Improvement in Exercise Tolerance and Symptoms of Congestive Heart Failure During Treatment With Candesartan Cilexetil

G.A.J. Riegger, MD; H. Bouzo, MD; P. Petr, MD; J. Münn, MD; R. Spacek, MD, PhD; H. Pethig, MD; V. von Behren, MD; M. George, MD; H.-J. Arens, PhD; for the Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators

Background—The renin-angiotensin system plays an important part in the pathogenesis of congestive heart failure (CHF). This study evaluated the effect of an angiotensin II type 1 receptor antagonist on exercise tolerance and symptoms of CHF.

Methods and Results—In this multicenter, double-blind, parallel-group study, 844 patients with CHF were randomized to 12 weeks’ treatment with placebo (n=211) or candesartan cilexetil 4 mg (n=208), 8 mg (n=212), or 16 mg (n=213) after a 4-week placebo run-in period. Changes in exercise time, Dyspnea Fatigue Index score, NYHA functional class, and cardiothoracic ratio were determined. Candesartan cilexetil produced a dose-related improvement in exercise time. For the intention-to-treat population, the increase produced by candesartan cilexetil 16 mg was significantly greater than that produced by placebo (47.2 versus 30.8 seconds, \( P=0.0463 \)). All doses of candesartan cilexetil significantly improved the Dyspnea Fatigue Index score relative to placebo. NYHA class improved more frequently in the candesartan cilexetil groups; the differences relative to placebo were not significant. The decrease in cardiothoracic ratio with candesartan 4 to 16 mg was small but statistically significant compared with placebo (all \( P<0.05 \)). In all candesartan cilexetil groups, plasma renin activity and angiotensin II levels increased from baseline and aldosterone levels decreased in the 8- and 16-mg treatment groups. Candesartan cilexetil was well tolerated at all doses.

Conclusions—In summary, treatment with candesartan cilexetil demonstrated significant improvements in exercise tolerance, cardiothoracic ratio, and symptoms and signs of CHF and was well tolerated. (Circulation. 1999;100:2224-2230.)

Key Words: heart failure • angiotensin • receptors • exercise

Congestive heart failure (CHF) is an increasingly common condition, estimated to affect 1% to 2% of the US population.\(^1\) CHF is a highly symptomatic condition associated with significant morbidity and mortality and has a profound economic impact on healthcare resources.

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The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of CHF. Block of the RAAS in CHF with ACE inhibitors can improve signs, symptoms, and survival in CHF patients.\(^2,3\) Although the precise mechanisms by which these agents decrease morbidity and mortality are uncertain, their beneficial effects on symptoms are at least partly attributable to their hemodynamic effects.\(^4\) Although ACE inhibitors are clinically beneficial in CHF, there is increasing evidence that as the disease progresses the RAAS can “escape” the effects of ACE inhibition, partly because of the existence of ACE-independent pathways for the generation of angiotensin II (AngII).\(^5\)

Recent evidence indicates that AngII receptor antagonists can be beneficial in the management of CHF.\(^6\) This multicenter, double-blind, parallel-group study investigated the effects of candesartan cilexetil, a novel, long-acting AngII type 1 (AT\(_1\)) receptor antagonist,\(^7\) on exercise time and signs and symptoms in patients with CHF.

Methods

Study Population

Male and female patients 21 to 80 years of age with mild to moderate symptomatic CHF (NYHA class II or III) were enrolled. Patients

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From the Department of Internal Medicine II, University of Regensburg, Regensburg, Germany (G.A.J.R.); private practice, Munich, Germany (H.B.); Interne Oddeleni, Klinike Farmakologie, Ceske Budejovice, Czech Republic (P.P.); Interne Oddeleni, Nemocnice Milosrdnych (J.M.), and Interni Klinik, Fakultni Nemocnice Krakovsko Vinohrady (R.S.), Prague, Czech Republic; private practice, Kleve, Germany (H.P.); private practice, Wiesbaden, Germany (V.v.B.); Takeda Eureka R&D Centre Ltd, London, UK (M.G.); and Takeda Euro R&D GmbH, Frankfurt/Main, Germany (H.-J.A.).

