetime risk of developing heart failure is estimated at about 20%. Despite marked, recent progress regarding improved identification and treatment of patients with heart failure, prognosis remains poor: 1-year mortality rates for older patients with heart failure are about 25–35%.

Approximately 50–70% of patients with heart failure have preserved ejection fraction (i.e. HF-PEF), and this percentage increases with age. Guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) suggest that this figure may be as high as 70%, because studies have used different ‘cut-offs’ for categorisation of preserved ejection fraction. Furthermore, over the last two decades, the prevalence of HF-PEF appears to have increased, in part because of population ageing. Patients with HF-PEF were traditionally considered to have a better prognosis than those with HF-REF. However, survival in patients with HF-PEF now also appears to be as poor as that in patients with HF-REF. Survival depends on geographic region, and the ejection fraction threshold used for definition of HF-PEF. Over a mean follow-up period of approximately 3 years, the Digitalis Investigation Group reported a mortality rate of about 35% in patients with HF-REF (ejection fraction ≤45%), compared with a rate of approximately 25% in patients with HF-PEF (ejection fraction >45%). In general, the prognosis for heart failure has been documented as worse than that for some malignant cancers.

Another important consideration is frailty. Approximately three-quarters of patients with heart failure are frail elderly individuals, and this phenotype is associated with an increased risk of comorbidities, medication AEs, falls, hospitalisation, and mortality. Implementation of appropriate multidisciplinary, guideline-directed strategies for the management of frail elderly individuals is therefore particularly important. So is the provision of appropriate palliative care support and decision-making.

Diagnosis

The principal aspect of HF-REF diagnosis is identification and characterisation of systemic and pulmonary congestion, whereas HF-PEF is largely a diagnosis based on exclusion of factors such as myocardial ischaemia and valvular disease (Table 2). As already outlined, HF-REF is primarily caused by CHD and valvular heart disease, whereas HF-PEF is more common in elderly individuals and women, and is primarily due to hypertension and age-related fibrosis, hypertrophy, obesity and diabetes.

In suspected HF-REF, early confirmation of left ventricular dysfunction is vital, because early initiation of guideline-directed treatment can prevent or slow heart failure progression. The principal components of diagnosis are clinical features, chest X-ray, and echocardiography. The latter is especially important, since physical signs are frequently normal in early heart failure, and diagnosis based on clinical signs may be unreliable in elderly or obese patients, or those with concurrent pulmonary disease. Plasma BNP or N-terminal pro-BNP (NT-proBNP) measurements are appropriate (but are seldom used in Australia as their estimation is not funded) if echocardiography cannot be performed in a timely fashion, or if the diagnosis remains dubious (Figure 3).

ESC guidelines for the diagnosis and treatment of heart failure suggest that in the non-acute setting, electrocardiogram (ECG) and natriuretic peptide measurements can be used to identify patients most suitable for echocardiography; that is, a BNP level ≥35 pg/mL or NT-proBNP level ≥125 pg/mL suggests a need for echocardiography. However, measurement of natriuretic peptide levels may be confounded by elevated levels in patients aged ≥75 years, and in patients with atrial fibrillation, left ventricular hypertrophy, COPD, or chronic kidney disease; moreover, heart failure therapy may itself reduce natriuretic peptide levels, which may not necessarily be raised in patients with HF-PEF.

Additional tests, and responses to treatment, can facilitate: confirmation of the heart failure diagnosis; identification of causes (e.g. left ventricular dysfunction, valvular heart disease, CHD) and precipitating factors (e.g. anaemia, arrhythmias, infection, ischaemia, pulmonary embolism); determination of prognosis; and relevant guidance of treatment. All patients with suspected heart failure should undergo an ECG, echocardiography, and chest X-ray, even if physical signs are normal. A full blood count, and testing for plasma urea, creatinine, and electrolytes, should also be performed. Other investigations that may be useful include liver and thyroid function testing, stress testing, coronary angiography, invasive haemodynamic testing, and spirometry.

### Table 2. Key factors in the diagnosis of HF-REF and HF-PEF

<table>
<thead>
<tr>
<th>General diagnosis of HF</th>
<th>HF-REF</th>
<th>HF-PEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical signs and symptoms, HF history, chest X-ray</td>
<td>• Echocardiography: impaired LV contraction (EF &lt;40%)</td>
<td>• Echocardiography: impaired LV relaxation and/or raised filling pressure; normal LV function (EF &gt;40%)</td>
</tr>
<tr>
<td>• Exclude myocardial ischaemia and valvular disease</td>
<td>• +/- cardiac catheterisation</td>
<td>• Exclude myocardial ischaemia and valvular disease</td>
</tr>
<tr>
<td>• Echocardiography or cardiac catheterisation may indicate diastolic dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A normal chest X-ray does not exclude HF. Specific abnormalities can exclude HF, conversely, cardiomegaly, pulmonary venous changes, and interstitial oedema in pulmonary fields support a diagnosis of HF. EF, ejection fraction; HF, heart failure; LV, left ventricular; PEF, preserved ejection fraction; REF, reduced ejection fraction.

