Leading Article

The place of ACE inhibitors in the current treatment of chronic heart failure

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In assessing the place of any therapy for chronic heart failure (CHF) there are two main considerations – does the treatment make patients feel better and does it make them live longer? It is then important to see whether this treatment offers any advantages over other treatments; here the side effect profile may be a crucial determinant.

There is now sufficient evidence to compare angiotensin converting enzyme (ACE) inhibitors to diuretics and other vasodilators in these respects (but not enough to make any comparison with digoxin).

With regard to symptomatology, several well designed large scale, placebo-controlled trials have shown that ACE inhibitors improve symptoms and exercise tolerance in advanced CHF when added to diuretics (and other treatments).^{1–3} In less severe CHF the evidence is different. Richardson *et al.* have shown that an ACE inhibitor alone may be an insufficient treatment in patients with mild heart failure compared to a diuretic alone, especially if there is a previous history of acute pulmonary oedema.⁴ It has also been suggested that increasing the dose of diuretic may improve symptoms and exercise tolerance more than adding an ACE inhibitor in patients with mild to moderate CHF.⁵ The combination of an ACE inhibitor, it should be stressed, does cause some clinical improvement and considerations other than symptomatic benefit may be important in deciding whether to add an ACE inhibitor or more diuretic (see below).^{6,7}

In contrast to the case with diuretics, there is good evidence to suggest that ACE inhibitors are superior to other vasodilators in terms of symptomatic benefit and also in terms of side effects, tachyphylaxis and neuroendocrine suppression.^{8,10}

Turning to mortality, there is no evidence to show that diuretics improve prognosis in CHF and some suspicion that they may contribute to

progression of the syndrome (see below). Certain vasodilators, on the other hand, may reduce mortality. The VHeFT-1 trial compared a high dose hydralazine – isosorbide dinitrate (ISDN) combination (300 mg/160 mg daily respectively), prazosin (20 mg daily) and placebo as adjunctive therapy in patients with mild to moderate heart failure.¹¹ Prazosin was not superior to placebo but the hydralazine – ISDN combination reduced mortality from 19.5% to 12.1% after 1 year. The patients in this study were, however, atypical – there was a high incidence of alcohol-related disease (40%), a somewhat low incidence of coronary artery disease (44%) and all patients were male and relatively young (mean 58 years). Even more importantly approximately one-third of patients had to have a reduction in dosage, or the discontinuation of either or both drugs, during this study because of adverse effects. More recently the Consensus trial study group have reported that the addition of enalapril (mean daily dose 18.4 mg) to maximal conventional treatment in patients with severe CHF resulted in a reduction in 1 year mortality from 52% to 31%.¹² The patients in this study were much more typical of British hospital practice – 73% had coronary artery disease, they were of both sexes and had a mean age of 70 years. Also in contrast to the VHeFT-1 trial, there was a much lower incidence of serious adverse effects (17% withdrawn on enalapril compared with 14% on placebo). Crucially, 44% of the enalapril-treated patients were already receiving other vasodilators (mainly ISDN) and yet still showed a reduction in mortality.

All this information suggests that ACE inhibitors do indeed make patients with CHF feel better and live longer. They seem to be more effective than other vasodilators in these respects and certainly have fewer adverse effects.⁹ ACE inhibitors must, however, remain complementary to diuretics. The latter offer initially superior symptom control but do not improve prognosis. There are also other reasons to believe that ACE inhibitors and diuretics

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are complementary. Francis *et al.* have postulated that neuroendocrine activation in CHF may be deleterious and suggest that diuretics may contribute to this.¹³ Recently Bayliss *et al.* have confirmed that the introduction of diuretics in CHF stimulates the renin-angiotensin system.¹⁴ Angiotensin II is a powerful vasoconstrictor with important direct and indirect (via aldosterone, antidiuretic hormone and possibly the sympathetic nervous system) renal effects.¹⁵ It is therefore attractive to suggest that concomitant treatment with an ACE inhibitor might limit these potentially adverse consequences of diuretic therapy. Similarly by often enabling a reduction in diuretic dose other metabolic disturbances may be minimized.¹⁶ ACE inhibitors also correct hyponatraemia and diuretic-induced hypokalaemia, perhaps more effectively than potassium-sparing diuretics in the latter case.^{17,18}

When and how then should ACE inhibitors be used in CHF? The symptomatic and prognostic evidence relates mainly to advanced CHF though there is a preliminary report that captopril may improve life expectancy in mild to moderate heart failure.¹⁹ The neuroendocrine benefits of ACE inhibition argue for earlier use. A reasonable course is probably to introduce these drugs when 40–80 mg of frusemide (or its equivalent) is required.^{20,21} Because of the risk of hypotension, reduction or temporary (24–48 h) withdrawal of diuretic prior to

initiation of treatment is advisable; screening for patients with hyponatraemia, hyperkalaemia, and proteinuria is important.²² A small starting dose (captopril 6.25 mg or enalapril 2.5 mg) should be given under observation in hospital and titration against blood pressure (and any adverse effects) should take place over the next two or three doses. Diuretics can be reinstituted at their original dose though early review in clinic is advised as less diuretic is often required following treatment with an ACE inhibitor.¹⁶ Maximum symptomatic benefit (if it occurs) may take several weeks to develop and it is helpful to inform the patient of this and to avoid potentially confusing treatment alterations in this interval.¹

Because of the risks of renal impairment, hyperkalaemia, haematological disturbances and proteinuria careful follow-up is mandatory.¹⁶ There is one report that renal dysfunction and hyperkalaemia may be more of a problem with long-acting rather than short-acting ACE inhibitors. These findings require confirmation, however, as the evidence is based on only one study which compared relatively large, fixed, doses of enalapril (40 mg daily) and captopril (150 mg daily) in patients with severe chronic heart failure. In these patients concomitant diuretic therapy (80–100 mg frusemide daily) was not altered as would now be considered normal practice.²³

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