ADEPT: Addition of the AT_1 receptor antagonist eprosartan to ACE inhibitor therapy in chronic heart failure trial: Hemodynamic and neurohormonal effects

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Background Persistent activation of the renin-angiotensin-aldosterone-system (RAAS) is known to occur in patients with chronic heart failure (CHF) despite treatment with angiotensin-converting enzyme inhibitor (ACE) therapy. When added to ACE inhibitors, angiotensin II type 1 (AT_1) antagonists may allow more complete blockade of the RAAS and preserve the beneficial effects of bradykinin accumulation not seen with AT_1 receptor blockade alone.

Methods Thirty-six patients with stable New York Heart Association class II-IV CHF receiving ACE inhibitor therapy were randomly assigned in a double-blind manner to receive either eprosartan, a specific competitive AT_1 receptor antagonist (400 to 800 mg daily, n = 18) or placebo (n = 18) for 8 weeks. The primary outcome measure was left ventricular ejection fraction (LVEF) as measured by radionuclide ventriculography, and secondary measures were central hemodynamics assessed by Swan-Ganz catheterization and neurohormonal effects.

Results There was no change in LVEF with eprosartan therapy (mean relative LVEF percentage change [SEM] +10.5% [9.3] vs +10.1% [5.0], respectively; difference, 0.4; 95% confidence interval [CI], −20.8 to 21.7; $P = .97$). Eprosartan was associated with a significant reduction in diastolic blood pressure and a trend toward a reduction in systolic blood pressure compared with placebo (−7.3 mm Hg [95% CI, −14.2 to −0.4] diastolic; −8.9 mm Hg [95% CI, −18.6 to 0.8] systolic). No significant change in heart rate or central hemodynamics occurred during treatment with eprosartan compared with placebo. A trend toward an increase in plasma renin activity was noted with eprosartan therapy. Eprosartan was well tolerated, with an adverse event profile similar to placebo, whereas kidney function remained unchanged.

Conclusions When added to an ACE inhibitor, eprosartan reduced arterial pressure without increasing heart rate. There was no change in LVEF after 2 months of therapy with eprosartan. (Am Heart J 2001;141:800-7.)

Angiotensin-converting enzyme (ACE) inhibitors and spironolactone, drugs that inhibit the renin-angiotensin-aldosterone-system (RAAS), improve prognosis in chronic heart failure (CHF).[1,2] Plasma concentrations of angiotensin II and aldosterone, however, remain elevated in patients with CHF despite treatment with an ACE inhibitor.[3,4] This persistent activation of the RAAS may be explained, at least in part, by the existence of non-ACE pathways that convert angiotensin I to angiotensin II.[5,6] Angiotensin II receptor antagonists may therefore allow more effective blockade of the RAAS.

ACE inhibitors have another potentially important action in addition to RAAS blockade: the inhibition of bradykinin breakdown. Recent evidence suggests that this action does contribute to the pharmacologic effects of these drugs in human beings.[7] Combination therapy with an ACE inhibitor and angiotensin II receptor antagonist may therefore offer the best therapeutic approach to blockade of the RAAS in CHF.

The acute and chronic hemodynamic and neurohormonal actions of adding losartan[8,9] and valsartan[10] to an ACE inhibitor have been reported. The neurohormonal and left ventricular remodeling effects of adding candesartan celexitil to an ACE inhibitor have also been described.[11]

Eprosartan is a highly selective, nontetrazole, nonbiphenyl, nonpeptide AT_1 receptor antagonist that has

