Hemodynamic and Neurohumoral Effects of Selective Endothelin A (ET\textsubscript{A}) Receptor Blockade in Chronic Heart Failure

The Heart Failure ET\textsubscript{A} Receptor Blockade Trial (HEAT)

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Background—The endothelin (ET-1) system is activated in chronic heart failure (CHF). Whether, what type, and what degree of selective ET blockade is clinically beneficial is unknown. We investigated hemodynamic and neurohumoral effects of 3 weeks of treatment with various dosages of the orally available ET\textsubscript{A} antagonist darusentan in addition to modern standard therapy in patients with CHF.

Methods and Results—A total of 157 patients with CHF (present or recent NYHA class III of at least 3 months duration), pulmonary capillary wedge pressure $\geq 12$ mm Hg, and a cardiac index $\leq 2.6$ L · min$^{-1}$ · m$^{-2}$ were randomly assigned to double-blind treatment with placebo or darusentan (30, 100, or 300 mg/d) in addition to standard therapy. Short-term administration of darusentan increased the cardiac index, but this did not reach statistical significance compared with placebo. The increase in cardiac index was significantly more pronounced after 3 weeks of treatment ($P<0.0001$ versus placebo). Pulmonary capillary wedge pressure, pulmonary arterial pressure, pulmonary vascular resistance, and right atrial pressure remained unchanged. Heart rate, mean artery pressure, and plasma catecholamines remained unaltered, but systemic vascular resistance decreased significantly ($P=0.0001$). Higher dosages were associated with a trend to more adverse events (including death), particularly early exacerbation of CHF without further benefit on hemodynamics compared with moderate dosages.

Conclusions—This study demonstrates for the first time in a large patient population that 3 weeks of selective ET\textsubscript{A} receptor blockade improves cardiac index in patients with CHF. However, long-term studies are needed to determine whether ET\textsubscript{A} blockade is beneficial in CHF. (Circulation. 2002;106:2666-2672.)

Key Words: endothelin  heart failure  hemodynamics

The endothelium produces endothelin (ET-1), nitric oxide, and prostacyclin and thereby plays a fundamental role in the regulation of vascular tone and structure.\textsuperscript{1,2} ET\textsubscript{A} and ET\textsubscript{B} receptors mediate the vasoconstrictor effects of ET-1.\textsuperscript{3} ET-1 also induces the proliferation of vascular and myocardial hypertrophy.\textsuperscript{4} In contrast, endothelial ET\textsubscript{B} receptors cause vasodilatation via nitric oxide and/or prostacyclin, which exert antithrombotic and antiproliferative effects.\textsuperscript{5} Further, pulmonary ET\textsubscript{B} receptors are important for the clearance of ET-1.\textsuperscript{6}

Apart from activating the sympathetic nervous and renin-angiotensin systems,\textsuperscript{7} increased ET-1 production contributes to neurohormonal activation in chronic heart failure (CHF). Indeed, plasma levels of ET-1 and of its precursor big ET-1 are elevated and strong independent predictors of death in CHF.\textsuperscript{8,9}

ET receptor antagonists might be useful in the treatment of CHF. ET\textsubscript{A} and ET\textsubscript{A/B} receptor antagonists have demonstrated beneficial effects on endothelial dysfunction,\textsuperscript{10} cardiovascular remodeling,\textsuperscript{11,12} and survival.\textsuperscript{12,13} Early use of ET receptor blockade after myocardial infarction may cause adverse left ventricular remodeling, but it improves pulmonary artery pressure after infarction in the rat.\textsuperscript{14} In patients with CHF, nonselective ET\textsubscript{A/B} blockade improves pulmonary and systemic hemodynamics and potentially exerts beneficial clinical effects long-term.\textsuperscript{15,16} Although an increasing body of evidence suggests beneficial effects of selective ET\textsubscript{A} antagonists...
in heart failure, it remains controversial whether nonselective ET$_{A/B}$ antagonists or selective ET$_A$ antagonists should be used. The hemodynamic effects of a single oral dose of darusentan (1, 10, 30, 100, or 300 mg) were recently investigated in a multicenter study involving 95 patients with CHF (NYHA functional class II or III). In this study, a single oral dose of darusentan improved hemodynamics in a dose-dependent manner without activation of other neurohumoral systems. Therefore, we investigated the hemodynamic and neurohumoral effects of 3 weeks of treatment with darusentan, a selective ET$_A$ antagonist, in patients with CHF.

