Leading Article

Angiotensin converting enzyme inhibitors for hypertension and heart failure?

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Introduction

Over the last decade, angiotensin converting enzyme (ACE) inhibitors have established a major role for the management of patients with hypertension and heart failure. However, to what extent are the real indications for these agents obscured by the plethora of research? New scientific tools for the investigation of disease, combined with the more widespread use of advanced technology, may well obscure rather than clarify the indications for a particular therapy.

The goals in the management of hypertension are simply to reduce the morbidity and mortality associated with the condition while causing minimal inconvenience and side effects in a largely asymptomatic population. In patients with symptomatically mild heart failure, the aims are somewhat similar to those of hypertension, though an improvement in symptoms, even if mild, may be a worthy goal. Although symptoms may be mild, left ventricular function is already severely compromised and the average life expectancy is only about 5 years, so the potential benefits of effective therapy are great. In patients with more severe heart failure, even though the prognosis is very poor, a treatment which only improves longevity without improving symptoms might be regarded as a failure. With these goals in mind, the role of ACE inhibitors in cardiovascular medicine may be defined more clearly.

Hypertension

There is, as yet, no evidence that ACE inhibitors reduce mortality or major morbidity in patients with hypertension. ACE inhibitors do appear to slow the decline in renal function in patients with

hypertension and diabetes mellitus, but this has not yet been shown to reduce requirements for dialysis or renal transplantation.¹ Some have argued that ACE inhibitors should be used as first line therapy based on the following line of reasoning. Lowering blood pressure with beta-blockers or diuretic reduces the morbidity associated with mild to moderate hypertension, therefore, as ACE inhibitors also reduce blood pressure effectively they should be at least as effective in reducing mortality. The argument then runs that because ACE inhibitors have less adverse metabolic effects they are likely to be more effective. However, it is equally possible that there are side effects of ACE inhibitors of which we are as yet unaware which would negate such theoretical advantages. To justify the increase in prescription costs, ACE inhibitors have to demonstrate in a properly controlled trial that they live up to expectation before they can be recommended for use as first-line agents in hypertension.

However, ACE inhibitors do have a major role in the management of hypertension. Many patients have side effects from standard therapies such as diuretics and beta-blockers. Even if these are mild, many patients would not be willing to tolerate them for a decade or more and it may be reasonable to make the assumption that equivalent benefits can be derived with an ACE inhibitor. Other patients fail to respond to beta-blockers and diuretics alone and a third-line agent may be required.

Hypertension commonly antedates myocardial infarction or heart failure; many patients who have a myocardial infarction or heart failure have concomitant hypertension.² In the absence of a trial specifically addressing mortality in hypertension, it is not unreasonable to use the data in mortality studies in these related conditions to obtain some general idea of the likely effect of a particular anti-hypertensive therapy. ACE inhibitors have been shown to reduce mortality in patients with heart failure^{3–7} although a recent study showed no

mortality benefit after myocardial infarction.⁸ Conducting a similar exercise with prazosin indicates no benefit with this therapy.⁹ In contrast, there is accumulating evidence of an increased mortality associated with the dihydropyridine calcium antagonist, nifedipine.^{10,11} Hydralazine is not widely used in the UK, but there is evidence of a modest benefit in mortality in patients with heart failure.⁹ Although a great deal of caution should be placed on the above speculation until there is better evidence, it would seem reasonable to consider ACE inhibitors as the preferred therapy when a beta-blocker or diuretic are contra-indicated or as the third-line agent of choice.

ACE inhibitors in severe heart failure

ACE inhibitors are of clear benefit in this group of patients.^{4,5} They reduce symptoms, improve functional capacity and prolong life. The CONSENSUS study demonstrated that for every 100 patients treated with enalapril, 16 more patients would be alive at one year than without such treatment. This is probably more cost effective than any other cardiovascular intervention other than advising the patient not to smoke. Further follow-up of this group of patients suggests continuing benefit beyond the year of treatment included in the CONSENSUS study.¹² Patients who exhibit intense neuro-endocrine activation have the worst prognosis and appear to derive the greatest benefit from addition of an ACE inhibitor.¹³ This may be a statistical phenomenon in the group who had most to gain. However, ACE inhibitors may prevent the direct cardiotoxic actions and secondary metabolic disturbances of angiotensin II.^{14,15}

Of course, death is not prevented but merely delayed. The prognosis of these patients remains poor despite treatment with an ACE inhibitor. Although symptoms are initially improved by the ACE inhibitor, progression of the underlying disease may lead to an apparent, though not real, loss of effect. ACE inhibitors do not confer immortality and in this group of patients other therapeutic avenues need to be explored. Large scale studies are being set up to assess the effect of combining an ACE inhibitor with a vasodilator such as hydralazine or one of the newer vasodilator agents. However, as hypotension leading to symptoms and pre-renal uraemia is often a problem in these patients, this therapeutic approach may prove deleterious.