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Supported by the Medical Research Council (D. R. M., T. A. M, R. F., J. J. M., J. J .V. M., and H. J. D.) and by a grant from SmithKline Beecham Pharmaceuticals.
Presented in part at the 20th Congress of the European Society of Cardiology, Vienna, Austria, August 1998.
Submitted July 24, 2000; accepted February 1, 2001.
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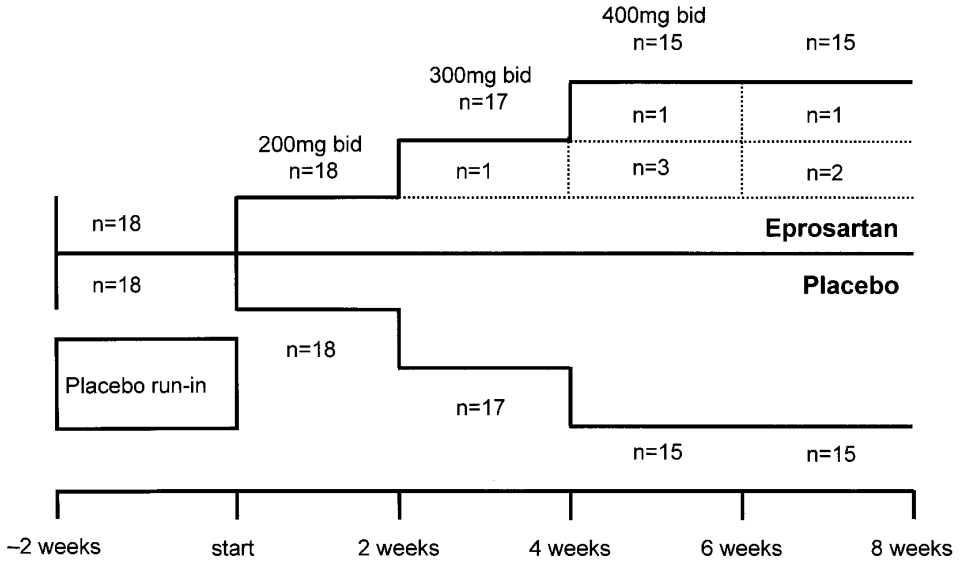
0002-8703/2001/$35.00 + 0 **4/1/114802**
doi:10.1067/mhj.2001.114802

Figure 1



Study design and patient dosage details according to study progress.

been shown to be well tolerated and effective in the management of hypertension at a starting dose of 600 mg given once daily.[12,13] Of particular importance in the treatment of heart failure, eprosartan exhibits no major drug interactions and can be safely administered with warfarin and digoxin,[14,15] it does not require dose adjustment in the elderly or those with renal impairment,[16,17] and preclinical data show that it inhibits sympathetic outflow more effectively than losartan, valsartan, or irbesartan.[18] The objectives of this study were to evaluate the hemodynamic and neurohormonal effects of the addition of eprosartan to conventional ACE inhibitor therapy in CHF.

Methods

Ethical approval

The study was conducted in accordance with good clinical practice and the Declaration of Helsinki as amended in Hong Kong (1989). The study was approved by the local committee on medical ethics, and all patients gave written informed consent.

Study patients

Male or female patients (≥18 years of age) with CHF were eligible for enrollment if they had received ACE inhibitor therapy for at least 4 weeks, were stable in New York Heart Association (NYHA) class II-IV heart failure and had a left ventricular ejection fraction (LVEF) ≤35%. Patients had to have heart failure caused by ischemic heart disease or nonischemic dilated cardiomyopathy, with at least a 2-month history of symptoms of dyspnea and/or fatigue at rest or on exertion. Patients with significant concomitant disease, including significant renal or hepatic dysfunction (defined as creatinine >250 μmol/L or transaminases >3 times normal, respectively), malignancy, or chronic lung disease were excluded.

Study design

Trial design and patient dosage details are given in Figure 1.

This was an 8-week, prospective, randomized, double-blind, parallel-group, placebo-controlled, single-center study. Patients were randomly assigned to receive either eprosartan (400 mg daily, given as 200 mg twice daily) or matching placebo. Patients' ACE inhibitor therapy was continued throughout the study and given at the normal time, including during hemodynamic and neurohormonal assessment. At baseline, after a 2-week placebo run-in period, patients were admitted to the hospital after an overnight fast for radionuclide ventriculography (performed before administration of the first dose of randomized study medication), invasive hemodynamic assessments by right heart catheterization (performed before administration of the first dose of randomized study medication), and blood sampling for neurohormonal assessment (performed before administration of study medication). During the 8-week double-blind treatment period, patients were seen at 2-week intervals for dose titration purposes. In the absence of significant side effects, the initial dose of eprosartan was increased in a stepwise fashion to 600 mg daily, given as 300 mg twice daily, and then to the target dose of 800 mg daily, given as 400 mg twice daily. Patients unable to tolerate higher doses could have their dose maintained or decreased and subsequently increased at a later date. On completion of the study, patients were again admitted to the hospital after an overnight fast for radionuclide ventricu-

lography and invasive hemodynamic and neurohormonal assessment as before.

