The role of ACE inhibitor therapy in treating cardiovascular disease

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ACE inhibitors inhibit the conversion of an inactive hormone, angiotensin I, to an active one, angiotensin II. Angiotensin II increases blood pressure by constricting blood vessels and making their walls thicker and, therefore, the lumen smaller. It also stimulates aldosterone production, which in turn stimulates salt and water retention. The reduction of angiotensin II allows arteries to vasodilate and blood pressure to drop.

The action of the ACE also prevents further degradation of bradykinin. Bradykinin causes vasodilatation by stimulating nitric-oxide production and causes natriuresis through direct tubular effects. The increased circulating levels of bradykinin may play a key role in the cardioprotective actions of ACE inhibitors.

ACE inhibitors do not result in a compensatory tachycardia as they cause a reduction of noradrenaline release and endothelin formation. ACE inhibitors have been shown to act as anti-ischaemic agents. ACE inhibitors may:

- Reduce myocardial oxygen consumption through a decrease in afterload, preload, and left-ventricular myocardial mass;
- Improve myocardial oxygen supply through a reduction in perivascular and interstitial fibrosis and an improvement in endothelial-dependent vasodilatation;
- Inhibit the migration and proliferation of the smooth muscle and inflammatory cells, with slowing of the atherosclerosis progression;
- Favour endogenous thrombolysis through its mild antiplatelet action and the enhancement of the plasminogen activator inhibitor activity.

This suggests that ACE inhibitors may have structural effects on the underlying pathophysiology, rather than acute haemodynamic effects altering myocardial oxygen demand/supply balance.

Heart failure

Heart failure is a common condition with an annual mortality of between 10 and 50 per cent, depending on the severity. This means that between three and 20 people per 1,000 have the condition. Approximately five per cent of hospital admissions are due to heart failure and half of these could be prevented with appropriate management (Department of Health, 2000). ACE inhibitors should be considered for all patients with heart failure due to left ventricular systolic dysfunction (LVSD) (National Institute for Clinical Excellence, 2003).

After myocardial infarction

ACE inhibitors can reduce the remodelling that occurs following an acute myocardial infarction (MI). These changes are precursors to the development of symptomatic heart failure and premature death.

In unselective one-year trials ISIS-4 (ISIS-4 Collaborative Group, 1995) and GISSI-3 (GISSI-3 Study Group, 1994) there was a mortality reduction in the range of seven to 12 per cent at 35–42 days post MI. These trials randomised patients within 24 hours of an MI and had few exclusion criteria.

In selective trials in which high-risk patients were given ACE inhibitors or placebo, the mortality reduction was greater. These include the Survival and Ventricular Enlargement (SAVE) trial (Pfeffer et al, 1992) (19 per cent reduction), the AIRE trial (AIRE Study Investigators, 1993) (27 per cent reduction) and the TRACE trial (Kober et al, 1995) (22 per cent reduction).

The extension to the AIRE study (AIREX) showed that giving ramipril for one year provided continuing mortality benefit for up to 59 months (Hall et al, 1997).

All of these trials showed reduced progression to congestive heart failure. Pertinent research findings in relation to ACE inhibitors and myocardial infarction suggest that:

- Long-term ACE therapy should be considered for all those who have had an MI with or without LVSD, unless there are contraindications;
- Patients with LVSD should be considered for treatment within 48 hours;
- Caution should be exercised when using ACE inhibitors in patients who are hypotensive, have moderate renal failure, or who are known to have renal artery stenosis;
- Most of the benefits appear to occur during the first few days when mortality is highest;

REFERENCES


ACE inhibitors should not be prescribed under the following circumstances:
- During pregnancy;
- For patients with bilateral renal artery stenosis;
- In left ventricular outflow obstruction.

- Use ACE inhibitors with caution in patients with aortic stenosis especially if symptomatic;
- Start with a low dose (starter packs available) and titrate upwards every four to eight weeks;
- Discontinue potassium sparing diuretics and potassium supplements, temporarily withdraw dose of high-dose loop diuretic (such as frusemide >80mg daily), this may cause rebound pulmonary oedema;
- Monitor renal function before and during the period of treatment.
- High doses may have to be introduced in hospital.
- Aim for the dosages reached in trials, not to those necessary to achieve a symptomatic response.
- For all ACE inhibitors, reduce the initial dose in older people and in patients with impaired renal or hepatic function and monitor supine and standing blood pressure.
- If cough is a problem, some patients tolerate reinstitution of drug after a drug-free period.
- An angiotensin-receptor blocker (ARB) may be used if the patient cannot tolerate an ACE inhibitor.