Clinical distinction between HF-REF and HF-PEF is important because of the divergent disease-management implications. Thus, when diagnosing HF-PEF, cardiac factors such as pericardial or valvular disease, high-output disorders (e.g. anaemia, arteriovenous fistula, thyrotoxicosis), and left ventricular hypertrophy, should be excluded. Non-cardiac factors, such as COPD, liver disease, obesity, and obstructive sleep apnoea, should also be excluded. Moreover, in elderly patients, heart failure symptoms may present gradually and atypically, and may include reduced appetite and body mass index; traditional symptoms such as dyspnoea may be absent, or difficult to interpret because of comorbidities (e.g. pulmonary disease). Issues such as poor vision, confusion, and osteoarthritis, with consequently reduced mobility and exertion, and sleep disturbances, may also confound the clinical picture.

In addition, primary care physicians may be less likely than cardiologists to utilise diagnostic procedures such as echocardiography and natriuretic peptide levels, particularly in patients with comorbidities that may mask symptoms of heart failure (e.g. pulmonary disease). Elderly patients hospitalised with heart failure may also have a reduced likelihood of undergoing echocardiography or evaluation by a cardiologist during hospitalisation.
Figure 3. Suggested diagnostic algorithm for chronic heart failure (adapted from National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines), BNP, B-type natriuretic peptide; CV, cardiovascular; ECG, electrocardiogram; HF-PEF, heart failure-preserved ejection fraction; HF-REF, heart failure-reduced ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PND, paroxysmal nocturnal dyspnoea.

Disease burden

Heart failure represents a swiftly escalating public health issue that currently affects almost 40 million people worldwide. The high prevalence in the elderly, and a traditional lack of effective treatments, particularly for HF-PEF, underscores the major disease burden posed by the condition. Indeed, heart failure is a leading cause of hospitalisation in the elderly and, in the US, total annual medical costs for patients with heart failure have been projected to more than double, to almost US$55 billion, over the next 15 years. In Australia, the annual cost of chronic heart failure has been estimated at more than $1 billion, with the largest expenditure being on hospital care. A substantial portion of this overall cost is linked to preventable heart failure admissions, and indeed, it is widely recognised that up to two-thirds of all heart-failure hospitalisations can be prevented by providing relevant, non-hospital, multidisciplinary healthcare services. However, rehospitalisation rates for heart failure within 1 month of initial discharge may be as high as 20%, and within 3–6 months of discharge as high as 30–50%. Mean costs associated with hospital admissions for simple and complex heart failure have been documented as $3,440 and $7,260, respectively. Metropolitan areas of Queensland have led the way in introducing multidisciplinary healthcare services, which besides producing major cost savings due to fewer unplanned hospitalisations or rehospitalisations for heart failure, have the following health and clinical benefits:

- Improved patient education about diet and exercise.
- Enhanced symptom and clinical management.
- Improved clinical outcomes.
- Better patient adherence to treatments.
- Improved patient mental health and QoL.
- Enhanced palliative care support and decision-making.

Despite implementation of such coordinated multidisciplinary services, many patients with heart failure are not referred to these services in the first place, and in some urban, rural, and remote areas, these services are not adequately resourced and staffed.

Treatment of heart failure in the elderly

Although Australian guidelines for the management of chronic heart failure are now slightly outdated (last updated October 2011), there are still significant areas of concordance with more recent guidelines from the ACCF/AHA and ESC. The principal goals of treatment are to prevent chronic heart failure in at-risk individuals, and identify asymptomatic left ventricular dysfunction as early as possible. In manifest heart failure, fundamental goals are to relieve symptoms, enhance QoL, slow disease progression, and prolong survival. Allied to these factors are the aims of enhancing exertion tolerance, and reducing hospital admissions. An Australian ‘snapshot’ of acute heart failure admissions recently audited data from almost 1,000 patients from 24 centres in Australian Capital Territory and New South Wales. The audit found that average patient age was 77 years, 58% of patients were male, and 42% of patients had preserved ejection fraction (>50%). In addition, the median Charlson Comorbidity Index score was 3, and almost three-quarters of patients were frail. The median duration of hospital stay was 6 (range 3–12) days, and approximately 60% of patients were subsequently referred to a multidisciplinary heart failure service. Discharge medications comprised ACE inhibitors or ARBs (59% of patients), β-blockers (66%), and loop diuretics (88%), thus indicating that evidence-based therapies — especially ACE inhibitors and β-blockers — were under-utilised. In elderly, Australian patients with heart failure, there is therefore an urgent need to enhance overall disease management, particularly regarding the development of strategies for improving access to multidisciplinary care programs and increasing the uptake of evidence-based therapies.