At present, inotropic agents new and old have proved disappointing. There is no clear evidence from larger scale studies that digoxin is more effective than a placebo in those patients in sinus rhythm,^{16,17} although the subset of patients with a persistent sinus tachycardia and third heart sound

may benefit.¹⁸ At present there is no evidence that digoxin worsens prognosis.⁴ Newer inotropic agents are generally associated with increased mortality with little evidence of an improvement in symptoms or exercise performance.¹⁹

It might be thought that the most rational approach to the problem would be prevention. Unfortunately, this view is in part naive. Cardiac function declines with age. Even though we have agents which may delay the onset of coronary disease, reduce the size of myocardial infarctions or slow down progressive ventricular dysfunction, if these therapies concomitantly reduce mortality, then, perversely, they will increase the prevalence of heart failure in the community. The major advantage in preventative measures is to 'prolong active life'. In purely economic terms death is cheap, life is inevitably more expensive.

ACE inhibitors in mild to moderate heart failure

Two recently published papers have confirmed that ACE inhibitors are effective in reducing the mortality and morbidity associated with milder degrees of heart failure treated with diuretics.^{6,7} The V-HeFT study showed that at 2 years, mortality was reduced by 28% when enalapril twice daily was compared to a combination of hydralazine and isosorbide dinitrate. Retrospective comparison to patients treated with diuretics alone suggested that enalapril could reduce mortality rates by up to 50%. This suggests that ACE inhibitors have the same absolute but greater relative benefits in terms of mortality in patients with mild compared to severe heart failure.

The SOLVD study compared enalapril with 'conventional' therapy and suggested a more modest reduction in mortality, around 23% at 2 years. However, during the course of the study, those randomized to conventional treatment generally received vasodilator agents such as hydralazine and isosorbide dinitrate, while towards the end of the study, 30% of patients who were randomized to conventional therapy were prescribed open-label ACE inhibitor. Thus the SOLVD study is more likely to have under-estimated the beneficial effects of the ACE inhibitor on mortality than if diuretic therapy alone had been the standard therapy.

These studies both emphasize that treatment with an ACE inhibitor also reduces the rate of hospitalization, both all cause and those specifically for heart failure. However, as patients live longer the total number of admissions may be little affected. Unfortunately, neither of these studies gives us a clear idea of what severity of heart failure was being treated. The mean ejection fraction was 24–29% and peak oxygen consumption around 14 ml/kg/min in both studies, which some have suggested is a severity requiring cardiac transplan-

tation.²⁰ Unfortunately, in neither study is the diuretic dose recorded. Fortunately, the SOLVD study has a second arm called the SOLVD prevention study, with over 4,000 patients recruited. The majority of patients in the SOLVD prevention study are not receiving a diuretic and constitute a group of patients with genuinely mild heart failure. The SOLVD prevention study should be reported in 1992 and will clarify whether very early introduction of enalapril really is of benefit.

The maintenance dose of enalapril in the above studies was 10–20 mg twice daily. A recent trial noted a higher mortality in those patients receiving smaller doses of ACE inhibitors compared to regimes designed to produce more intense ACE inhibition.²¹ Doses of captopril and enalapril that are considered moderately high may be unable to suppress angiotensin II formation throughout the 24 hours.²² Higher doses of ACE inhibitors, which inhibit the production of angiotensin II throughout the 24 hours, may be required to obtain full benefit at least with respect to mortality.

The V-HeFT II data suggest that the reduced mortality in moderate heart failure is confined to those without coronary artery disease. The SOLVD data also shows a trend to greater benefit in those with heart failure not due to ischaemic heart disease. This result may be fortuitous, but recent data from the Framingham study, showing that patients with a previous myocardial infarction and a low arterial pressure have an increased mortality,²³ may indicate that some patients with coronary disease do less well with reductions in coronary perfusion pressure. This is borne out to some extent by a recent report from the CONSENSUS II study, which investigated the effects of an ACE inhibitor on mortality after myocardial infarction.⁸ Enalapril was introduced very early as intravenous enalaprilat. The study showed no difference in mortality between enalapril and placebo, but did suggest that those patients who developed a low arterial pressure on the introduction of the ACE inhibitor had a worse outcome. The excess mortality in this group was spread out over the 3 months after myocardial infarction. The ACE inhibitor may have reduced coronary perfusion pressure acutely causing an increase in the size of the myocardial infarction. A recent clinical study has confirmed that ACE inhibitors may exacerbate angina in patients with concomitant heart failure probably through such a mechanism.²⁴

