

Angiotensin-Converting Inhibitors in Patients with Congestive Heart Failure: A Class Effect?

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Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve exercise performance, patient well-being and survival in patients with heart failure.¹⁻⁴ Both captopril and enalapril have been approved for use in heart failure and it is likely that several other ACE inhibitors will be approved within the near future. Although they differ in duration of action and side-effect profile, it has generally been thought that one ACE inhibitor is equal to another in effectiveness.⁵ This concept has now been challenged by Pouleur et al,⁶ who found in a retrospective analysis of baseline therapy in the Xamoterol Mortality Trial that patients receiving baseline therapy with captopril had a significantly higher mortality than those receiving enalapril.

Pouleur et al postulate that the higher mortality of patients receiving captopril in their study was due to the fact that captopril's duration of action is shorter than that of enalapril. Because captopril is recommended to be used 3 times daily, compared with 2 times daily for enalapril in patients with heart failure, compliance may have been worse with captopril, thereby leaving patients exposed to the adverse effects of renin-angiotensin system activation. Furthermore, many investigators in their study administered captopril at a lower than recommended dose or on a twice-daily rather than a three-times daily schedule in order to reduce the cost of chronic therapy. However, one should be skeptical of any retrospective analysis such as that performed by Pouleur et al. Their trial was not designed, nor statistically empowered, to explore the relative difference in effectiveness between captopril and enalapril. Nevertheless, one cannot ignore the possibility that significant differences in the effectiveness of various ACE inhibitors might exist.

If differences in the effectiveness of ACE inhibitors do exist, how might they be explained? One explanation is that proposed by Pouleur et al.⁶ Should the

neuroendocrine hypothesis for heart failure prove to be valid—i.e., that activation of neurohormones, in particular the renin-angiotensin system, is important in determining survival in patients with heart failure—one could postulate that failure to provide adequate and continuous blockade of the renin-angiotensin system could lead to an increase in the incidence of manifest heart failure and death. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial of enalapril in patients with class IV heart failure, Swedberg et al⁷ showed that enalapril was effective in reducing the incidence of progressive heart failure and mortality only in patients with marked activation of the renin-angiotensin system. The Veterans Administration Vasodilator Heart Failure Trial-II (VHEFT-II) comparing a strategy of direct-acting vasodilators with isosorbide dinitrate-hydralazine to an ACE inhibitor strategy with enalapril has shown that enalapril was more effective in reducing mortality (Cohn J, personal communication). The reduction in mortality with enalapril in the VHEFT-II occurred despite the fact that the isosorbide dinitrate-hydralazine combination appeared to be the more effective vasodilator, as evidenced by a greater improvement in left ventricular ejection fraction and exercise performance. The improved mortality with enalapril in both the CONSENSUS trial and the VHEFT-II is therefore likely due to the fact that it is an inhibitor of the renin-angiotensin system rather than a pure vasodilator.

Other explanations for a potential difference in the efficacy of captopril and enalapril can also be postulated. Toussaint et al⁸ showed in a study of human volunteers that there may be significant differences in the effectiveness of loop diuretic-induced natriuresis with different ACE inhibitors. They compared the natriuretic effect of furosemide alone and after pretreatment with 3 ACE inhibitors: 100 mg of captopril, 5 and 10 mg of ramapril, and 20 mg of enalapril by mouth. In those pretreated with captopril, there was significantly less natriuresis than with ramapril or enalapril. They found that captopril interfered with the delivery of furosemide to the distal renal tubule and, hence, natriuresis. In patients with heart failure, a relative decrease in effective diuresis and natriuresis with 1 ACE inhibitor

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versus another could lead to a higher incidence of salt and water retention, manifest heart failure, and further activation of neurohormones, thereby leading to the well-known vicious cycle of heart failure. Although their study needs to be confirmed and repeated in patients with heart failure, it does raise the possibility that there may be important differences among the various ACE inhibitors.

The possibility that the major effects of ACE inhibitors may not be through blockade of the serum angiotensin system, but rather through the tissue ACE system is even more intriguing.⁹⁻¹¹ The tissue ACE system has important effects on vascular and myocardial remodeling. Differences in lipophilicity and chemical structure among the various ACE inhibitors results in differential effectiveness in inhibiting ACE activity, in particular tissues and organs.⁹⁻¹¹ Whether or not the differential effects of various ACE inhibitors in specific organ systems are of importance needs to be determined by appropriate, prospective, well-controlled comparative studies.