It should be re-emphasised that heart failure is primarily a disease of the elderly, and that up to 70% of heart failure patients have HF-PEF. In clinical trials of pharmacotherapies, however, elderly patients with chronic heart failure have been under-represented (see Risk factors and comorbidities), and community-based studies indicate that the mean age for new-onset heart failure is >75 years. Thus, some debate exists regarding extrapolation of clinical-trial data from nonelderly populations to the community setting of elderly patients aged ≥70 years with heart failure. Nonetheless, with increased awareness of the apparently growing prevalence of HF-PEF in ageing populations, more data are now starting to accumulate, and more clinical trials are now starting to evaluate pharmacotherapies (e.g. PARAGON-HF) in this condition, specifically in elderly and very elderly patients (see subsequent sections).
Nonpharmacological intervention

Routine nonpharmacological measures, such as restricting dietary sodium (<2 g/day) and fluid intake (<2 L/day), and limiting caffeine to 1–2 drinks per day, should form a central component of all disease-management strategies for chronic heart failure. The need for physical activity should also be emphasised, as should the need to restrict alcohol intake (<2 standard drinks per day). Patients should be advised to quit smoking, should be vaccinated against influenza and streptococcal pneumonia, and should undertake bed rest whenever they have disease exacerbations. After discharge from hospital, all heart failure patients should have access to best-practice multidisciplinary care.

Devices

Biventricular pacing (with or without an implantable cardioverter defibrillator; ICD) is now considered a safe and viable clinical option to provide symptomatic and haemodynamic improvement in heart failure patients with the following: NYHA class III–IV disease and receiving pharmacotherapy; ejection fraction <35%; QRS duration ≥120 msec; and sinus rhythm. ICD implantation should be considered in any of the following patients with: a history of cardiac arrest due to ventricular fibrillation or tachycardia; spontaneous sustained ventricular tachycardia and attendant structural CHD; ejection fraction <35%; QRS duration >120 msec; and sinus rhythm. When ICD implantation is used to reduce sudden death risk, cardiac resynchronisation therapy can also be considered to reduce the risk of heart failure events and mortality; this applies if ejection fraction is ≤30% and QRS duration is ≥150 msec (left bundle-branch block), and if patients have mild heart failure (NYHA class II), despite optimum treatment. Left ventricular assist devices are used primarily as transient ‘bridges’ to cardiac transplantation, or during recovery after cardiac surgery.

Pharmacological intervention

General principles

For the prevention of worsening heart failure in at-risk individuals, ACE inhibitors should be used, if tolerated, in all patients with asymptomatic left ventricular dysfunction (NYHA class I). β-Blockers, if tolerated, are also appropriate for use in this setting. In addition, ACE inhibitors should be considered in patients in NYHA class I with a history of myocardial infarction or other cardiovascular disease; at least one antihypertensive should be prescribed to prevent heart failure in patients with hypertension; and β-blocker therapy should be started early after myocardial infarction, irrespective of ejection fraction. Statins should be used, according to National Heart Foundation of Australia guidelines, to manage dyslipidaemias appropriately.

Traditional management of comorbidities

In heart failure patients with concurrent atrial fibrillation, digoxin can be used to control ventricular rate; β-blockers are appropriate if heart failure is stabilised. Amiodarone can also be considered for the control of atrial or ventricular fibrillation, but neither digoxin nor amiodarone reduce mortality in HF.

In concurrent CHD, low-dose aspirin should be prescribed, together with statin therapy to achieve recommended lipid levels: low-density lipoprotein cholesterol <1.8 mmol/L; high-density lipoprotein cholesterol >1.0 mmol/L; and triglycerides <1.5mmol/L. After optimum drug treatment is started, patients can be assessed for possible coronary revascularisation.

In concurrent hypertension, combination antihypertensive schedules should be used to attain blood pressure goals. If needed, a dihydropyridine calcium-channel blocker (e.g.amlodipine or felodipine) can be added to ACE inhibitor or β-blocker therapy, but diltiazem and verapamil should be avoided in HF-REF as they are negative inotropes.

The management of comorbidities in heart failure is important to reduce overall morbidity and mortality, and enhance QoL. Nevertheless, drugs that exacerbate heart failure (Table 3) should generally be avoided.

### Table 3. Drugs that should generally be avoided in patients with heart failure

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antianthyratic agents</td>
<td>Other than amiodarone and β-blockers</td>
</tr>
<tr>
<td>Clozapine</td>
<td>–</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>e.g. glucocorticoids, mineralocorticoids</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Contraindicated in heart failure because of an increased risk of mortality</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Contraindicated in heart failure because of an increased risk of mortality</td>
</tr>
<tr>
<td>Non-dihydropyridine calcium-channel blockers</td>
<td>e.g. diltiazem, verapamil</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Including cyclo-oxygenase type 2 inhibitors</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>e.g. pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Contraindicated in patients with symptomatic heart failure or ejection fraction &lt;45%</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>–</td>
</tr>
<tr>
<td>Tumour necrosis factor antagonists</td>
<td>e.g. adalimumab, etanercept</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>e.g. sunitinib; may cause hypertension, reduced ejection fraction, and heart failure</td>
</tr>
</tbody>
</table>