Correspondence to Professor G.A.J. Riegger, Department of Internal Medicine II, University of Regensburg, Franz-Josef-Strauß-Allee 11, D-93053 Regensburg, Germany.

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were eligible for inclusion if they had impaired left ventricular function (ejection fraction, 30% to 45%) confirmed by echocardiography, ventriculography, or scintigraphy. The study was conducted according to the Declaration of Helsinki, the European Guidelines on Good Clinical Practice, and relevant national and regional authority requirements and ethics committees. Patients were excluded from the study for the following reasons: severe or malignant hypertension; symptomatic hypotension; myocardial infarction within 3 months of the trial; hemodynamically relevant arrhythmias and the use of pacemakers or implanted cardioverters; hemodynamically relevant valvular defect or insufficiency; angina pectoris; clinically significant disease; autoimmune or wasting disease; psychological illness; drug or alcohol addiction; type 1 diabetes mellitus; uncontrolled diabetes mellitus or diabetes requiring insulin therapy; and limitation of exercise capacity for a reason other than CHF. Pregnant or lactating women, patients unable or unwilling to comply with the study protocol, those participating in another clinical trial within 1 month of study enrollment, and those requiring concomitant β-blockers were excluded.

**Study Design**

In this phase 2, double-blind, prospective, randomized, placebo-controlled, multicenter, parallel-group study, eligible patients underwent a 4-week placebo run-in period during which patients were stabilized on optimal therapy with diuretics, cardiac glycosides, and long-acting nitrates (Figure 1). Patients receiving prior ACE inhibitor therapy underwent an initial 2-week washout before the placebo run-in period during which patients were kept constant throughout the treatment period. Nitrates were not to be taken on visit days before ergometry testing. Concomitant therapy with cardiac glycosides, long-acting nitrates, or diuretics was kept constant throughout the treatment period. Nitrates were not to be taken on visit days before ergometry testing. Treatment with antihypertensive, other agents causing systemic vasodilation or vasoconstriction, nonsteroidal anti-inflammatory drugs, antiarrhythmics, immunosuppressive or cytotoxic agents, insulin, or any drug altering gastrointestinal absorption was not permitted.

Patients could withdraw from the study at any time at their own request, at the discretion of the investigator, if adverse events required discontinuation, or if an exclusion criterion occurred.

**Efficacy Assessment**

The primary efficacy parameter was total exercise time at study end point determined by bicycle ergometry. Ergometry tests were performed ≥2 times during placebo run-in and twice during the randomized treatment period (Figure 1). During ergometry testing, patients cycled in the upright position starting with a workload of 25 W. The workload was increased in 25-W steps every 2 minutes until the patient was unable to continue because of dyspnea or fatigue. A 12-lead ECG was recorded during the last 10 seconds of each minute of exercise and 1, 3, and 5 minutes after exercise testing. Secondary efficacy variables included signs and symptoms of CHF, NYHA functional class, cardiothoracic ratio, and neuroendocrine parameters.

NYHA functional class was rated after the placebo run-in period and after 6 and 12 weeks of randomized treatment. At the same time points, patients’ signs and symptoms of CHF were assessed with the Dyspnea Fatigue Index score, which measured impairment of normal daily activities using the parameters “functional impairment,” “magnitude of task,” and “magnitude of effort” and yielded a total score of between 0 and 12. Patients rated their dyspnea 3 minutes after each exercise test using a 10-cm visual analog scale (VAS; 0 cm indicates no dyspnea, 10 cm, severe dyspnea).

Cardiothoracic ratio was assessed from chest x-rays performed after the placebo run-in and treatment periods. Blood samples were taken after the placebo run-in and after 6 and 12 weeks of randomized treatment for determination of aldosterone. AngII levels, plasma renin activity, adrenaline, and noradrenaline. Postbaseline blood sampling for neuroendocrine parameters took place at trough and peak serum concentrations in subjects in the supine position.

