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Scientific Update™

The Therapeutic Role of Vasopeptidase Inhibition in Heart Failure – Late-breaking Results of the OVERTURE Trial

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The syndrome of congestive heart failure (CHF) is associated with the activation of several endogenous vasoconstrictive as well as counter-regulatory vasodilator neurohormonal systems. In patients with moderate to severe CHF, the actions of the vasoconstrictor neurohormonal systems predominate over the vasodilator systems. Accordingly, an attractive therapeutic approach in these patients is to inhibit the vasoconstrictor peptides and simultaneously augment the actions of the vasodilator peptides. Omapatrilat belongs to a novel class of agents, the vasopeptidase inhibitors (VPI), that inhibit both the angiotensin-converting enzyme (ACE), as well as the neutral endopeptidase (NEP) enzyme that degrades vasodilator peptides. The results of an earlier phase II study (the Inhibition of MetalloProtease in the Randomized Exercise and Symptom Study in heart failure [IMPRESS]) in patients with moderate CHF suggested improved clinical outcomes in patients treated with omapatrilat as compared to an ACE inhibitor. The OVERTURE study was a large-scale, randomized, controlled trial designed to test the hypothesis that omapatrilat improves clinical outcomes compared to ACE inhibition in patients with moderate to severe CHF. In this *Cardiology Scientific Update*, the results of the OVERTURE study and the role of VPI in the treatment of CHF will be discussed.

Congestive heart failure (CHF) is a syndrome associated with the activation of several neurohormonal systems.[1] Excessive activation of the vasoconstrictor, antidiuretic, and neurohormonal systems results in abnormal myocyte growth, myocyte loss, and cardiac fibrosis. Accordingly, inhibition of some of the vasoconstrictor systems (ie, the renin-angiotensin-aldosterone system and the sympathetic nervous system), has become standard therapy for patients with CHF. Besides the vasoconstrictor peptides, the human body also possesses several vasodilative diuretic neurohormonal systems that exert effects that are opposite to those of the vasoconstrictor neurohormones. These neurohormonal systems – including the natriuretic peptides, (ie, atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], and C-type natriuretic peptide [CNP]), vasodilative prostaglandins, and adrenomedullin – play a counter-regulatory role in maintaining circulatory homeostasis in CHF.

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Accordingly, augmentation of these endogenous vasodilative peptides is an attractive, novel, and relatively unexplored approach to treating CHF. Neutral endopeptidase 24.11 (NEP) is a metalloprotease that is co-localized with ACE in great abundance in organs such as the kidneys.[2] NEP inactivates the endogenous vasodilative peptides, including bradykinin, adrenomedullin, and natriuretic peptides.[3,4] The VPIs belong to a new class of agents that simultaneously block both ACE and NEP, thereby resulting in concomitant reduction of angiotensin II and augmentation of the vasodilator peptides.[5]

Omapatrilat, the first of the VPIs, is at the most advanced stage of development. In animal models of CHF, omapatrilat has consistently been shown to improve cardiovascular and renal function.[6-9] To date, omapatrilat has been tested in more than 24,000 patients. In those with CHF, omapatrilat improves clinical status and exerts favorable hemodynamic, renal, and neurohormonal effects.[10] In the IMPRESS trial, omapatrilat (40 mg once daily) improved clinical outcome, when compared to ACE inhibitor alone (lisinopril, 20 mg once daily), in 573 patients with moderate CHF (New York Heart Association [NYHA] II-IV symptoms).[11] This finding, though encouraging, needed to be confirmed since the study involved a relatively small number of patients and was not designed to assess clinical outcome.

OVERTURE

Accordingly, the Omapatrilat Vs Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study was created. OVERTURE was an international, multicentre, double-blind, ACE inhibitor-controlled trial designed to assess the effect of omapatrilat versus the ACE inhibitor enalapril on clinical outcomes.