Traditional management of HF-REF

Approximately 30–50% of elderly patients with heart failure have reduced ejection fraction. If ACE inhibitors are tolerated, and not contraindicated, they should be started in all patients with ejection fraction <40%, irrespective of symptom severity. ARBs are appropriate alternatives for patients unable to tolerate ACE inhibitor-induced cough. β-Blockers (e.g. bisoprolol, carvedilol, extended-release metoprolol, nebivolol) should also be started in all patients with stable HF-REF, since these agents have been shown to prolong survival and normalise left ventricular function. Loop diuretics are used to manage symptoms of fluid overload; however, diuretics should not be used as monotherapy, and should always be administered with an ACE inhibitor (Figure 4). The most widely used diuretic is frusemide, but there is no definitive evidence to suggest that this loop diuretic is any more effective or better tolerated than thiazide diuretics, although it is more potent. The MRA spironolactone is advocated for use in individuals with NYHA class III–IV heart failure, despite optimum ACE inhibitor + diuretic therapy; eplerenone is appropriate for consideration in patients with heart failure (NYHA class II or above) early after myocardial infarction, besides standard ACE inhibitor + β-blocker therapy. Icdarabine, a direct sinu node inhibitor, is recommended for consideration in patients on standard therapy with ejection fraction <35%, and who are in sinus rhythm with heart rate >77 beats per minute.
Management of HF-PEF

As mentioned throughout this review, there is limited clinical-trial data to direct treatment of HF-PEF in the approximately 50–70% of heart failure patients with this disease phenotype.²⁶,²⁷ Although pathophysiological understanding of the condition has improved, treatments with a definitive mortality benefit in HF-PEF have not yet been identified. Indeed, ACE inhibitors, ARBs and the MRA spironolactone have all failed to show a significant mortality advantage, although ARBs and spironolactone did show a trend towards improved morbidity.³⁷ In the CHARM-Preserved trial, for example, candesartan versus placebo reduced hospitalisation due to heart failure (p=0.017), and reduced the composite endpoint of nonfatal myocardial infarction and nonfatal stroke (p=0.078).³⁸ In the TOPCAT trial, spironolactone versus placebo also significantly reduced the risk of hospitalisation due to heart failure (p=0.04), although there was marked regional variation.³⁹ Clearly, definitive large-scale studies of novel treatments (e.g. ARNi) and existing therapies (e.g. nebivolol) as monotherapy, and of appropriate combination-therapy schedules, are now warranted in elderly patients with HF-PEF. Thus, the PARAGON-HF study of sacubitril/valsartan is ongoing (see subsequent sections).⁴² Traditionally, disease management in HF-PEF has focused on prevention of left ventricular hypertrophy with ACE inhibitor or ARB therapy, as for HF-REF, and on the appropriate treatment of underlying causes of HF-PEF: for example, strict blood pressure control in hypertension; and strict glycaemic control in diabetes.⁴³

Management of advanced or end-stage heart failure

Short-term treatment with positive inotropes (e.g. dobutamine, levosimendan) to enhance cardiac pumping may be beneficial in individuals with advanced HF-REF unresponsive to other interventions. For patients in whom continuous inpatient infusion cannot be stopped, domiciliary continuous ambulatory infusion can be considered. In patients with acute pulmonary oedema, continuous positive airway pressure or bilevel positive airway pressure can reduce the need for invasive ventilation. For patients in whom death within months is likely, and with reduced QoL on standard treatment, palliative care should be considered. Risk factors for impending death comprise: advanced age; cardiac cachexia; hyponatraemia and refractory hypotension requiring treatment withdrawal; NYHA class IV symptoms; recurrent hospitalisation for decompensated heart failure; and severe renal impairment.⁴⁴

Specific pharmacotherapies

β-Blocker use in elderly patients

β-Blockers (i.e. bisoprolol, carvedilol, extended-release metoprolol, nebivolol) are a cornerstone of heart failure management,⁴⁶ and are advocated for use in all patients with stable disease,⁴⁷,⁴⁸ since these agents significantly improve symptoms, slow disease progression, and reduce hospital admissions and mortality.⁴⁷,⁴⁹ This is evident from the CIBIS-II,⁴⁸ COPERNICUS,⁵⁰ and MERIT-HF trials, and more recently, from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS).⁴ Nineteen large-scale meta-analysis of data from >12,000 patients, and which included the CIBIS-II, COPERNICUS, and MERIT-HF trials, also revealed a statistically significant reduction in the risk of all-cause mortality for β-blockers relative to placebo in subgroup analyses of elderly patients with heart failure (risk ratio 0.76; 95% confidence interval [CI] 0.64, 0.90; p=0.002).⁵¹ Regarding individual studies, however, earlier trials generally included younger patients and excluded those aged ≥80 years, and focused specifically on HF-REF;⁴⁷ whereas the SENIORS study specifically included elderly patients aged ≥70 years, and a substantial proportion of patients (36%) had HF-PEF.⁴² Nebivolol, the β-blocker evaluated in SENIORS, is a third-generation, cardioselective, β₁-adrenoceptor antagonist that also has an effect on the vascular endothelium to cause nitric oxide-dependent vasodilation.⁵² Although the question of whether nebivolol improves left ventricular diastolic function has not been answered definitively, potential pharmacodynamic actions of nebivolol that may explain efficacy in HF-PEF comprise:

