Heart Failure

Hemodynamic and Neuroendocrine Effects for Candoxatril and Frusemide in Mild Stable Chronic Heart Failure

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OBJECTIVES

The study aimed to assess the hemodynamic and neuroendocrine effects of candoxatril and frusemide compared with placebo in patients with mild chronic heart failure.

BACKGROUND

Candoxatril is an atriopeptidase inhibitor. It increases circulating levels of atrial natriuretic peptide leading to natriuresis and diuresis, which alleviate the symptoms of a failing heart.

METHODS

This was a multicenter, randomized, double-blind study. Forty-seven patients with mild stable chronic heart failure received candoxatril 400 mg/day, frusemide 40 mg/day or placebo for up to six weeks. Cardiac indices were determined at rest and during exercise, and blood samples were taken for laboratory analysis. Assessments were performed at baseline (day 0) and after six weeks (day 42).

RESULTS

In comparison with placebo, both drugs significantly reduced mean pulmonary capillary wedge pressure following the first dose administration. Only candoxatril significantly reduced pulmonary capillary wedge pressure during exercise on day 0, while both drugs significantly reduced this parameter on day 42. Changes in the remaining hemodynamic parameters were comparable for both drugs relative to placebo. Frusemide significantly increased mean plasma renin activity (days 0 and 42), and the mean aldosterone concentration (day 42) in comparison with placebo, whereas candoxatril caused no significant changes in any of the hormonal parameters assessed.

CONCLUSIONS

These results show that candoxatril, 400 mg/day, has a similar hemodynamic profile to frusemide, 40 mg/day, but it does not induce adverse neuroendocrine effects. Candoxatril therefore appears to offer a clinically significant advantage over frusemide, providing an alternative therapeutic approach to the treatment of patients with mild stable chronic heart failure. (J Am Coll Cardiol 1999;34:1794–801) © 1999 by the American College of Cardiology

Despite the advances that have been made in the understanding and treatment of heart failure over the past decade, the incidence of the disease continues to rise (1). Once diagnosed, patients have a prognosis worse than for many cancer patients, with a five-year mortality rate of about 50% (1). With improved survival among acute myocardial infarction patients, and an aging population, more people are progressing to a failing heart, and this significant public health problem will certainly continue to grow (1).

Symptoms of a failing heart are alleviated by measures such as rest, restriction of sodium and fluid to unload the decompensating heart, with inotropic agents to improve the mechanical performance of the heart, and with agents to counteract the activated sympathetic nervous system and the renin-angiotensin-aldosterone system (2). These symptoms, however, still limit the everyday activities of most heart failure patients (1), highlighting the need for new therapies in this setting.

Heart failure therapy continues to improve, and angiotensin-converting enzyme (ACE) inhibitors are the most important recent development (1,3). These agents reduce the harmful long-term consequences of neurohormonal/autocrine–paracrine effects, and they slow the progression of left ventricular (LV) dysfunction or ventricular remodeling (4). Other therapies include treatment with beta-blockers and diuretics, while concomitant vasodilator therapy with some of the newer calcium channel blockers is currently under investigation (3). These therapies aim to provide symptomatic control, leading to an increase in exercise tolerance.

Atriopeptidase inhibitors are a new class of agent producing natriuresis and diuresis. Studies are currently inves-
tigating whether these agents have a role in the pathophysiology and therapy of various diseases, such as congestive heart failure and certain forms of hypertension (5). Angiotensin-converting enzyme inhibitors have been shown to alleviate symptoms of a failing heart (5,6) and to increase exercise tolerance. Candoxatril is an orally active prodrug of candoxatrilat, an angiotensin-converting enzyme inhibitor that has been shown to lower blood pressure in animals with established hypertension.

Current studies are investigating the dose-response relationship, duration of action, hemodynamic effects and safety of oral candoxatril for the treatment of patients with hypertension and heart failure. In early placebo-controlled clinical studies, candoxatril has been shown to confer beneficial acute hemodynamic effects in patients with congestive heart failure and to be well tolerated (7,8). Furthermore, its efficacy is maintained with chronic therapy (7,9). These results indicate that candoxatril has therapeutic potential in chronic congestive heart failure (7,8).

