Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure

The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)

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Background—Combined inhibition of the angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) may produce greater benefits in heart failure than ACE inhibition alone.

Methods and Results—We randomly assigned 5770 patients with New York Heart Association class II to IV heart failure to double-blind treatment with either the ACE inhibitor enalapril (10 mg BID, n=2884) or to the ACE-NEP inhibitor omapatrilat (40 mg once daily, n=2886) for a mean of 14.5 months. The primary end point—the combined risk of death or hospitalization for heart failure requiring intravenous treatment—was used prospectively to test both a superiority and noninferiority hypothesis (based on the effect of enalapril in the Studies of Left Ventricular Dysfunction [SOLVD] Treatment Trial). A primary end point was achieved in 973 patients in the enalapril group and in 914 patients in the omapatrilat group (hazard ratio 0.94; 95% CI: 0.86 to 1.03, \(P=0.187\))—a result that fulfilled prespecified criteria for noninferiority but not for superiority. The omapatrilat group also had a 9% lower risk of cardiovascular death or hospitalization (\(P=0.024\)) and a 6% lower risk of death (\(P=0.339\)). Post hoc analysis of the primary end point with the definition used in the SOLVD Treatment Trial (which included all hospitalizations for heart failure) showed an 11% lower risk in patients treated with omapatrilat (nominal \(P=0.012\)).

Conclusion—Omapatrilat reduces the risk of death and hospitalization in chronic heart failure but was not more effective than ACE inhibition alone in reducing the risk of a primary clinical event. Between-group differences in favor of omapatrilat observed in secondary and post hoc analyses warrant further study. (Circulation. 2002;106:920-926.)

Key Words: heart failure ■ angiotensin-converting enzyme inhibitors ■ omapatrilat

Recent studies have shown that several endogenous peptides (ie, natriuretic peptides, bradykinin, and adrenomedullin) can attenuate vasoconstriction and sodium retention as well as retard cardiac and vascular hypertrophy and remodeling, thus acting to ameliorate many of the pathophysiological abnormalities of heart failure.1-3 This observation has led to the hypothesis that enhancing the effects of these endogenous vasodilators by blocking neutral endopeptidase (NEP)—one of the key enzymes responsible for the breakdown of these peptides4—may exert favorable effects in the treatment of this disorder.5,6 Single molecules that inhibit both the angiotensin-converting enzyme (ACE) and NEP (vasopeptidase inhibitors) have been developed in recent years.7 Simultaneous inhibition of both ACE and NEP produces greater short-term and long-term benefits in experimental models of heart failure than does ACE inhibition alone.8,9

Omapatrilat is a dual inhibitor of both ACE and NEP, which has been evaluated for the treatment of hypertension and heart failure. In patients with hypertension, omapatrilat produces greater decreases in both systolic and diastolic blood pressure than does ACE inhibition alone.10 In patients with heart failure, omapatrilat has been reported to reduce the risk of death or hospitalization for heart failure to a greater degree than ACE inhibition alone,11 but this effect was based on a small number of clinical events observed in patients who...
were treated for only 6 months. The OVERTURE trial was conducted as a definitive study to compare the efficacy of omapatrilat to that of a conventional ACE inhibitor in patients with heart failure.

Methods

The institutional review board of each of the 704 participating institutions (in 42 countries) approved the protocol, and all patients gave written informed consent.

Study Patients

Patients were eligible for the study if they had New York Heart Association class II, III, or IV heart failure because of an ischemic or nonischemic cardiomyopathy for ≥2 months or had a left ventricular ejection fraction ≤30% and had been hospitalized for heart failure within the previous 12 months. All patients were treated with diuretics and were encouraged to have received all other appropriate treatment for heart failure, including digitalis, an ACE inhibitor, or angiotensin II receptor antagonist, β-blocker, or spironolactone.

Patients were excluded from participation in the study if they had a surgically correctable or reversible cause of heart failure; had received or were likely to receive a cardiac transplant or left ventricular assist device; had severe primary pulmonary, renal, or hepatic disease; or had a history of intolerance to an ACE inhibitor. In addition, patients were not allowed to have had an acute coronary syndrome within the previous month or have had coronary revascularization or an acute cerebral ischemic event within the previous 3 months. Patients with a history of ventricular tachycardia, ventricular fibrillation, or sudden death were not enrolled unless an implantable cardioverter-defibrillator had been placed and had not fired within 2 months. Patients were eligible for the study if they had New York Heart Association class II, III, or IV heart failure because of an ischemic or nonischemic cardiomyopathy for ≥2 months or had a left ventricular ejection fraction ≤30% and had been hospitalized for heart failure within the previous 12 months. All patients were treated with diuretics and were encouraged to have received all other appropriate treatment for heart failure, including digitalis, an ACE inhibitor, or angiotensin II receptor antagonist, β-blocker, or spironolactone.