Efficacy assessments

Radionuclide ventriculography. The primary efficacy parameter for this study was the relative percentage change from baseline in LVEF measured with radionuclide ventriculography. After an injection of stannous pyrophosphate, 800 MBq of technetium as sodium pertechnate (Tc^{99m}) was given. The heart was first imaged in the left anterior oblique projection, giving optimal separation of right and left ventricles; LVEF was calculated from the best septal view with a single planar region of interest.

Hemodynamic measurements. Secondary efficacy measurements included the change from baseline at rest in resting sitting systolic and diastolic blood pressure, pulmonary capillary wedge pressure, right atrial pressure, pulmonary artery pressure, cardiac output, and systemic vascular resistance as assessed by right heart catheterization. A balloon-tipped pulmonary artery thermodilution catheter was inserted through the femoral vein and advanced to an appropriate position within the pulmonary artery. After a period of stabilization of at least 1 hour, measurements of pulmonary capillary wedge pressure, right atrial pressure, and pulmonary artery pressure were made at end expiration. Cardiac output was measured by the thermodilution method, and systemic vascular resistance was derived. The mean of at least 3 measurements of each parameter (5 for cardiac output) was calculated. Blood pressure was measured noninvasively, in triplicate, by an automated inflatable cuff placed around the upper arm, and the mean was recorded.

Sample collection for neurohormonal measurements. Fifty milliliters of venous blood was drawn from the femoral venous catheter after at least 1 hour supine rest and stabilization of pulmonary pressures at the time of hemodynamic assessment but before administration of study medication. Samples were collected into chilled tubes containing potassium ethylenediaminetetra-acetic acid (EDTA) (1 mg/mL blood) and aprotinin (50 KIU/mL blood) for assay of brain natriuretic peptide and N-terminal atrial natriuretic peptide; lithium heparin (20 U/mL) for assay of plasma aldosterone and norepinephrine; EDTA (125 mmol/L), *o*-phenanthroline (25 mmol/L), and human renin inhibitor (H142, 20 μmol/L) for assay of plasma angiotensin II; and potassium EDTA (1 mg/mL blood) for assay of plasma renin activity. The samples were separated in a refrigerated centrifuge at 4°C and the plasma stored at −20°C until assay. All samples were assayed as a single batch in a blinded fashion within 4 weeks of collection.

Neurohormonal measurements. Secondary efficacy measurements also included the percentage change from baseline in angiotensin II, norepinephrine, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, and renin activity. Brain natriuretic peptide was assayed without prior extraction of plasma by means of a direct, specific monoclonal antibody radioimmunoassay kit supplied by Shionogi & Co, Ltd (Settsu-shi, Osaka, Japan), as previously described.[19,20] Plasma N-terminal atrial natriuretic peptide (ANP 1-30) was assayed by radioimmunoassay after extraction from acidified plasma with C18 reverse-phase columns (Sep-Pak, Waters Associates Ltd, Watford, UK) with the use of a modification of a previously described method.[21] A Peninsula Laboratories antibody, RAS 9129 (Belmont, Calif), was used for identification of N-terminal atrial natriuretic peptide. The between-assay coefficients of variation were 15% for the N-terminal atrial natriuretic peptide assay and <10% for the brain natriuretic peptide assay, respectively. Plasma renin activity was measured by an in-house antibody trapping technique in the presence of added excess renin substrate.[22] The coefficient of variation was 3.4%. An in-house radioimmunoassay was used for plasma angiotensin II as previously described.[23] Angiotensin II was preextracted from plasma before assay. The coefficient of variation was 10%. Plasma aldosterone was measured with a solid-phase (coated tube) radioimmunoassay kit supplied by Diagnostic Products (UK) Ltd. The coefficient of variation was <8.3%. Plasma norepinephrine was measured by high-performance liquid chromatography.

