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

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Background—ACE inhibitors may not adequately suppress deleterious levels of angiotensin II in patients with heart failure. An angiotensin receptor blocker added to an ACE inhibitor may exert additional beneficial effects.

Methods and Results—Eighty-three symptomatic stable patients with chronic heart failure receiving long-term ACE inhibitor therapy were randomly assigned to double-blind treatment with valsartan 80 mg BID, valsartan 160 mg BID, or placebo while receiving their usual ACE inhibitor therapy. Studies were performed before and after the first dose of the test drug and again after 4 weeks of therapy. A single dose of lisinopril was administered during study days to ensure sustained ACE inhibition. Compared with placebo, the first dose of valsartan 160 mg resulted in a significantly greater reduction in pulmonary capillary wedge pressure at 3, 4, and 8 hours and during the prespecified 4- to 8-hour interval after the dose and in systolic blood pressure at 2, 3, 6, 8, and 12 hours and 4 to 8 hours after the dose. A pressure reduction from valsartan 80 mg did not achieve statistical significance. After 4 weeks of therapy, net reductions in 0-hour trough pulmonary capillary wedge pressure (−4.3 mm Hg; \(P=0.16\)), pulmonary artery diastolic pressure (−4.7 mm Hg; \(P=0.013\)), and systolic blood pressure (−6.8 mm Hg; \(P=0.013\)) were observed in the valsartan 160 mg group compared with placebo. After 4 weeks of therapy, plasma aldosterone was reduced by valsartan 80 mg BID (−52.1 pg/mL; \(P=0.001\)) and 160 mg BID (−47.8 pg/mL; \(P<0.001\)) compared with placebo, and there was a trend for a reduction in plasma norepinephrine (−97 pg/mL; \(P=0.10\)). Seventy-four of the 83 patients completed the trial.

Conclusions—Physiologically active levels of angiotensin II persist during standard long-term ACE inhibitor therapy.

Key Words: heart failure ■ angiotensin ■ hemodynamics ■ hormones

The effectiveness of ACE inhibitor drugs in patients with heart failure is thought to reflect their action to inhibit the renin-angiotensin system.1 Because plasma renin activity (PRA) is increased in heart failure and angiotensin II (AngII) is a potent stimulator of vasoconstriction, aldosterone release, and cardiovascular cellular growth, the hemodynamic benefit and mortality reduction from these drugs have been attributed to a reduction of AngII levels.2–4

Controversy has nonetheless arisen regarding the ability of ACE inhibitors to produce long-term suppression of AngII levels. The inhibition of converting enzyme by most of these drugs may not be sustained throughout the drug-dosing interval.5 ACE inhibitors are also competitive inhibitors whose blockade could be overridden by increased AngI levels that result from the loss of feedback inhibition of renin activity.6,7 Even if circulating AngII levels are reduced, the ability of different ACE inhibitors to suppress various tissue levels of AngII remains unclear.8 Furthermore, there is growing evidence that alternative pathways of conversion of AngI to AngII, including a chymase pathway, may restore circulating or tissue levels despite ACE inhibition.9–13 Indeed, circulating AngII levels tend to return toward pretreatment levels during long-term ACE inhibitor therapy.12,13 Furthermore, data in some experimental models of ventricular dysfunction suggest that at least some of the benefit of ACE inhibitors may be mediated by kinin stimulation rather than by AngII suppression.14,15

Angiotensin AT1 receptor blockers inhibit the vasoconstrictor, hormone-stimulating, and growth-promoting effects of AngII.16,17 Their antihypertensive and hemodynamic ac-
tions appear to mimic those of the ACE inhibitors. The absence of ACE inhibitor side effects, such as cough, during their clinical administration has made them attractive alternatives to ACE inhibitors for management of hypertension. Valsartan is an angiotensin AT1 receptor blocker that has been shown to be efficacious and safe when administered once daily in the treatment of hypertension. Because ACE inhibitors have become standard therapy for heart failure, owing to their survival benefit, and because long-term therapy may not completely inhibit the adverse effects of AngII stimulation, we evaluated the hemodynamic and hormonal effects of valsartan added to long-term ACE inhibitor therapy in patients with heart failure.

