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Scientific Update™

# Vasopeptidase Inhibition and Improved Cardiovascular Outcomes

## A Report from the 49th Scientific Sessions of the American College of Cardiology

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**Cardiovascular disease remains the number one cause of mortality in the western world. Although there has been an important reduction in age-adjusted death rates from heart disease, the overall incidence of myocardial infarction (MI) and heart failure continues to increase consequent to an aging population. Hypertension, an important risk factor for MI, heart failure and stroke, is often unrecognized and inadequately treated in the elderly patient. A recent meta-analysis has confirmed that drug treatment of isolated systolic hypertension is justified to prevent cardiovascular complications, particularly in those with wider pulse pressure.[1] The introduction of the vasopeptidase inhibitors (VPIs) provides enhanced prospects for a more successful achievement of target blood pressure goals with greater reduction of cardiovascular complications. Furthermore, the same agents show promise of improved outcomes for patients with heart failure beyond those provided by the current standard of care with angiotensin-converting enzyme (ACE) inhibitors.**

### Controlled hypertension – the tip of the iceberg

Not only is hypertension under-diagnosed, but for patients taking medication, blood pressure reduction frequently does not achieve targets recommended by the International Society of Hypertension and the World Health Organization. The Canadian Heart Health survey[2] (1986-92) showed that 42% of Canadian hypertensives are not aware they have hypertension, and that 23% of hypertensives are treated, but inadequately controlled. The NHANES III study (1988-91) also showed that 47% of subjects were aware they had hypertension, but only 50% of these patients were on treatment, with 24% reaching target blood pressures of ≤140/90 mm Hg.[3] At the recent Scientific Sessions of the American College of Cardiology, an analysis of the NHANES III data confirmed the urgency for physicians to focus on the needs of patients with systolic hypertension.[4] In this analysis, hypertension was classified as:

- **isolated diastolic hypertension (IDH)** (SBP ≤140 and DBP ≥90 mm Hg)
- **systolic/diastolic hypertension (SDH)** (SBP ≥140 and DBP ≥90 mm Hg)
- **isolated systolic hypertension (ISH)** (SBP ≥140 and DBP ≤90 mm Hg).

The 19,661 hypertensive patients were stratified according to age (≥ or <50 years of age), and whether they were currently receiving treatment. 74% of both the treated and untreated hypertensives were ≥50 years old. The distribution of the types of hypertension in the untreated and treated patients is shown in Table 1.

Isolated diastolic hypertension was more common in the younger population (<50 years 78.5%, ≥50 years 21.4%); whereas isolated systolic hypertension was more confined to the over-50 population (<50 years 8.8%, ≥50 years 91.2%). Systolic/diastolic hypertension was observed with a similar incidence in both age groups ( <50 years 42.9%, ≥50 years 56.9%). Two-thirds of hypertensive subjects over 50 years old were not on treatment, and over 80% were in the ISH group. Inadequate treatment was seen in 86% of the subjects ≥50 years of age, of whom the large majority had ISH.

The results of this analysis highlight the large number of older individuals who are at high risk of cardiovascular events due to unrecognized and inadequately treated higher systolic pressures, wide pulse pressures, and an increased incidence of co-morbidity. Successful treatment of SBP in



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**Table 1: Distribution of the types of hypertension in treated and untreated patients in the NHANES III Study**

| | Type % | | |
|---|---|---|---|
| | IDH | SDH | ISH |
| **Untreated <50 years** | 46.9 | 32.5 | 20.6 |
| **Untreated ≥50 years** | 3.7 | 16.6 | 79.7 |
| **Treated <50 years** | 26.7 | 45.1 | 28.2 |
| **Treated ≥50 years** | 4.4 | 15.5 | 80.1 |

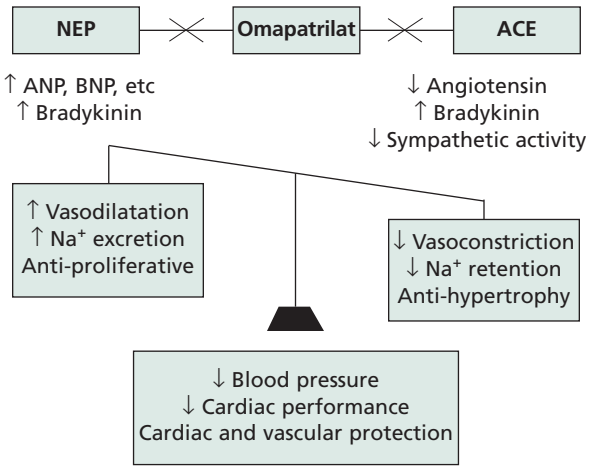
patients over the age of 50 will require more effective antihypertensive medications than are currently used. Vasopeptidase inhibitors, such as omapatrilat, are a promising new class of agents that appear to meet this need.