**Tolerability**

All adverse events were recorded regardless of their relationship to study medication and their intensity was rated as mild, moderate, or severe. Blood pressure and heart rate were recorded at each visit, and 12-lead ECGs were recorded at enrollment, after the washout and placebo run-in periods, and at weeks 1, 6, and 12 of randomized treatment. Laboratory safety parameters were assessed at study enrollment, after the placebo run-in, and after 6 and 12 weeks of randomized treatment.

**Statistical Analysis**

The intention-to-treat (ITT) population was defined as all randomized patients with bicycle ergometry data available at baseline and after 6 and/or 12 weeks of double-blind treatment. For patients who dropped out during the treatment period, the last available value after randomization was used, and those who had no exercise time measurement after randomization were excluded from this analysis. The per-protocol (PP) population included all patients in the ITT group with no major protocol violations. All patients who took ≥1 dose of randomized medication were included in the safety analysis.

On the basis of previous findings, sample size was calculated according to the expectation that the total exercise time with candesartan cilexetil would increase by ≥45 seconds compared with placebo. Assuming a type I error of α=0.05, a type II error of β=0.1, a treatment difference of 45 seconds, and an SD of 120 seconds, the number of evaluable patients required per treatment group was 151 (2-sided t test). With a dropout rate of ~25% assumed, ~850 patients were required.

Treatment groups were compared using ANCOVA with the factor treatment and the covariates total exercise time at baseline, use of cardiac glycosides and diuretics, age, and sex. The effect of each
Results

We enrolled 926 patients in 86 centers in Germany, the Czech Republic, and Slovenia. Of these, 513 patients (59%) had previously received ACE inhibitors and started the 2-week washout phase. Eighty-two patients discontinued the study during the washout or placebo run-in period, mainly because dyspnea, influenzalike symptoms, or peripheral edema. Thus, 844 evaluable patients (safety population) were randomized to treatment with placebo (n=211) or candesartan cilexetil 4 mg (n=208), 8 mg (n=212), or 16 mg (n=213). Of these patients, 55 discontinued the trial early for the following reasons: adverse events (n=29), patient’s request (n=11), occurrence of exclusion criteria (n=8), noncompliance (n=1), and other unspecified reasons (n=6). The number of patients withdrawing from treatment was lowest in the candesartan cilexetil 4 mg group (n=7) but was similar across other treatment groups (n=12 to 19). There were no marked between-group differences in the reasons for discontinuation.

The demographic and baseline characteristics of the safety population were similar across groups (Table 1). There was a greater proportion of male (68.4%) than female (31.6%) patients, and except for 2 Oriental patients, all were Caucasian. In the safety population, 739 patients (87.6%) had been treated for CHF in the 3 months before the trial. The most frequently prescribed agents were cardiac drugs (62.1% of patients) with cardiac glycosides (42.4%), vasodilators (31.5%), ACE inhibitors (59.0%), and diuretics (54.7%). There were no differences between groups with regard to the types of previous treatment received.

All but 1 patient had concomitant diseases, most commonly chronic ischemic heart disease (73.1%), lipid metabolism disorders (37.8%), essential hypertension (37.2%), and diabetes mellitus (22.3%). There were no clinically relevant differences between groups with respect to concomitant diseases. A total of 819 patients (97.0%) received concomitant treatment during the study (Table 2).

Of those randomized to double-blind treatment, 37 (4.4%) were ineligible for efficacy analysis because valid bicycle ergometry data, either at baseline or during treatment, were lacking. Of those in the ITT population (n=807), 161 patients (20.0%) had ≥1 major protocol violation, most frequently for taking prohibited concomitant medication or failure to take study medication between 7 and 9 AM. Thus, 629 patients were included in the PP analysis. The demographic characteristics of the ITT and PP populations were similar to those of the safety population.
Analysis of Efficacy: Exercise Time

Baseline values for total exercise time were similar across groups (Table 1). Increases in total exercise time from baseline to study end point with candesartan cilexetil were dose related (Figure 2); the difference from placebo reached statistical significance (ITT population) for candesartan cilexetil 16 mg ($P=0.046$) and approached significance for candesartan cilexetil 8 mg ($P=0.069$). For the PP population, the effects of candesartan cilexetil were more marked, with changes with both candesartan cilexetil 8 and 16 mg being significantly greater than with placebo ($P=0.027$ and $P=0.019$, respectively; Figure 3). After 6 weeks of treatment, increases in exercise time were observed in all treatment groups, with changes for candesartan cilexetil groups being greater than for the placebo group. These changes were not statistically significant.