Methods

Patients with stable symptomatic congestive heart failure (CHF) (NYHA functional class II, III, or IV) were eligible for enrollment in this multicenter trial. The study protocol was approved by each center's institutional review board, and all patients gave written informed consent. Background ACE inhibitor therapy in a predefined minimum therapeutic dose that was stable for a period of 1 month was mandatory. Concomitant stable digitalis or diuretic therapy was permitted but not required. Other vasodilator therapy was interdicted. Exclusionary criteria included an acute ischemic event within the preceding 3 months or hospitalization for decompensated CHF within the preceding month, angina pectoris requiring >5 tablets of nitroglycerin per week, creatinine >2.3 mg/dL, or blood pressure <80/50 mm Hg.

Initial treatment consisted of a 2-week, single-blind placebo phase to confirm the clinical stability of each patient's heart failure and to ensure compliance. Thereafter, patients were randomly assigned to receive 4 weeks of therapy with valsartan 80 mg BID, valsartan 160 mg BID, or placebo. The first (day 0) and last (day 28) doses of the test drug were administered under direct observation for 12 hours in the laboratory with hemodynamic monitoring. Patients were stratified at baseline into low-dose or high-dose ACE inhibitor groups on the basis of their background ACE inhibitor dose. High dose was defined as a total daily ACE inhibitor dose of >10 mg of either enalapril, lisinopril, fosinopril, or benazepril; >5 mg of ramipril; >20 mg of quinapril; or >75 mg of captopril. Low dose was defined as a dose less than or equal to these doses. On the days of the 12-hour hemodynamic assessments, at the same time as they received valsartan or placebo, patients in the low-dose ACE inhibitor group received a single dose of 10 mg lisinopril orally, whereas those taking the high dose received 20 mg orally as a substitute for their usual ACE inhibitor dose. Each patient's usual diuretic dose was withheld on hemodynamic assessment days.

Hemodynamic assessment was performed after placement of a balloon-tipped thermodilution catheter in the pulmonary artery with continuous ECG monitoring. In the majority of cases, the qualifying right heart catheterization was performed the afternoon of admission before the day of test drug administration. Owing to limited availability of monitored beds, right heart catheterization was performed the morning of study in a minority of cases. A minimum mean pulmonary capillary wedge pressure (PCWP) of 15 mm Hg 1 hour after catheterization on 2 hemodynamic assessments 10 minutes apart was required for eligibility for the randomized study phase.

After an overnight fast, the patients began a prolonged hemodynamic measurement period (day 0). Hemodynamic measurements at 0 hour were repeated at 10-minute intervals until 2 consecutive mean PCWP values exhibited 10% variability. This was considered the baseline measurement for all statistical evaluations. Systolic and diastolic blood pressures were measured with an automated sphygmomanometer. Heart rate (HR) was recorded by standard ECG monitoring. Thermodilution cardiac output (CO) measurements at each time point were averaged from 5 successive measurements, with the highest and lowest values excluded. PCWP measurements were determined by taking the average of 2 measurements. Mean right atrial pressure (RAP) and mean systolic and diastolic pulmonary artery pressures were each measured once at each time point. Cardiac index and systemic vascular resistance (SVR) were calculated from the measured parameters. Patients then received valsartan 80 mg, valsartan 160 mg, or placebo in a randomized, double-blind fashion, along with lisinopril 10 or 20 mg as previously described. After administration of trial medication, oral fluids were given at a rate of 30 mL/h plus the equivalent of the urine output per hour. The amount of oral fluid intake did not exceed 100 mL/h and consisted of only noncaffeinated beverages. All hemodynamic measurements were performed after a minimum 15-minute rest in the supine position. A light meal was provided after the 4- and 12-hour measurements. Repeat hemodynamic measurements were made at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after the dose. Blood samples were obtained at baseline and 6 and 12 hours after dosing for measurement of atrial natriuretic peptide (ANP), PRA, AngII, norepinephrine, and aldosterone. Fasting samples were obtained at baseline for complete blood counts, chemistries, and urinalysis. After 4 weeks of randomized therapy, all assessments, including neurohormones and invasive hemodynamics, were repeated over a similar time period and in a similar manner. Hard copies of selected recorded pressures were routinely submitted to a core laboratory for quality control assessment.