Safety assessments

All reported adverse events were recorded. Standard laboratory safety tests and a 12-lead electrocardiogram were performed at baseline and at 2-week intervals throughout the study to identify any significant changes.

Statistical analyses

Changes from baseline for the primary and secondary parameters were assessed for effects of treatment by means of a 1-way analysis of variance (PROC GLM in SAS) (Cary NC, SAS Institute; 1990: User's guide version 6, 4th edition; SAS/Stat; Volumes 1 and 2). Probability values were considered statistically significant at $P < .05$.

Results

Study patients

Thirty-six patients were randomly assigned and received at least one dose of study medication (placebo, n = 18; eprosartan n = 18). ACE inhibitor therapy was captopril in 8 patients (mean [SEM] daily dose 103.1 [13.7] mg); enalapril in 12 (21.7 [1.8] mg); lisinopril in 10 (15.2 [3.5] mg); and trandolapril (2.0 [0.0] mg), perindopril (4.0 [0.0] mg) and quinapril (25.0 [15.0] mg) in 2 each (see Figure 1).

Patient details are given in Table I. In general, no differences were observed between treatment groups in the severity of heart failure, LVEF, or concomitant treatment.

Safety assessments

Plasma creatinine rose in both treatment groups; however, this was more pronounced with placebo than eprosartan. The mean (SEM) change with placebo was 12.0% (2.9) compared with 4.4% (3.1) with eprosartan. The difference between treatments was of borderline statistical significance: −7.7% (95% confidence interval [CI], −16.4 to 1.1). No other significant changes in biochemistry or hematology were noted. No significant electrocardiographic changes were noted.

Withdrawals

Fifteen of the 18 patients randomly assigned to receive eprosartan and 15 of the 18 patients randomly assigned to receive placebo completed the study. The reasons for withdrawal from the study were adverse events in 5 patients (eprosartan, n = 2; placebo, n = 3) and withdrawal of consent in 1 patient taking eprosartan.

LVEF assessments

LVEF tended to increase in both treatment groups, although the percentage change from baseline was not significantly different between patients taking eprosartan or placebo (Table II).

Hemodynamic changes

Resting systolic and diastolic blood pressures were similar between groups at baseline (Table I). The addition of eprosartan was, however, associated with a significant reduction in diastolic blood pressure (between-group difference, −7.3 mm Hg [95% CI, −14.2 to −0.4]) and a trend toward a reduction in systolic blood pressure (between-group difference, −8.9 mm Hg [95% CI, −18.6 to 0.8) (Figure 2). No significant change in heart rate occurred during treatment with eprosartan compared with placebo (between treatment, −0.8 beats/min [95% CI, −6.7 to 5.0]).

No significant between-group difference was found in any central hemodynamic measurement (Table II).

Neurohormonal changes

The addition of eprosartan was associated with nonsignificant trends toward increases in angiotensin II and plasma renin activity. No significant changes in the concentration of the natriuretic peptides or norepinephrine were observed in any patient group (Table III).

Adverse experiences

Eprosartan was well tolerated, with an adverse event rate similar to placebo. Of those receiving eprosartan, 14 (77.8%) of 18 patients reported one or more adverse events compared with 16 (88.9%) of 18 patients receiving placebo. The most commonly occurring adverse events were eprosartan fatigue (n = 4), diarrhea (n = 4) or myalgia (n = 5), placebo headache (n = 3), dizziness, dyspepsia, myalgia, or cough (n = 2 each).

A total of 4 patients had treatment-emergent adverse reactions that led to dose reductions. Of these, 2 patients were taking placebo, whereas the other 2 were taking eprosartan. One of the patients receiving eprosartan had diarrhea and the other had angina pectoris and hypotension. Both of these patients had their eprosartan dosage reduced from 300 mg twice daily to 200 mg twice daily. All adverse reactions were considered by the investigator to be possibly related to study medication. However, by reducing the study medication dosage, all patients completed the study without being withdrawn.

