Cardiovascular Drugs

Vasopeptidase Inhibitors
A New Therapeutic Concept in Cardiovascular Disease?
Roberto Corti, MD; John C. Burnett, Jr, MD; Jean L. Rouleau, MD; Frank Ruschitzka, MD; Thomas F. Lüscher, MD

Abstract—The cardiovascular system is regulated by hemodynamic and neurohumoral mechanisms. These regulatory systems play a key role in modulating cardiac function, vascular tone, and structure. Although neurohumoral systems are essential in vascular homeostasis, they become maladaptive in disease states such as hypertension, coronary disease, and heart failure. The clinical success of ACE inhibitors has led to efforts to block other humoral systems. Neutral endopeptidase (NEP) is an endothelial cell surface zinc metallopeptidase with similar structure and catalytic site. NEP is the major enzymatic pathway for degradation of natriuretic peptides, a secondary enzymatic pathway for degradation of kinins, and adrenomedullin. The natriuretic peptides can be viewed as endogenous inhibitors of the renin-angiotensin system. Inhibition of NEP increases levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) of myocardial cell origin, and C-type natriuretic peptide (CNP) of endothelial cell origin as well as bradykinin and adrenomedullin. By simultaneously inhibiting the renin-angiotensin-aldosterone system and potentiating the natriuretic peptide and kinin systems, vasopeptidase inhibitors reduce vasoconstriction, enhance vasodilation, improve sodium/water balance, and, in turn, decrease peripheral vascular resistance and blood pressure and improve local blood flow. Within the blood vessel wall, this leads to a reduction of vasoconstrictor and proliferative mediators such as angiotensin II and increased local levels of bradykinin (and, in turn, nitric oxide) and natriuretic peptides. Preliminary clinical experiences with vasopeptidase inhibitors are encouraging. Thus, the combined inhibition of ACE and neutral endopeptidase is a new and promising approach to treat patients with hypertension, atherosclerosis, or heart failure. (Circulation. 2001;104:1856-1862.)

Key Words: hypertension ■ heart failure ■ treatment

Structural, humoral, and neuronal factors are involved in cardiovascular regulation, among them the sympathetic and parasympathetic nervous systems and renin-angiotensin-aldosterone system (RAAS). The endothelium is a source of paracrine mediators such as nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and endothelin (Figure 1). Circulating and local regulatory mediators exhibit complex synergisms and interactions; the sympathetic nervous system stimulates secretion of renin and angiotensin (Ang) II, which centrally and at the presynaptic level increase sympathetic nerve activity and enhance endothelin and vasopressin production. The natriuretic peptide system, consisting of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), of myocardial origin, and C-type natriuretic peptide (CNP), of endothelial origin, on the other hand, counteracts the RAAS and endothelin. Endothelial substances act primarily locally and exhibit vasoconstrictor, vasodilating, and mitogenic effects. Some endothelial substances stimulate the production of cytokines and growth factors, leading to vascular smooth muscle cell proliferation. All these regulatory systems are crucial for proper circulatory homeostasis and for structural vascular and myocardial regulation.

Vascular Effects of ACE Inhibitors
ACE is located mainly on endothelial cells, where it transforms Ang I into Ang II and degrades bradykinin, a potent stimulus of the l-arginine and cyclooxygenase pathways1 (Figure 1). Therefore, ACE inhibitors not only prevent the formation of a potent vasoconstrictor with proliferative properties but also increase local concentrations of bradykinin and, in turn, the production of NO2 and prostacyclin.3 The latter may participate in the vascular protective effects of ACE inhibitors by improving local blood flow and preventing platelet activation. Accordingly, pretreatment of human saphenous vein and coronary artery with ACE inhibitors enhances endothelium-dependent relaxation to bradykinin. The decreased degradation of bradykinin could therefore explain the improved endothelial function observed with ACE inhibitors in normotensive and particularly in hypertensive rats.

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The improvement of endothelial function by ACE inhibitors in NG-nitro-L-arginine methyl ester–induced hypertension, however, suggests that they also enhance endothelium-dependent mediators other than NO (ie, EDHF), because the activity of endothelial NO synthase (eNOS) remains suppressed in this model. Moreover, ACE inhibitors stabilize the activity of B1-bradykininergic receptors independently of effects on bradykinin metabolism, because stable analogues of bradykinin, which are not inactivated by chymase II or ACE, also exhibit enhanced endothelium-dependent relaxation in the presence of an ACE inhibitor. The effects of ACE inhibitors need time to develop and can be reproduced only in part in the short term, again suggesting that mechanisms other than ACE inhibition that are rapid are involved. Indeed, in salt-induced hypertension in Dahl rats and in postinfarction rats, diminished eNOS expression is restored during long-term ACE inhibition.