Hormone Measurement

Blood samples for hormone measurements were processed locally; the plasma was separated, frozen, and then transported to the Core Laboratory at the University of Minnesota, where the assays were performed. Plasma norepinephrine (PNE) was measured by high-performance liquid chromatography (HPLC). PPRa, plasma ANP, and plasma aldosterone (PA) were measured by radioimmunoassay. Plasma AngII was determined by HPLC separation of AngII from AngI and III followed by radioimmunoassay with a Peninsula (Peninsula Laboratories, Inc) antibody.

Statistical Analysis

The baseline value used for comparisons for each of the variables was the last predose measurement before double-blind treatment for that variable. For the hemodynamic variables, the 0-hour day-0 measurement was used as the baseline measurement for all subsequent measurements. On the basis of prior clinical pharmacological studies, we expected the 4- to 8-hour mean value to provide information about peak effect.

The primary variable for analysis was the change from baseline in PCWP. Secondary prespecified variables analyzed included changes from baseline in systolic blood pressure (SBP), CO, RAP, pulmonary artery diastolic pressure (PAP), cardiac index, SVR, HR, PRA, ANP, PA, AngII, and PNE. Baseline characteristics were compared by Fisher's exact or Cochran-Mantel-Haenszel test for categorical variables. ANOVA was used to test for treatment-group baseline differences for continuous variables. Hemodynamic and hormonal responses to various doses of valsartan were compared by parametric ANCOVA, with the baseline level used as the covariate. A retrospective analysis was also performed for between-treatment comparisons of hemodynamic and neurohormonal variables by Student's t test. Between-group differences for the changes (from baseline) for each variable were evaluated by both an area under the curve and a time-point–by–time-point analysis. Bonferroni adjustment for multiple comparisons was used to maintain an overall 2-sided significance level of 0.05, with between-treatment comparisons of valsartan versus placebo considered statistically significant for P<0.025. Within-treatment analyses of change from baseline were performed at the 0.05 significance level by use of Student's t test.

Results

Of 143 patients who entered the single-blind phase of the study, 83 met all of the entry criteria, including prebaseline PCWP ≥15 mm Hg, and were randomized. Baseline charac-
teristics in the 3 groups were generally similar (Table 1). Because 14 of the 15 centers were in Veterans Affairs hospitals, the study was restricted to male patients; 65% of the patients were white, 27% were black, 93% were receiving diuretics, and 90% were receiving digoxin. The origin of the heart failure was ischemic in the majority of patients, with the remainder classified as hypertensive or idiopathic. Differences in average baseline characteristics were partially adjusted for by ANCOVA.

Immediate Effects (Day 0)
Mean PCWP decreased significantly compared with baseline in all 3 blinded study groups. The placebo response was presumably related to the lisinopril dose given at baseline to all patients. There were statistically significantly (P < 0.025: ANCOVA and t test) greater reductions in PCWP in the valsartan 160 mg group than with placebo at 3, 4, and 8 hours (Figure 1) and during the prespecified primary variable of the mean from 4 to 8 hours (Figure 3). No consistent immediate effect on PCWP was noted with valsartan 80 mg. Changes in PADP were similar to those in PCWP.

Valsartan 160 mg also produced a statistically significant reduction in SBP compared with placebo at 2, 3, 6, 8, and 12 hours after the dose (Figure 2) and during the prespecified 4- to 8-hour interval (Figure 3). The reduction from valsartan 80 mg did not achieve statistical significance.

RAP was significantly (P < 0.025) reduced by valsartan 160 mg compared with placebo at 4, 6, and 12 hours, as well as from 4 to 8 hours. A peak net reduction of 2 mm Hg compared with placebo was noted at 6 hours. RAP tended to decrease in the valsartan 80 mg group, but the reduction did not achieve statistical significance. HR tended to decrease slightly in the valsartan 160 mg group, with a statistically significant reduction only at the 12-hour time point (net decrease of 6.8 bpm compared with placebo). In the valsartan 80 mg group, HR remained generally unchanged. Valsartan demonstrated no discernible effect on CO. SVR tended to decrease in both valsartan-treatment groups. Net mean reductions over the 12-hour monitoring period in the valsartan 80 and 160 mg groups were 94.7 and 119.6 dynes cm⁻², respectively.