Table I. Baseline demographics and variables according to treatment allocation

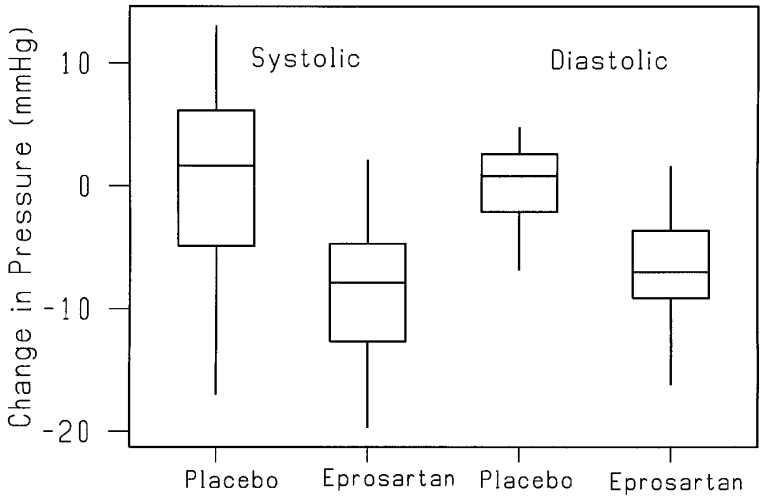
	Eprosartan (n = 18)	Placebo (n = 18)
Demographic (mean ± SEM)		
Age (y)	65.7 ± 1.8	61.2 ± 1.6
Male:female	15:3	14:4
Weight (kg)	79.6 ± 2.0	78.1 ± 3.1
Height (cm)	171.1 ± 1.3	166.8 ± 1.9
Mean sitting systolic blood pressure (mm Hg)	116.6 ± 2.2	119.1 ± 3.2
Medical history [n (%)]		
Myocardial infarction	18 (100)	17 (94)
Hypertension	1 (6)	2 (11)
Angina pectoris	11 (61)	14 (78)
Cardiac arrhythmia	3 (17)	2 (11)
Diabetes mellitus	3 (17)	6 (33)
Clinical (n)		
NYHA class I/II/III/IV	0/11/6/1	0/7/9/2
NYHA class (mean)	2.4 (0.1)	2.7 (0.2)
LVEF (%)	21.8 (2.0)	23.5 (1.7)
Drug therapy [n (%)]		
Diuretics	8 (44)	11 (61)
Digoxin	4 (22)	4 (22)
Nitrates	10 (56)	14 (78)
Ca^{++} blockade	3 (17)	5 (28)
β-Blockade	9 (50)	8 (44)
Aspirin	17 (94)	14 (78)
Warfarin	2 (11)	2 (11)
Statin	7 (39)	8 (44)
Amiodarone	2 (11)	2 (11)
Completed study	15	15

Discussion

The addition of an AT_1 receptor blocker to standard ACE inhibitor therapy in CHF significantly reduced blood pressure without reflex tachycardia, although no clear-cut central hemodynamic changes were observed. The lack of significant hemodynamic changes with eprosartan may have a number of explanations.

First, as an outpatient study, few of our patients had severe symptoms (ie, NYHA class IV), and normal therapy was continued throughout. This was reflected in relatively normal pulmonary artery pressure and capillary wedge pressure values at baseline. As might be expected, these values were certainly lower than in previous hemodynamic studies of AT_1 receptor blockade in which many patients had rest symptoms and pulmonary capillary wedge pressures that were elevated at baseline.[24,25] Other hemodynamic measures, such as systemic vascular resistance, were, however, still grossly abnormal, and the addition of eprosartan was only associated with a relatively small, nonsignificant reduction. We have previously made this observation in

Figure 2



Box-and-whisker plot of median change, interquartile range, and range in systolic and diastolic blood pressure according to treatment allocation.