The principal inclusion criteria included a diagnosis of CHF for > 2 months, NYHA II-IV symptoms, left ventricular (LV) ejection fraction (LVEF) < 30% (implying more advanced CHF), and a history of hospitalization for CHF within 12 months. Patients had to be on therapy for CHF symptoms including diuretics with or without digitalis, ACE inhibitors, or ß-blockers. Patients on ACE inhibitors had their medication withheld prior to randomization. Eligible patients were randomized to either:

- enalapril, initiated at 2.5 mg orally twice daily, and up-titrated to 5 mg twice daily and subsequently 10 mg twice daily, or
- omapatrilat, 10 mg once daily, 20 mg once daily, and subsequently 40 mg once daily.

The dose of enalapril was chosen on the basis of the Studies of Left Ventricular Dysfunction (SOLVD) trial in which 10 mg twice daily was shown to produce a survival benefit over placebo.[12] The dose of omapatrilat 40 mg once daily was the same dose used in the IMPRESS study that demonstrated a benefit in clinical outcome over lisinopril.[11] In OVERTURE, the predefined primary outcome was composite all-cause mortality or CHF hospitalization. The secondary outcomes were all-cause mortality, combined risk of cardiovascular (CV) death or CV hospitalization, combined ischemic events, (defined as a composite of CV death, myocardial infarction [MI], stroke or revascularization), NYHA functional class, and patient global assessment of clinical well being.

The study was prospectively designed to test the following two hypotheses.

- First, that omapatrilat was superior to enalapril; this would be achieved if the upper boundary of the one-sided 97.5% confidence interval (CI) was < 1.0.
- Second, that omapatrilat was non-inferior (equivalent) to the ACE inhibitor enalapril; this would be achieved if the upper boundary of the one-sided 97.5% CI was < 1.09.

The sample size was calculated with > 98% power to detect a 15% difference in combined death and CHF hospitalization and > 90% power to detect a 20% difference in all-cause mortality. The trial was event-rate driven with a target of 850 deaths and a minimum follow-up of 8 months.

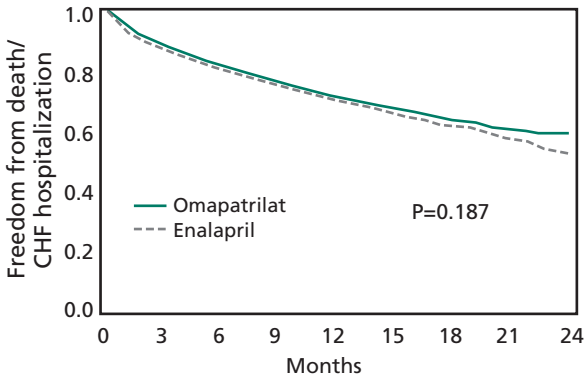
ACC Late-breaking Trial Results

A total of 5770 patients were randomized. The results were presented at the recent American College of Cardiology meeting and published.[13] The baseline demographic data are shown in Table 1. The two treatment groups are comparable in all baseline data. The more than 50% of patients using ß-blockers as background therapy at baseline reflects contemporary treatment guidelines[14] and is more extensive than the background therapy of other

Table 1: Baseline data

	Enalapril (n = 2884)	Omapatrilat (n = 2886)
Age (years)	63.5	63.4
Male (%)	78	80
Average LVEF	23.5%	23.5%
NYHA II/III/IV (%)	48/48/4	48/48/4
History of diabetes (%)	31	30
Blood pressure (mm Hg)	124/74	123/74
Digitalis use (%)	66	59
ß-blocker use (%)	52	51
Spironolactone use (%)	42	42

Figure 1: OVERTURE – primary endpoint



recent CHF trials.[15] Importantly, almost half those enrolled were on an aldosterone receptor antagonist at baseline, attesting to the severity of CHF in some of these patients.

Results of the primary endpoint – death/CHF hospitalizations – are shown in Table 2 and Figure 1. Compared to enalapril, there was a 6% relative risk reduction (RRR) in favour of omapatrilat. This difference was not statistically significant. However, the upper CI of the hazard ratio was 1.03 which was lower than the predefined upper boundary of CI for non-inferiority (equivalence) of 1.09, indicating that omapatrilat is at least equivalent to enalapril in reducing the primary outcome if compared to placebo.

Results of the secondary endpoints, namely CV death or CV hospitalization, and combined ischemic events (death, MI, stroke or revascularization) are shown in Table 2. A 9% RRR in CV death and CV hospitalization by omapatrilat was statistically significant. A 7% RRR of combined ischemic events with omapatrilat did not reach statistical significance.