There were no significant between-group differences in baseline neurohormone values for PRA, PA, and AngII (Table 2). However, slightly higher baseline values for PNE were observed in the valsartan 160 BID group. PNE did not change significantly during the 12-hour monitoring period (Table 3). PRA increased in all 3 groups at 6 hours, but this

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<tr>
<th>TABLE 1. Baseline Values (±SD)</th>
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<td>Placebo</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>High-dose ACE inhibitor, %</td>
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<tr>
<td>Duration of CHF, y</td>
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<td>Ischemic origin, %</td>
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<tr>
<td>PADP, mm Hg</td>
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<td>PCWP, mm Hg</td>
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<tr>
<td>SVR, dynes · s⁻¹ · cm⁻⁵</td>
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<td>RAP, mm Hg</td>
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Figure 1. Sequential mean ± SEM change in pulmonary artery wedge pressure on day 0 after administration of lisinopril plus valsartan 80 mg (V80; ▲), valsartan 160 mg (V160; ●), or placebo (■). Plotted data are not adjusted for baseline differences.

Figure 2. Sequential mean ± SEM change in arterial SBP in the 3 groups depicted in Figure 1.
effect waned at 12 hours. ANP and PA levels decreased in both valsartan cohorts. AngII levels were not significantly altered by the drugs. Between-treatment comparisons with placebo by ANCOVA were not statistically significant, with the exception that valsartan 160 mg produced greater lowering of PA at the 6-hour time point ($P=0.02$).

**Long-Term Effects (Day 28)**

**0 Hour (Trough)**

After 4 weeks of therapy, before administration of medications, hemodynamic measurements were compared with those at baseline on day 0. Mean PCWP had decreased from a baseline value of 24.9 to 18.7 mm Hg for patients receiving valsartan 160 mg BID and from 20.6 to 18.4 mm Hg for patients receiving placebo. The net (compared with placebo) reduction in PCWP was slightly higher in the valsartan 160 mg BID group than in the baseline group. ANP levels tended to rise in the placebo group and fall in the valsartan groups, but the differences did not quite reach statistical significance. AngII levels tended to increase in all 3 treatment groups, but the between-treatment changes were not statistically significant.

**Hours 0 to 12**

Mean PCWP decreased in all 3 groups after drug administration, but when adjusted for baseline differences by ANCOVA, the effect was not significantly different between the valsartan and placebo groups. PA levels were lower in the valsartan 160 mg BID group than in the placebo group throughout the 12-hour monitoring period, with or without baseline adjustment. RAP tended to decrease in valsartan-treated patients, and the adjusted decrease was statistically significantly greater (by 2.2 mm Hg at 1 hour; $P=0.019$) in the valsartan 160 mg BID cohort than in the placebo group.

In the valsartan 160 mg BID group than with placebo throughout the 12 hours of monitoring, with a significant adjusted net reduction of 8.7 mm Hg at 30 minutes ($P=0.019$). No statistically significant net change in SBP was seen with valsartan 80 mg BID. HR tended to decrease in valsartan-treated patients. No effect was observed on CO or SVR.

**Safety**

Trial medications were well tolerated over the 4-week period. Seventy-four (89%) of 83 patients completed the protocol. Of the 9 patients who failed to complete the protocol, 8 had received valsartan, 4 from each dosage group. The reasons for withdrawal were hypotension (2 patients after receiving their initial doses of 80 mg of valsartan), gastrointestinal disturbance (1 patient receiving 160 mg BID), concomitant illness

### TABLE 2. Baseline Neurohormonal Values (Mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Valsartan 80 mg BID</th>
<th>Valsartan 160 mg BID</th>
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</thead>
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<tr>
<td></td>
<td>n</td>
<td>Mean±SD</td>
<td>n</td>
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<tr>
<td>Renin activity, ng · mL⁻¹ · h⁻¹</td>
<td>28</td>
<td>5.2±9.0</td>
<td>27</td>
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<tr>
<td>Atrial peptide, pg/mL</td>
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<td>330±339</td>
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<tr>
<td>Aldosterone, pg/mL</td>
<td>28</td>
<td>94±92</td>
<td>26</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>28</td>
<td>303±173</td>
<td>27</td>
</tr>
<tr>
<td>AngII, pg/mL</td>
<td>25</td>
<td>3.4±3.5</td>
<td>25</td>
</tr>
</tbody>
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unrelated to the study drug (1 patient), death unrelated to trial medication (1 patient receiving 80 mg BID and 1 patient receiving 160 mg BID), and administrative reasons (3 patients). Hypotension and dizziness were the most common adverse events reported. Hypotension related to the study drug was documented in 10.9% of valsartan patients and 3.6% of patients receiving placebo.