Table II. Hemodynamic parameters at baseline and study end point according to treatment allocation

Parameter*	Placebo	Eprosartan	*P* value
LVEF (%), n			
Baseline	21.8 (2.0), n = 18	23.5 (1.7), n = 17	.968
End of study	23.7 (1.3), n = 15	24.6 (1.7), n = 14	
PCWP (mm Hg), n			
Baseline	11.2 (1.4), n = 18	12.3 (1.3), n = 18	.363
End of study	8.2 (0.9), n = 13	11.5 (1.1), n = 15	
RAP (mm Hg), n			
Baseline	5.4 (0.7), n = 18	4.6 (0.6), n = 18	.406
End of study	3.5 (0.6), n = 13	3.6 (0.4), n = 15	
PAP (mm Hg), n			
Baseline	16.3 (1.3), n = 18	16.8 (1.4), n = 18	.288
End of study	15.0 (1.4), n = 13	15.4 (1.1), n = 15	
CO (L/min), n			
Baseline	4.0 (0.1), n = 18	3.8 (0.2), n = 18	.473
End of study	3.8 (0.2), n = 13	3.6 (0.1), n = 15	
SVR (dyne · cm^{-5}), n			
Baseline	1698 (60), n = 18	1840 (116), n = 18	.109
End of study	1817 (66), n = 13	1812 (84), n = 15	

LVEF, Left ventricular ejection fraction; *PCWP,* pulmonary capillary wedge pressure; *RAP,* right atrial pressure; *PAP,* mean pulmonary artery pressure; *CO,* cardiac output; *SVR,* systemic vascular resistance.
*All measurements are given as mean (standard error of the mean).

patients treated with very high doses of ACE inhibitors and in some cases the AT_1 blocker losartan in combination.[26]

A second possible explanation for the lack of effect of the addition of AT_1 receptor blockade was that all patients were already receiving treatment with ACE inhibitors and in many cases additional vasodilators, which were continued throughout the study, including the days of hemodynamic assessment (Table I). Indeed, the mean doses of ACE inhibitors used in our study exceeded the doses achieved in the randomized trials that established their effectiveness and, in some cases, also exceeded the target doses used in these studies. For example, in the SOLVD treatment trial,[27] the target dose of enalapril was 20 mg daily (10 mg twice daily); however, the mean dose achieved was actually 16.7 mg. Similarly, in GISSI-III,[28] the target dose of lisinopril was 10 mg daily; however, only 47.5% of patients

Table III. Neurohormonal parameters at baseline and study end point and baseline according to treatment allocation

Parameter*	Placebo	Eprosartan	*P* value
Angiotensin II (pg/mL), n			
Baseline	6.8 (15.3), n = 18	3.6 (2.1), n = 18	.511
End of study	5.0 (5.8), n = 15	8.7 (13.5), n = 14	
Norepinephrine (nmol/L), n			
Baseline	3.9 (1.7), n = 18	3.6 (1.7), n = 18	.677
End of study	3.1 (1.2), n = 15	3.3 (1.1), n = 14	
Aldosterone (ng/100 mL), n			
Baseline	8.8 (8.1), n = 18	5.1 (3.8), n = 18	.215
End of study	8.2 (4.6), n = 15	4.4 (5.2), n = 14	
Atrial natriuretic peptide (pg/nL), n			
Baseline	7.4 (5.5), n = 18	8.3 (5.1), n = 18	.696
End of study	6.7 (4.6), n = 15	8.4 (4.5), n = 14	
Brain natriuretic peptide (pg/nL), n			
Baseline	41.2 (25.5), n = 18	38.9 (25.5), n = 18	.669
End of study	35.2 (26.7), n = 15	34.9 (18.3), n = 14	
Renin activity (μmol/mL), n			
Baseline	111.4 (170.6), n = 18	81.1 (67.5), n = 18	.120
End of study	41.7 (47.6), n = 15	143.6 (16.5), n = 14	

*All measurements are given as mean (SD).

reached this dose. In comparison, in this study, mean enalapril doses were 25.0 mg and 19.3 mg, and mean lisinopril doses were 13.7 mg and 12.9 mg in placebo- and eprosartan-treated patients, respectively. This would inevitably have limited the magnitude of the possible effects of combination treatment with eprosartan and have contributed to the relatively normal baseline hemodynamics, thereby reducing the potential for improvement.