**Methods**

**Study Population**

Between October 1998 and July 1999, 179 patients with CHF of any underlying cause (except primary organic valvular heart disease) were recruited at 12 medical centers in Europe (see Appendix). Each patient gave written informed consent, and this study was approved by the ethics committees of each of the participating centers. Only patients with an ejection fraction $\geq 35\%$ by echocardiography or isotope ventriculography were included. Inclusion criteria consisted of clinical signs of CHF of at least 3 months duration and recent or recent history of NYHA functional class III, pulmonary capillary wedge pressure of $\geq 12$ mm Hg, and a cardiac index $\geq 2.6$ L $\cdot$ min$^{-1}$ $\cdot$ m$^{-2}$. Exclusion criteria were acute heart failure, sustained or symptomatic systemic hypotension (systolic blood pressure $\leq 90$ mm Hg), acute myocardial infarction within the last 3 months before study enrollment, unstable angina pectoris, primary valvular heart disease, pacemaker rhythm, stroke within the last 6 months, introduction of $\beta$-blocker therapy within the last 3 months, pregnancy or lactation, liver disease, renal failure (creatinine $>110$ mmol/L), recent history of NYHA functional class III, pulmonary capillary wedge pressure of $\geq 12$ mm Hg, and a cardiac index $\geq 2.6$ L $\cdot$ min$^{-1}$ $\cdot$ m$^{-2}$. Exclusion criteria were acute heart failure, sustained or symptomatic systemic hypotension (systolic blood pressure $\leq 90$ mm Hg), acute myocardial infarction within the last 3 months before study enrollment, unstable angina pectoris, primary valvular heart disease, pacemaker rhythm, stroke within the last 6 months, introduction of $\beta$-blocker therapy within the last 3 months, pregnancy or lactation, liver disease, renal failure (creatinine $>220$ mmol/L), and exposure to any investigational drug during the last month.

**Study End Points**

The prespecified primary end point was the change from baseline of cardiac index and wedge pressure 3 weeks after start of therapy.

**Experimental Protocol**

Seven visits were scheduled during the study period. After a preinvestigational eligibility check, the individual study course consisted of 2 periods, a 3-week double-blind dosing period and a 1-week double-blind follow-up period. Patients continued their usual medications unchanged during the entire study period, except for the morning of the baseline and the final visit. Different doses of darusentan (30, 100, and 300 mg once daily; LU 135252, Knoll, Ludwigshafen, Germany) and placebo were studied in different patient groups. After clinical examination and recording of a 12-lead ECG, a Swan-Ganz catheter was placed. During a 30-minute period of supine rest, blood samples were drawn to determine laboratory parameters for darusentan and neurohormones. Afterward, hemodynamic baseline measurements were determined at trough levels of routine medication. If patients met the hemodynamic selection criteria, they were asked to take their routine medication. Two hours later, a second measurement of hemodynamic parameters took place; this occurred at the anticipated peak levels of the drugs. Directly thereafter, darusentan or placebo was administered orally with 200 mL of water. Hemodynamic measurements were repeated 60, 120, 180, and 240 minutes after oral administration of the drug or placebo. ECG monitoring was performed throughout the entire investigational period. Four hours after administration of darusentan, the Swan-Ganz catheter was removed. For safety reasons, patients spent the following 2 hours in the hospital.

For safety reasons, the first visit was scheduled on day 3; this was followed by 3 other visits at weekly intervals after the baseline visit until the end of dosing. After 3 weeks of treatment, hemodynamics were determined as described above. On day 28, patients were assessed for adverse events.