Assessment of Dyspnea and Fatigue

In the ITT population, all candesartan cilexetil groups experienced a significant improvement in Dyspnea Fatigue Index scores (1.0±1.4, 1.0±1.4, and 1.0±1.4 for 4-, 8-, and 16-mg groups, respectively) compared with placebo (0.5±1.2; all $P<0.001$). Similar results were obtained for the PP population ($P<0.002$).

Subjective assessment of dyspnea after bicycle ergometry with the use of a VAS showed that dyspnea decreased over

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**TABLE 2. Concomitant Medications at Baseline (Visit 5) of the Safety Population**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=211)</th>
<th>4 mg (n=208)</th>
<th>8 mg (n=212)</th>
<th>16 mg (n=213)</th>
<th>Total (n=844)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac therapy</strong></td>
<td>133 (63.0)</td>
<td>137 (65.9)</td>
<td>140 (66.0)</td>
<td>149 (70.0)</td>
<td>559 (66.2)</td>
</tr>
<tr>
<td><strong>Cardiac glycosides</strong></td>
<td>82 (38.9)</td>
<td>83 (39.9)</td>
<td>91 (42.9)</td>
<td>90 (42.3)</td>
<td>346 (41.0)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>123 (58.3)</td>
<td>126 (60.6)</td>
<td>133 (62.7)</td>
<td>123 (57.7)</td>
<td>505 (59.8)</td>
</tr>
<tr>
<td><strong>Diuretics and potassium-sparing agents in combination</strong></td>
<td>27 (12.8)</td>
<td>32 (15.4)</td>
<td>36 (17.0)</td>
<td>28 (13.1)</td>
<td>123 (14.6)</td>
</tr>
<tr>
<td><strong>Potassium-sparing agents</strong></td>
<td>0 (0.0)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong>*</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td>5 (2.4)</td>
<td>4 (1.9)</td>
<td>5 (2.4)</td>
<td>4 (1.9)</td>
<td>18 (2.1)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong>*</td>
<td>107 (50.7)</td>
<td>96 (46.2)</td>
<td>102 (48.1)</td>
<td>108 (50.7)</td>
<td>413 (48.9)</td>
</tr>
<tr>
<td><strong>Serum lipid-reducing agents</strong></td>
<td>51 (24.2)</td>
<td>38 (18.3)</td>
<td>49 (23.1)</td>
<td>48 (22.5)</td>
<td>186 (22.0)</td>
</tr>
<tr>
<td><strong>Mineral supplements</strong></td>
<td>26 (12.3)</td>
<td>27 (13.0)</td>
<td>27 (12.7)</td>
<td>23 (10.8)</td>
<td>103 (12.2)</td>
</tr>
<tr>
<td><strong>Diuretics and potassium-sparing agents in combination</strong></td>
<td>27 (12.8)</td>
<td>32 (15.4)</td>
<td>36 (17.0)</td>
<td>28 (13.1)</td>
<td>123 (14.6)</td>
</tr>
<tr>
<td><strong>Potassium-sparing agents</strong></td>
<td>0 (0.0)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>5 (2.4)</td>
<td>4 (1.9)</td>
<td>5 (2.4)</td>
<td>4 (1.9)</td>
<td>18 (2.1)</td>
</tr>
</tbody>
</table>

Values are n (%).

*Not permitted concomitant medication.

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Figure 2. Mean change from baseline to last value in total exercise time (bicycle ergometry) among patients with CHF treated with placebo or candesartan cilexetil 4 to 16 mg for ≥12 weeks (ITT population, n=807). *P<0.05 vs placebo.

