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Vasopeptidase Inhibition (VPI): An important step towards improved hypertension control and CHF management

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Hypertension is a major risk factor for coronary artery disease, stroke, peripheral vascular disease, and renal failure. Hypertension is also an important cause of heart failure. The need for novel therapeutic agents that will more effectively control blood pressure is clear. Ideally, these new agents would also have a favorable impact on cardiac remodeling and heart failure. Vasopeptidase inhibition (VPI) is a novel concept in cardiovascular therapy. VPI involves the simultaneous inhibition, using a single agent, of two key enzymes involved in cardiovascular homeostasis, namely neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). Omapatrilat, the most clinically advanced VPI, is currently under priority review by both the FDA in the United States and the TPP in Canada. The following discussion explores the rationale for the use of VPIs in the treatment of hypertension and congestive heart failure and reviews the preclinical and clinical data of omapatrilat.

How well are we controlling hypertension in Canada?

The awareness, treatment, and control of hypertension in Canada has recently been examined and reported in the Canadian Heart Health Survey.[1] This survey took place in 10 provinces between 1986 and 1992. The survey involved 23,129 non-institutionalized, randomly selected subjects, aged 18 to 74 years. Hypertension, as defined by systolic or diastolic blood pressure ≥140 and 90 mm Hg, respectively, was found in 22% of participants, representing 4.1 million Canadians. Overall, 16% of respondents were treated *and* controlled; 23%, or 960,000 people, were treated but not controlled; 19% were not treated and not controlled; and 42% (47% of men and 35% of women), or 1.7 million people, were not even aware of their hypertension. Among the younger hypertensives (aged 18 to 34 years old), 64% of men and 19% of women were unaware of their hypertension.

To see how well we are controlling blood pressure in Canada, it is useful to compare our data with that from the United States as represented by the first (1971-1974), second (1976-1980), and third (1988-1991) National Health and Nutrition Examination Surveys (NHANES I, II, and III, respectively).[2,3] The US surveys involved subjects aged 18 to 74 years. During the interval between NHANES II and III, the threshold for defining hypertension was changed from 160/95 to 140/90 mm Hg. Age-adjusted prevalence of blood pressure ≥140/90 mm Hg peaked at 36.3% in NHANES I and declined to 20.4%, representing 43 million Americans, in NHANES III. Age-specific prevalence rates have decreased for every age-sex-race subgroup except for black men aged ≥50 years. In NHANES II (1976-80), only 10% had their blood pressure controlled <140/90 mm Hg, in NHANES III (1988-1991), this figure has increased to 29% (as compared to 16% in the Canadian Heart Health Survey). In NHANES III, 89% of those with blood pressure ≥160/95 mm Hg and 47% of those with blood pressure ≥140/90 mm Hg were aware of their hypertension.

Notwithstanding the limitations of comparing two national surveys with slightly different designs, the control of hypertension in Canada appears to be less optimal than that of the United States (Figure 1).

Vasopeptidase inhibition: a new concept in cardiovascular disease management

Fluid volume and arterial blood pressure are regulated in part by an interaction of several neurohormonal systems.

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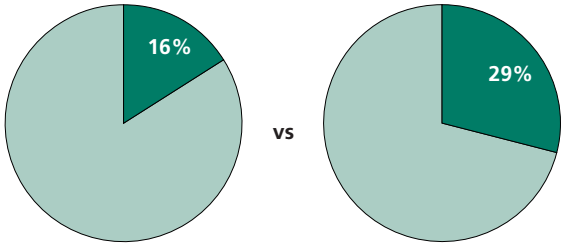
Figure 1: Control of hypertension; % patients with BP controlled <140/90 mm Hg[1,3]



Among these are the "vasoconstrictor" renin-angiotensin-aldosterone system (RAAS), as well as the counter-regulatory "vasodilator" kallikrein-kinin system, and the natriuretic peptide (NP) system. While the RAAS has been used extensively as a therapeutic target in the treatment of various cardiovascular disorders, the endogenous vasodilator systems have not been as extensively explored or utilized.