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Study Design

Patients fulfilling these entry criteria were randomly assigned in a double-blind fashion to receive either omapatrilat or enalapril (in a 1:1 ratio). Before the first dose of the study medication, any ongoing therapy with an ACE inhibitor or angiotensin receptor blocker was stopped (but other treatments for heart failure were continued), and patients were started on omapatrilat 10 mg once daily or enalapril 2.5 mg twice daily. If these doses were well tolerated after 3 to 14 days, they were increased, omapatrilat to 20 mg once daily and enalapril to 5 mg twice daily, and then (if tolerated for an additional 3 to 14 days) to a target dose of omapatrilat 40 mg once daily or enalapril 10 mg twice daily. The target dose of enalapril was selected on the basis of its ability to reduce the risk of death or hospitalization for heart failure in the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial.12 The target dose of omapatrilat was selected on the basis of its apparent superiority to ACE inhibition in an earlier trial.11 Patients were maintained on the highest tolerated doses of the study medication and were evaluated as an outpatient every 1 to 4 months until the end of the study. During this maintenance period, the dose of omapatrilat or enalapril could be reduced or temporarily discontinued, but investigators were encouraged to reinstate partial or full doses of the study drugs at a later time. If necessitated by the patient’s condition, investigators adjusted the doses of any concomitant drug and could utilize any interventions that were clinically indicated, but they were instructed not to institute open-label treatment with an ACE inhibitor or angiotensin receptor blocker.

Statistical Analysis

The primary end point of the study was the combined risk of all-cause mortality or hospitalization for heart failure. Protocol-specified secondary measures of outcome included all-cause mortality; the combined risk of cardiovascular death or cardiovascular hospitalization; and the combined risk of cardiovascular death, myocardial infarction, stroke, or myocardial revascularization. Between-group differences in the Kaplan-Meier survival curves for these end points were analyzed according to the intention-to-treat principle and were tested for significance by the log-rank statistic. Cox proportional hazards regression models were used to estimate hazard ratios and 2-sided 95% confidence intervals (CIs).

The primary end point was used prospectively to test two hypotheses: (1) that omapatrilat was superior to enalapril (which would be concluded if the upper bound of the 1-sided 97.5% CI was <1.00); and (2) that omapatrilat was not inferior to enalapril (which would be concluded if the upper bound of the 1-sided 97.5% CI was <1.09). Fulfillment of this latter criterion would indicate that omapatrilat would have been superior to placebo (if placebo had been studied) and that the magnitude of such benefit would have been ≥80% of the magnitude of the effect of enalapril on this end point observed in the SOLVD Treatment Trial,12 which was the protocol-specified reference standard. In testing the superiority hypothesis, hospitalization for heart failure was defined in the protocol as an admission for or with worsening heart failure that required an intravenous treatment for heart failure within the first 3 days after admission; the cause of all hospitalization was adjudicated by a blinded End Point Committee. This protocol-specified definition was also used to test the noninferiority hypothesis, but it was recognized during discussions with the FDA after completion of the study that a comparison of the treatment effects in the present trial with those observed in the SOLVD Treatment Trial would most appropriately be performed with the use of the definition of hospitalization for heart failure specified in that trial, which relied on investigator judgment (rather than an adjudication process) to determine the cause of hospitalization and included all hospitalizations for heart failure (regardless of the use of intravenous therapy).

The sample size was estimated on the basis of the following assumptions: the 18-month mortality rate in the placebo group would be 17%; the risk of death would be altered by 20% as a result of treatment with omapatrilat when compared with enalapril; and the study would have 90% power (2-sided α=0.05) to detect a significant difference between the treatment groups in all-cause mortality. To maintain statistical power should the event rate estimate prove inaccurate, the trial was designed to continue until 850 deaths had occurred and the last randomized patient had been monitored for 8 months. These design features provided 96% power to test for the possibility of a 15% difference between omapatrilat and enalapril on the primary end point of all-cause mortality or hospitalization for heart failure.