Patients at higher risk appear to benefit to a greater extent (ACE Inhibitors MI Collaborative Group, 1998).

**The National Service Framework for Coronary Heart Disease** (DoH, 2000) states that after four to six weeks ACE inhibitor therapy should be reviewed and discontinued in those with preserved left ventricular function. The HOPE trial (HOPE Study Investigators, 2000) suggests continued benefit for at least four to five years and the EUROPA study (EUROPA Study Investigators, 2003) confirms this.

**Hypertension**

Patients with hypertension are at greater risk of cardiovascular and renal disease. An ACE inhibitor alone controls high blood pressure in half of the people with mild to moderate hypertension (Kostis, 1998). When used with a thiazide or calcium antagonist they control about 80 per cent of patients. Evidence from recent studies such as HOPE (HOPE Study Investigators, 2000), PROGRESS (PROGRESS Management Committee, 1999) and EUROPA (EUROPA Study Investigators, 2003) provide strong evidence demonstrating that ACE inhibitors may well be of use in a much wider group of patients.

The following points contain information, evidence and guidelines from a variety of sources on how and why to use ACE inhibitors in patients who are hypertensive:
- There are strong indications for ACE inhibitors in the treatment of hypertension with:
  - Heart failure;
  - LVSD;
  - Diabetes;
  - Protein-losing nephropathy;
  - After MI;
- ACE inhibitors are specifically indicated as first-line treatment of hypertension in patients with type 1 diabetes, proteinuria or LVSD;
- The Captopril Prevention Project (CAPPP) trial showed reduced cardiovascular mortality compared with conventional treatment with diuretics and beta-blockers (Hansson et al, 1999);
- Use with caution in older people. Check serum creatinine level 1–2 weeks after starting an ACE inhibitor. Use with caution if serum creatinine is >150µmol/L, although in many patients with renal failure the creatinine will fall with therapy. The British Hypertension Society Guidelines (Ramsay et al, 1999) state that older people respond well to monotherapy with ACE inhibitors or beta blockers and that calcium antagonists and diuretics are more effective in this group;
  - A once-daily dosage may also promote adherence;
- The British Hypertension Guidelines state that Afro-Caribbean patients are more responsive to calcium channel blockers and diuretics. ACE inhibitors and beta blockers may be ineffective as a monotherapy in Afro-Caribbeans and others with a suppressed renin angiotensin system;
- The New European Guidelines concluded that ACE inhibitors are suitable for initiation and maintenance of anti-hypertensive therapy (De Backer et al, 2003).

**Diabetes**

The morbidity and mortality rates from cardiovascular disease are two to five times higher in patients with diabetes. The Scottish Intercollegiate Guidelines Network (SIGN) (2001) states that women with diabetes have a greater risk of death from cardiovascular disease than men, although the absolute risk of cardiovascular disease is lower. Patients with diabetes are also at more risk of developing renal disease. ACE inhibition can be used to reduce blood pressure, incidence of stroke and cardiovascular events, and improve renal function.

The HOPE study (HOPE Investigators, 2000) looked at 3,577 patients with diabetes on ramipril (10mg once daily) or placebo and generated the following results:
- A 25 per cent reduction in MI, death, and stroke;
- A reduction in diabetic microvascular complications.

The cardiovascular mortality rate of patients who have diabetes and renal microalbuminuria is two to four times higher than it is in comparable patients without renal microalbuminuria. The decline in renal function and progression to end-stage renal failure were both reduced in the HOPE study (2000).

The EUROPA study (2003) included 1,502 patients with a coronary condition and diabetes and showed that use ACE inhibitors in patients who are hypertensive.

For related articles on this subject and links to relevant websites see www.nursingtimes.net

**REFERENCES**


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Box 1. Administration considerations in heart failure

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perindopril similarly reduced the primary composite of cardiovascular death, MI, and cardiac arrest among patients with diabetes than in patients with a coronary condition who did not have diabetes.

The Hypertension Optimal Treatment (HOT) Study (Hansson et al, 1998) suggests that it is beneficial to reduce blood pressure in high-risk groups such as those with diabetes, even if it is within the ‘normal’ range. For every 10mmHg reduction in blood pressure there is a 15 per cent reduction in cardiovascular events over 10 years.