The NP family consists of atrial, brain, and C-type natriuretic peptide (ANP, BNP and CNP, respectively) with strikingly similar morphology and biologic activity.[4] As summarized in Table 1, many of the biologic actions of the NP family are the opposite of those of the RAAS, suggesting that the NP system may play a key role in modulating the effects of RAAS. In addition, the NP system acts in a paracrine manner to inhibit proliferation of vascular smooth muscle and collagen, effects that may ameliorate vascular and cardiac remodeling.[4,5] The NP system exerts its effects through activation of receptors linked to *particulate* guanylate cyclase, resulting in the generation of the second messenger cGMP. On the other hand, nitric oxide (NO) acts through receptors linked to *soluble* guanylate cyclase. The NP and NO system can therefore be considered as dual vasodilator humoral pathways that act through cGMP. The latest addition to the endogenous vasodilator peptide family is adrenomedullin, a 52 amino acid peptide originally discovered in human pheochromocytoma tissue.[6] Adrenomedullin possesses a multitude of biologic effects that include vasodilation and diuresis. Unlike the NP family, the biologic actions of adrenomedullin are mediated by a number of second messenger systems including cAMP, NO, intracellular calcium, and tissue prostaglandins.

Neutral endopeptidase (NEP) is a membrane-bound metalloenzyme with zinc at its center that serves to cleave endogenous peptides on the amino side of hydrophobic residue.[7] The enzyme is located at the cell surface of many organ systems and is the principal enzyme responsible for the degradation of NP, bradykinin (BK), as well as adrenomedullin.[8-10] Because of the vasodilatory and potentially cardioprotective effects of these endogenous vasodilator systems,

Table 1: Biologic actions of the RAAS and the NP system

	Biologic actions
RAAS	Vasoconstriction
	Sodium retention
	↑aldosterone release
	↑cell growth
	↑sympathetic activity
NP system (ANP, BNP CNP)	Vasodilation
	Sodium excretion
	↓ aldosterone
	Inhibition of sympathetic activity
	Vasodilation
	↓ vascular smooth muscle cell growth
	↓ aldosterone

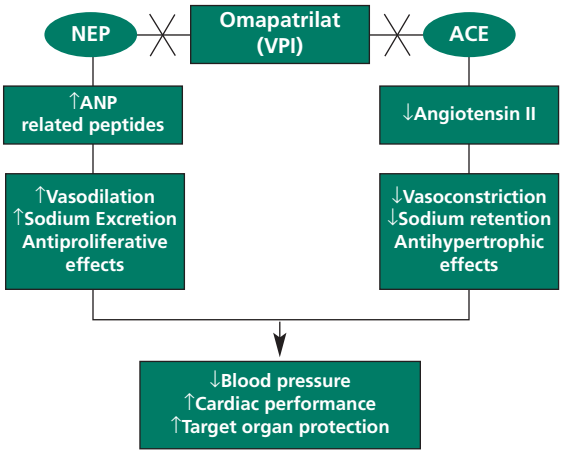
RAAS = renin-angiotensin-aldosterone system
NP = natriuretic peptide
ANP, BNP and CNP = atrial, brain and C-type natriuretic peptide, respectively

a logical therapeutic strategy is to enhance these systems by selectively inhibiting NEP. However, clinical trials that examined the effects of NEP inhibition alone revealed relatively limited ability of these agents to lower systemic blood pressure despite an increase in urinary ANP and cGMP excretion.[10] It is quite likely that, at least in the case of heart failure, increased angiotensin II and other vasoactive peptides may compromise the beneficial effects of selective NEP inhibition.[12,13] It has been appreciated for some time that the active sites of ACE and NEP share some structural and functional properties. Both ACE and NEP are cell membrane-bound zinc metallopeptidases, with close homology at their catalytic sites and several common substrates. Based on these considerations, inhibition of ACE and NEP using a single molecule is both feasible and may be potentially of therapeutic benefit (Figure 2).[11]

The development of omapatrilat, a VPI, allows for the first time the simultaneous inhibition of ACE and NEP.[11] Omapatrilat (Figure 3) inhibits both ACE (Ki 6.0 nM) and NEP (Ki 8.9 nM). Thus, omapatrilat has *similar* potency against both enzymes, a very important attribute in the design of a molecule to simultaneously inhibit two enzyme systems.