There are also other differences that need to be considered relative to the clinical effectiveness of various ACE inhibitors. Captopril has, in contrast to enalapril, a sulfhydryl (SH) group. Although this was originally thought to be a disadvantage due to the side effects inherent to the SH group, recent studies have suggested that the SH group could be an asset. Captopril prevents the oxidation of catecholamines and has been shown to be more effective than enalapril in protecting against myocardial stunning.¹¹⁻¹⁴

What can the clinician infer from the study of Poulleur et al? First, I believe that we should continue to use both captopril and enalapril for heart failure therapy. Both have been shown to reduce the incidence of manifest heart failure and its consequences.^{1-4,15} Captopril should, however, be prescribed only as recommended in the package insert, 3 times daily. The clinician should be wary of using any new ACE inhibitor or vasodilator in patients with heart failure based solely on evidence of benefit in another indication, such as hypertension, or comparability in improving exercise performance. Approval for use of an ACE inhibitor or vasodilator should not, in my opinion, be based on demonstration of an improvement in exercise performance alone without demonstration of a reduction in the incidence of manifest heart failure, if not mortality. Our knowledge of the pathophysiology of heart failure is as yet incomplete. The use of surrogate end points, such as exercise performance, which appear to depend on vasodilation for approval and clinical use of ACE inhibitors, although convenient, may not be justified. Although we want our patients to feel better and to exercise more,

we also need to know that we can prevent the development of manifest heart failure, with all of its deleterious consequences and costs. Prevention of the development of manifest heart failure and improvement of survival may depend on completeness in blockade of the serum or the tissue renin angiotensin system, or both. Until we have greater understanding of these effects, it would be prudent to prescribe only ACE inhibitors that have been shown to prevent the development of manifest heart failure or improve survival, or both, and only in doses shown to be effective in the pivotal trials.

Before new ACE inhibitors or vasodilators are approved for use in heart failure, we need to have more data on the effective as well as the minimally effective dose. We still do not know the minimally effective dose of captopril or enalapril for preventing manifest heart failure and death. This may or may not be the same dose that blocks the serum renin-angiotensin system. If Poulleur et al⁶ are correct, many of our patients currently treated with ACE inhibitors may not be adequately protected.

The concept of class effectiveness is being challenged not only for ACE inhibitors, but also for β -adrenergic blocking agents. A recent study by Ablad et al¹⁶ suggests that lipophilic β -adrenergic blockers might be more effective than hydrophilic β blockers in reducing sudden cardiac death.¹⁶ Although both lipophilic and hydrophilic β -adrenergic blocking agents were equally effective in reducing heart rate and evidence of ischemia in their animal model, the lipophilic β blocker was more effective in reducing sudden death by increasing central vagal tone.

We need well-controlled, prospective, comparative trials to determine whether or not claims of class effectiveness are valid. It is possible that we may need to reevaluate our current concepts of class effectiveness in the light of new understanding of pathophysiology.

REFERENCES

1. The Captopril Multicenter Research Group. A placebo controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983;2:755-763.
2. The Captopril-Digoxin Multicenter Research Group. Comparative effects of captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539-544.
3. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Comparative North Scandinavian Enalapril Survival Study (Consensus). *N Engl J Med* 1987;316:1429-1435.
4. Sharpe DN, Murphy J, Goxon R, Hannan SF. Enalapril in patients with chronic heart failure; a placebo controlled, randomized, double blind study. *Circulation* 1984;70:271-298.
5. Cody RJ. Pharmacology of angiotensin-converting enzyme inhibitors as a guide to their use in congestive heart failure. *Am J Cardiol* 1990;66:7D-15D.
6. Poulleur H, Rousseau MF, Oakley C, Rydén L, for the Xamoterol in Severe Heart Failure Study Group. Difference in mortality between patients treated with

captopril or enalapril in the xamoterol in severe heart failure study. *Am J Cardiol* 1991;68:71-74.

7. Swedberg K, Encroth P, Kjekshvs J, Snappin S, for the Consensus Trial Study Group. Effects of enalapril and new endocrine activation on prognosis in severe congestive heart failure (follow-up of the Consensus Trial). *Am J Cardiol* 1990;66:40D-45D.

8. Toussaint C, Massclink A, Gentes A, Wambach G, Bonner G. Interference of diuretic ACE-inhibitors with the diuretic action of furosemide and hydrochlorothiazide. *Klin Wochenschr* 1989;67:1138-1146.