The diuretic frusemide has beneficial effects on the hemodynamic profile, but it has an adverse effect on levels of renin and aldosterone. Initial placebo-controlled trials in patients with LV dysfunction have shown that candoxatril has a similar hemodynamic profile to frusemide but no adverse neuroendocrine effects in an acute setting (10). This six-week study compared the hemodynamic and neuroendocrine effects of candoxatril 400 mg/day and frusemide 40 mg/day with placebo in patients with mild stable chronic heart failure to evaluate whether long-term administration of candoxatril maintained the beneficial effects shown earlier in acute investigations.

METHODS

Selection of patients. Patients aged 18 to 75 years with stable mild chronic heart failure and an ejection fraction <50% were eligible for inclusion into this multicenter, double-blind, double-dummy, parallel-group comparison. Stable mild heart failure was defined as New York Heart Association (NYHA) class I or II heart failure that had been in the same functional class for the previous two weeks.

The patient population comprised those currently on no therapy, but requiring monotherapy with diuretics, or those already on diuretic treatment who could, in the opinion of the investigator, be safely discontinued. After a two-week placebo run-in, patients with a pulmonary capillary wedge pressure (PCWP) of ≥25 mm Hg (exercise) and <21 mm Hg (rest) were randomized to receive either candoxatril 200 mg twice daily, frusemide 40 mg once daily, or placebo for six weeks.

Exclusion criteria covered women of childbearing potential, patients who had suffered a myocardial infarction, cerebrovascular accident or those who had undergone cardiac surgery, in the preceding three months. Also excluded were patients with any other clinically significant disease likely to affect the degree of heart failure or the hemodynamic response to exercise, patients who required continued therapy with other cardiovascular drugs, or patients whose weight gain was ≥2.5 kg in the initial two-week placebo run-in period.

Forty-three patients were receiving concomitant medication (mostly anti-inflammatory drugs) on entry into the study. All patients gave their written informed consent before entry. Experimental procedures were reviewed and approved by the appropriate independent Ethics Committees, and conducted in compliance with the revised declaration of Helsinki.

Study protocol. Patients who met the selection criteria underwent a screening visit during which demographic data, medical history, intercurrent illnesses, allergies and concomitant therapy were documented. In addition, patients underwent a full physical assessment that included measurement of blood pressure, heart rate, body weight and height. Blood and urine samples were obtained for routine laboratory investigation and a 12-lead electrocardiogram (ECG) was performed. Left ventricular ejection fraction had been measured within the preceding eight weeks.

On the first (day 0) and last (day 42) days of treatment, patients underwent a cardiovascular examination that included measurement of blood pressure, heart rate and assessment of NYHA class. A 12-lead resting ECG, blood samples for hematological and biochemical testing, and a urine sample for analysis were obtained. Patients were instructed not to take their morning medication before attendance, and invasive hemodynamic measurements were taken before and after double-blind medication was given.

The primary efficacy parameters were PCWP and cardiac index (CI) at rest and during exercise on days 0 and 42 and discontinuation due to worsening heart failure. Systemic vascular resistance and pulmonary vascular resistance at rest and exercise together with NYHA classification and circulating hormone levels were also determined on days 0 and 42.

Hemodynamic analysis. Hemodynamic measurements were taken on day 0 and day 42. Patients underwent a supine bicycle exercise test to determine the load required to produce fatigue, shortness of breath, or for the heart rate to exceed 150 beats/min. Patients then underwent cardiac catheterization and measurement of PCWP at rest. Catheterization was performed with a four-channel thermodilution catheter (Swan-Ganz) inserted through an antecubital...
fossa vein. The catheter was positioned in the right atrium, right ventricle and pulmonary artery; a brachial or radial artery cannula was also inserted. Systemic blood pressure was continuously monitored using a transducer attached to the arterial line, and the heart rate was simultaneously taken from the ECG.