**Hemodynamic Measurements**

Cardiac output (average of at least 3 measurements) was determined by thermodilution with a Swan-Ganz catheter inserted through a sheath introducer system in a jugular or cubital vein and propagated to the pulmonary artery. Mean right atrial, systemic, and pulmonary artery pressure and pulmonary capillary wedge pressure were measured. Cardiac index and systemic and pulmonary vascular resistance were calculated. Heart rate was obtained from the ECG. The hemodynamic analyses focused on the comparison of the trough values (values assessed before intake of standard and study medication) at visits 2 and 6.

**Adverse Events**

An adverse event was defined as any event during the study, including intercurrent illness or accident, that impairs the well-being of the patient. The adverse event of worsening heart failure was defined as symptoms, signs, or findings that are regularly associated with chronic heart failure (ie, edema, dyspnea, or weight gain).

**Blood Sample Measurements**

Blood samples were drawn at baseline and 120 minutes after administration of standard medication. Plasma, obtained by centrifugation, was stored at $-170^\circ$C until analysis. Plasma levels of ET-1 and catecholamines were assayed using a methodology described previously. The hemodynamic analyses focused on the comparison of the trough values (values assessed before intake of standard and study medication) at visit 2 and visit 6. The population of interest for the hemodynamic analysis is the patients who did not have a serious adverse event leading to discontinuation of treatment (n=143). Changes from visit 2 to visit 6 for each time point were analyzed using an ANOVA with repeated measurements. When a significant result was found, we applied unpaired t tests with a Bonferroni correction as post hoc tests (to detect which of the darusentan groups differed from placebo). Changes from the visit-specific trough values were analyzed using a classic ANOVA to test for differences between the 4 groups (active treatment was compared with placebo). Again, unpaired t tests with a Bonferroni correction were applied as post hoc tests. For the statistical analysis of adverse events, we used the data of all patients who received darusentan or placebo (n=157). Statistical analysis of the adverse events was done using the $\chi^2$ test. For the adverse events, we compared active treatment versus placebo. Throughout the study, $P<0.05$ was considered significant.

**Results**

**Patient Characteristics and Medication**

Baseline demographics (Table 1) and concomitant cardiovascular medication were similar among groups. All patients were on ACE inhibitors or angiotensin II antagonists, 70% were on diuretics, 65% were on digitalis glycosides, 65%
were on nitrates, 46% were on oral anticoagulation, 46% were on β-blockers, 11% were on platelet aggregation inhibitors without heparin, 25% were on statins, 25% were on amiodarone, 24% were on aldosterone antagonists, and 5% were on calcium-channel blockers.

A total of 179 patients were enrolled at 12 centers. Twenty-two patients discontinued the study before randomization (21 did not meet hemodynamic inclusion criteria; 1 patient withdrew because of administrative reasons) and were not included in the hemodynamic analysis. All of the 157 randomized patients received double-blind study medication. A total of 14 patients did not complete the protocol; 3 patients withdrew consent, and the other 11 did not complete the study because of adverse events (Table 2).

### Hemodynamic Effects

In addition to standard therapy, short-term administration of darusentan increased cardiac index by 1.3%, 7.9%, and 12.6% after 30, 100, and 300 mg of darusentan, respectively, which was not significant when compared with placebo (Figure, A). The improvement of cardiac index was significantly more pronounced after 3 weeks of treatment compared with placebo ($P<0.0001$; Figure, A).

Pulmonary capillary wedge pressure (Figure, B; $P=0.35$ versus placebo), mean pulmonary arterial pressure (Figure, C; $P=0.48$ versus placebo), pulmonary vascular resistance (Figure, D; $P=0.32$ versus placebo), right atrial pressure (Figure, E; $P=0.052$ versus placebo), heart rate (Figure, G; $P=0.27$ versus placebo), and mean arterial pressure (Figure, H; $P=0.08$ versus placebo) were significantly reduced by darusentan compared with placebo ($P=0.052$ versus placebo).