The mortality of the patients (at an annualized rate of approximately 12%) reflected the severity of CHF. Omapatrilat reduced mortality by 6% compared to enalapril (*P*=0.339, Table 2). Once again, the upper CI of the hazard ratio of 1.07 was lower than the predefined upper boundary of 1.09, indicating equivalence with enalapril (in the reduction of total mortality if compared to placebo). All predefined subgroups, namely age, NYHA class, LVEF, ischemic etiology and ß-blocker use, demonstrated similar results, with modest trends towards benefit with omapatrilat, but none reached statistical significance.

Data for the frequency of adverse events are shown in Table 3. More patients in the enalapril group reported

Table 2: OVERTURE – Results of the primary and secondary endpoints

	Enalapril (BID)	Omapatrilat (OD)	Hazard ratio% (97.5% CI)	Relative Risk Reduction	*P*-value
Primary endpoint Death or CHF hospitalization requiring I.V. treatment	973/2884 (33.7%)	914/2886 (31.7%)	0.94 (0.86,1.03)	6%	0.187
Secondary endpoints CV death and CV hospitalization	1275/2884 (44.2%)	1178/2886 (40.8%)	0.91 (0.84,0.99)	9%	0.024
Combined ischemic events	578/2884 (20.0%)	537/2886 (18.6%)	0.93 (0.83,1.05)	7%	0.233
All-cause mortality	509/2884 (17.6%)	477/2886 (16.5%)	0.94 (0.83,1.07)	6%	0.339

Table 3: Adverse events		
Event	**Enalapril**	**Omapatrilat**
CHF	25.6%	22.6%
Hypotension	11.5%	19.5%
Dizziness	13.9%	19.5%
Impaired renal function	3.6%	2.3%
Angioedema	0.5%	0.8%

CHF as adverse events and experienced worsening of renal function. However, more patients in the omapatrilat group experienced hypotension and dizziness. The incidence of angioedema was very low in both groups and was only slightly higher in the omapatrilat group.

Discussion

The OVERTURE study is the largest study of the use of a new drug in patients with CHF. Results of the OVERTURE study indicate that omapatrilat is at least equivalent to enalapril in reducing mortality and CHF hospitalization in patients with severe CHF (Figure 1). This finding implies that combined NEP and ACE inhibition with VPI produced a lesser incremental benefit over ACE inhibition than expected on these predefined clinical outcomes in patients on optimal contemporary therapy.

The mechanisms for the lack of superiority of combined NEP and ACE inhibition over ACE inhibition alone in CHF are unclear, although several possible explanations have been considered.

- The first possibility is that the dose or the dosing regimen of omapatrilat might have been suboptimal. This possibility is not very likely since, in the IMPRESS study, omapatrilat 40 mg daily, but not lisinopril 20 mg daily, increased plasma ANP levels.[11]
- The second possible explanation is that patients in the OVERTURE study have already reached a "ceiling" beyond which they would not benefit further from neurohormonal inhibition. This argument may apply if the study drug were another agent that inhibited the vasoconstrictor, antidiuretic, neurohormonal systems. However, omapatrilat exerts its effect, in part, through the vasodilator systems that may not have yet been intervened with to any great extent in these patients.
- The third possible explanation is that patients with severe CHF have developed target organ resistance to the actions of endogenous vasodilator peptides. This hypothesis is supported by previous observations that the biologic effect of exogenous infusion of ANP is attenuated in patients with CHF when compared to subjects with normal LV function.[16,17] This hypothesis was reviewed in the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study, as presented in a recent issue of *Cardiology Scientific Update*.
- The fourth possible explanation is that greater blood pressure lowering by omapatrilat (Figure 2), especially in patients with low baseline blood pressure, might have negated its other beneficial effects. This hypothesis is suggested by an unplanned analysis of mortality according to pretreatment systolic blood pressures: ≥140 mm Hg, 130-139 mm Hg, 120-129 mm Hg, 110-119 mm Hg, and <110 mm Hg. Patients with pretreatment systolic pressure ≥140 mm Hg appeared to benefit most from omapatrilat. The benefit decreased progressively with lower quintiles of blood pressure. Patients with baseline systolic pressure <110 mm Hg appeared not to benefit at all.