Hemodynamic measurements included mean right atrial pressure, systolic, diastolic and mean pulmonary artery pressure, PCWP, mean arterial pressure and cardiac output. These were made in duplicate in the supine position, and cardiac output was determined by thermodilution. From these parameters, the CI, systemic vascular resistance and pulmonary vascular resistance were calculated.

Patients underwent a second exercise test and hemodynamic measurements were made at 1-min intervals during exercise. Resting hemodynamic measurements were then taken until four consecutive measurements of PCWP, cardiac output and mean arterial pressure showed a stable baseline. Resting hemodynamic measurements were made at 1, 2, 3, 4 and 6 h following administration of medication. Patients underwent supine bicycle exercise tests using the same load and protocol as in the first exercise test.

Hormonal analysis. Distributions of the hormonal parameters in the three treatment groups were assessed for plasma renin activity and norepinephrine, aldosterone and angiotensin II concentrations. Blood samples were taken on days 0 and 42 immediately after exercise before the dose and at 2 and 6 h after administration.

Adverse event analysis. All adverse events, concomitant illnesses and therapeutic interventions were recorded by the investigator at each visit and assessed for causality. Serious adverse events were categorized as fatal, life-threatening, permanently disabling, requiring in-patient hospitalization, congenital anomaly, cancer or the result of an overdose, significant enough to merit immediate reporting. Abnormal values in laboratory tests of hematology, clinical chemistry, urinalysis and hepatitis battery were followed up with appropriate medical management if necessary.

On completion of these measurements, patients were discharged unless they had developed complications, standing systolic blood pressure was ≤85 mm Hg, or hemostasis was not established.

Statistical analysis. Hemodynamic variables were analyzed using one way analysis of variance (ANOVA) with treatment as the grouping factor. The baseline term was included in each model as a covariate as was the interaction between the baseline term and the treatment. Least-square means, adjusted for the baseline terms, were used in the comparisons. The sample size was sufficient to detect a difference of 4 mm Hg in PCWP between treatments using a significance level of α = 0.05 and with a power of 80%. This assumed a between-subject standard deviation of changes from baseline of 3.8 mm Hg. No direct statistical comparisons were made between the two active treatment groups.

The hormonal data were log-transformed to improve the normality of these data and analyzed using the same model as for the hemodynamic data. Worsening of heart failure was compared between the active-treatment and placebo groups using a continuity adjusted chi-square test. Pairwise comparisons of each active treatment with placebo were made using a pooled estimate of error from the ANOVA model, and 95% confidence intervals for treatment differences were calculated.

All statistical analyses were performed using SAS (version 6.09), and all tests were two-tailed at the 5% significance level.

RESULTS

Of the 72 patients screened, 47 were eligible for inclusion in the study. Of these, 15 patients were randomized to receive candoxatril, 16 patients were randomized to receive frusemide, and 16 patients were randomized to receive...
placebo. A summary of the baseline characteristics of the patient population is shown in Table 1. All patients in the candoxatril and frusemide groups, and 14 of the 16 patients in the placebo group completed the study. One patient discontinued owing to tiredness, the other because of an adverse event considered to be related to a concurrent illness.

**Hemodynamics.** The primary variables analyzed at rest were the maximum change (increase or decrease) from the predose baseline during the 6-h postdose period (defined as peak effect), and the time to achieve this, on both day 0 and day 42. In addition, the differences between the predose baselines on day 42 and day 0 were analyzed. After exercise, the 6-h value was used in the same comparisons and analyses as the “peak effect” at rest.

**Pulmonary capillary wedge pressure.** REST. On day 0, the peak fall in the mean PCWP from baseline (minimum at 3.7 h postdose) relative to placebo was statistically significant for both candoxatril (−2.5 ± 0.91 mm Hg, p = 0.009) and frusemide (−2.4 ± 0.91 mm Hg, p = 0.012). The PCWP rose at 6 h postdose in both groups. The adjusted mean time to peak effect was statistically significantly higher for candoxatril only (3.7 h ± 0.36), compared with placebo (2.4 h ± 0.35, p = 0.017). On day 42, the adjusted mean change from baseline to peak effect between 0 and 6 h postdose reached statistical significance compared with placebo in the frusemide group only (−2.4 ± 1.09 mm Hg, p = 0.037) (Table 2).