To achieve the treatment goal of SBP ≤140 mm Hg, the NHANES III analysis showed the required reduction of systolic pressure would be greater in the older population for both the systolic/diastolic hypertensive group (<50 years -9.9 mm Hg, ≥50 years -22.9 mm Hg) and in the isolated systolic hypertensives (<50 years -9.8 mm Hg, >50 years -13.3 mm Hg).[4] Although attention has previously focused on reduction of DBP, the benefits of SBP reduction have been confirmed by the results of at least 8 randomized controlled trials that included elderly patients with isolated systolic hypertension. These benefits have been summarized in a recent meta-analysis[1] that showed that treatment of isolated systolic hypertension reduces total mortality by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23%. Reduction of SBP will usually reduce pulse pressure, a recently recognized prognostic marker for cardiovascular morbidity and mortality.

## Omapatrilat and optimal blood pressure control

Vasopeptidase inhibition is a novel approach to antihypertensive therapy. These compounds inhibit both neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE): enzymes that not only play a role in the modulation of vascular tone, but also have important effects on fluid homeostasis and cellular hypertrophy and growth (Figure 1). ACE inhibition, a well recognized approach to blood pressure control inhibits the synthesis of the vasoconstrictor angiotensin II, as well as preventing the breakdown of the vasodilator bradykinin. NEP inhibition prolongs the availability of the vasodilatory peptides (atrial [ANP], brain [BNP], and C-type [CNP] natriuretic peptides). NEP inhibitors do not appear to be effective as antihypertensive agents, probably due to compensatory activation of the renin angiotensin axis. Yet vasopeptidase inhibitors, which combine both ACE inhibition and NEP inhibition, results in vasodilatation, sodium excretion, reduced cellular growth, and diminished sympathetic nervous system activity, all of which promote increased blood pressure reduction.

**Figure 1: Vasopeptidase inhibition with omapatrilat improves balance of vasoconstriction/vasodilation and limits vascular and cardiac remodelling.**




NEP = neutral endopeptidase
ACE = angiotensin-converting enzyme
ANP, BNP = atrial and brain natriuretic peptides

Omapatrilat, the first vasopeptidase inhibitor to be investigated in clinical trials shows considerable promise as a highly effective anti-hypertensive agent. The properties of omapatrilat have been compared in randomized controlled trials to an ACE inhibitor (lisinopril)[5] and a calcium channel blocker (amlodipine)[6] using ambulatory blood pressure recording in hypertensive subjects. Omapatrilat resulted in a dose-dependent decrease in average 24-hour blood pressure, as well as a reduction in mean pressure throughout the 24-hour monitoring period. SBP was reduced more than DBP, with a consequent reduction of pulse pressure. Mean 24-hour SBP was reduced by 19 mm Hg with omapatrilat 80 mg daily, compared to 12.2 mm Hg with lisinopril 40 mg daily, and DBP by 10.5 mm Hg with omapatrilat vs 7.5 mm Hg with lisinopril. Omapatrilat 80 mg daily reduced both SBP and DBP significantly more than amlodipine 10 mg daily (SBP: 20.4 mm Hg vs 14.5 mm Hg, DBP 13.6 mm Hg vs 9.3 mm Hg $p<0.001$). Again the reduction of SBP with omapatrilat was greater than the fall of DBP.

Omapatrilat has the potential of providing both improved blood pressure control by reducing systolic and pulse pressure and limiting end organ damage by diminishing adverse cardiac remodelling and vascular damage. Improved outcomes depend on modification of conventional cardiovascular risk factors such as hypertension. However, more effective blood pressure control using agents that protect the heart and vasculature, such as the

vasopeptidase inhibitors, is likely to provide superior event-free survival.