- Reduced heart rate prolongs diastolic filling and reduces diastolic pressures.⁵³,⁵⁴
- Longer diastole leads to increased myocardial perfusion.⁵⁵
- Anti-ischaemic activity enhances ventricular relaxation, maintains ventricular structure, and prevents myocardial fibrosis.⁵⁶
- Reduced afterload leads to reduced left ventricular hypertrophy, and prevention of diastolic dysfunction. Afterload is additionally reduced by enhanced nitric oxide production, which leads to peripheral vasodilation.⁵⁷
- In a SENIORS substudy in patients with HF-PEF, nebivolol versus placebo reduced the risk of sudden cardiac death by 51% (not statistically significant).⁵⁸
- A direct, nitric oxide-mediated, downward shift of the left ventricular pressure–volume relationship may enhance early diastolic relaxation.⁵⁹

![Diagram](https://example.com/diagram.png)
Importantly, principal results from SENIORS, which included 2,128 patients aged ≥70 years with HF-REF or HF-PEF, and from key SENIORS subgroup analyses, are as follows for nebivolol versus placebo:43

- Significant reduction in the primary composite endpoint of all-cause mortality or cardiovascular hospitalisation [hazard ratio (HR) 0.86; 95% CI: 0.74, 0.99; p = 0.039].44
- Significant reduction in the risk of cardiovascular hospitalisation or mortality (HR 0.90; 95% CI: 0.72, 0.98; p = 0.02).45
- Ejection fraction substudy: nebivolol tended to reduce the primary composite endpoint, both in patients with HF-REF (HR 0.86; 95% CI: 0.72, 1.04) and those with HF-PEF (HR 0.81; 95% CI: 0.63, 1.04).46
- Echocardiographic substudy: nebivolol significantly increased ejection fraction (+4.6%; p = 0.008) and significantly reduced end-systolic volume (p = 0.016) in HF-REF, but produced no significant changes in left ventricular structure or function in HF-PEF.47
- Cost-effectiveness model: a Markov model applied to SENIORS data projected that the total cost per nebivolol-treated patient was US$18,120, compared with US$14,298 for standard medical therapy. Incremental cost-effectiveness ratios for nebivolol were calculated as US$4,322 per quality-adjusted life-year gained, and US$2,888 per life-year gained, which were considered highly cost-effective.48

What should be remembered is, in clinical practice, although about two-thirds of elderly patients with heart failure can tolerate β-blocker therapy, the doses used have traditionally been about 40–70% of those identified as effective in randomised controlled trials. Reasons for this include polypharmacy, and possible drug interactions and AEs, due to the large number of comorbidities. Besides this potential for suboptimal β-blocker utility and efficacy, β-blockers may reduce all-cause mortality to a lesser extent in very elderly and frail patients than in younger patients. Thus, despite the pivotal place of β-blockers in guideline-directed management strategies for heart failure in the elderly, some clinicians may consider the quality of evidence for β-blocker use to be less in elderly than younger patients, as elderly patients were generally not included in the definitive trials.49 Consequently, in some settings, β-blockers may not be as widely used as they should be, but the concept of a ‘highest tolerable dose’ rather than a specific ‘target dose’ should be carefully considered in elderly patients with heart failure. Observational studies indicate that, in terms of prognosis with β-blockers, a ‘low dose’ is better than ‘no dose’. Overall, ‘... nebivolol should be considered as an alternative first-line treatment option in selected elderly patients with heart failure.’49

### Availability of nebivolol (Nebilet®) in Australia

Nebivolol is indicated for the treatment of essential hypertension, and for the treatment of stable chronic heart failure, as an adjunct to standard therapies, in patients aged ≥70 years.43 Nebivolol is subsidised on the Pharmaceutical Benefits Scheme only for the treatment of moderate-to-severe heart failure; for subsidy, patients must be stabilised on conventional therapy, which must include an ACE inhibitor or ARB, if tolerated.

As previously outlined, SENIORS included a mixed population of elderly patients with HF-REF or HF-PEF. It is interesting that, despite marked efficacy for nebivolol in both heart failure subtypes, large observational studies with β-blockers — for example, the OPTIMIZE-HF study44 — revealed that patients with HF-PEF had a poor prognosis, and β-blockers had no significant influence on hospitalisation or mortality rates in HF-PEF. Thus, ‘... nebivolol is so far the only β-blocker shown to be effective in elderly patients with chronic heart failure, regardless of systolic function.’49 Nonetheless, further targeted clinical trials and observational studies of β-blocker efficacy and tolerability, specifically in patients with HF-PEF, are urgently needed to unequivocally demonstrate improved clinical outcomes and a favourable benefit/risk ratio in elderly patients, irrespective of comorbidities, frailty, and polypharmacy.44