**EXERCISE.** On day 0, the fall in mean PCWP from predose baseline to 6 h postdose relative to placebo was statistically significantly greater for candoxatril (−10.6 ± 2.69 mm Hg, p < 0.001) but not for frusemide (−4.1 mm Hg ± 2.67, p = 0.13). On day 42, the fall in mean PCWP relative to placebo reached statistical significance, and was greater for both treatment groups (candoxatril: −5.2 ± 2.29 mm Hg, p = 0.028; frusemide: −6.1 ± 2.29 mm Hg, p = 0.011 [Table 2]). There was no statistically significant difference in the mean change in PCWP relative to placebo between the day 0 and day 42 results for either group.

**Cardiac index.** REST. The reduction in the mean CI on day 0 was statistically significantly greater in both active treatment groups compared with placebo (candoxatril: −0.32 ± 0.107 liter/min/m², p = 0.004; frusemide: −0.29 ±

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**Table 2.** Pulmonary Capillary Wedge Pressure, mm Hg, Days 0 and 42 (Mean ± SE)

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment Group</th>
<th>Baseline (predose)</th>
<th>Change from Baseline</th>
<th>Difference in Change from Baseline to Peak Effect Compared with Placebo (significance)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>At Peak Effect (0–6 h)—Resting</td>
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<td></td>
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<tr>
<td>0</td>
<td>Candoxatril (n = 15)</td>
<td>9.3 ± 1.0</td>
<td>−5.6 ± 0.6</td>
<td>−2.5 ± 0.9 (p = 0.009)</td>
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<td>Frusemide (n = 16)</td>
<td>11.2 ± 1.4</td>
<td>−5.5 ± 0.6</td>
<td>−2.4 ± 0.9 (p = 0.012)</td>
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<tr>
<td></td>
<td>Placebo (n = 16)</td>
<td>8.9 ± 1.0</td>
<td>−3.1 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>42</td>
<td>Candoxatril (n = 15)</td>
<td>8.6 ± 1.0</td>
<td>−4.0 ± 0.8</td>
<td>−1.4 ± 1.1 (p = 0.22)</td>
</tr>
<tr>
<td></td>
<td>Frusemide (n = 16)</td>
<td>10.7 ± 1.6</td>
<td>−5.0 ± 0.7</td>
<td>−2.4 ± 1.1 (p = 0.037)</td>
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<td>Placebo (n = 14)</td>
<td>8.9 ± 1.5</td>
<td>−2.7 ± 0.8</td>
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<tr>
<td></td>
<td>At 6 h Postdose—After 6-min Exercise</td>
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<tr>
<td>0</td>
<td>Candoxatril (n = 15)</td>
<td>32.0 ± 1.8</td>
<td>−14.4 ± 1.9</td>
<td>−10.6 ± 2.7 (p &lt; 0.001)</td>
</tr>
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<td></td>
<td>Frusemide (n = 15)</td>
<td>34.5 ± 2.1</td>
<td>−7.9 ± 1.9</td>
<td>−4.1 ± 2.7 (p = 0.13)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 15)</td>
<td>33.5 ± 1.9</td>
<td>−3.8 ± 1.9</td>
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</tr>
<tr>
<td>42</td>
<td>Candoxatril (n = 15)</td>
<td>28.7 ± 2.0</td>
<td>−5.3 ± 1.6</td>
<td>−5.2 ± 2.3 (p = 0.028)</td>
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<td></td>
<td>Frusemide (n = 16)</td>
<td>34.6 ± 2.3</td>
<td>−6.2 ± 1.5</td>
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</tr>
<tr>
<td></td>
<td>Placebo (n = 13)</td>
<td>32.3 ± 2.6</td>
<td>−0.1 ± 1.7</td>
<td>—</td>
</tr>
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</table>
0.105 liter/min$^{-1}$/m$^2$, p = 0.008). The mean time to peak effect was not statistically significant compared with placebo for candoxatril or frusemide on either day 0 or day 42.

