

Heart failure: the role of ACE inhibitors

Heart failure is significant cause of death and disability in the elderly population, with over one in seven of those over 85 years having the condition. Recent evidence has shown that ACE inhibitors could prevent heart failure as well as treat it. In this article, **Dr Mark Davis** examines the evidence and discusses the role of angiotensin converting enzyme (ACE) inhibitors in the management of heart failure.

Hear failure is a significant cause of morbidity and mortality in the elderly population¹. The estimated prevalence of heart failure in the UK is about 900,000 with the incidence increasing significantly with age¹. The incidence per 1000 population is less than 0.2 in the under 55 years age group, increasing to 3.0 in those aged 65–74 years, 7.4 in the 75–84 years age group and 11.6 in those aged 85 years and over^{1,2}. This equates to one in 35 people aged 65–74 years in the UK having heart failure, one in 15 aged between 75 and 84 years, and over one in seven aged over 85 years^{1,3}.

The total annual cost of heart failure to the NHS is estimated to be £716m; approximately 1.8 per cent of the total NHS budget⁴. Hospital inpatient care is the single biggest cost, accounting for over 60 per cent of the total healthcare costs, and hospital admissions are projected to rise by 50 per cent over the next 25 years¹.

Indeed, currently heart failure accounts for two per cent of all inpatient bed days, a total of one million bed days in England¹, and five per cent of all emergency medical admissions to hospital⁴. Furthermore the costs increase with disease severity – severe symptoms can result in costs between eight and 30 times greater than the costs of mild symptoms^{4,5}.

Heart failure is thought to be a significant cause of death in the UK; however, the extent is difficult to establish exactly because guidance on death certificates – that heart failure is not a cause but a mode of death – discourages doctors from noting heart failure as the underlying cause of death. This means that other causes of death, such as coronary heart disease, are more commonly given as the cause of death on the death certificates of people with heart failure¹. It was estimated that in 2000, although just under 10,000 deaths due to heart failure were officially recorded, the true number was closer to 24,000 – accounting for at least five per cent of all deaths in the UK¹.

The progression of heart failure to severe physical limitation and ultimately death can be gauged by the New York Heart Association (NYHA) functional classification of the patient. The overall risk of death (i.e. across all risk classifications) is particularly high within the first few weeks of a diagnosis of heart failure – about 20 per cent of patients die within one month and 40 per cent within one year⁶ – thereafter, mortality is less than 10 per cent per year⁴.

Quality of life is severely affected in people with heart failure and declines markedly as the severity of disease increases¹. Symptoms such as breathlessness and fatigue can substantially limit

physical activity; indeed, heart failure has been shown to have a greater impact on the physical functioning domain of the short-form 36 (SF-36) quality of life questionnaire than chronic lung disease, arthritis or angina⁷.

Heart failure can result from any structural or functional cardiac disorder that impairs the ability of the heart to pump blood⁴. The most common cause of heart failure in the UK is coronary artery disease (CAD), including past myocardial infarction (MI), which is responsible for around 50 per cent of all new cases^{1,8}. Other causes include chronic hypertension, cardiomyopathy, atrial fibrillation, heart valve disease, congenital heart or blood vessel defects, and excess alcohol^{1,8}.

The treatment of heart failure aims to reduce symptoms, delay progression of the disease, reduce hospitalisation and improve quality of life^{1,4}. Lifestyle changes such as regular exercise (as part of an exercise or rehabilitation programme), smoking cessation and reduction in alcohol consumption are recommended for all heart failure patients⁴.

Angiotensin converting enzyme (ACE) inhibitors, beta-blockers and diuretics are commonly used in the treatment of heart failure; however, non adherence is a common problem and a significant cause of readmission^{4,9,10}. Consequently simple drug regimens are recommended, with a once-daily administration preferred⁴.

In some patients coronary revascularisation and other interventions may be considered, particularly if symptoms prove refractory to drug treatment⁴.

ACE inhibitors and heart failure

European, UK and US guidelines for the treatment of heart failure all agree that ACE inhibitors should be used as first-line therapy in patients with reduced Left Ventricular (LV) function, with or without heart failure symptoms, in the absence of contraindications^{4,11,12}. Furthermore, ACE inhibitors should be used to prevent/delay the development of heart failure in high-risk patients including those with CAD (particularly those with previous MI) or hypertension^{4,11,12}.