ACE inhibitors for asymptomatic left ventricular dysfunction

If a patient has no symptoms, then prevention of progression of disease, or a reduction in mortality, become the most important goals. However,

although many patients claim to be asymptomatic, this is because they have altered their lifestyle to prevent the occurrence of symptoms. Regular exercise programmes do appear to confer benefit, at least in symptoms and possibly in terms of mortality and progression of disease. The SOLVD prevention study will clarify whether ACE inhibitors can prevent the progression of disease to the symptomatic stage.

What is the mechanism by which ACE inhibitors reduce mortality?

The CONSENSUS and SOLVD studies both suggest that ACE inhibitors act by retarding the progression of heart failure, while the SOLVD data also noted a trend to reduced incidence of myocardial infarction. However, the V-HeFT II data is in marked contrast to this, suggesting that the reduction in mortality was confined to a reduction in sudden death. The V-HeFT II study had fewer patients with coronary artery disease as the cause of heart failure and only men were recruited to this study which may account for the differences. However, it is far more likely that the differences were due to dissimilarities in the classification of death by the end points committee. These studies emphasize that mortality should be classified as far as possible according to the facts and not opinions. There is no doubt in anybody's mind that intractable pulmonary oedema or cardiogenic shock may be classified as deaths due to pump failure. A sudden death, whether it occurs in the setting of worsening heart failure or in a stable situation, should be classified as sudden as this has major implications for further strategies to reduce mortality. There seems no need for the pointless confusion, especially evident in the SOLVD paper when sudden death occurring in the setting of worsening symptoms was classified as a death due to progressive heart failure.

ACE inhibitors after myocardial infarction

Myocardial infarction leads to activation of the renin-angiotensin system, sympathetic nervous system and anti-diuretic hormone. The intensity of this activation is roughly proportional to the size of the myocardial infarction.²⁵ While several smaller studies have indicated possible benefits in terms of progressive ventricular dysfunction and mortality after myocardial infarction with the use of an ACE inhibitor,^{26,27} the only large scale study reported to date failed to show benefit.⁸ Possibly the ACE inhibitor was introduced too early and had a deleterious effect on infarct size, especially in those who had a marked fall in blood pressure and

therefore coronary perfusion.^{24,28,29} This could have offset any later benefit. However, the majority of patients with a first myocardial infarction do not develop heart failure and it is possible that ACE inhibitors have no benefit to confer in this group.

ISIS-IV will be conducted on a far larger number of patients, but again with early introduction of the ACE inhibitor and again all infarcts will be included as in CONSENSUS II.³⁰ Although the design similarities to CONSENSUS II are worrying, investigators in addition will be studying the effects of isosorbide mononitrate and intravenous magnesium in a factorial study design. If they do come up with a different result from CONSENSUS II, this may indicate a specific effect of captopril due either to its duration of action or its sulphhydryl group.

Other studies are being conducted in specifically targeted high risk groups after myocardial infarction. The SAVE study³⁰ is being conducted on those with an ejection fraction less than 45% after the myocardial infarction. The AIRE study has an even more clinically pragmatic approach, recruiting solely those patients with evidence of heart failure after myocardial infarction.³¹ In both these studies patients do not receive the ACE inhibitor until several days after the infarct to avoid the

problems of acute haemodynamic instability. It is likely that the latter study design will make more sense to the clinician trying to determine the optimal use of these drugs. The larger studies should be useful in showing the limitations of this sort of therapy if not the benefits.

Conclusion

ACE inhibitor use is likely to expand many-fold in the next decade. It is likely that they confer benefit in all grades of heart failure, though the reduction in mortality in patients with very mild heart failure needs to be confirmed. However, used for the wrong patient or in the wrong situation, these drugs also have the power to do harm. Heart failure is a malignant condition and deserves thorough investigation. Patients incorporated into clinical studies are investigated and those patients who would benefit from surgery or at high risk of complications of therapy are withdrawn. The benefits observed in trials are an indication not only that ACE inhibitors should be more widely used, but also that the causes of heart failure should be more thoroughly investigated.

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