ACE inhibitors in mild heart failure: first-line or second-line therapy?

J. G. F. Cleland

Department of Medicine (Cardiology Section), Hammersmith Hospital, London, U.K.

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Despite the successful therapeutic applications of angiotensin-converting enzyme (ACE) inhibitors to date, knowledge of how they work and guidelines for their use are still incomplete. On their role as monotherapy in congestive heart failure, we have scarce and conflicting data. Nor is there a clear answer to the question, when should an ACE inhibitor be started in a patient with heart failure? In patients with severe heart failure, the addition of an ACE inhibitor to a diuretic regimen has been shown to improve prognosis. In patients with mild heart failure, a benefit has not been demonstrated. In one preliminary report, monotherapy with the ACE inhibitor quinapril was shown to improve exercise time and functional class in patients with mild heart failure compared to placebo.

Introduction

Although it is unlikely that angiotensin-converting enzyme (ACE) inhibitors will be valuable as monotherapy in patients with severe congestive heart failure, there are advantages, at least in terms of safety, to initiating ACE inhibitor and diuretic therapy concurrently in more severe cases of heart failure. In this regard, ACE inhibitors can be considered first-line therapy. There is a paucity of data concerning the place of ACE inhibitors in mild heart failure. The definition of mild heart failure is a subject in its own right. For purposes of this review, 'mild' is defined as New York Heart Association (NYHA) grade II or III heart failure in patients not receiving diuretics, or NYHA I or II heart failure in patients receiving 40 mg day⁻¹ of frusemide (or equivalent) or less.

Large controlled trials designed to answer the question, 'When should ACE inhibitors be started in patients with heart failure?' have not been formally reported. However, the medical practitioner rarely has sufficient data at his or her disposal to be sure how any individual patient will respond to therapy. This review will attempt to summarize the limited information available in an attempt to optimize our use of these very important compounds.

Neuroendocrine systems in heart failure

WHY ACE INHIBITORS MIGHT HELP

As is well known, the primary effect of ACE inhibitors in heart failure is to prevent the conversion of angiotensin I into angiotensin II. Putative effects on bradykinin degradation remain largely unconfirmed in vivo and of uncertain significance, partly due to the problem of finding a reliable assay. Angiotensin II has a series of undesirable effects (Fig. 1) in heart failure, including direct arterial constriction, activation of the sympathetic nervous system with resultant venoconstriction, vagolytic effects and stimulation of thirst. In addition, angiotensin II may stimulate salt and water retention by a direct effect on the renal tubule and, indirectly, by stimulation of aldosterone and anti-diuretic hormone secretion. Angiotensin II has also been reported to cause direct myocardial necrosis. Theoretically, reduction in angiotensin II might prevent fluid retention and protect the failing heart.

WHY ACE INHIBITORS MIGHT NOT HELP

Angiotensin II may have beneficial effects in heart failure as well. It has direct inotropic effects. Angiotensin II is important in maintaining blood pressure, at least at the onset, in heart failure. It can also help maintain glomerular filtration rate by causing preferential constriction of the efferent arteriole, especially if arterial pressure has declined (Fig. 2). A reduction in venous tone with a fall in right atrial pressure can cause a fall in atrial...
Figure 1  Actions of angiotensin II  SNS = sympathetic nervous system; ADH = anti-diuretic hormone.

Figure 2  Diagrammatic representation of the renal glomerulus. The efferent arteriole is more sensitive to angiotensin II than the afferent arteriole.

natriuretic peptide, with loss of its desirable sodium-loosing effects (Fig. 3). Theoretically, ACE inhibitors could cause an exacerbation of sodium retention in heart failure for a number of reasons.

Conclusion
On theoretical grounds, ACE inhibitors could be useful, but we cannot be sure.

Neuroendocrine activation in heart failure
WHY ACE INHIBITORS MIGHT HELP
Animal experimental work has demonstrated that activation of the renin-angiotensin-aldosterone system, and the sympathetic and atrial natriuretic peptide systems, occurs in concert in the initial stages of heart failureª,7º. In some animal models, inhibition of an increase in aldosteroneª and angiotensin IIº has prevented or ameliorated many of
The manifestations of heart failure (i.e. sodium retention, fall in cardiac output). Studies of post-myocardial infarction patients have also shown early activation of neuroendocrine systems. Administration of an ACE inhibitor in this setting causes a fall in atrial pressures but also a reduction in arterial pressure that may not always be desirable.

**WHY ACE INHIBITORS MIGHT NOT HELP**

Although animal models of acute heart failure show activation of neuroendocrine systems at the onset, this activation becomes attenuated with time. Models of chronic heart failure show much less consistent activation. Fluid retention and blood volume expansion probably cause a secondary inactivation of the renin-angiotensin system, unless heart failure is very severe. In that case, vascular volume cannot expand adequately and oedema develops. In patients with untreated chronic heart failure there appears also to be little increase in renin-angiotensin activity. It has been argued that such low levels of activity indicate that therapy targeted against this system would be of no value. Other animal experiments on untreated recent-onset heart failure have shown that ACE inhibition actually causes hypotension and continued sodium retention in animals that had previously been able to establish circulatory and salt and water equilibrium.