Prevention of heart failure

The benefits of ACE inhibitors in patients without signs and symptoms of heart failure

have been established in a number of landmark clinical trials¹³⁻¹⁸.

In the HOPE¹⁴ study, ramipril was shown to reduce the risk of new onset heart failure by 23 per cent, and hospitalisation for heart failure by 12 per cent (although this did not reach statistical significance), in high risk patients with cardiovascular disease but without heart failure or low ejection fraction (mean age 66 years). Analysis of these results suggested that the benefits seen were not explained by blood pressure reduction alone and that ACE inhibitors may have additional beneficial mechanisms. These findings were supported by EUROPA¹⁵, which investigated patients (mean age 60 years) with stable CAD without heart failure. It found that treatment with perindopril resulted in a significant 39 per cent relative risk reduction in hospital admissions for heart failure ($p < 0.01$).

More recently, looking specifically at an elderly population (average age 72 years) with acute MI and preserved LV function, the PREAMI¹⁹ study found that perindopril reduced the composite primary endpoint of death, hospitalisation for heart failure and cardiac remodelling by 38 per cent. This was driven by a significant 46 per cent reduction in the extent of cardiac remodelling, a major cause of heart failure in elderly patients who have had an MI.

The benefit of ACE inhibition use in patients who do have LV dysfunction is also well established. The SOLVD¹³ study found that ACE inhibitors have beneficial effects on morbidity and mortality in patients with asymptomatic heart failure as well as those with overt, severe heart failure symptoms. Patients with a reduced LV ejection fraction ≤ 35 per cent were divided into those already receiving treatment for heart failure (mean age 60.8 years) and those who were not (the preventive arm - mean age 59.1 years). Significant risk reductions in death or hospitalisation for heart failure were seen with enalapril in both the treatment (26 per cent) and prevention (20 per cent) arms.

Furthermore, in the prevention arm, enalapril treatment resulted in significantly fewer first hospitalisations for congestive heart failure and fewer patients developing the signs and/or symptoms of heart failure (risk reduction 37 per cent). In fact, progression to either hospitalisation or development of heart failure was delayed by over a year.

Key points

- > Heart failure is a significant cause of morbidity and mortality in the elderly population; it is estimated to cost the NHS £716m per year.
 - > Hospital admissions for heart failure are projected to rise by 50 per cent over the next 25 years.
 - > ACE inhibitors are the recommended first line therapy in patients with reduced LV function.
 - > There is growing evidence that ACE inhibitors can prevent or delay the development of heart failure in high risk patients such as those with CAD or hypertension.
- The incidence of stroke more than doubles in each successive decade over the age of 55 years. However, it has been shown that ACE inhibitors can also prevent heart failure in patients with cerebrovascular disease.

Cerebrovascular disease

The incidence of stroke more than doubles in each successive decade over the age of 55 years. However, it has been shown that ACE inhibitors can also prevent heart failure in patients with cerebrovascular disease. The PROGRESS¹⁷ study demonstrated that in patients (mean age 64 years) with a history of stroke or transient ischaemic attack, perindopril plus the diuretic indapamide reduced non fatal MI by 38 per cent and heart failure by 26 per cent compared with placebo¹⁸.

Conclusion

Heart failure is a common cause of morbidity and mortality in elderly patients. It produces a substantial burden on patients, carers and the NHS. In large randomised trials ACE inhibitors have demonstrated benefits, not only in the treatment of existing heart failure but also in preventing the development of heart failure in patients at risk. Unfortunately, data suggest that ACE inhibitors are under prescribed, particularly in women and older patients, and the doses used are too low^{1,20}.

As stated in several guidelines, ACE inhibitors should be prescribed in all patients with reduced LV function (with or without heart failure symptoms) and all those at high risk of developing heart failure (such as those with CAD, previous MI or chronic hypertension) in the absence of contraindications^{4,11,12}. Use of ACE inhibitors has

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the potential to improve patients' quality of life, delay or prevent disease progression and reduce the need for hospitalisation – providing benefits to the patient, carers and the NHS.

Conflict of interest: Dr Davis has undertaken speaking engagements and attended advisory boards, which have been supported by companies that make and market angiotensin receptor blockers and ace inhibitors.