ACE inhibitors for heart failure: a question of dose

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Few treatments for cardiovascular disease have been shown to have such an impact on symptoms, morbidity, and mortality as have the angiotensin converting enzyme (ACE) inhibitors when used for the treatment of heart failure. A reduction in mortality has also been shown in patients treated with ACE inhibitors after myocardial infarction, particularly if heart failure or obvious ventricular dysfunction is present. The outcome of recent trials would be expected to lead to major changes in clinical practice, but, despite what seems overwhelming evidence of benefit, only a minority (10–20%) of patients who stand to benefit currently receive an ACE inhibitor.¹ The lack of impact on prescribing habits may indicate a reluctance on the part of physicians to change current practice or merely reflect a reasonable time delay as physicians learn the nuances of a new class of drug to be used in the clinical context of heart failure or myocardial infarction.

An additional concern is that up to 80% of patients who are receiving an ACE inhibitor are taking doses that are not known to be effective in reducing morbidity or mortality.² Caution on the part of cardiovascular physicians has often been appropriate. Ten years ago thiazide diuretics were being used in doses 4–8 times higher than they are today and captopril was commonly used in doses in excess of 450 mg/day.^{3–5} Reductions in dose of both agents have led to a fall in the incidence of side effects. As a consequence of an understandable zeal to reduce doses to avoid side effects physicians may also be forfeiting benefit.

ACE inhibition

ACE inhibitors bind reversibly to ACE and dissociate from the enzyme as the plasma concentration of free drug falls.⁶ ACE inhibitors that have a high affinity for the enzyme dissociate slowly, and, although the plasma concentration of free drug may fall rapidly, the half life of the fraction bound to ACE can be very long.⁶ The drug may finally be eliminated only when ACE itself is degraded; in the case of tissue bound ACE this may take days. ACE is not the rate limiting enzyme for the formation of angiotensin II under normal circumstances, and about 80% of the activity of the enzyme must be inhibited before plasma concentrations of angiotensin II begin to fall.⁷ Detection of reduced formation of angiotensin II is a better marker of the efficacy of ACE inhibition than the degree of inhibition of the activity of the enzyme itself. If no free drug is present in the plasma to

inhibit newly formed ACE, production of angiotensin II will resume. A higher dose of an ACE inhibitor, by maintaining the plasma concentration of unbound drug for longer, may not only inhibit the ACE more completely but also inhibit production of angiotensin II for longer.⁶

Theoretical arguments for using low doses

Although substantial doses of ACE inhibitors are required to suppress the formation of angiotensin II for more than a few hours, some investigators suggest that high doses of ACE inhibitors are not necessary to exert clinical benefit. Preliminary studies have suggested that small doses of an ACE inhibitor—for example, captopril 1 mg—can enhance renal salt and water excretion without altering circulating neuroendocrine factors or haemodynamics.⁸ Animal data suggest that small doses of ramipril can prevent ventricular hypertrophy without reducing blood pressure, a potentially dangerous effect.⁹ These data await confirmation but suggest that inhibition of circulating ACE to reduce plasma angiotensin II may not be a necessary or important action of ACE inhibitors.

Many, though not all, investigators believe that the haemodynamic effects of ACE inhibitors are poorly related to the activity of the plasma renin-angiotensin system.^{10 11} There are several explanations for these observations. Tissue ACE may be more sensitive to the effects of ACE inhibitors, or their effects in tissues may persist for longer.^{12 13} Tissue ACE is found mainly on the luminal surface of the vascular endothelium¹⁴ and is the main source of plasma ACE. ACE inhibitors bound to tissue and plasma ACE are probably in a dynamic equilibrium during long term treatment. Alternative metabolic pathways for the conversion of angiotensin I to II by chymases,¹² changes in electrolyte homeostasis, altered tone of the vascular smooth muscle cell, changes in plasma volume, secondary effects on the bradykinin-prostaglandin system, and long term structural changes in the arterial wall itself are options to explain the dissociation of the haemodynamic effects of ACE inhibition from plasma renin-angiotensin system activity. Only small doses of an ACE inhibitor may be required to reduce the degradation of bradykinin, which may be an important mediator of ACE inhibitor action.¹²

Brief periods of suppression of angiotensin II have been argued to be preferable to prolonged inhibition. Allowing angiotensin II

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to rise periodically might ameliorate the decline in glomerular filtration rate observed with ACE inhibitors in heart failure, by allowing blood pressure and efferent arteriolar tone to rise at regular intervals.¹⁵ High doses of long acting ACE inhibitors result in a greater decline in glomerular filtration rate, but the effect is generally small. On balance, however, long acting ACE inhibitors have an equal or greater benefit on clinical symptoms so long as the decline in renal function is not prominent.¹⁶

During long term ACE inhibition in patients with hypertension,¹⁷ after myocardial infarction,¹⁸ or with heart failure¹⁹ enalapril up to 10 mg twice daily or ramipril 10 mg once daily have failed to reduce plasma angiotensin II concentrations. These data need to be confirmed by others as the assay for angiotensin II is prone to technical problems, especially cross reactivity with angiotensin I, concentrations being greatly raised during long term ACE inhibition.²⁰ Lower doses of ACE inhibitors could be more effective in lowering angiotensin II concentrations long term, as described below.