Laboratory changes documented included a serum urea nitrogen rise of >50% above baseline in 9 (19%) of the valsartan-treated patients (none in placebo). Creatinine rose >50% in 1 placebo patient (4%) and 2 valsartan patients (4%). Mean serum potassium rose slightly in valsartan-treated patients from 4.2 to 4.4 mEq/L, whereas it declined slightly from 4.2 to 4.0 mEq/L in the placebo group. Potassium rose >20% in 4 patients (9%) treated with valsartan (none in placebo). Only 2 patients receiving valsartan developed potassium values outside the upper limit of normal, 1 of whom was dehydrated and the other of whom was taking potassium supplements.

**Discussion**

The data from this 4-week trial indicate that an angiotensin receptor blocker, valsartan, produces hemodynamic and hormonal effects when given to patients with heart failure chronically treated with an ACE inhibitor. An additive blood pressure and renin effect of single doses of losartan and captopril in mildly sodium-depleted volunteers has previously been demonstrated by Azizi et al.25 These studies represent the first evidence in humans that hemodynamic and hormonally active levels of AngII persist during long-term administration of standard clinical doses of ACE inhibitors augmented by a dose of the long-acting drug lisinopril at the time of administration of test medication.

The design of this trial allowed assessment of the response to both the first dose of valsartan and a dose given after 4 weeks of therapy, as well as assessment of the long-term response to a 4-week treatment regimen. Valsartan was given twice daily in the present study, despite the fact that the drug is effective as a once-daily antihypertensive,22 to ensure sustained inhibition of the AT1 receptor. The 160 mg BID regimen exerted a hemodynamic effect on the first day of therapy, a sustained hemodynamic effect at trough drug effect after 4 weeks of continuous therapy, and a hormone-inhibiting effect at that time demonstrated by suppression of PA and a trend for suppression of PNE. The 80 mg BID regimen did not exert a significant hemodynamic effect but also suppressed PA levels. Because the patients entered into this trial were selected to have a persistently elevated PCWP, the efficacy and safety of valsartan is not established in patients who do not meet this criterion.

Several mechanisms may account for physiologically persistent AngII levels despite long-term ACE inhibitor therapy.11,26 Renin is activated during long-term ACE inhibitor therapy, and AngI levels are elevated.6,7 The increased substrate levels may therefore be adequate to overcome the competitive inhibition of the converting enzyme, especially
during the intervals between dosing. In addition, tissue levels of AngII could persist even if circulating levels of the hormone are suppressed by the drug. Furthermore, there is growing evidence that alternate pathways for conversion of AngI to AngII reside in the actions of chymase and other proteolytic enzymes, present particularly in certain tissues. If these systems are active in humans, then the favorable effects of ACE inhibitors in hypertension and heart failure would need to be attributed at least in part to alternative mechanisms, including the activation of bradykinin, which appears to account for the favorable vascular and cardiac effects of ACE inhibitors in some animal models.

Neurohormonal measurements performed in the present study help to explore some of the mechanisms. AngII plasma levels at baseline with long-term ACE inhibitor therapy were within the normally reported range. Because no values are available in these patients in the absence of ACE inhibition, it is not possible to know whether the therapy produced some long-term suppression. Although a rise in circulating AngII would be anticipated in response to valsartan, this increase was not observed either acutely or chronically, possibly because of the coadministration of an ACE inhibitor. A similar inhibition by ACE inhibitor of a losartan-induced rise in plasma AngII level has been reported by Azizi et al. Thus, it appears that ACE inhibition suppresses the activation of AngII but not its resting levels. This observation raises interesting speculations about the feedback controls of the renin-angiotensin system and also indicates that combined therapy may not be associated with the excessive stimulation of AT1 receptors that is thought to accompany AT1 receptor blockade.

The trend for PNE suppression during long-term valsartan therapy raises the possibility that combined ACE inhibitor and AT1 receptor blocking treatment in heart failure may be more effective than ACE inhibitor therapy, which is accompanied by an “escape” from suppression of PNE after the first year of treatment.