Many previous studies either have examined ACE-naive patients, have stopped ACE inhibitors before hemodynamic assessment,[24,25,29] or have only examined acute hemodynamic effects.[24,29] This study was, however, designed to investigate whether additional treatment with AT_1 blockade would be of benefit to such patients. Indeed, data from the Val-HeFt pilot trial showed that significant acute central hemodynamic effects were restricted to the highest dose of valsartan (160 mg), and these were attenuated with chronic therapy.[9] Furthermore, Jorde et al[30] have recently shown that angiotensin I continued to have a pressor effect when given to patients with CHF treated with conventional doses of ACE inhibitors. Although this pressor effect was blunted by the addition of an AT_1 receptor antagonist, doubling the dose of the ACE inhibitor had the same effect. This suggests that it may be difficult to document incremental hemodynamic effects of the addition of an AT_1 antagonist when patients are already taking high doses of ACE inhibitors, as they were in this study.

Third, we should consider whether we used a sufficiently high dose of eprosartan. Our target dose was greater than that shown to have equipotent hypotensive effects to enalapril in other studies[12,13] and significantly reduced blood pressure in our study, so inadequate dosing seems unlikely.

Finally, the period of 2 months of treatment may also have been too short for differences in left ventricular remodeling to become apparent. In the RESOLVD pilot study, no significant change in LVEF was noted throughout the study, and significant differences between groups in change in left ventricular systolic and diastolic volumes only became apparent after 43 weeks of therapy with the highest dose of candesartan.[11]

Interestingly, despite the absence of significant central hemodynamic effects, the addition of eprosartan was associated with trends toward increases in angiotensin II and plasma renin activity. This confirms that despite high doses of ACE inhibitors, there was persistent activation of the RAAS and production of angiotensin II through non-ACE pathways (such as chymase), which was blocked by eprosartan. Eprosartan also reduced blood pressure substantially and significantly in a patient population already receiving various hypotensive therapies in addition to ACE inhibitors (mean change, –7.3/–8.9 mm Hg). The magnitude of the blood pressure–lowering effect is surprising in light of the mean change of blood pressure with the introduction of the ACE inhibitor ramipril in the HOPE study (mean change, –3/–2 mm Hg).[31] The mechanism of the addition of AT_1 receptor blockade here, therefore, appears to be neurohormonal.

The long-term mortality and morbidity effects of combination therapy involving an AT_1 receptor antagonist and an ACE inhibitor require further study. Trials such as CHARM and Val-HeFt will assess the effects of these drugs, either singly or in combination, on morbidity and mortality in CHF.[32,33]

Study limitations

The numbers of patients that can be recruited in invasive hemodynamic studies are necessarily limited, especially if the long-term effects of therapy are to be examined, necessitating two invasive procedures. However, our results are consistent with the only other hemodynamic study to examine long-term combination therapy.[9] Our failure to demonstrate significant long-term hemodynamic changes therefore may be a consequence of the continued use of an ACE inhibitor and other vasodilators in our study rather than inadequate numbers of participants.

Conclusions

Although the addition of the AT_1 receptor blocker eprosartan was associated with little change in LVEF or central hemodynamic measurements, significant reductions in diastolic blood pressure were noted, whereas heart rate remained constant. Such an approach was well tolerated, with a side-effect profile similar to placebo.

We thank Dr V. Rayan, BSc, PhD, of FSP International, for assistance in preparation of the manuscript.