Reduction in angiotensin II concentration leads to a loss of feedback inhibition on renin secretion and to upregulation of angiotensin II receptors.²¹ Long term ACE inhibition leads to hypertrophy of the juxtaglomerular apparatus and increases in plasma concentrations of active renin of up to 100-fold.²² Increases in renin concentration lead to increased conversion of angiotensinogen to angiotensin I.²³⁻²⁴ The accumulation of angiotensin I then competes with the ACE inhibitor for binding to the enzyme, leading to renewed formation of angiotensin II. Angiotensin I may also be converted to angiotensin II by enzymes other than ACE such as cardiac chymase.¹¹ Periodic loss of effective ACE inhibition could prevent an excessive rise in renin concentration, accumulation of angiotensin I, and upregulation of angiotensin II receptors, thereby preserving the ability of ACE inhibitors to suppress effectively angiotensin II long term.

The argument is speculative. Evidence that alternative pathways of conversion of angiotensin I to angiotensin II are clinically relevant in humans is not available, and less reactive hyperreninaemia may merely reflect less effective suppression of angiotensin II formation.

Theoretical arguments for using high doses

Prevention of the formation of angiotensin II is believed to be the fundamental mechanism of action of ACE inhibitors by many investigators. On starting treatment with an ACE inhibitor small doses—for example, captopril 6.25 mg—can completely inhibit the formation of angiotensin II for brief periods (10–15 minutes) in patients with heart failure.²⁵ During long term ACE inhibition plasma concentrations of active renin rise up to 100-fold, resulting in a greatly increased capacity to synthesise angiotensin I, which

competes with the inhibitor for binding to the enzyme.²²⁻²⁶ Moderately large doses of ACE inhibitors can suppress, long term, the formation of angiotensin II in heart failure partially,²⁶⁻²⁷ while doses of enalapril at 40 mg/day can suppress angiotensin II more or less completely throughout 24 hours.²² Small increases in ACE activity, through partial loss of ACE inhibition, will lead to the rapid rise in plasma angiotensin II concentration. Doses of an ACE inhibitor that adequately suppress angiotensin II formation throughout the day initially, may fail to do so during long term treatment. Additionally, during long term ACE inhibition angiotensin II receptor upregulation may result in smaller plasma concentrations of angiotensin II having more profound effects on vascular tone or aldosterone secretion. This may explain why, after an initial fall, aldosterone concentrations tend to rise during long term ACE inhibition, though adrenal stimulation secondary to an increase in potassium concentration is an alternative explanation.

Complete suppression of angiotensin II throughout the 24 hours may be important in obtaining not only the greatest haemodynamic benefit but also the most benefit from the prevention of the direct effects of angiotensin II on tissues and the sympathetic nervous system.²⁵ More profound ACE inhibition results in a greater rise not only in serum creatinine concentration but also in potassium concentration.¹⁵ Hyperkalaemia may be important in preventing arrhythmias and improving skeletal and cardiac muscle function. Intense ACE inhibition during long term treatment also enhances a frusemide induced diuresis.²⁸

The doses of ACE inhibitors used in clinical studies so far may not completely suppress angiotensin II over 24 hours.^{17-19, 26} Higher doses of ACE inhibitors than used heretofore might produce even greater benefit. Even larger doses of ACE inhibitors than those required to suppress angiotensin II may be required for optimal effects on bradykinin-prostaglandin mediated effects or other as yet poorly described effects of ACE inhibitors on other systems, such as erythropoietin, substance P, nitric oxide, and vasoactive intestinal polypeptide. Animal studies have shown that high doses of ACE inhibitors (human dose equivalent of 3000 mg/day of captopril) can retard the development of atherosclerosis.²⁹ Such large doses would not be tolerated by many patients, but the upper end of the therapeutic dose-response relation with ACE inhibitors has not been fully explored.