### Mineralocorticoid receptor antagonists (MRAs)

Despite definitive guidelines advocating the use of MRAs in HF-REF, MRA uptake by physicians has generally been poor because of concerns about hyperkalemia and renal dysfunction. Careful patient selection for treatment, monitoring of plasma potassium levels and renal function, and relevant patient education about the potassium content of frequently ingested foods are all important clinical considerations if MRAs are to be used. Such considerations can facilitate adverse event (AE) reduction and further reduce hospitalisation rates and cardiovascular mortality.44

Speculation suggests that, in future, nonsteroidal MRAs (e.g., finerenone) might develop important mono- and combination-therapy roles in the specific management of heart failure in elderly patients,46–48 especially in patients with HF-REF and concurrent diabetes mellitus.49 Definitive research is clearly needed in this regard, since large meta-analyses outnumbered that although some clinical benefits occurred, MRAs did not improve all-cause mortality in patients with HF-PEF.50 The large-scale TOPCAT study in almost 3,500 patients with HF-PEF also revealed that spironolactone did not significantly reduce the composite primary endpoint of cardiovascular mortality, halted cardiac arrest, or hospitalisation for heart failure; however, it did significantly reduce (p=0.04) the individual endpoint of hospitalisation for heart failure.50 It is also important to recognise that patients in the USA included in this study did not have significant benefit from spironolactone.44 Importantly, for a planned population of approximately 6,000 patients with HF-REF, and type 2 diabetes mellitus and/or chronic kidney disease, including elderly patients, the 18–36-month FINESSE-HF study of finerenone versus placebo is now recruiting; this multinational study includes centres in Australia and New Zealand, and preliminary results are anticipated towards the end of 2017.51,49

### Angiotensin receptor neprilysin inhibitors (ARNIs)

Exciting results from the PARADIGM-HF trial recently heralded the arrival of a new class of drug treatments for HF-REF: the ARNI.7 The forerunner of this drug class is the fixed-dose combination sacubitril/valsartan, which is now approved for use in Australia. This ARNI has a dual mechanism of action: inhibition of neutral endopeptidase (neprilysin) via the active metabolite of sacubitril, LBQ657; and blockade of angiotensin II type-1 receptors by valsartan. Thus, the beneficial effects of endogenous natriuretic peptides are enhanced, and the deleterious effects of angiotensin are reduced.52

In the PARADIGM-HF trial,53 which was stopped early, because overwhelming benefit was identified for sacubitril/valsartan, the fixed-dose combination versus enalapril significantly reduced the relative risks of:

- Cardiovascular mortality and hospitalisation due to heart failure (–20%; p < 0.001).
- All-cause mortality (–16%; p < 0.001).
- Cardiovascular mortality (–20%; p < 0.001).
- Hospitalisation due to heart failure (–21%; p < 0.001).

Whether the dramatic results of this trial will ultimately shift the treatment paradigm for HF-REF in elderly patients, and whether ARNI will eventually replace ACE inhibitors as first-line RAAS blockers in heart failure treatment guidelines, remains to be seen. Indeed, additional clinical experience and long-term safety and tolerability data are needed for ARNI before such a major guideline change can occur.4 Meanwhile, the efficacy of sacubitril/valsartan in HF-REF is currently being evaluated in the PARAGON-HF trial, which is recruiting approximately 4,300 patients with NYHA class II–IV heart failure and ejection fraction <45%.54 This international study, which includes several sites in Australia, is being conducted in patients aged ≥50 years, and has a primary composite outcome of cardiovascular death and total (first and recurrent) heart failure hospitalisations; the study is due for completion in May 2019 (NCT01920711).
Clinical studies

Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)

Authors: Flather MD, et al.

Background: Unequivocally, β-blockers reduce hospitalisations and mortality in patients with heart failure. However, in most clinical trials, elderly patients with a wide range of ejection fractions (i.e. HF-REF or HF-PEF) have been under-represented. The SENIORS study was conducted specifically to evaluate efficacy of the cardioselective β-blocker nebivolol in elderly patients (aged ≥70 years), irrespective of ejection fraction.

Methods: A total of 2,128 patients with a history of heart failure (i.e. hospitalisation in the previous year or documented ejection fraction ≤35%) were randomised to receive nebivolol 1.25–10 mg once daily (n=1,067) or placebo (1,061). The primary study endpoint was a composite of total mortality or time to first cardiovascular hospitalisation.

Results: Mean patient age was 76 years, and patients were followed-up for a mean of 21 months. Mean ejection fraction was 36% (a total 35% of patients had ejection fraction >35%), and approximately two-thirds of patients had a history of CHD. The primary study endpoint occurred in 31.1% of nebivolol-treated patients, compared with 35.3% of placebo recipients (HR 0.86; 95% CI: 0.74, 0.99; P=0.039; Figure 5). Age, sex, and ejection fraction did not influence the effect of nebivolol on the primary study outcome. All-cause mortality was lower, but not significantly lower, in nebivolol versus placebo recipients (15.8% vs 18.1%; HR 0.88; 95% CI: 0.71, 1.08).