Until recently, the benefits seen with ACE inhibitors in heart failure were mainly attributed to the prevention of angiotensin II formation. It is now postulated that blockade of angiotensin II with ACE inhibitors only account for a part of the associated benefit. A substantial proportion of the cardiovascular protective properties attributed to ACE inhibition are due to a reduction in bradykinin metabolism

Figure 2: VPI mode of action

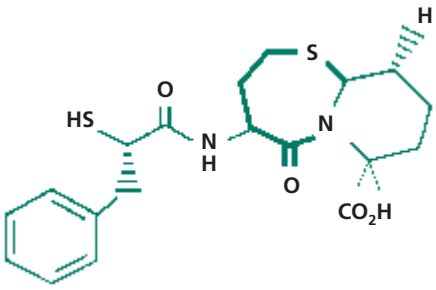


and an increase in desirable molecules like nitric oxide. If a significant proportion of ACE inhibitor benefit is due to its ability to increase endogenous vasodilator compounds, it is reasonable to expect that VPIs, which block both NEP and ACE and increase NO even more than ACE inhibitors alone, may provide an additional benefit in hypertension and heart failure than standard therapy.

Bradykinin: A potential target for therapy

The vasodilatory and anti-proliferative effects of bradykinin (BK)[14] make it a potential target of therapy for cardiovascular disorders. Indeed, experimental data have suggested that the cardiac anti-remodeling effect of angiotensin-converting enzyme (ACE) inhibitors might be mediated predominantly by the preservation of BK .[14,15]

Figure 3: Omapatrilat – Potent vasopeptidase inhibitor



Enzyme	K_i (nM)
Neutral endopeptidase (NEP)	8.9
Angiotensin-converting enzyme (ACE)	6.0

No inhibition (100 µM) of metalloproteases (collagenase, carboxypeptidase A carboxypeptidase B, aminopeptidase, endothelin converting enzyme, matrix metalloproteases)

In vitro, several enzymes, including the metallopeptidases, have been shown to metabolize BK.[16] *In vivo*, ACE is the key enzyme responsible for the metabolism of BK in many biologic systems, including cardiac membranes.[17,18] Neutral endopeptidase (NEP) is also an important metabolic pathway for BK in the endothelium of the rat coronary vascular bed and becomes evident when ACE is inhibited.[19]

The relative role of ACE and NEP in the degradation of BK in pathophysiologic state was recently examined in the rat with myocardial infarction (MI) induced by coronary artery ligation.[20] Co-incubation with the ACE inhibitor enalaprilat significantly increased the half-life of BK. This was further increased with the VPI omapatrilat. These data indicate that both ACE and NEP participate in the degradation of BK in this MI model, suggesting that inhibition of both ACE and NEP may augment BK. This may have beneficial effects in the treatment of left ventricular remodeling and heart failure.

Pre-clinical pharmacology of omapatrilat

Omapatrilat lowers blood pressure in experimental models of hypertension regardless of sodium status or the degree of activation of the RAAS.[11,21,22] In a recent study,[22] omapatrilat was demonstrated to reduce arterial blood pressure to a similar magnitude in conscious rats with low renin, the deoxycoticosterone-acetate (DOCA) rats; normal renin, sodium-replete spontaneously hypertensive rats (SHR); and high renin (sodium-depleted SHR) hypertension. The ability of omapatrilat to reduce blood pressure regardless of renin status suggests the possibility that VPI can be more effective than ACE inhibition alone in the treatment of hypertension because of its potential applicability to a broad range of patient subsets.