**Conclusion**

The data are conflicting. ACE inhibitors could be useful in some cases, harmful in others.

**Trials of ACE inhibitors in moderate/severe heart failure**

In patients who have heart failure already requiring diuretic therapy, the addition of an ACE inhibitor appears to be markedly beneficial. In addition to beneficial effects on symptoms, functional capacity, and haemodynamics, ACE inhibitors can correct hypokalaemia, intracellular potassium depletion, hypomagnesaemia, and disturbances in autonomic function, as well as reduce the frequency of ventricular arrhythmias. The CONSENSUS study has shown that these beneficial effects can be translated into an improvement in prognosis in patients with severe heart failure.

Even in this group of patients, there are potential disadvantages with ACE inhibitor therapy. ACE inhibitors generally cause a decline in glomerular filtration rate due to a reduction in glomerular efferent arteriolar tone, an effect of reducing angiotensin II. This is not progressive. Possibly owing to an acute decline in glomerular filtration rate or, more likely, a reduction in atrial natriuretic factor, sodium and water retention is the rule rather than the exception during the first few days of ACE inhibitor therapy. Over the ensuing weeks this effect is reversed, and long-term therapy (longer than 3 months) is associated with a net natriuresis (unpublished data).

**Trials of ACE inhibitors in mild heart failure**

**INDICATIONS THAT ACE INHIBITORS MIGHT BE HELPFUL**

In a large study of patients with mild heart failure symptoms, some of whom were not receiving diuretics, captopril was found to be superior to placebo in reducing symptoms and improving exercise performance. Digoxin generally had intermediate effects that differed little from placebo (apart from an increase in ejection fraction),
although captopril was not clearly better than digoxin, apart from producing a reduction in ventricular arrhythmias.

In another study adding captopril to frusemide 40 mg day\(^{-1}\) was as effective as doubling the dose of diuretic\(^{22}\).

**INDICATIONS THAT ACE INHIBITORS MIGHT NOT BE HELPFUL**

The inability to perceive a clear difference between digoxin and placebo in recent large studies\(^{21,23}\) renders interpretation of trials comparing ACE inhibitors and digoxin in mild heart failure difficult. One fairly large trial, comparing the effects of enalapril with digoxin in patients on small doses of frusemide, demonstrated similar efficacy\(^{24}\). However, since the benefit of digoxin in this setting is doubtful, the benefit of enalapril is also uncertain. Similarly, in a study comparing captopril and digoxin, there was no significant difference in the increase in exercise time\(^{25}\). In another elegant study design\(^{26}\), diuretic therapy was discontinued and ACE inhibitor or placebo therapy initiated. By one year 25% of those on captopril required reinitiation of diuretic therapy, compared with 36% of those on placebo. The difference was not statistically significant, nor was the exercise time different between the two groups.

**ACE inhibitor monotherapy**

**THEY DON'T WORK**

The only controlled trial specifically designed to address the effectiveness of ACE inhibitors as monotherapy in mild heart failure suggested that ACE inhibitor monotherapy was of limited use\(^{27}\). Several of the patients developed pulmonary oedema and required diuretic therapy. However, patient selection may have been inappropriate: most of the patients recruited for the study had been withdrawn from diuretics, and several had previously had pulmonary oedema.

**THEY DO WORK**

In a preliminary report on the results of a large study with quinapril in mild heart failure\(^{28}\), an overall benefit was demonstrated. Importantly, 26 of the patients who were not receiving diuretics showed the same beneficial response as did patients receiving quinapril plus concomitant digitalis and/or diuretics. The increase in exercise time was up to three times greater in patients receiving quinapril monotherapy compared with those on placebo.

**Can ACE inhibitor monotherapy prevent heart failure from occurring?**

Early animal experiments\(^{29,30}\) suggested that captopril could reduce mortality and ventricular dysfunction in animals undergoing experimental infarcts. Subsequently, it was shown that captopril, given to patients some days after an anterior myocardial infarction, could prevent ventricular dilatation\(^{31}\). The significance of these findings remains uncertain, but a recent placebo-controlled study suggested that captopril could prevent the deterioration in exercise performance observed in a group of patients after large myocardial infarctions\(^{32}\).

**Conclusions**

In some circumstances, ACE inhibitors do seem to be effective in preventing progression of ventricular dysfunction, which may delay or prevent the appearance of heart failure. Data on ACE inhibitor monotherapy in heart failure are scarce and conflicting. In patients with mild heart failure already receiving diuretics, the addition of an ACE inhibitor rather than digoxin is preferred. Nonetheless, the best available information to date suggests that monotherapy with an ACE inhibitor (quinapril) in very mild heart failure is beneficial.

**References**