### Table 1. Main Baseline Demographic and NYHA Functional Class of the Study Patients (n=143)

<table>
<thead>
<tr>
<th>Description of event</th>
<th>Placebo (n=33)</th>
<th>30 mg of Darusentan (n=36)</th>
<th>100 mg of Darusentan (n=39)</th>
<th>300 mg of Darusentan (n=49)</th>
<th>All Darusentan (n=124)</th>
<th>$P$ (All Darusentan vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Sex, male/female</td>
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<tr>
<td>Weight, kg</td>
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<td>Height, m</td>
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<td>Body mass index, kg/m²</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>NYHA functional class, n</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>II</td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
<td>7 (17.9)</td>
<td>14 (28.6)</td>
<td>21 (16.9)*</td>
<td>0.04</td>
</tr>
<tr>
<td>III</td>
<td>136 (99.3)</td>
<td>31 (86.1)</td>
<td>34 (87.2)</td>
<td>32 (84.2)</td>
<td>39 (96.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>IV</td>
<td>3 (2.3)</td>
<td>1 (2.8)</td>
<td>0 (0.0)</td>
<td>2 (4.1)</td>
<td>3 (2.4)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values are n (%) of patients experiencing at least one adverse event (n=157). $^*$P<0.05. $^*$P values are given for all darusentan vs placebo.

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### Table 2. Frequently Reported Adverse Events

<table>
<thead>
<tr>
<th>Description of event</th>
<th>Placebo (n=33)</th>
<th>30 mg of Darusentan (n=36)</th>
<th>100 mg of Darusentan (n=39)</th>
<th>300 mg of Darusentan (n=49)</th>
<th>All Darusentan (n=124)</th>
<th>$P$ (All Darusentan vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>7 (17.9)</td>
<td>14 (28.6)</td>
<td>21 (16.9)*</td>
<td>0.04</td>
</tr>
<tr>
<td>Flushing</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td>3 (7.7)</td>
<td>5 (10.2)</td>
<td>9 (7.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (5.1)</td>
<td>4 (8.2)</td>
<td>6 (4.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>4 (12.1)</td>
<td>5 (13.9)</td>
<td>6 (15.4)</td>
<td>18 (36.7)</td>
<td>29 (23.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (5.1)†</td>
<td>2 (4.1)†</td>
<td>3 (2.4)†</td>
<td>0.30</td>
</tr>
<tr>
<td>Discontinuation due to serious adverse event</td>
<td>1 (3.0)§</td>
<td>1 (2.8)§</td>
<td>2 (5.1)§</td>
<td>4 (8.2)§</td>
<td>6 (4.8)§</td>
<td>0.09</td>
</tr>
<tr>
<td>Discontinuation (withdrawal of consent)</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td>0 (0.0)</td>
<td>2 (4.1)</td>
<td>3 (2.4)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Values are n (%) of patients experiencing at least one adverse event (n=157). $^*$P<0.05. $^*$P values are given for all darusentan vs placebo.

†One patient with dilated cardiomyopathy who was on the waiting list for heart transplantation died of unexplained sudden death 4 days after first intake of study medication; the other patient, who had coronary artery disease and coronary artery bypass grafting, died of unexplained sudden death after 6 days on study medication.

‡One patient with coronary artery disease died of cardiogenic shock after 6 days on study medication; the other patient, who had dilated cardiomyopathy, died of ventricular fibrillation after 7 days on study medication.

§Patient with worsening heart failure.

¶Patient with myocardial infarction.

‖Patient with worsening heart failure.