The following points and recommendations relate to using ACE inhibitors in the people with diabetes:

- ACE inhibitors would be the first-line treatment in patients with microalbuminuria, as they are more effective in reducing albumin loss;
- ACE inhibitors can delay the onset of diabetic nephropathy in people who have diabetes and microalbuminuria (Doh, 2000);
- ACE inhibitors given for four-and-a-half years in patients with type 2 diabetes with albuminuria reduces cardiovascular events by 25 per cent (SIGN, 2001);
- Most studies use ACE inhibitors at the higher end of the therapeutic dose range.

**Stroke**

Stroke is the third leading cause of morbidity and mortality worldwide (Bonita, 1992). Patients who have suffered a first transient ischaemic attack (TIA) or ischaemic stroke are at high risk of any vascular event, most commonly MI and recurrence of stroke.

The PROGRESS study researchers gave 4mg of perindopril once daily or placebo to patients with a history of recent cerebrovascular disease (PROGRESS Management Committee, 1999). The findings of the PROGRESS report state:

- Active treatment decreased systolic and diastolic blood pressure by 9mmHg and 4mmHg respectively;
- The risk reduction of stroke recurrence was 28 per cent;
- The risk reduction in patients with a history of haemorrhagic stroke was 50 per cent;
- The benefits were not limited to hypertensive patients;
- The occurrence of dementia was reduced by 30 per cent and there was an improvement in cognitive function;
- The results strengthen the vasoprotective properties of blood pressure reduction in patients with previous stroke.

The HOPE study gave ramipril 10mg daily or placebo once daily to a group who were at high risk of cardiovascular events but who did not have left ventricular dysfunction or heart failure (HOPE Study Investigators, 2000). There was a reduction in rates of death, MI, and stroke. The rate of stroke in the ramipril group was 3.4 per cent and 4.9 per cent in the placebo group.

**Renal protection**

Diabetic nephropathy is one of the leading causes of end-stage renal failure in the developed world, therefore any measures that impact favourably on this are of benefit. These include:

- The rate of decline of renal function in overt diabetic nephropathy is slowed by blood pressure reduction and treatment with ACE inhibitors (Lewis et al, 1993);
- ACE inhibitors reduce micro and macroalbuminuria in patients with diabetes and hypertension;
- The British Hypertension Society (Ramsay et al, 1999) recommends the use of ACE inhibitors as first-line therapy for hypertensive patients with type 1 diabetes and incipient or overt nephropathy. It also states that normotensive patients with type 1 diabetes and persistent microalbuminuria may benefit;
- ACE inhibitors benefit people without diabetes who are hypertensive and have proteinuria and renal impairment.

**Stable coronary disease**

The impact of ACE inhibitor therapy on mortality and morbidity was seen only after at least 12 months of taking ACE inhibitors. This suggests that ACE inhibitors may have structural effects on the underlying pathophysiology, rather than acute haemodynamic effects altering myocardial oxygen demand/supply balance.

This has led to studies looking at the effects on atherosclerosis. The HOPE study (2000) found that ramipril at 10mg daily reduced the rates of death, MI, strokes, revascularisations, cardiac arrest, complications from diabetes, and heart failure in high-risk patients.

The EUROPA study (2003) looked at a low-risk group with known coronary heart disease and compared perindopril with placebo. The results demonstrated a reduction in cardiovascular death, MI, resuscitated cardiac arrest, and unstable angina in patients with or without diabetes, with or without hypertension, and whether male or female. It is unlikely that the modest reduction in blood pressure was responsible for the cardiovascular benefits – this may be due to changes in the arterial wall. About 50 patients would need to be treated for four years to prevent one major cardiac event. The benefits became evident after one year and increased over the duration of the study.

**Nursing implications of ACE inhibitors**

Nurses have a responsibility as part of the multidisciplinary team to have knowledge of various aspects of ACE inhibitors, including: contraindications; indications for use; target doses; side-effects; guidelines; and any interactions with other drugs.

Non-compliance with medications is a factor in the exacerbation of heart failure and admission to hospital. This may be for various reasons such as a lack of knowledge, poor motivation, depression and anxiety, poor understanding, or lack of support. Nurses can improve compliance by providing information and support.

Further developments, such as clinical nurse specialist roles and nurse prescribing, mean that the nurse’s role will expand in the future. This will be of great benefit to the patient.

The key responsibilities are to educate, support and encourage the patient and their carer or family to comply with the therapeutic regimen, which will maintain clinical stability and function, reduce hospital admissions, and improve quality of life.