In animal models of heart failure, omapatrilat has been shown to improve hemodynamic status as compared to ACE inhibition alone.[18] In a model of tachycardia-induced heart failure, omapatrilat improved myocyte basal contractility and improved ß-adrenergic receptor sensitivity.[23] The effects of omapatrilat and the ACE inhibitor captopril were compared recently in a cardiomyopathic hamster model.[24] As expected, omapatrilat increased urinary ANP excretion and reduced left ventricular end diastolic pressure. Importantly, compared to controls, animals treated with omapatrilat had a 98% increase in survival versus a 51% improvement in survival observed in the animals treated with captopril.

Omapatrilat, systolic and pulse pressure control: raising the standard for hypertension management

Until recently, diastolic blood pressure (DBP) has been considered more important than systolic blood pressure (SBP) in the management of hypertension. The large meta-analysis of nine prospectively observational studies by MacMahon et al[25] focused mainly on DBP. Indeed, in the recently published

HOT study,[26] a blood pressure treatment target goal was defined only for DBP. However, recent epidemiologic data have confirmed that SBP may be more important than DBP as a risk factor.[27,28] Treatment benefits also appear to correlate more closely with reduction in SBP than DBP.[29] Without a doubt, elevated SBP appears to be much more difficult to control than DBP, as evident from observations from the HOT and ALLHAT trials.[26,30] Because elevated SBP is an important risk factor for cardiovascular events, it is important that studies include SBP in the assessment of therapeutic efficacy; agents that reduce SBP most efficiently will likely be the most effective in reducing risk.

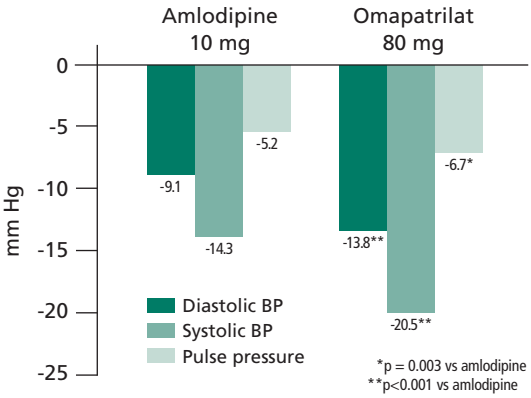
Pulse pressure has recently received attention as a prognostic marker. Pulse pressure increases substantially in the elderly because of increasing SBP and declining DBP with advancing age. Recent studies have suggested that pulse pressure may be a more important risk factor than SBP or DBP measured separately.[31,32] In the study by Madhavan et al,[31] patients at the highest tertile of pulse pressure (ie, 63 mm Hg) had significantly greater risk for MI, stroke, and cardiovascular deaths.

Controlling blood pressure alone, whether it is DBP, SBP, or pulse pressure, may still not be sufficient to prevent unfavorable clinical events. Attention should be given to the management of other risk factors, as well as protection from organ damage. Indeed, antihypertensive agents that have strong organ-protection properties will likely be most effective in reducing clinical events.

VPI, through its unique and novel mechanism of action reviewed earlier, is particularly promising in this regard. In a recent study, the effects of omapatrilat at 5 to 40 mg daily were compared with the ACE inhibitor lisinopril, 20 mg daily, and placebo in a 9-week trial in patients with DBP 95-110 mm Hg.[33] Omapatrilat produced significant and dose-dependent reduction in trough and peak SBP and DBP. At a dose of 20 mg, 40 mg, and 80 mg of omapatrilat, the reductions in SBP were significantly greater than that of lisinopril at doses of 20 mg and 40 mg. In African-American patients, the changes in SBP/DBP/pulse pressure were -16.8/-11.4/-5.5 mm Hg with 40 mg of omapatrilat versus only -0.9/-5.1/+4.2 mm Hg with 20 mg of lisinopril. In patients >65 years of age, the changes in SBP/DBP/pulse pressure were -17.1/-10.6/-6.4 mm Hg with 40 mg of omapatrilat versus -8.5/-10.6/+2.1 mm Hg with 20 mg of lisinopril. The number of drug-related adverse events were similar to lisinopril. These data therefore suggest that omapatrilat at 20, 40, and 80 mg reduces blood pressure more effectively than lisinopril. Furthermore, the superiority of VPI over ACE inhibition in blood pressure lowering appears to be maintained regardless of race or the age range studied in these trials.