## Improved outcomes in cardiac failure

Heart failure is associated with a substantial reduction in life expectancy, with survival related to severity of symptoms and cardiac function. ACE inhibitors improve survival in moderate and severe heart failure, and prevent the progression to heart failure in patients with left ventricular dysfunction. Consequently ACE inhibitors are a current standard of care for patients with heart failure and left ventricular dysfunction.

The vasopeptidase inhibitors have unique properties which make them potentially powerful therapeutic agents for the management of heart failure. Not only are vasopeptidase inhibitors effective ACE inhibitors, but in addition, they promote vasodilatation, sodium excretion, and diminish adverse cardiac and vascular remodelling by enhancing the availability of the vasodilatory peptides such as ANP, BNP, and CNP (Figure 1). Omapatrilat has been extensively investigated in both pre-clinical and clinical trials and has been shown to provide a sustained hemodynamic benefit and prevention of left ventricular dilatation. Holzgreffe et al reported the effect of medications in a canine pacing model of heart failure at the recent ACC.[7] They compared the cardiovascular response to a diuretic (furosemide), an ACE inhibitor (fosinopril), the combination of the ACE inhibitor and diuretic, and omapatrilat. Although all treatments lowered left ventricular filling pressures, only omapatrilat reduced the relative increase in left ventricular end diastolic volume. Consequently, omapatrilat, by reducing left ventricular diastolic wall stress and ventricular dilatation, appeared to have significantly greater benefits for the management of heart failure than those obtained from an ACE inhibitor alone.

McClean et al[8] presented the effect of omapatrilat on volume homeostasis in patients with cardiac failure. After a 12-week period of treatment, omapatrilat 20-40 mg daily significantly reduced total blood volume by 749±164 ml ($p<0.05$). The change in blood volume was associated with a significant increase in plasma ANP which correlated with the observed decrease in left ventricular end diastolic and systolic volumes, as well as the increase in 24-hour urinary sodium excretion. These recent data support the hypothesis that omapatrilat, by potentiating natriuretic and vasodilator peptides, as well as limiting the adverse effects of angiotensin II (Figure 1), could have a major role in limiting left ventricular remodelling in patients with cardiac failure.

## IMPRESS

The largest completed randomized controlled trial of omapatrilat to date is the IMPRESS trial, which was reported in detail in a previous *Cardiology Scientific Update*. In this study, patients with heart failure and NYHA class II-IV symptoms were randomized to a 24-week treatment with either omapatrilat (target dose 40 mg daily) or lisinopril (target dose 20 mg daily). There was no significant difference between the omapatrilat and lisinopril groups for the primary endpoint of treadmill walking time. However, the composite endpoint of death, hospitalization for heart failure, and discontinuation of the medication for worsening heart failure was significantly reduced by omapatrilat (48%), with a trend in favour of omapatrilat for each of the components of the composite endpoint. Furthermore, serious adverse events, and worsening of renal function was less frequent in omapatrilat-treated patients compared to those receiving lisinopril.

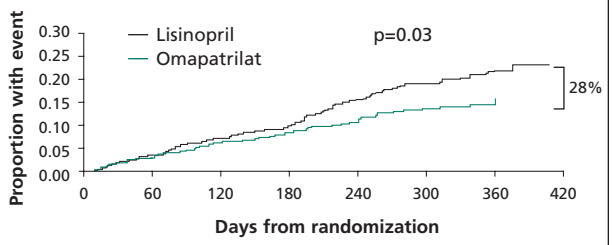
## Combined Analysis: IMPRESS and Safety Study

At the recent American College of Cardiology meeting, Kostis et al[9] reported further information about the benefits of omapatrilat for patients with cardiac failure. This report examined combined outcome data from the IMPRESS (CV137-28) and the Safety Study (CV137-08), which were similar randomized controlled trials comparing omapatrilat to lisinopril for patients with cardiac failure. In contrast to the exercise endpoint of IMPRESS, the Safety Study had adverse outcomes and discontinuation of medication as primary endpoint. The Safety Study used the same dose of lisinopril as IMPRESS, although the omapatrilat target dose was 20 mg as compared to 40 mg in IMPRESS.