Conclusion: Importantly, ‘… nebivolol is well tolerated and effective in reducing mortality and morbidity in patients of age >70 years with heart failure, regardless of the initial ejection fraction.’

Comment: Heart failure is the most frequent cause of hospital admission in the elderly, but elderly patients were under-represented in the seminal heart-failure studies upon which guidelines are based. There is no reason to think that evidence-based therapies will be any less effective in the elderly, and it is reassuring to see that in the SENIORS trial this was the case with nebivolol. There are no evidence-based treatments for HF-PEF, but in the SENIORS study, nebivolol reduced morbidity and mortality in patients with ejection fraction >35%. Trials of ARBs and ACE inhibitors in patients with HF-PEF have not shown clinically meaningful improvements in outcomes, although spironolactone may have benefit when used in Western populations. Given the magnitude of the HF-PEF problem, further study of nebivolol in elderly HF-PEF patients would seem reasonable, especially in combination with ARNIs now that encouraging results from the PARADIGM study are available.


Full article

Figure 5. Time to primary composite endpoint in the SENIORS study.\(^2\)

Beta-blockade with nebivolol in elderly heart failure patients

Authors: van Veldhuisen DJ, et al.

Background: The definitive effects of β-blockers in HF-PEF remain unclear. This study, a pre-specified subanalysis of the SENIORS study, therefore aimed to determine the effects of nebivolol on cardiovascular outcomes in patients with impaired ejection fraction (≤35%) and preserved ejection fraction (>35%).

Methods: A total of 2,111 patients were evaluated: 1,359 with impaired ejection fraction, and 752 with preserved ejection fraction. The follow-up period was 21 months, and the primary study endpoint was the composite of cardiovascular hospitalisations and total mortality.

Results: The primary endpoint occurred in 34.2% of patients with impaired ejection fraction, compared with 31.2% of patients with preserved ejection fraction. Nebivolol versus placebo reduced the relative risk of the primary endpoint by 14% in patients with impaired ejection fraction (HR 0.86; 95% CI: 0.72, 1.04), and by 19% in patients with preserved ejection fraction (HR 0.81; 95% CI: 0.63, 1.04). Effects on all secondary study endpoints were similar between the two study groups.

Conclusions: These are ‘… the first large-scale data for a potentially beneficial effect of beta-blockade in HF patients with a preserved EF … Larger, adequately powered studies with beta-blockers in this population are clearly needed.’

Comment: The SENIORS study is the only trial to demonstrate improved outcomes with a specific treatment in patients with HF-PEF (ejection fraction >35%). This may be due to nebivolol’s combined β-blocking properties and vasodilation due to nitric oxide activation, which could potentially improve left ventricular compliance by improving endothelial function. If a β-blocker is to be used in HF-PEF, nebivolol is the only proven treatment to improve outcomes.


Full article
Angiotensin-neprilysin inhibition versus enalapril in heart failure

Authors: McMurray JJ, et al.

Background: Unequivocally, enalapril improves survival and is a first-line treatment in HF-REF. The current trial compared a novel fixed-dose combination, sacubitril/valsartan, with enalapril in patients with HF-REF.

Methods: A total of 8,442 patients with NYHA class II–IV heart failure and ejection fraction <40% were randomised, in double-blind fashion, to receive sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily, plus standard treatment. The primary study outcome was a composite of hospitalisation for heart failure or cardiovascular mortality.

Results: After a median follow-up period of 27 months, the study was stopped prematurely because of overwhelming benefit for sacubitril/valsartan. The primary study outcome manifested in 21.8% of patients treated with the fixed-dose combination, compared with 26.5% of enalapril-treated patients (HR 0.80; 95% CI: 0.73, 0.87; p<0.001). All-cause mortality was significantly lower in the fixed-dose combination than enalapril group (17.0% vs 19.8%; HR 0.84; 95% CI: 0.76, 0.93; p<0.001); the same was true for cardiovascular mortality (13.3% vs 16.5%; HR 0.80; 95% CI: 0.71, 0.89; p<0.001). Sacubitril/valsartan also significantly reduced the risk of hospitalisation due to heart failure (~21%; p<0.001), and significantly reduced (p=0.001) the symptoms and physical restrictions of heart failure.

Conclusion: 'This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin-angiotensin system alone in patients with chronic heart failure.'

Comment: The demonstration that RAAS blockade with the ARNI sacubitril/valsartan (Entresto®; Novartis Pharmaceuticals Australia Pty Ltd, Macquarie Park, Sydney, NSW) is superior to enalapril has the potential to create a paradigm shift in the management of stable patients with HF-REF. The magnitude of the benefits, including reduced all-cause mortality, is extremely clinically meaningful and should promote a transition to this therapy as the standard for patients with HF-REF. Although sacubitril/valsartan has been approved by the Therapeutic Goods Administration for HF-REF it is not yet subsidised on the Pharmaceutical Benefits Scheme, but it can be prescribed privately.


Spironolactone for heart failure with preserved ejection fraction

Authors: Pitt B, et al.