Clinical evidence for the effectiveness of high doses

Most of the major studies on the effect of ACE inhibitors on symptoms and all the major studies of the effects on prognosis have used high doses of ACE inhibitors.³⁰⁻³⁴ Moreover, ACE inhibitors have usually been given more frequently than is common clinical practice. Enalapril 10 mg twice daily is a more effective

antihypertensive regimen than 20 mg once daily, probably because it suppresses production of angiotensin II over 24 hours more effectively.^{35 36} Captopril 25 mg thrice daily probably does not inhibit angiotensin II production effectively over 24 hours in patients with heart failure during long term dosing, though 50 mg thrice daily may do so.²⁶

The early studies that conclusively showed the benefits of ACE inhibitors on symptoms and exercise performance used fairly high doses—for example, captopril 50–100 mg thrice daily and enalapril 40 mg.^{22 26 37} High doses in these studies were generally well tolerated, and about 80% of patients took full doses.

The target dose of enalapril in the original CONSENSUS study was 20 mg twice daily.³⁰ Despite the fact that the patients in this study had severe heart failure and were receiving high doses of diuretics, 22% achieved the top dose. More patients would probably have tolerated this dose if the investigators had applied the study protocol more rigorously; only 45% of patients randomly allocated to placebo achieved the target “dose,” indicating a reluctance on the part of the investigators even to try high doses. Nevertheless, the mean daily dose was 18.4 mg/day—that is, about 9.2 mg twice daily—and this was associated with a 50% reduction in mortality in patients with heart failure due to ischaemic heart disease.³⁸ The table shows the mean dose of ACE inhibitor in the other major studies. In these landmark trials ACE inhibitors, used in high doses, were able not only to reduce mortality but also to prevent progressive ventricular dysfunction.

Clinical evidence for the effectiveness of low doses

Properly designed clinical trials showing clinical benefit with low doses of ACE inhibitors are few. Brilla *et al* found an improvement in symptoms in a single blind placebo controlled trial of enalapril 5 mg once daily.³⁹ Two small double blind studies of enalapril in

doses of 5 mg twice daily have also shown beneficial effects on symptoms and exercise performance.^{40 41} The study by Kleber *et al* in 170 patients with mild heart failure is the only placebo controlled trial that shows an improvement in a combined morbidity-mortality end point with a fairly low dose of an ACE inhibitor (captopril 25 mg twice daily).⁴²

Several clinical trials of ACE inhibitors after myocardial infarction show that doses of captopril as low as 75–100 mg/day modify ventricular remodelling.^{43 44} Thus, doses of captopril one half that targeted in the SAVE study are associated with some clinical evidence of benefit.

Clinical comparisons of high and low dose ACE inhibition

No adequate comparisons of the symptomatic or prognostic benefits of low versus high doses of ACE inhibitors yet exist.

Riegger found a dose-response relation with quinapril in doses ranging from 5 mg to 20 mg twice daily, patients receiving higher doses having greater increments in exercise performance.⁴⁵ However, during a subsequent one year open label follow up study the most popular choice of quinapril dose was the lowest, with 71% of patients taking 5 mg twice daily. These data need to be substantiated in further clinical trials.

Pacher *et al* in a non-randomised comparison of more than or less than 25 mg captopril thrice daily found that patients taking higher doses were less likely to undergo transplantation or die.⁴⁶ Patients taking the higher dose were also more likely to have a reduction in plasma concentrations of aldosterone and atrial natriuretic peptide. As the study was not randomised the sicker patients may have tolerated high doses of captopril less well. Thus the ability to tolerate high doses of captopril may indicate an intrinsically better prognosis. Also, transplantation is not a satisfactory trial end point because the indications for referral and the criteria for acceptance on to a waiting list vary. Factors

Relative efficiency in terms of lives saved per month's treatment in trials of ACE inhibitors

Trial	Agent	Frequency	Total daily dose of ACE inhibitor (target/achieved)	Comparator	Mean duration of trial (months)	Survival	
						Absolute benefit*	Relative benefit (% risk reduction)
CONSENSUS	Enalapril	Twice daily	40 mg/18.4 mg	Placebo	6.3	22.9	27
V-HeFT II	Enalapril	Twice daily	20 mg/15 mg	Hydralazine-nitrate	30	1.8	11
SOLVD:							
Treatment	Enalapril	Twice daily	20 mg/16.6 mg	Placebo	41.4	1.1	16
Prevention	Enalapril	Twice daily	20 mg/16.7 mg	Placebo	37.4	0.3	8
SAVE	Captopril	Thrice daily	150 mg (79% achieved target)	Placebo	42	1.0	19
AIRE	Ramipril	Twice daily	10 mg (77% achieved target)	Placebo	15	3.5	27
ISIS-4	Captopril	Twice daily	100 mg (83% on active treatment at end)	Placebo	1	4.6	7
GISSI-3	Lisinopril	Once daily	10 mg (data awaited)	Placebo	1.5	5.3	12
ISIS-2†	Streptokinase	—	Not applicable	Placebo	1.2	22.2‡	25
MRC trial of mild hypertension†	Thiazide or propranolol	—	Not applicable	Placebo	66	Death 0.0049 Stroke 0.048	45

*No of lives saved (all cause) during one month's treatment of 1000 patients.