**EXERCISE.** No statistically significant different changes occurred in CI relative to placebo in either the candoxatril or frusemide groups on either day 0 or day 42.

**Systemic vascular resistance.** **REST.** On day 0, the mean change from baseline to peak effect for systemic vascular resistance relative to placebo between 0 and 6 h postdose was not statistically significant for candoxatril (127.86 ± 73.635 dynes/s/cm$^{-5}$, p = 0.09) but increased and reached statistical significance for frusemide (174.76 ± 72.123 dynes/s/cm$^{-5}$, p = 0.02). The mean time to peak effect relative to placebo was not statistically significantly different for either drug on day 0 or day 42.

**EXERCISE.** There were no statistically significant changes in systemic vascular resistance relative to placebo in the active treatment groups on either day 0 or day 42.

**Pulmonary vascular resistance.** The mean change from baseline, or mean time to peak effect relative to placebo, was not statistically significant for either candoxatril or frusemide after rest or exercise on days 0 or 42 (Table 3).

**Neuroendocrine effects.** Candoxatril induced no statistically significant change in plasma renin activity, aldosterone angiotensin II or norepinephrine on day 0. On day 42, the mean difference (log transformed) between the candoxatril and placebo groups reached statistical significance for the plasma renin activity parameter at 2 h postdose (p = 0.011), but this difference was no longer statistically significant at 6 h postdose. Frusemide caused a statistically significant increase in the plasma renin activity on days 0 and 42 (Fig. 1). The mean difference between plasma renin activity (log transformed) at baseline and 6 h postdose relative to placebo was +0.436 ± 0.1226 µg/liter/h, p = 0.001, on day 0, and +0.305 ± 0.1247 µg/liter/h, p = 0.019, on day 42. Frusemide also caused a statistically significant change in the mean aldosterone concentration relative to placebo on day 42 (+0.281 ± 0.0958 nmol/liter, p = 0.006), but not in any of the other parameters (Fig. 2, Table 4).

**Cardiovascular examination.** Most patients did not experience any symptoms of paroxysmal nocturnal dyspnea,
orthopnea or ankle/pedal edema at screening or on days 0 and 42. There was a decrease in dyspnea (after climbing one flight of stairs) on days 0 and 42 in all treatment groups compared with the screening visit.

Worsening of heart failure. One patient in the candoxatril group and five in the frusemide group experienced a worsening of heart failure. The incidence was not statistically significantly different compared with placebo (two patients).

Figure 1. Plasma renin activity (µg/liter/h). Geometric mean over time on day 0 and day 42.

Hormonal Data: Geometric Mean Over Time

Plasma Renin Activity (µg/liter/h)

Day 0

Day 42

Figure 2. Aldosterone concentration (nmol/liter). Geometric mean over time on day 0 and day 42.
Potential explanations. The fall in CI compared to placebo in both groups of patients at rest was not seen in

<table>
<thead>
<tr>
<th>Day</th>
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<th>Plasma Renin Activity (µg/liter/h)</th>
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<td>Frusemide</td>
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<td>42</td>
<td>Candoxatril</td>
<td>−0.27 ± 0.09</td>
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<td>Frusemide</td>
<td>0.06 ± 0.08</td>
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<td></td>
<td>Placebo</td>
<td>−0.24 ± 0.09</td>
<td>—</td>
<td>−0.14 ± 0.071</td>
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### DISCUSSION

We have demonstrated that candoxatril (200 mg twice daily) is associated with a beneficial hemodynamic effect, both at rest and during exercise. The effects were comparable to those observed following frusemide (40 mg once daily). We also observed that the beneficial hemodynamic effects associated with candoxatril are maintained during long-term therapy in the absence of harmful, activating effects on neuroendocrine function. Both candoxatril and frusemide significantly improved hemodynamic parameters compared with placebo. The most common adverse events reported during candoxatril treatment were symptoms of the central and peripheral nervous system including dizziness (one), headache (one), and one placebo-treated patient was considered by the investigator to be treatment-related. One patient had a serious adverse event during placebo treatment (hematuria with congestion over seven days duration and moderate severity).