In two randomized, double-blind, multi-center, 24-hour ambulatory BP trials, omapatrilat also reduced

Figure 4: Omapatrilat vs amlodipine: 24-hr ambulatory BP at week 10.



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both SBP and DBP significantly better than several classes of agents, achieving reductions of around 20 mm Hg. One study compared 80 mg of omapatrilat to 40 mg of lisinopril in hypertensive patients after 10 weeks. Mean 24-hour SBP was reduced by 19 mm Hg with omapatrilat vs 12.2 mm Hg with lisinopril, and DBP was reduced by 10.5 mm Hg with omapatrilat vs 7.5 mm Hg with lisinopril (n=347, p<0.001).[34]

Another study compared omapatrilat 80 mg to amlodipine 10 mg in 430 patients with mild to moderate hypertension. The study also demonstrated that 24-hour SBP and DBP reductions, as measured by ambulatory monitoring, were significantly greater with omapatrilat over the 10-week study period. Mean 24-hour SBP was reduced by 20.5 mm Hg with omapatrilat vs 14.3 mm Hg with amlodipine, and DBP was reduced by 13.8 mm Hg with omapatrilat vs 9.1 mm Hg with amlodipine (n=430, p<0.001) (Figure 4).

Omapatrilat: potential utility in heart failure

The unique mechanism of action and the organ-protective effects of VPI also make omapatrilat a potentially useful agent in the treatment of heart failure. The potent beneficial hemodynamic effects of omapatrilat have been reviewed in detail in a previous edition of *Cardiology Scientific Update*. In brief, the *long term* hemodynamic effects of omapatrilat were assessed in a study that involved a 12-week administration of a wide range of doses of omapatrilat to patients with heart failure with New York Heart Association (NYHA) class II to IV symptoms and left ventricular ejection fraction <40%. Patients underwent two invasive hemodynamic assessments, the first after receiving the first dose of omapatrilat and the second after taking the final dose of omapatrilat at the end of 12 weeks. Three hundred and sixty nine patients were

randomized to doses up to 40 mg of omapatrilat daily. Omapatrilat produced a dose-dependent reduction of pulmonary capillary wedge pressure. These hemodynamic effects were *sustained* at 12 weeks. Furthermore, these beneficial effects were also observed at both the baseline and 12-week assessment. There was a significant dose-dependent decline in systolic arterial pressure. Importantly, there was no significant change in heart rate. Cardiac index did not increase significantly, but there was a trend for left ventricular ejection fraction to increase over the 12-week period (22% at baseline to 27% at 12 weeks for the 40 mg dose, odds ratio 2.3, CI -0.8, 5.4) observed in this study.

IMPRESS

The largest randomized controlled trial of omapatrilat completed to date on patients with heart failure is the "Inhibition of MetalloProtease in a Randomized Exercise and Symptom Study in heart failure" (IMPRESS) trial. In this multicenter trial, 573 patients with heart failure and NYHA class II-IV symptoms were randomized to 24-week therapy of omapatrilat, uptitrated from 10 mg to a target dose 40 mg daily, or lisinopril, uptitrated from 5 mg to a target of 20 mg daily. The *primary* endpoint of the study was treadmill exercise tolerance determined at week 12 of treatment. The *secondary* endpoints were NYHA functional class and the combined clinical endpoint of mortality, hospitalization due to heart failure, and discontinuation of study medication. The two groups were comparable in baseline characteristics. The majority had NYHA class II symptoms and over 60% had ischemic etiology for the heart failure.