The combined analysis chose the combined endpoint of death or rehospitalization for worsening heart failure. In the SOLVD treatment study, the ACE inhibitor enalapril had been shown to reduce this combined endpoint by 30% after a period of one year versus placebo. This combined analysis showed that over one year of omapatrilat significantly reduced the risk of death or rehospitalization for worsening heart failure, compared to lisinopril (Relative Risk (RR) 0.72, 95% CI, 0.53-0.97): Figure 2. There was a trend towards a reduction of all-cause mortality in the omapatrilat group (RR 0.75; 95% CI, 0.48-1.17). Omapatrilat also improved symptoms more than lisinopril, with a trend to greater improvement with the 40 mg dosage as compared to the 20 mg dose.

The reduced adverse outcomes in the omapatrilat-, compared to lisinopril-treated patients, were almost entirely the result of less cardiovascular events. Hospitalization for heart failure, invasive cardiac procedures, and syncope were all less in the omapatrilat group. Adverse side effects of treatment were less with omapatrilat than with lisinopril. Although hypotension was reported more frequently in the omapatrilat group, syncope occurred more often in patients treated with lisinopril. Renal function deteriorated less with omapatrilat compared to lisinopril. An increase in creatinine to more than 50% greater than baseline or to 1.5 times above the normal upper limit was observed in 9% of patients receiving lisinopril in comparison to 5.5% of the omapatrilat group ($p< 0.023$). A possi-

**Figure 2: Reduction of combined endpoint of death and hospitalization for heart failure by omapatrilat compared to lisinopril in the combined analysis of IMPRESS (CV137-28) and the Safety Study (CV137-08)**




ble explanation for this different effect on renal function is the drug's different vasodilatory effects on afferent and efferent glomerular arterioles. Whereas ACE inhibitors primarily dilate efferent arterioles and reduce glomerular perfusion pressure, NEP inhibition dilates both afferent and efferent vessels, thereby maintaining the pressure gradient for glomerular filtration.

These studies suggest potential advantages of VPIs above those of ACE inhibitors in the prevention of death and hospitalization for worsening heart failure. Furthermore, in these CHF studies, omapatrilat was better tolerated than lisinopril, with less symptomatic side-effects and serious renal dysfunction. Although the results of these preliminary studies are encouraging, we should wait for the results of randomized, controlled outcome trials. The definitive trial OVERTURE will enrol 4420 patients to either omapatrilat 40 mg daily or enalapril 10 mg twice daily. The primary endpoint of this trial is all-cause mortality or hospitalization for worsening heart failure.

## Safety and tolerability of omapatrilat

Omapatrilat is well tolerated with a safety record and side-effect profile similar to that observed with the ACE inhibitors. The application for FDA approval in the US was voluntarily delayed to collect more data to better establish the incidence and severity of angioedema. In the approximately 10,000 subjects exposed to omapatrilat, the incidence of angioedema was 0.5% in non-black subjects, which is similar to that observed with ACE inhibitors in the same population (0.1-1.0%).[10] The recently published HOPE study reported that angioedema occurred in 0.4% of subjects treated with ramipril.[11] As with ACE inhibitors,[12] black Americans had a four-fold increase in the incidence of angioedema as compared to non-black subjects. The severity of the angioedema observed with omapatrilat was relatively mild, with only 4 cases of airway compromise, all of which made a full recovery.

## Conclusions

Controlled clinical trials with omapatrilat show improved blood pressure control, with significantly greater reductions in pressures than with maximum doses of either amlodipine or lisinopril. In addition, pre-clinical studies suggest that vascular and cardiac remodelling may be improved by omapatrilat, which may result in reduced adverse vascular outcomes in hypertensive patients.

The studies in patients with heart failure suggest that omapatrilat reduces cardiac mortality and early rehospitalization for heart failure in comparison to treatment with the ACE inhibitor lisinopril. Trials currently underway, such as OVERTURE in heart failure and OPERA in hypertension, will further define clinical evidence to support the use of this promising new vasopeptidase inhibitor.

Omapatrilat has potential as a more effective antihypertensive agent and treatment modality for patients with heart failure than the current standards. The incidence of side-effects is similar to that observed with the ACE inhibitors, yet the benefits appear to be considerably greater.

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