Figure 3. Mean change from baseline to last value in total exercise time (bicycle ergometry) among patients with CHF treated with placebo or candesartan cilexetil 4 to 16 mg for ≥12 weeks (PP population, n=629). *P<0.05 vs placebo.
the course of the study in both ITT and PP populations. The largest mean reduction in VAS score from baseline to last value occurred in the 16-mg group (−9.5 versus −6.5 mm for placebo), but differences were not statistically significant.

### NYHA Functional Class

NYHA functional class improved more frequently in those groups treated with candesartan cilexetil than placebo (Table 3). Results for ITT and PP populations were comparable, although differences relative to placebo did not reach statistical significance.

### Cardiothoracic Ratio

Although the changes in cardiothoracic ratio were small in absolute terms, in the ITT population, the decrease relative to placebo was statistically significant for all doses of candesartan cilexetil (−0.013, −0.006, and −0.013 for 4, 8, and 16 mg, respectively, versus no change with placebo; P<0.05). In the PP population, improvements in cardiothoracic ratio were significantly greater than for placebo in the groups receiving candesartan cilexetil 4 and 16 mg.

### Neuroendocrine Parameters

Neuroendocrine parameters were assessed in a subpopulation of 467 patients before and 3.75 hours after drug intake (Figure 4). Adrenaline and noradrenaline levels were unchanged throughout the study. Aldosterone serum levels were unchanged in the placebo and 4-mg groups but decreased slightly from baseline with both 8 and 16 mg. Plasma renin activity and AngII serum levels increased from baseline for all candesartan groups but were unchanged in the placebo group. Increases in both plasma renin activity and serum AngII levels tended to be dose related and were particularly pronounced at the time of peak candesartan serum levels.

### Tolerability

During double-blind treatment, 480 adverse events were reported by 280 patients (33.2%). Of these, 281 adverse events were considered at least possibly related to treatment and were predominantly mild to moderate in intensity. The incidence of adverse events and the proportion of patients reporting events were similar across all treatment groups (Table 4). Fifteen patients experienced adverse events (dizziness, orthostatic vertigo) possibly related to symptomatic hypotension. For all groups, the incidence was very low (placebo, 1.9%; 4 mg, 1.5%; 8 mg, 2.8%; 16 mg, 0.5%); none were regarded as serious, and treatment was discontinued prematurely in only 2 patients.

A total of 35 patients withdrew as a result of adverse events. The withdrawal rate was lowest in the 4-mg group (placebo, 4.3%; 4 mg, 1.9%; 8 mg, 4.7%; 16 mg, 5.6%).

A total of 40 serious adverse events were reported by 37 patients. The incidence of serious adverse events was lower with candesartan cilexetil 4 mg (1.4%) than with placebo (4.7%) or candesartan cilexetil 8 mg (5.7%) or 16 mg (5.6%), but differences between groups were not statistically significant. There were a total of 11 deaths. Except for 2 deaths in the 16-mg group (1 caused by pancreatic carcinoma and another by pulmonary embolism in a man with severe dilated cardiomyopathy who had taken study medication for 2 days), all were cardiac in origin (exacerbation of heart failure, sudden death, or myocardial infarction). Of these, 1 death occurred in the placebo group, 1 in the 4-mg group, 4 in the 8-mg group, and 3 in the 16-mg group.

No clinically relevant changes in laboratory safety parameters were observed, although a trend to lower hematocrit, hemoglobin, and erythrocyte values was obtained in the candesartan groups. There was a small decrease in blood pressure and heart rate among active treatment groups, but effects were not dose related (Table 5).

### Discussion

Increasing evidence highlights the crucial role of the neuroendocrine axis in the pathophysiology and prognosis of heart failure,11,12 particularly the role of the RAAS. Despite the benefits of ACE inhibitor therapy, CHF remains a progressive and highly symptomatic condition with high morbidity and mortality. RAAS activation is a marked feature of CHF,13 becoming an increasingly maladaptive phenomenon as CHF progresses. There is accumulating evidence that despite suppression by ACE inhibitors, breakthrough of the RAAS can occur.14,15 AngII antagonists specifically block the deleterious effects of AngII at the AT1 receptor in target organ tissues and are effective regardless of the pathway of AngII generation. Furthermore, stimulation of the AT2 receptor may increase the effects seen after blocking AT1 receptors, because activation of the AT2 receptor antagonizes the effects of the activated AT1 receptor.16