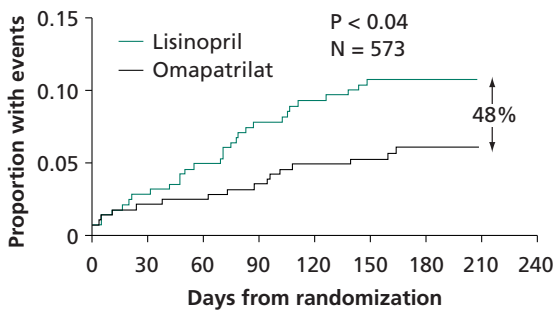
At the end of the three-week titration period, 88% of the omapatrilat group and 94% of the lisinopril group reached the target dose. Thirty-one patients in the omapatrilat group and 34 patients in the lisinopril groups discontinued their study medications. There was no significant difference between the omapatrilat and the lisinopril group in the change in treadmill walking time. Slightly more patients improved their NYHA functional class in the omapatrilat group than in the lisinopril group. When only NYHA class III-IV patients were considered, the differences were significant. Overall, there was a significant 48% reduction in the composite clinical endpoint of death, hospitalization for heart failure, and discontinuation of study drug with a trend favoring omapatrilat in each of the components (Figure 5). These clinical outcomes are very encouraging. However, IMPRESS was not designed primarily to assess events. Research with omapatrilat is now underway to confirm these results in heart failure.

Table 2: The IMPRESS study: renal function

	Omapatrilat (n=289)	Lisinopril (n=284)
BUN 2 times normal	2.5%	6.8%*
Creatinine 1.5 times normal	1.8%	6.1%*
Renal failure as adverse event	1.0%	2.1%*

* p<0.05 versus omapatrilat

Figure 5: IMPRESS: Event curves for death/HF hospitalization/discontinuation due to worsening HF



Frequency of serious adverse events in IMPRESS was less in the omapatrilat group (17%) than in the lisinopril group (23%). Data for abnormalities of renal function are displayed in Table 2. The omapatrilat-treated patients experienced significantly less worsening of renal function compared to the lisinopril-treated patients. Data from the IMPRESS study therefore suggest that omapatrilat is superior to lisinopril in improvement of symptoms in patients with NYHA class II-IV heart failure. Omapatrilat also produces less drug-related adverse events and worsening of renal function.

OVERTURE

The ongoing "Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events" (OVERTURE) is an international, randomized, controlled, double-blind study designed to compare the effect of omapatrilat and enalapril on hard clinical outcomes. The primary endpoint will be all-cause mortality or hospitalization for heart failure. Secondary endpoints will include all-cause mortality, cardiovascular death or hospitalization, NYHA class, and composite endpoint of cardiovascular death, stroke, MI, or revascularization. It is estimated that 4,400 patients will be randomized and that the study will last for 1.5 to 3 years. Dr. Malcolm Arnold (London) is the Canadian Coordinator of the study whose executive committee includes Dr. J.L. Rouleau (Toronto).

Omapatrilat: future development

At the time of writing of this review, close to 10,000 patients have participated in the clinical research program of omapatrilat. The greatest experience with the use of omapatrilat is in hypertension with >6950 patients evaluated, followed by heart failure with >1550 patients studied. The rest are spread between the stable angina program with >600 patients, as well as clinical pharmacokinetic studies with >730 patients evaluated. Large-scale clinical outcome studies of omapatrilat include the OVERTURE study (reviewed above), as well as the "Omapatrilat in Patients with Enhanced Risk of Atherosclerotic events" (OPERA) study. The OPERA study will evaluate the impact of omapatrilat on strokes, MI, heart failure, and cardiovascular deaths in about 12,600 patients at risk for these clinical events. Dr. Pierre Larochelle (Montreal) is the Canadian coordinator of the OPERA Trial and is on its steering committee.

Conclusion

National and international guidelines for the management of hypertension recommend aggressive targets which, for the most part, are not being achieved with current therapies. Clearly, in order to decrease morbidity and mortality associated with hypertension and heart failure, better options are needed.

Data from the first agent in the VPI class is promising as it can dramatically lower systolic, diastolic, and pulse pressure while maintaining the potential for benefits beyond BP reduction associated with ACE inhibition, and increased natriuretic peptides (ANP, BNP, etc.) on the sympathetic system and endothelial function, cellular growth and proliferation.

The results from ongoing international morbidity and mortality trials in hypertension (OPERA) and heart failure (OVERTURE) will be important additions to the currently available evidence for the benefits of VPIs.

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