SUMMARY

1. Despite the plethora of new ACE-inhibitors they offer little advantage over the earlier products captopril and enalapril.

2. While diuretics and beta-blockers remain first-line antihypertensive drugs, in specific patient groups ACE-inhibitors should be considered.

3. ACE-inhibitors, in combination with diuretics if required, can improve symptoms and prolong life in many patients with heart failure and are superior to digoxin.

4. New indications include diabetic nephropathy and post myocardial infarction.

INTRODUCTION

There are nine ACE-inhibitors currently available in Ireland. The different preparations vary in their pharmacology but produce similar effects. Earlier fears regarding the frequency of serious adverse effects were exaggerated. Cough is the commonest adverse reaction.

CLINICAL INDICATIONS

Hypertension

• ACE-inhibitors are known to be effective in treating hypertension whether used alone or in combination with other drugs. Approximately 50% of all hypertensive patients have a satisfactory response to ACE-inhibitors as monotherapy. Combination therapy with a diuretic or calcium antagonists can increase efficacy to 80% (1,2).

• ACE-inhibitors are associated with regression of left ventricular hypertrophy secondary to hypertension but so also are beta-blockers and methyldopa (2). However unlike thiazides and beta-blockers their effects on long term morbidity and mortality is unknown.

• Guidelines (3) recommend the use of ACE-inhibitors as first-line antihypertensive agents in patients who have co-existing disease such as asthma, diabetes, heart failure or gout in whom other classes of antihypertensives is unacceptable. Their routine use in uncomplicated hypertension is debated and there is no evidence that ACE-inhibitors are superior to diuretics or beta-blockers to justify their greater expense.

Heart Failure

ACE-inhibitors represent a significant advance in the treatment of heart failure and are proven to reduce symptoms and improve prognosis (4, 5). In many instances of uncomplicated mild to moderate heart failure treatment can be initiated and managed in general practice. Heart failure may be first stabilised with a thiazide diuretic e.g. bendrofluazide 5mg daily or loop diuretic e.g. frusemide 40mg daily followed by an ACE-inhibitor (6). The risk of first dose hypotension may be reduced by stopping the diuretic for 24 hrs. before commencing with low doses of ACE-inhibitors e.g. captopril 6.25mg, enalapril
2.5mg daily or lisinopril 2.5mg daily. The dosage should be increased gradually. For maximum benefit many patients may require captopril 75-150mg daily (in divided doses), enalapril 20mg daily or lisinopril 20mg daily (7). Once the patient is stable it may be possible to reduce or discontinue the diuretic.

Patients with severe disease or certain risk factors should be referred to hospital for initiation of ACE-inhibitor treatment. These include, patients on high dose diuretic treatment, hypovolemia, hyponatremia, unstable heart failure, renal impairment and age of over 70 years (8).

NEW INDICATIONS

- The use of ACE-inhibitors after myocardial infarction (MI) has been assessed (9,10,11,12) and thought to improve symptoms and reduce mortality especially in those with left ventricular dysfunction. While the balance of evidence supports the use of ACE-inhibitors post-MI this practice is not yet universal. However some hospitals are incorporating ACE-inhibitors into their treatment protocols for MI patients with left ventricular dysfunction and GP's may find their patients discharged on this medication. Captopril and ramipril are usually given three days post MI while lisinopril is usually commenced within 24 hours. The duration of therapy post-MI is uncertain and currently the topic of debate. Lisinopril (Zestril) is licensed for six weeks only but can be continued for longer if signs of cardiac failure are present. In contrast captopril has no time restriction.

- Beneficial effects of ACE-inhibitors on renal function are particularly noteworthy in diabetic patients in whom hypertension and renal failure are a major cause of death. Captopril has been shown to have a marked effect in reducing the rate of progression to end stage renal disease in patients with type 1 diabetes mellitus. Captopril is licensed for this indication with the recommended dose of 75 to 100mg daily in divided doses (13,14).

ANY SIDE EFFECTS

These are common to all ACE-inhibitors:

- **First dose hypotension.** It is less common in patients treated for hypertension than heart failure (15) and is minimised by a low starting dose.

- **Impaired renal function** is more likely to occur in patients with renal impairment. These patients are at high risk of a sharp rise in urea and creatine. It is advised to check each patients urea and electrolytes before commencing treatment and at regular intervals afterwards. Proteinuria may also occur (16).

- **Metabolic: Hyperkalemia** is more likely to occur in patients with impaired renal function or those on potassium supplements, potassium sparing diuretics or combination diuretics containing potassium. **Hypoglycemia** may occur in diabetics when treated with antidiabetic medicines and ACE-inhibitors concurrently due to an increased glucose lowering effect (17). Unlike diuretics and beta-blockers the ACE-inhibitors have no adverse effects on serum lipids, calcium, or uric acid.

- **Persistant dry cough** occurs in up to 20% of patients on ACE-inhibitors. It is more common in women and in non-smokers. The cough can occur at any dose but may
improve by dose reduction. It usually begins within one month of starting and resolves within one month of stopping treatment. Substituting another ACE-inhibitor is unlikely to help. (18)

- **Rash** occurs in up to 7% of patients and may be associated with pruritis. Photosensitivity and angioedema has occurred rarely. (16)
- **Taste** perception is altered in about 2 - 4% of patients. Its onset is usually within the first three months of therapy and takes three months to resolve after its discontinuation.
- **Rare** side effects include neutropenia and hyponatremia.

**DRUG INTERACTIONS**

**ACE-inhibitors**

- May have their efficacy reduced when taken concurrently with non-steroidal anti-inflammatory drugs (NSAID's).
- May enhance the effect of oral hypoglycemics/insulin especially in the first few weeks of treatment.
- May reduce the excretion of lithium.

**ACE-INHIBITORS IN PREGNANCY**

- ACE-inhibitors are contraindicated during pregnancy and are both teratogenic and toxic to the foetus during the second and third trimesters (19).
- Methyldopa or beta-blockers should be used to treat hypertension during pregnancy.
COSTS

Over 325,000 prescriptions for ACE-inhibitors were dispensed at a cost of over £5 million by the GMS in 1994.
REFERENCES