Until data of outcome trials become available, clinical data on the effects of AngII receptor antagonists on the signs and symptoms of CHF are essential to optimize therapeutic strategies to improve management of patients of those highly symptomatic conditions. This study is the first to provide clear evidence of both symptomatic and exercise tolerance improvement with an AngII receptor antagonist in patients with CHF. Treatment with candesartan cilexetil significantly increased exercise time and significantly improved both the Dyspnea Fatigue Index score and cardiothoracic ratio relative to placebo. A dose-related effect on exercise time was evident with candesartan cilexetil 4 to 16 mg once daily. The Dyspnea Fatigue Index score and cardiothoracic ratio were significantly improved for all doses of candesartan cilexetil, despite concurrent increases in exercise time.

The increase in plasma renin and AngII levels and decrease in aldosterone observed with candesartan cilexetil are consistent with its known pharmacological effects. Reduced aldo-
Figure 4. Mean ± 2 SEM values for neuroendocrine parameters before (trough) and 3.75 hours after (peak) drug intake in patients with neuroendocrine status (n = 467).
Candesartan cilexetil was well tolerated, and withdrawal rates because of adverse events were low in all treatment groups. The incidence and profile of adverse events were similar with all doses of candesartan cilexetil and placebo and were similar to those reported with the use of candesartan cilexetil in hypertension. Several cases of increases in blood urea nitrogen and nonprotein nitrogen were reported in each treatment group, but this was not dose dependent and could be expected to occur in some CHF patients regardless of the type of therapy. Hypokalemia was reported more often with placebo than with other treatments and was probably related to the use of diuretics. The potassium-sparing effect of candesartan cilexetil may have afforded some protection.

Although the trial was not designed to investigate morbidity or mortality, data on clinical outcome were collected as part of the safety analysis. The mortality rate was very low, compares favorably with reports in the literature, and was within the range reported with ACE inhibitors.

In summary, candesartan cilexetil significantly improved the signs and symptoms of CHF, with dose-dependent improvements in exercise time. Candesartan cilexetil was well tolerated; there were no excess of reports of hypotension and no increase in heart rate. The observed incidence and profile of adverse events were similar to those with placebo.

### Table 4. Adverse Events With an Onset During the Double-Blind Treatment Period Reported by >2% of Patients in ≥1 Treatment Group for the Safety Population

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=211)</th>
<th>4 mg (n=208)</th>
<th>8 mg (n=212)</th>
<th>16 mg (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>4 (1.9)</td>
<td>6 (2.9)</td>
<td>3 (1.4)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Increase in serum creatinine</td>
<td>4 (1.9)</td>
<td>6 (2.9)</td>
<td>9 (4.2)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Increase in BUN</td>
<td>2 (0.9)</td>
<td>7 (3.4)</td>
<td>2 (0.9)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (2.8)</td>
<td>4 (1.9)</td>
<td>3 (1.4)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7 (3.3)</td>
<td>1 (0.5)</td>
<td>3 (1.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (2.4)</td>
<td>1 (0.5)</td>
<td>4 (1.9)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (0.5)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
<td>5 (2.3)</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen. n=844. Values are n (%).

### Table 5. Mean Change From Baseline to Last Value in Systolic and Diastolic Blood Pressures and Heart Rate for the Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=211)</th>
<th>4 mg (n=208)</th>
<th>8 mg (n=212)</th>
<th>16 mg (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>-1.2±12.8</td>
<td>-5.3±13.3</td>
<td>-4.6±14.3</td>
<td>-5.1±13.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.0±7.5</td>
<td>-2.9±7.4</td>
<td>-2.5±8.2</td>
<td>-2.6±8.1</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>0.5±10.9</td>
<td>-1.3±10.2</td>
<td>-1.2±10.6</td>
<td>-0.3±10.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. n=844.

References

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for the Symptom Tolerability Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators

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