†Given as comparator.

‡Vascular deaths only.

These data should be interpreted with caution, however. Although the effect of one month's treatment in some of the postinfarction trials is striking, this may reflect a short term benefit during a period of high risk; little greater benefit may be had by longer term treatment in patients without marked ventricular dysfunction. In other words, the apparent absolute benefit per month of treatment will diminish with longer term treatment. Nevertheless, these data provide proof that to treat all patients with high doses of ACE inhibitors after infarction is one inexpensive method of saving lives. The studies do not provide conclusive evidence that high dose treatment of all patients is optimal or the least expensive clinical practice.

other than the severity of heart failure, such as blood group, may influence which patients undergo transplantation.

Pouleur *et al* reported a retrospective analysis of a trial of xamoterol in severe heart failure.⁴⁷ The abrupt introduction of xamoterol increased mortality, but patients taking captopril had a higher mortality than those taking enalapril. The authors suggested that the long acting ACE inhibitor had superior prognostic benefits to the shorter acting one. It is difficult to judge whether the dose of enalapril and captopril were equivalent. An alternative explanation is that the dose of captopril was effectively lower than the dose of enalapril and that no difference would have been observed had equipotent doses been used. Any ACE inhibitor, including captopril, will induce 24 hour suppression of angiotensin II concentrations if given in large enough doses, at least in the short and medium term.

The only randomised dose ranging study so far purporting to investigate morbidity in heart failure included only 27 patients, but the results showed that patients taking enalapril 15 mg twice daily were less likely to deteriorate than patients taking 2.5 mg twice daily.⁴⁸

Practical issues

The major goals of treating severe heart failure are to ameliorate symptoms, improve quality of life, and reduce mortality. In severe heart failure the prognosis is poor even in patients treated with ACE inhibitors and a reduction in mortality alone may be a critical end point only in exceptional groups of patients such as those awaiting transplantation. On the other hand, in frail elderly patients prognosis may not be an issue at all. In these circumstances use of the smallest dose that adequately relieves symptoms but minimises side effects is justified. Several properly controlled studies have shown that ACE inhibitors are effective in improving symptoms and exercise performance when given at low doses and that only a minority need to be titrated to higher doses to improve clinical status.⁴⁹⁻⁵⁰ Alternatively, if symptoms are already well controlled, prognosis is the principal reason for treating a patient with an ACE inhibitor. Since myocardial infarction and progression of heart failure may be irreversible and death certainly so, physicians, on current evidence, should titrate up to the dose used in the large clinical trials when treating to delay worsening heart failure or death.

There are a few exceptions to this last statement. Most ACE inhibitors are excreted by the kidney, and even at small doses they may have a protracted effect if the glomerular filtration rate is low. Patients with renal dysfunction may not require high doses. All elderly patients with heart failure have renal dysfunction. The large clinical trials have enrolled few patients over 70, yet this group constitutes most patients with heart failure. The optimal dose of ACE inhibitor to improve prognosis in elderly patients is not known,

although titration of the dose against symptoms may be optimal management in many. Dose will need to be adjusted according to the patient's size and body type.

Studies under way

Two large trials have been initiated to determine whether high doses of ACE inhibitors are superior to lower doses. The NETWORK study, due to complete in 1994, will randomly allocate 1500 patients to enalapril 2.5 mg, 5 mg, or 10 mg twice daily for six months. The primary end point is the combined end point of death, admission to hospital for heart failure, and worsening heart failure. The study is designed to detect a difference between the highest and lowest dose, with the middle dose occupying an intermediate position. The ATLAS study has the primary end point of all cause mortality. This study will randomly allocate 3000 patients to receive lisinopril either at low dose (2.5 mg or 5 mg once daily, according to local practice) or at high dose (32.5 mg or 35 mg once daily); the expected minimum follow up time is two years, recruitment has been completed this year, and reporting is expected in 1996. A further study (ACHIEVE) will also consider the dose of quinapril in relation to the cost effectiveness of ACE inhibitor treatment. These studies should add significantly to our current knowledge of how to treat heart failure.

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