Valsartan was generally well tolerated when added to an ACE inhibitor in this population. In both the 80 and 160 mg BID groups, hypotension did occasionally occur, but usually only after the first dose, while the patient was fasting and had already received lisinopril. Two patients, both of whom had underlying atrial fibrillation, developed hypotension after a single 80-mg dose of valsartan accompanied by lisinopril 10 or 20 mg. The patients’ background ACE inhibitors were captopril 25 mg TID and fosinopril 20 mg/d, respectively. The patients recovered uneventfully and were released from the study as mandated by the protocol. A rise in serum urea nitrogen was observed in nearly 20% of the patients but did not require dose adjustment or cessation. Because dose titration was not used in this trial, it is likely that hypotension and azotemia would be less common in clinical practice. An increase in serum potassium in patients receiving combination therapy provided further evidence that aldosterone suppression was augmented by the combination therapy.

The hemodynamic and hormonal effects of valsartan could theoretically have been replicated if a higher dose of ACE inhibitor had been used; however, 75% of the participants were receiving doses of ACE inhibitors that approached or equaled those recommended by established heart failure guidelines. Adjustments in background therapy did not contribute to the valsartan effect, because only 2 patients had either a permanent reduction in ACE inhibitor dose or diuretic dose subsequent to randomization. Furthermore, all patients received an appropriate dose of the long-acting drug lisinopril at the time of the double-blind administration of valsartan or placebo. A recently completed long-term study to evaluate the effect of a higher dose of lisinopril (35 mg) has not provided persuasive evidence for efficacy greater than that of conventional doses.

Despite optimal medical therapy with digoxin, diuretics, and ACE inhibitors, CHF remains a major cause of morbidity and mortality. Because AngII is a potent vasoconstrictor and cardiovascular tissue growth stimulator, its possible role in the progression of structural and functional alterations in heart failure has been widely entertained. The evidence from the present study that physiologically active levels of angiotensin persist during long-term ACE inhibitor therapy mandates a long-term study to evaluate the possible benefits on morbidity and mortality of adding an angiotensin receptor blocker to currently practiced ACE inhibitor therapy. Such a trial, the Valsartan Heart Failure Trial (Val-HeFT), has already been initiated to target the higher dose of valsartan identified as effective in the present study.

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Appendix

The following individuals and institutions participated in this trial:

**Study Chairman’s Office (Minneapolis, Minn):** Jay N. Cohn, MD, study chairman; Susan Ziesche, RN, study coordinator.

**Medical Centers:** VA Medical Center, Albuquerque, NM—Milton Icenogle, MD, Jean Pierre Letellier; VA Medical Center, Bronx, NY—Lawrence Baruch, MD, Pros Patacsil, RN; VA Medical Center, Dallas, Tex—Eric Eichhorn, MD, Lucille Marcoux, RN; VA Medical Center, Decatur, Ga—Robert Taylor, MD, Alberta Lane, RN; VA Medical Center, Durham, NC—Frederick Cobb, MD, Gwen Dodson, RN; VA Hospital, Loma Linda, Calif—Thomas Heywood, MD, Karen Okubo, RN; Tower Cardiology Medical Group, Los Angeles, Calif—Robert Davidson, MD, Carolyn Mandel, RN; VA Medical Center, Milwaukee, Wis—Vincent Hughes, MD, Grace Daniels, LPN; VA Medical Center, Minneapolis, Minn—Inder Anand, MD, Amy Holmstrom, RN, Susan Ziesche, RN; VA Medical Center, Nashville, Tenn—Raphael Smith, MD, Barbara Smith, RN; VA Medical Center, Philadelphia, Pa—Bruce Dunkman, MD, Ken Gebhardt, RN; VA Medical Center, San Diego, Calif—Ralph Shabetai, MD, Rosemary Cremo, RN, Stacie Reynolds, RN; VA Medical Center, Tucson, Ariz—Gregory Pennock, MD, Beth Gregorio, RN; VA Medical Center, Washington, DC—Peter Carson, MD, Dottie Lee, RN; VA Medical Center, West Haven, Conn—Ira Cohen, MD, Luisa Canestri, RN.

**Core Laboratory:** Central Norepinephrine Laboratory, Minneapolis, Minn—Jay N. Cohn, MD; Dionne Judd, director; Flor Dizon, technician.

**References**

Angiotensin Receptor Blocker Plus ACE Therapy in HF


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