An independent Data and Safety Monitoring Board periodically reviewed the unblinded results and was empowered to recommend early termination of the study if it observed a treatment effect on all-cause mortality that exceeded prespecified boundaries. To protect against increasing the false-positive error rate with repeated interim analyses, an O’Brien-Fleming-type boundary computed with the use of the Lan-DeMets procedure13 was used to guide a recommendation for early stopping if omapatrilat proved to be superior to enalapril. The effect of omapatrilat (when compared with enalapril) on the combined risk of death and hospitalization was prospectively assessed in subgroups defined by the following prerandomization variables: age; sex; race; ejection fraction; cause of heart failure; New York Heart Association class; diabetes; or use of aspirin, β-blocker, or spironolactone. In addition, given the efficacy of omapatrilat in the treatment of hypertension, a post hoc analysis was performed to evaluate the influence of the baseline systolic blood pressure on the magnitude of any observed difference between omapatrilat and enalapril.

All reports of adverse events were included whether or not they were deemed by the investigator to be related to treatment.

Results

A total of 5770 patients were randomized into the trial, of which 2886 were assigned to treatment with omapatrilat and...
2884 to treatment with enalapril. The two treatment groups were similar with regard to all pretreatment characteristics (Table 1). Target doses of the study medications were reached by 82.5% and 86.4% of the patients in the omapatrilat and enalapril groups, respectively, and these doses were generally maintained until the end of the study. The mean duration of follow-up was 14.5 months. During this time, 26.8% and 25.3% of the omapatrilat and enalapril groups, respectively, stopped taking their study medication; 1.0% and 0.8%, respectively, were lost to follow-up for assessment of vital status; and 0.9% and 0.4%, respectively, withdrew consent to be monitored for end points.

Effect on Primary End Point
There were 973 patients who died or were hospitalized for heart failure requiring intravenous treatment in the enalapril group and 914 in the omapatrilat group (hazard ratio 0.94 [95% CI, 0.86 to 1.03], \( P=0.187 \))—a result that fulfilled prespecified criteria for noninferiority but not for superiority (Figure 1).

In a post hoc analysis of noninferiority that included all hospitalizations for heart failure (the definition used in the SOLVD Treatment Trial [the protocol-specified reference standard for noninferiority]), there were 1041 patients who died or were hospitalized for heart failure in the enalapril group and 941 in the omapatrilat group (hazard ratio 0.89 [95% CI, 0.82 to 0.98]), nominal \( P=0.012 \). The difference between this post hoc analysis and the prespecified analysis of the primary end point reflected the occurrence of hospitalizations for heart failure that were treated only with an intensification of oral drugs.

Effect on Secondary End Points
There were 509 and 477 deaths in the enalapril and omapatrilat groups, respectively; the hazard ratio was 0.94 (95% CI, 0.83 to 1.07), \( P=0.339 \), Figure 2. In addition, there were 1275 patients who died or were hospitalized for a cardiovascular reason in the enalapril group and 1178 such patients in the omapatrilat group (hazard ratio 0.91 [95% CI, 0.84 to 0.99]), \( P=0.024 \). Finally, there were 578 patients in the enalapril group and 537 in the omapatrilat group who experienced a cardiovascular death, myocardial infarction, stroke, or myocardial revascularization (hazard ratio 0.93 [95% CI, 0.83 to 1.05]), \( P=0.233 \).

Subgroup Analyses
Differences between omapatrilat and enalapril on the primary end point were generally similar in direction and magnitude in subgroups defined by 10 prespecified pretreatment variables (Figure 3). Post hoc analysis of the influence of systolic blood pressure on the magnitude of the difference between omapatrilat and enalapril suggested that patients who had hypertension (systolic blood pressure >140 mm Hg) at the start of the study showed the greatest difference between omapatrilat and enalapril for the primary end point. The interaction of baseline systolic blood pressure and treatment difference was significant (\( P=0.009 \)) for the combined risk of cardiovascular death or cardiovascular hospitalization.