#One patient with heart transplantation (already on waiting list before entry in the study), one patient with angina pectoris, and 2 patients with worsening heart failure vs placebo.
Hemodynamic variables at each time point during acute treatment and after 3 weeks of treatment with darusentan at different dosages compared with placebo. Values are mean±SEM. Solid arrow indicates administration of standard medications at time point 0; dotted arrow, administration of study drug at 2 hours.
Headache was the most frequent adverse event, was reported in 3% of the patients in receiving the higher dosages of darusentan, thus indicating a difference in frequency between the placebo group and the darusentan groups (P=0.04 versus placebo; Table 2). However, these events did not differ statistically between darusentan versus placebo (P=0.40 for all darusentan versus placebo). The statistical analyses for the combination of worsening heart failure and death did not show a significant difference between the placebo group and the darusentan groups (P=0.17 for all darusentan versus placebo).

Four fatal adverse events (2 each in the 100 mg and 300 mg groups) occurred; two were unexplained sudden death, and the others were cardiogenic shock and ventricular fibrillation (Table 2). However, these events did not differ statistically between the placebo group and the darusentan groups (P=0.3 versus placebo). Symptomatic hypotension was reported in the higher dosage groups (2 in the 100 mg and 4 in the 300 mg group each; P=NS versus placebo); the events did not lead to discontinuation of the drug. Similarly, asymptomatic bradycardia and first-degree atrioventricular block occurred in 2 patients in the 100 mg and 300 mg groups, respectively. Moderate, transient elevation of liver enzymes was observed in 2 patients in the placebo and 100 mg groups, respectively. The rates of other adverse events were similar among the groups.

### Parameters of Neurohormonal Activation

Treatment with different dosages of darusentan did not induce neurohormonal activation (Table 3). In particular, noradrenaline and natriuretic peptide levels did not change significantly, but ET-1 plasma levels increased after 3 weeks of treatment with darusentan.

### Plasma Levels of Darusentan

Plasma levels of darusentan increased dose-dependently after 3 weeks of treatment. Trough plasma levels at the final visit were 266±165 ng/mL (30 mg group), 854±1074 ng/mL (100 mg group) and 2303±2328 ng/mL (300 mg group).

### Discussion

This study demonstrates for the first time that 3 weeks of treatment with a selective ET_{A} receptor antagonist improves cardiac index and systemic vascular resistance in patients with CHF. Importantly, these favorable effects occurred in the absence of neurohormonal stimulation or increases of heart rate and were most pronounced at moderate doses.

ET-1 plasma levels are elevated in patients with CHF and correlate with hemodynamic compromise. As in previous studies with other ET-1 receptor antagonists, ET-1 plasma levels increased after the administration of darusentan, presumably because of the displacement of ET-1 from its receptors.
receptors. Most likely, however, ETs have a predominant paracrine action and are primarily released abluminally toward the medial layer of the vessel wall; thus plasma levels represent spill-over to the circulation and poorly reflect the activation of local ET-1 in disease states. The increase in ET-1 levels with higher dosages of darusentan may be explained by a reduced pulmonary clearance and reflect the lack of improvement in pulmonary hemodynamics and/or decreased clearance by nonselective blockade of ET_β receptors. Direct toxic effects of increased circulating ET, however, cannot be ruled out, but they seem less likely to be of pathophysiological importance in the presence of efficient ET receptor blockade.

Selective ET_A blockade with darusentan reduced systemic vascular resistance and caused a pronounced increase in cardiac output in the absence of an increase in heart rate. The neutral effect on pulmonary capillary wedge pressure is most likely because of the fact that this study evaluated hemodynamics in addition to standard medication (ie, all patients were on an ACE inhibitor and/or an angiotensin-II receptor antagonist and/or on diuretics). In addition, >40% were on β-blockers and/or an aldosterone receptor antagonist. Of note, in a study that investigated the short-term effects of darusentan in heart failure patients who did not take their standard medication on the day of the hemodynamic evaluation, darusentan lowered pulmonary capillary wedge pressure significantly. Short-term beneficial effects on hemodynamics, as seen in that study and in the present study, are shared by other ET antagonists, such as sitaxentan. Furthermore, the present study demonstrates, for the first time, beneficial effects after 3 weeks of selective ET_A receptor antagonism in CHF in addition to current standard therapy, including ACE inhibitors and/or angiotensin II antagonists, β-blockers, and aldosterone antagonists. Thus, ET antagonists may have a role in CHF in addition to the currently used drugs. However, there was no clear dose-dependency detectable. Indeed, the increase of cardiac index was more pronounced in patients receiving 100 mg than 30 mg of darusentan, but it did not differ between the highest dosage groups when compared with placebo. Importantly, the beneficial hemodynamic effects were not accompanied by an activation of the sympathetic nervous system; both plasma catecholamine levels and heart rate remained stable despite the marked hemodynamic effects.