References

1. Garg R, Yusuf S, for Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273:1450-6.
2. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: the Randomized Aldactone Evaluation Study (RALES). N Engl J Med 1999;341:709-17.
3. Struthers AD. Aldosterone escape during ACE-inhibitor therapy in chronic heart failure. Eur Heart J 1995;16:103-6.
4. Benedict CR, Francis GS, Shelton B, et al. Effect of long-term enalapril therapy on neurohormones in patients with left-ventricular dysfunction. Am J Cardiol 1995;75:1151-7.
5. Voors AA, Pinto YM, Buikema H, et al. Dual pathway for angiotensin II formation in human internal mammary arteries. Br J Pharmacol 1998;125:1028-32.
6. Akasu M, Urata H, Kinoshita A, et al. Differences in tissue angiotensin II-forming pathways by species and organs in vitro. Hypertension 1998;32:514-20.
7. Gainer JV, Morrow JD, Loveland A, et al. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998;339:1285-92.
8. Hamroff G, Blaufarb I, Mancini D, et al. Angiotensin II receptor blockade further reduces afterload safely in patients maximally treated with angiotensin-converting enzyme inhibitors for heart failure. J Cardiovasc Pharmacol 1997;30:533-6.
9. Hamroff G, Katz SD, Mancini D, et al. Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. Circulation 1999;99:990-2.
10. Baruch L, Anand I, Cohen IS, et al. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure: Vasodilator Heart Failure Trial (Val-HeFT) Study Group. Circulation 1999;99:2658-64.
11. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: the RESOLVD pilot study investigators. Circulation 1999;100:1056-64.
12. Gavras I, Gavras H. Effects of eprosartan versus enalapril in hypertensive patients on the renin-angiotensin-aldosterone system and safety parameters: results from a 26-week, double-blind, multicentre study. Curr Med Res Opin 1999;15:15-24.
13. Argenziano L, Fratta L, Larrni F, et al. Comparison of efficacy of eprosartan with enalapril in elderly patients with hypertension [abstract]. New York: American Society of Hypertension; 1998.
14. Kazierad DJ, Martin DE, Ilson B, et al. Eprosartan does not affect the pharmacodynamics of warfarin. J Clin Pharmacol 1998;38:649-53.
15. Martin DE, Tompson D, Boike SC, et al. Lack of effect of eprosartan on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers. Br J Clin Pharmacol 1997;43:661-4.
16. Tenero DM, Martin DE, Miller AK, et al. Effect of age and gender on the pharmacokinetics of eprosartan. Br J Clin Pharmacol 1998;46:267-70.
17. Martin DE, Chapelsky MC, Ilson B, et al. Pharmacokinetics and protein finding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. J Clin Pharmacol 1998;38:129-37.
18. Ohlstein EH, Brooks DP, Feuerstein GZ, et al. Inhibition of sympathetic outflow by the angiotensin II receptor antagonist, eprosartan, but not by losartan, valsartan or irbesartan: relationship to differences in prejunctional angiotensin II receptor blockade. Pharmacology 1997;55:244-51.
19. Murdoch DR, Byrne J, Morton JJ, et al. Brain natriuretic peptide is stable in whole blood and can be measured using a simple rapid assay: implications for clinical practice. Heart 1997;78:594-7.
20. Kono M, Yamauchi A, Tsuji T, et al. An immunoradiometric assay for brain natriuretic peptide in human plasma. Kaku Igaku Gijutsu 1993;13:2-7.
21. Richards AM, Tonolo G, McIntyre GD, et al. Radio-immunoassay for plasma alpha human atrial natriuretic peptide: a comparison of direct and pre-extracted methods. J Hypertens 1987;5:227-36.
22. Millar JA, Leckie BJ, Morton JJ, et al. A microassay for active and total renin concentration in human plasma based on antibody trapping. Clin Chim Acta 1980;101:5-15.
23. Morton JJ, Webb DJ. Measurement of plasma angiotensin II. Clin Sci 1985;68:483-4.
24. Gottlieb SS, Dickstein K, Fleck E, et al. Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure. Circulation 1993;88:1602-9.
25. Crozier I, Ikram H, Awan N, et al. Losartan in heart failure: hemodynamic effects and tolerability: Losartan Hemodynamic Study Group. Circulation 1995;91:691-7.
26. Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison on the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1999;138:1126-32.

27. SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
28. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after myocardial infarction. Lancet 1994;343: 1115-22.
29. Parker AB, Azevedo ER, Baird MG, et al. ARCTIC: assessment of haemodynamic response in patients with congestive heart failure to telmisartan: a multicentre dose-ranging study in Canada. Am Heart J 1999;138:843-8.
30. Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. Circulation 2000;101:844-6.
31. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.
32. Swedberg K, Pfeffer M, Granger C, et al. Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM): rationale and design. J Card Fail 1999;5:276-82.
33. Cohn JN, Tognoni G, Glazer RD, et al. Rationale and design of the valsartan heart failure trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. J Card Fail 1999;5:155-60.