### Other safety parameters.

All laboratory test results outside the normal range were considered by the investigator to be unrelated to treatment. No patient reported changes in life style as a result of the study treatment. All patients had normal ECG findings at baseline and day 1 after exercise. There was no statistically significant difference in body weight recorded over the study period in the candoxatril group compared to placebo. The most common adverse events reported during frusemide treatment were symptoms of the central and peripheral nervous system including dizziness (one), headache (one), and one placebo-treated patient was considered by the investigator to be treatment-related. One patient had a serious adverse event during placebo treatment (hematuria with congestion over seven days duration and moderate severity).

Most patients showed either improvements or no change in NYHA classification at day 42 compared with day 0. Adverse events. In the candoxatril group, 6 of the 15 patients had adverse events. The most common adverse events were gastrointestinal symptoms and peripheral nervous system symptoms including dizziness (one), headache (one), and one placebo-treated patient was considered by the investigator to be treatment-related. One patient had a serious adverse event during placebo treatment (hematuria with congestion over seven days duration and moderate severity).

### Table 4. Neuroendocrine Effects, Change from Baseline at 6 h Postdose (Adjusted Log-Transformed Mean ± SE)

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patients after exercise, probably due to the low LV filling pressure in the resting state. However, it seems unlikely that the reduction in CI at rest should have any adverse effect on cardiac function.

The mechanisms for the fall in LV filling pressure in the candoxatril group might be an increase in plasma ANP as has been observed previously (9). In our study, plasma ANP was not measured, but the acute hemodynamic effect of candoxatril in this study is similar to earlier findings, indicating that the biological consequence of candoxatril treatment is caused by elevated ANP concentration. In addition, the effect of candoxatril on hemodynamic parameters was maintained after long-term use during exercise.

**Neuroendocrine effects.** Unlike frusemide, the beneficial hemodynamic effects of candoxatril are observed in the absence of clinically relevant effects on the renin-angiotensin-aldosterone system in patients with mild chronic heart failure. Although activation of this hormonal system may be beneficial in the short term, it results in long-term and progressive dysfunction of the heart (4). Candoxatril produced no statistically significant increase in any hormonal parameter. This is likely to be particularly beneficial as activation of neurohormones is thought to have a negative impact on the prognosis of patients with congestive heart failure (11).

High plasma renin levels are associated with an increased risk of myocardial infarction in hypertensive patients (12). Furthermore, increased levels of both renin and aldosterone are thought to negatively affect the prognosis of patients with congestive heart failure (13). In the SOLVD (14,15) prevention trial, only patients already on treatment with diuretics had elevated plasma renin levels. Candoxatril, in contrast to frusemide, does not have any adverse neurohormonal effects and might, therefore, be more useful than diuretics in the long-term treatment of congestive heart failure.

**Clinical effects and safety.** In congestive heart failure, changes in body weight might reflect variations in the water and sodium balance. Diuresis was not measured in this study, but all patients were told to maintain a constant diet and sodium intake, and not to change their normal levels of physical activity. Therefore, the slight but significant reduction in body weight observed in the candoxatril group is suggestive of a beneficial diuretic effect.

Only one patient treated with candoxatril experienced a worsening of heart failure compared with five patients in the group treated with frusemide. However, this frequency was not statistically significantly different from that observed in the placebo-treated group (two patients) for either drug. Both the frequency and the severity of other adverse events were minimal and similar in both the candoxatril and frusemide treatment groups compared with placebo.

**Clinical implications.** Taken together, the results of this study support the current evidence that candoxatril offers a new and effective therapeutic approach in the treatment of patients with mild heart failure (9,10) without the adverse activation of the renin-angiotensin-aldosterone neuroendocrine system. The reductions in LV filling pressure measured as PCWP might also have clinical implications by relieving congestion and dyspnea during physical effort. These beneficial effects may improve the well-being of patients during everyday activities. However, to show the real potential of this drug, further long-term studies in combination with ACE inhibitors are needed.

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