Safety
When measured before the next scheduled dose, systolic blood pressure decreased more in the enalapril group than in

TABLE 1. Pretreatment Characteristics of Patients in the Study

<table>
<thead>
<tr>
<th></th>
<th>Omapatrilat (n=2886)</th>
<th>Enalapril (n=2884)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.4±11.6</td>
<td>63.5±11.9</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Cause of heart failure, % ischemic</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>23.5±5.4</td>
<td>23.5±5.3</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1388</td>
<td>1381</td>
</tr>
<tr>
<td>III</td>
<td>1378</td>
<td>1379</td>
</tr>
<tr>
<td>IV</td>
<td>113</td>
<td>111</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123±18</td>
<td>124±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74±10</td>
<td>74±11</td>
</tr>
<tr>
<td>Patients receiving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis, %</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>Diuretic, %</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>48</td>
<td>47</td>
</tr>
</tbody>
</table>

All continuous data are expressed as mean±SD.

Figure 1. Kaplan-Meier analysis of time to death or hospitalization for heart failure requiring intravenous treatment in the omapatrilat and enalapril groups.

Figure 2. Kaplan-Meier analysis of time to death in the omapatrilat or enalapril groups.
the omapatrilat group throughout the uptitration period (−5.2 versus −3.6 mm Hg at end of uptitration). However, during the maintenance phase of the study, the decline in systolic blood pressures at trough was similar in the two groups.

Adverse events occurring in >5% of patients are listed in Table 2. Hypotension and dizziness were reported more frequently, but heart failure and renal impairment were reported less frequently with omapatrilat than with enalapril. The pretreatment systolic blood pressure was a major determinant of the frequency of hypotensive reactions and renal impairment (Figure 4). Angioedema was reported in 24 (0.8%) omapatrilat-treated and 14 (0.5%) enalapril-treated patients, of whom 3 (2 on enalapril and 1 on omapatrilat) required hospitalization for management; none required intubation or died. The study drug was withdrawn because of an adverse event in 17.9% of the omapatrilat group and 17.0% of the enalapril group.

Table 2. Adverse Events With a Frequency >5%

<table>
<thead>
<tr>
<th>Event</th>
<th>Enalapril</th>
<th>Omapatril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>737 (25.6)</td>
<td>653 (22.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>401 (13.9)</td>
<td>561 (19.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>332 (11.5)</td>
<td>564 (19.5)</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>291 (10.1)</td>
<td>196 (6.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>276 (9.6)</td>
<td>233 (8.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>259 (9.0)</td>
<td>279 (9.7)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>256 (8.9)</td>
<td>238 (8.2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>252 (8.7)</td>
<td>256 (8.9)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>223 (7.7)</td>
<td>207 (7.2)</td>
</tr>
<tr>
<td>Edema</td>
<td>195 (6.8)</td>
<td>152 (5.3)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>194 (6.7)</td>
<td>238 (8.2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>182 (6.3)</td>
<td>178 (6.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>170 (5.9)</td>
<td>202 (7.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>145 (5.0)</td>
<td>153 (5.3)</td>
</tr>
</tbody>
</table>

Values are n (%).

Discussion

Our principal finding—based on prespecified tests of superiority and noninferiority—was that omapatrilat reduced the morbidity and mortality of the patients with moderate-to-severe heart failure enrolled in the OVERTURE trial but was not more effective than ACE inhibition alone in decreasing the risk of a primary clinical event. However, secondary and post hoc analyses that relied on a broader definition of heart failure or focused on all cardiovascular events suggested the possibility that omapatrilat may have been more effective than enalapril in these patients, the difference between the two groups being ≈10%. Yet, even if present, this potential difference was less than that had been expected when the study was designed and was less than that observed in experimental studies and in an earlier clinical trial that compared ACE-NEP inhibition with ACE inhibition alone.9,11