Figure 2: OVERTURE – death or CHF hospitalization (post-hoc subgroups)

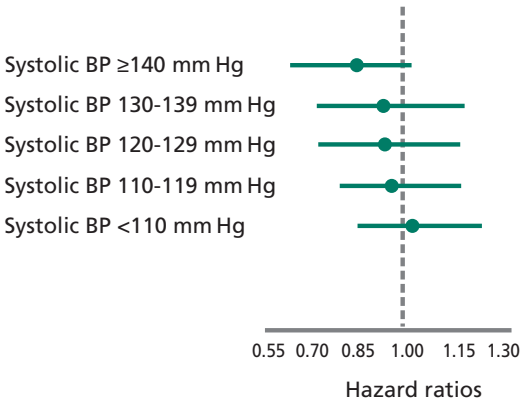


Table 4: OVERTURE primary endpoint using the same definition for hospitalizations as the protocol pre-specified reference standard for non-inferiority: SOLVD Trial

	Enalapril	Omapatrilat	Hazard ratio%	Relative risk reduction	Log-rank *P*-value
Death or all CHF hospitalization (as per SOLVD)	1041/2884	941/2886	0.89 (0.82, 0.98)	11%	0.012

Further analyses of the statistical significance of these potential differences, as well as changes in blood pressure over the course of the study, will be required to substantiate this hypothesis.

The findings of OVERTURE also contrast with those observed in the IMPRESS trial.[11] While omapatrilat produced a similar increase in treadmill walking time, the primary endpoint of the IMPRESS study, there was a trend in favor of omapatrilat on the secondary endpoint, a combined endpoint of death or CHF hospitalization (hazard ratio 0.52; 95% CI, 0.27-1.02; $P = 0.052$). The different observations in OVERTURE and IMPRESS underscore that caution should be applied in drawing conclusions from studies with a smaller sample size and short duration, as well as from analyses of secondary outcomes and patient subgroups such as studies of amlodipine and losartan in CHF.[18-20]

Nevertheless, it is useful to speculate on possible mechanisms besides chance alone that may account for the differences. First, the different inclusion criteria suggest that patients in the IMPRESS and OVERTURE studies differed in severity of CHF. The inclusion criteria of LVEF <30%, and more importantly, a history of CHF hospitalization within 12 months imply more severe CHF in OVERTURE patients. On the other hand, the inclusion criteria of LVEF <40% and the ability of patients to perform treadmill exercise testing in the IMPRESS study imply a CHF of lesser severity in these patients.[11] These observations raise the possibility that VPI may be more effective in patients with less severe CHF than in patients with advanced disease. In a canine model of pacing-induced CHF, acute NEP inhibition was effective in improving cardiorenal function only in mild CHF, but not in severe CHF.[21] Furthermore, in mild CHF, VPI was superior to ACE inhibitor alone.[7] These experimental data suggest that natriuretic peptides and other vasodilator peptides may play a more important role in early CHF than in advanced CHF. Accordingly, therapeutic approaches that target natriuretic peptides may be more effective in milder forms of CHF, and are at least as effective as enalapril in severe CHF.

Since commencing the preparation of this *Cardiology Scientific Update,* further analyses have been conducted, and the results were presented at the recent meeting of the American Society of Hypertension.

Although the reference standard for the OVERTURE trial was protocol-specified to be the SOLVD treatment trial, the criteria for the primary endpoint of non-inferiority was actually based on different criteria established by the endpoint committee. The re-analyses considered the OVERTURE results using the SOLVD criteria. The SOLVD data included all CHF hospitalizations by investigators, regardless of treatment or treatment duration. The original analysis by OVERTURE included hospitalizations as adjudicated, in which intravenous CHF treatment was required, or where hospitalization lasted for >24 hours. However, examination of the OVERTURE data indicated that approximately 200 CHF hospitalizations were treated only by an intensification of oral therapy, and therefore, had not been qualified as a CHF hospitalization according to the pre-specified analysis of the primary endpoint. Interestingly, using these new criteria that included oral therapy, the hazard ratio for the primary outcome becomes 0.89 with a *P*-value of 0.012, suggesting a 11% relative risk

reduction with omapatrilat (Table 4). The new data, while positive, should be considered in the proper context as an alternative analysis, since the SOLVD criteria were not the pre-specified criteria used for the primary endpoint of non-inferiority in the OVERTURE trial.