9. Unger T, Gohlke P. Tissue renin-angiotensin systems in the heart and vasculature: possible involvement in the cardiovascular vectors of converting enzyme inhibitors. *Am J Cardiol* 1990;65:31-101.

10. Hirsch AT, Pinto YM, Schunkert H, Dzau VJ. Potential role of the tissue renin-angiotensin system in the pathophysiology of congestive heart failure. *Am J Cardiol* 1990;66:22D-32D.

11. Cushman DW, Wang FL, Fung WC, Grover GJ, Harvey CM, Scalse RJ,

Mitch SL, Deforrest JM. Comparisons in vitro, ex vivo, and in vivo of the actions of severe structurally diverse inhibitors of angiotensin converting enzyme (ACE). *Br J Clin Pharmacol* 1989;28:115S-131S.

12. Westlin W, Mullane K. Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging her radicals? *Circulation* 1988;77:130-139.

13. Kukreja RC, Kontos HA, Eaton LR, Hiss ML. Captopril and enalaprilat do not scavenge the superoxide anion. *Am J Cardiol* 1990;65:241-271.

14. Przyklenk K, Kloner RA. Relationships between structure and effects of ACE inhibitors: comparative effects in myocardial ischemia/reperfusion injury. *Br J Clin Pharmacol* 1989;28:1675-1755.

15. Klever FX. Effects of captopril on survival in mild to moderate heart failure. *Herzinsuffizienz* 1987;12(suppl I):38-45.

16. Ablad B, Bguro T, Bjorkman JA, Edstrom T, Olsson G. Role of central nervous beta-adrenoreceptors in the prevention of ventricular fibrillation through augmentation of cardiac vagal tone. *J Am Coll Cardiol* 1991;17:165A.

Permanent Pacing as Treatment for Hypertrophic Cardiomyopathy

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The management of patients with hypertrophic cardiomyopathy (HC) is directed at 2 separate but interrelated goals: the amelioration of symptoms and the identification of those patients at risk of sudden cardiac death. Symptomatic improvement can be obtained in most patients with the use of standard pharmacotherapy.¹⁻³ Surgical intervention, either in the form of septal myectomy or mitral valve replacement, can be considered for those with obstructive disease who do not respond to medical therapy.³⁻⁵ Septal myectomy and mitral valve replacement are successful procedures that lessen both the resting and provokable outflow tract gradient, reduce left ventricular end-diastolic pressure and result in significant symptomatic improvement.^{4,5}

Unfortunately all of these treatments have disadvantages. Calcium antagonists are associated with major and minor side effects.⁶ Verapamil may precipitate pulmonary edema, especially in patients with significant resting outflow tract gradients and a high left ventricular end-diastolic pressure.⁶ Beta blockers in the doses prescribed often cause fatigue. Both groups of drugs may precipitate conduction disturbances.⁶ Surgical myectomy and mitral valve replacement, although successful in relieving symptoms, have an operative mor-

tality ranging from 3 to 16% and have not been shown to alter the natural history of this disease.^{7,8}

Because of these difficulties, it is important to search for alternative management options, especially for patients with HC who are refractory to the aforementioned standard therapy. Several centers, including our own, have pioneered the use of atrioventricular sequential pacing in the management of these patients.⁹⁻¹⁶ Pacing in these circumstances is being used to relieve symptoms and not to manage conduction system disease.

Hassenstein et al⁹ were the first to describe this approach. They reported a 56% reduction in left ventricular outflow tract gradient during paced rhythm in 4 patients, all of whom reported symptomatic improvement. These findings were confirmed by Duch et al,¹¹ who observed similar hemodynamic results in a series of 21 patients. Twelve patients in this group had a reduction of ventricular outflow tract gradient of $\geq 50\%$ in paced rhythm. Only 1 patient did not achieve any reduction in gradient in paced rhythm. The reduction in gradient was associated with a decrease in left ventricular filling pressure. These hemodynamic responses were not associated with any significant reduction in mean arterial pressure. This response mirrors the hemodynamic outcome from surgical interventions in this condition. Similar findings have been reported by both Dupont,¹⁰ Gardiner¹³ and their co-workers. Recently, preliminary data from the National Institutes of Health have shown a similar favorable hemodynamic and symptomatic response with pacing in this condition.¹⁶

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