The evaluation of drugs for the management of severe CHF has generally focused on measures of hemodynamic function in patients with a relatively stable clinical course. This approach is based on the assumption that hemodynamic improvements in such patients will translate into symptom relief. Favorable hemodynamic effects, however, may not necessarily be associated with improved prognosis in CHF.

The most common adverse effects, headache and worsening of heart failure, were more frequent in patients receiving the higher dosages. Indeed, headache, which usually was classified as mild, occurred in 17.9% and 28.6% of those receiving 100 mg or 300 mg of darusentan, respectively, but in none of the patients receiving 30 mg of darusentan. Importantly, 4 fatal adverse events (2 each in the 100 mg and 300 mg groups) occurred; 2 were unexplained sudden death, the others were cardiogenic shock and ventricular fibrillation, respectively. Although these events did not differ statistically between the placebo group and the darusentan groups, this may suggest a worrisome trend. The present study, however, included patients at high risk and was not designed to investigate mortality. Importantly, early exacerbation of heart failure was documented in 36.7% of the patients receiving 300 mg of darusentan, but in 12.1%, 13.9%, and 15.4% in the placebo, 30 mg, and 100 mg groups, respectively. Because initial worsening of heart failure was also observed in the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) and the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) trials (M. Packer, MD, unpublished data, 2002), a potential adverse effect of ET blockade on fluid and sodium retention may be implicated. Although a ceiling of benefit with neurohormonal blockade and too-pronounced blood pressure lowering effects may account for the observed incidence of adverse events in the REACH-1 and ENABLE studies, it is of note that blood pressure did not change significantly in the present study. By design, patients assigned to darusentan initially received the drug at the final dose without up-titration. Hence, large-scale clinical trials are needed to provide a definite answer on whether improvement in cardiac index and systemic vascular resistance after 3 weeks of treatment translates into long-term benefit in terms of morbidity and mortality in CHF. However, in these trials, low starting dosages with up-titration may, therefore, be required when starting ET antagonists in patients with CHF, particularly when compensatory mechanisms are blocked, as is the case in patients who are already receiving ACE inhibitors or β-blockers. In the still-ongoing Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH), darusentan was titrated upward over a 6-week period, starting at 10 or 25 mg/d to a maximum of 300 mg/d, with total treatment period being 24 weeks.

In summary, this study shows for the first time in a large patient population that the selective ET_A antagonist darusentan improves hemodynamics in patients with chronic CHF without neurohormonal stimulation and changes in heart rate. However, overall darusentan seemed to trend to an increased incidence of adverse events, particularly early exacerbation of heart failure, which was documented in 15.4% and 36.7% of the patients receiving 100 mg and 300 mg darusentan, respectively. As such, morbidity and mortality–based large-scale clinical trials, most likely using moderate dosages of the drug, will provide the answer to whether selective ET_A antagonists at low-to-medium dosages would be a valuable addition to the current treatment of patients with CHF.

Appendix

Participating Centers

Allgemeines Krankenhaus, Vienna, Austria (R. Pacher); Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark (C. Torp-Pedersen); Kerkhoff-Klinik GmbH, Bad Nauheim, Germany (V. Mitrovic); Herz- und Kreislaufforschungszentrum, Abteilung Kardiologie, Dresden, Germany (M. R. Schulze); Clinic of Cardiology, Clinical Hospital, Lodz, Poland (M.J. Kosmider); Clinic of Cardiology, Warsaw, Poland (W. Rzylko); Clinic of Cardiology, Silesian Med-
References


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