Our inability to demonstrate the anticipated difference between omapatrilat over enalapril may have been related to deficiencies in both the effectiveness of NEP inhibition or ACE inhibition achieved by omapatrilat in the doses and dosing regimens used in the present trial. At first glance, blockade of NEP may have been expected to yield few incremental benefits14 because patients with heart failure show a decrease in the ability of peripheral blood vessels and the kidney to respond to natriuretic peptides, adrenomedullin, or bradykinin14–16; this may be particularly true in patients with the most advanced disease.14 However, during the uptitration period, hypotension and dizziness were reported more frequently in omapatrilat-treated patients, even though trough blood pressure during this uptitration period was reduced more with enalapril than with omapatrilat. These observations suggest that combined ACE and NEP inhibition succeeded in producing greater vasodilator effects than ACE inhibition alone at peak drug effect, but these did not persist for the 24-hour interval between doses of omapatrilat.17,18 This hypothesis could not be tested by use of blood pressure measurements collected in the OVERTURE trial (as blood pressure was measured only at trough), but it is supported by the observations of an earlier study in patients with heart
failure,\textsuperscript{11} which showed that omapatrilat lowered blood pressure more than ACE inhibitor at peak but less than an ACE inhibitor at trough (Figure 5). These findings suggest that the benefits expected from inhibition of both ACE and NEP may have been largely offset by the failure of once-daily dosing with omapatrilat to maintain continuous ACE inhibition to the same degree as twice-daily dosing with enalapril.

Post hoc analysis of the influence of systolic blood pressure on the response to omapatrilat provides additional insights into the results of the present study. Differences in favor of omapatrilat were most apparent in patients with systemic hypertension, and the magnitude of the between-group difference decreased as the baseline systolic blood pressure decreased so that there was no apparent benefit of omapatrilat over enalapril in patients with systolic blood pressures $<110$ mm Hg. This relation may reflect the influence of disease severity on the responsiveness to endogenous vasodilators\textsuperscript{14,15} because systolic blood pressure was a powerful determinant of prognosis in the present trial. Alternatively, if omapatrilat lowered blood pressure more than enalapril in hypertensive patients with heart failure throughout most of the day, the apparent advantage of omapatrilat on the risk of a major clinical event in this subgroup may reflect more effective control of hypertension.

In addition to evaluating its efficacy relative to a conventional ACE inhibitor, an important prespecified objective of the present trial was to establish that omapatrilat was effective in reducing the morbidity and mortality of patients with chronic heart failure. Given the ethical mandate to treat patients with heart failure with an ACE inhibitor, it was impossible to evaluate this hypothesis in a long-term trial that compared omapatrilat with placebo. Instead, omapatrilat was compared with a conventional ACE inhibitor in a study that was sufficiently large to detect a meaningful difference between the two drugs if one existed. Fulfillment of the noninferiority hypothesis—when taken together with effects of enalapril seen in the SOLVD Treatment Trial—provides compelling evidence that omapatrilat would have been superior to placebo if placebo had been studied. When the data from the two trials are combined, the estimated hazard ratio of omapatrilat versus placebo is 0.66 (95% CI, 0.57 to 0.77, $P<10^{-5}$) for death or adjudicated hospitalization for heart failure and 0.72 (95% CI, 0.59 to 0.88, $P=0.0015$) for all-cause mortality. Finally, if the effects of omapatrilat on the primary end point were evaluated with the use of the same definition of hospitalization for heart failure as had been used in the SOLVD Treatment Trial, omapatrilat would have been deemed superior to enalapril—a result that would have conclusively demonstrated its efficacy in the treatment of heart failure.

Both omapatrilat and enalapril were well tolerated in patients with moderate-to-severe heart failure. As in an earlier study,\textsuperscript{11} hypotension and dizziness were more common in patients treated with omapatrilat, but despite these greater hypotensive effects, reports of worsening renal function were less frequent in the omapatrilat group. This pattern of response is similar to that reported in previous experimental and clinical studies, which showed that NEP inhibition can exert favorable effects on renal function and can counteract the risk of worsening renal function that predictably follows the use of ACE inhibitors.\textsuperscript{8,11,19} Although angioedema was reported more commonly with omapatrilat than enalapril, the absolute frequency, incremental risk, and severity in the present trial was less than that reported with omapatrilat in patients with hypertension, possibly because patients with heart failure are resistant to the ability of bradykinin to produce cutaneous exudation.\textsuperscript{20}

In conclusion, the OVERTURE trial demonstrates that omapatrilat reduced morbidity and mortality in patients with moderate-to-severe heart failure but was not was not more effective than ACE inhibition alone in reducing the risk of a primary clinical event. However, secondary and post hoc analyses based on a broader definition of heart failure or focused on all cardiovascular events suggested the possibility of between-group differences in favor of omapatrilat that warrant further study. Alternative dosing strategies that can provide for more continuous and intense inhibition of both ACE and NEP than that achieved by the doses of omapatrilat used in the present trial are of particular interest.

Appendix

Committees

Acknowledgment

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References

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