Conclusion

In conclusion, the OVERTURE study indicates that the VPI omapatrilat (once daily) is equivalent to the ACE inhibitor enalapril (twice daily) in reducing mortality and CHF hospitalizations in patients with CHF receiving optimal contemporary therapy, with a modest trend towards a benefit with omapatrilat. The mechanisms to fully explain these results remain to be determined. Further analyses of data from the OVERTURE study are likely to be forthcoming to address these mechanisms and will help define the role of vasopeptidase inhibition in the treatment of patients with heart failure.

References

1. Packer M. Evolution of the neurohormonal hypothesis to explain the progression of chronic heart failure. *Eur Heart J* 1995;16 Suppl F:4-6.
2. Ura N, Carretero OA, Erdos EG. Role of renal endopeptidase 24.11 in kinin metabolism in vitro and in vivo. *Kidney Int* 1987;32:507-13.
3. Kenny AJ, Bourne A, Ingram J. Hydrolysis of human and pig brain natriuretic peptides, urodilatin, C- type natriuretic peptide and some C-receptor ligands by endopeptidase- 24.11. *Biochem J* 1993; 291 (Pt 1):83-88.
4. Lisy O, Jougasaki M, Schirger JA, Chen HH, Barclay PT, Burnett JC Jr. Neutral endopeptidase inhibition potentiates the natriuretic actions of adrenomedullin. *Am J Physiol* 1998;275:F410-F414.
5. Corti R, Burnett JC Jr, Rouleau JL, Ruschitzka F, Luscher TF. Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? *Circulation* 2001;104:1856-62.
6. Cataliotti A, Boerrigter G, Chen HH, et al. Differential actions of vasopeptidase inhibition versus angiotensin-converting enzyme inhibition on diuretic therapy in experimental congestive heart failure. *Circulation* 2002;105:639-44.
7. Chen HH, Lainchbury JG, Matsuda Y, Harty GJ, Burnett JC Jr. Endogenous natriuretic peptides participate in renal and humoral actions of acute vasopeptidase inhibition in experimental mild heart failure. *Hypertension* 2001;38:187-91.
8. Trippodo NC, Robl JA, Asaad MM, et al. Cardiovascular effects of the novel dual inhibitor of neutral endopeptidase and angiotensin-converting enzyme BMS-182657 in experimental hypertension and heart failure. *J Pharmacol ExpTher* 1995;275:745-52.
9. Troughton RW, Rademaker MT, Powell JD, et al. Beneficial renal and hemodynamic effects of omapatrilat in mild and severe heart failure. *Hypertension* 2000;36:523-30.
10. McClean DR, Ikram H, Garlick AH, Richards AM, Nicholls MG, Crozier IG. The clinical, cardiac, renal, arterial, and neurohormonal effects of omapatrilat, a vasopeptidase inhibitor, in patients with chronic heart failure. *J Am Coll Cardiol* 2000;36:479-86.
11. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000;356:615-20.
12. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293-302.
13. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002;106:r21-r27.
14. Liu P, Arnold M, Belenkie I, et al. The 2001 Canadian Cardiovascular Society consensus guideline update for the management and prevention of heart failure. *Can J Cardiol* 2001;17 Suppl E:5E-25E.
15. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345:1667-75.
16. Cody RJ, Atlas SA, Laragh JH, Kubo SH, Covit AB, Ryman KS et al. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. *J Clin Invest* 1986;78:1362-74.
17. Moe GW, Canepa-Anson R, Armstrong PW. Atrial natriuretic factor: pharmacokinetics and cyclic GMP response in relation to biologic effects in severe heart failure. *J Cardiovasc Pharmacol* 1992;19:691-700.
18. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med* 1996;335:1107-14.
19. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.
20. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-87.
21. Chen HH, Schirger JA, Chau WL, et al. Renal response to acute neutral endopeptidase inhibition in mild and severe experimental heart failure. *Circulation* 1999;100:2443-48.

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