Background: MRAs are known to enhance prognosis in patients with HF-REF, but their effects on clinical outcomes in HF-PEF have not been rigorously tested. The TOPCAT trial therefore assessed the efficacy of spironolactone in patients with HF-PEF.

Methods: This was a large, double-blind study in which 3,445 patients with symptomatic heart failure and ejection fraction ≥45% were randomised to spironolactone 15–45 mg/day (n=1,722) or placebo (1,723) for a mean follow-up period of 3.3 years. Approximately 30% of patients in both groups were aged ≥75 years. The primary study endpoint was a composite of cardiac arrest, hospitalisation for heart failure, or cardiovascular mortality.

Results: Spironolactone versus placebo was associated with an 11% decrease in relative risk of the primary endpoint (incidence 18.6% vs 20.4% of patients; HR 0.89; 95% CI: 0.77, 1.04; not significant). Spironolactone significantly reduced the relative risk of hospitalisation for heart failure (12.0% vs 14.2%; HR 0.83; 95% CI: 0.69, 0.99; p=0.04), but had no significant effect on all-cause mortality or hospitalisations for any reason. Spironolactone was associated with double the incidence of hyperkalaemia than in the placebo group (18.7% vs 9.1% of patients).

Conclusion: In HF-PEF, the MRA spironolactone ‘... did not significantly reduce the composite primary end point of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.’

Comment: Although overall results of this study were disappointing, there was large regional variation in response to this therapy. In subgroup analyses, patients in the USA had a significant benefit with this therapy, and a significant reduction in blood pressure. This raises the possibility that the populations studied were different and that the criteria for hospitalisation in non-US centres were more liberal. If a diuretic or antihypertensive agent is needed in patients with HF-PEF, spironolactone would be a reasonable option, if it can be tolerated.


Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction

Authors: Yusuf S, et al.

Background: Approximately half of all patients with chronic heart failure have preserved left ventricular ejection fraction, but few interventions have been evaluated specifically in this patient subgroup. It is known that RAAS inhibition is clinically beneficial in patients with HF-REF or vascular disease and preserved left ventricular ejection fraction. The CHARM-Preserved study therefore assessed the efficacy of candesartan, as an addition to standard therapy, in patients with chronic heart failure and preserved left ventricular ejection fraction.

Methods: A total of 3,023 patients with NYHA class II–IV heart failure and ejection fraction ≥40% were randomised to receive candesartan (up to 32 mg/day; n=1,514) or placebo (1,509) for a median follow-up period of 36.6 months. The primary study endpoint was hospitalisation for heart failure or cardiovascular mortality.

Results: Candesartan versus placebo reduced (almost significantly) relative risk of the primary study outcome by 14% (22% vs 24% of patients; adjusted HR 0.86; 95% CI: 0.74, 1.0; p=0.051). Cardiovascular mortality was the same in both groups (170 deaths in each group), but candesartan significantly reduced the number of patients with one hospital admission for heart failure (230 vs 279; p=0.017).

Conclusion: The ARB candesartan had a modest effect in reducing hospital admissions for heart failure in patients with HF-PEF.

Comment: Although hospitalisations were modestly reduced with candesartan versus placebo in CHARM-Preserved, there was no improvement in harder outcomes, such as mortality. Similarly disappointing results were seen in I-PRESERVE (irbesartan) and PEP-CHF (perindopril) in the same population, but the potentially beneficial effect of RAAS blockade was thought to have been diluted in both studies, as there was a high rate of open-label ACE inhibitor and ARB use in the study populations. Reducing hospitalisations is a worthwhile and cost-effective strategy in patients with HF-REF or HF-PEF, so results of the CHARM study support the use of RAAS blockade in these patients. Results also provide encouragement for further study with ARNIs, particularly in HF-PEF. Ivabradine is also being studied in HF-PEF in the EDIFY study, although this treatment can only be used in patients in sinus rhythm.


Atrial Fibrillation

Subscribe free, visit www.researchreview.com.au and update your subscription to receive Atrial Fibrillation Research Review.
Nebivolol (versus placebo) significantly reduced the risk of all-cause heart failure by 28% in patients with HF-PEF, and 22% in patients with HF-REF. The risk reduction was 19% in patients with HF-PEF, and 14% in patients with HF-REF.

The TOPCAT study of spironolactone in HF-PEF showed that this MRA did not significantly reduce the composite of hospitalisation for heart failure or cardiovascular mortality.

Large-scale studies of novel treatments (e.g. sacubitril/valsartan) or existing therapies (e.g. nevirapine), either as monotherapy or in combination-therapy schedules, are urgently needed, specifically in elderly patients with HF-PEF.

References

This review was commissioned by A. Menarini Pty Ltd, Sydney, NSW, Australia. The content is entirely independent and based on published studies and the reviewer’s opinions. It may not reflect the views of Menarini.

This review was commissioned by A. Menarini Pty Ltd, Sydney, NSW, Australia. The content is entirely independent and based on published studies and the reviewer’s opinions. It may not reflect the views of Menarini.