In contrast to striking improvements in experimental hypertension, studies in hypertensives revealed controversial results. ACE inhibitors somewhat improved endothelial function in subcutaneous arteries and in the renal circulation. In the forearm circulation, however, captopril and enalapril or cilazapril failed to improve vasodilation to a muscarinic agonist, whereas lisinopril selectively improved vasodilation to bradykinin without restoring NO bioavailability. The reasons for this discrepancy are unclear. Different explanations have been suggested, including the fact that they have not been studied at comparable doses with respect to their dose-response curves. In addition, endothelial dysfunction certainly is treated at later stages in patients than in experimental hypertension. Alternatively, duration of therapy and differences in tissue selectivity may be important. Indeed, in normal subjects, ACE inhibitors, such as quinaprilat, with high tissue selectivity have vascular effects that are not shared by enalapril. In patients with coronary artery disease, 6 months of treatment with quinapril improved endothelium-dependent vasomotion to acetylcholine in epicardial coronary arteries and in part in the coronary microcirculation. Quinaprilat also improves flow-dependent dilation in congestive heart failure (CHF) as the result of increased availability of NO, whereas enalaprilat does not.

The mechanisms involved may be related to inhibition of angiotensin formation and/or stimulation of the L-arginine/NO pathway. Many studies documented the existence of a kallikrein-kinin system in myocardial and vascular tissue. The antihypertensive and cardioprotective effect of ACE inhibitors has been explained in part as a consequence of diminished kinin degradation, resulting in the increase of endothelial NO production (Figure 1). Indeed, studies of recombinant full-length ACE have shown that the Km of ACE for bradykinin is substantially lower than for Ang I, reflecting a greater affinity for metabolism of bradykinin than for the production of Ang II. ACE is the major enzyme responsible for the metabolism of bradykinin, the exact percentage varying according to the tissue and species being evaluated. In endothelium and cardiac tissues, ACE is the major enzyme involved in the degradation of bradykinin regardless of species. The other enzymes involved in the metabolism of bradykinin include carboxypeptidases, neutral endopeptidases, and aminopeptidase P. ACE is also a major metabolic pathway for the degradation of one of the metabolites of bradykinin, des-arg9-bradykinin, which in certain situations in which its receptors are expressed (inflammatory situations), the B1-receptor can have the same effects as bradykinin.

**Clinical Effects of ACE Inhibitors**

ACE inhibitors decrease systemic vascular resistance without increasing heart rate and promote natriuresis. The favorable effect of ACE inhibition has been documented in many large, randomized trials in hypertension, after myocardial infarction, and in CHF. More recently, they have been shown to decrease clinical events in high-risk patients with atherosclerosis with and without ventricular dysfunction and before and after myocardial infarction. Moreover, the HOPE study confirmed that ACE inhibitors are vascular-protective independent of their effects on blood pressure and ventricular remodeling.

The clinical effects of ACE inhibitors in the treatment of hypertension and CHF underline the importance of neurohumoral blockade. Since the introduction of captopril in 1975, many long-acting molecules have been developed. Despite their clinical efficacy, however, a substantial number of...
Natriuretic Peptides Have Contrasting Biological Effects to Ang II

<table>
<thead>
<tr>
<th>Angiotensin II</th>
<th>Natriuretic Peptides</th>
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<tr>
<td>↑ Blood pressure</td>
<td>↓</td>
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<tr>
<td>↓ Renal sodium secretion</td>
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<tr>
<td>↑ Aldosterone</td>
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<td>↓ Renin secretion</td>
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<td>↑ Cell proliferation</td>
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<td>↑ Hypertrophy</td>
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Natriuretic Peptides

The family of natriuretic peptides consists of 3 isoforms: ANP, BNP, and CNP. Both ANP and BNP are synthesized in the atrium of the heart under physiological conditions and in the ventricles (BNP) in the presence of ventricular hypertrophy, and CNP in endothelial cells. ANP infusion reduces blood pressure while increasing urine volume, urinary excretion of sodium, and cyclic GMP, inhibits renin and aldosterone secretion, and increases the hypertensive effect of BNP. Moreover, ANP inhibits endothelin production and proliferation of vascular smooth muscle cells and myocardial hypertrophy, and ANP has been shown to have significant sympatholytic effects as well. Because of its biological effect (as an antagonist to Ang II), ANP is an endogenous inhibitor of the RAAS (Table). ANP and BNP production in the myocardium is induced by increased atrial pressure, as may occur with increased sodium intake and by decreased left ventricular function (systolic and diastolic left ventricular dysfunction).

A hallmark of ventricular remodeling secondary to heart failure or left ventricular hypertrophy is the increase in plasma ANP and BNP. Although the increased circulating natriuretic peptides may prevent water and sodium retention, progressive CHF is associated with a relative decrease of ANP production in association with an escape phenomenon of the RAAS leading to increased water and sodium retention.

Circulating ANP, BNP, and CNP are quickly metabolized and inactivated by the specific enzyme, the widely scattered neutral endopeptidases (Figure 1), as well as by cell-surface clearance receptor. The short half-life of the natriuretic peptides, as well as the fact that a peptide is difficult to administer and expensive to produce, limits the option of an exogenous application of the peptide as a possible therapeutic strategy. It should be noted that BNP has emerged as an efficacious intravenous agent for the treatment of CHF. Therefore, pharmacological inhibition of the metabolism of hypertensives are not adequately controlled with ACE inhibitors and need combination therapy with diuretics, β-blockers, and/or calcium antagonists. Furthermore, clinical studies in early stages of CHF demonstrated that ACE inhibitors are less effective in patients with high levels of ANP, epinephrine, and renin activity. Also, morbidity and mortality remain high in patients with CHF on ACE. Thus, the development of new drugs that act on neurohumoral systems other than the RAAS may be advantageous.

Neutral Endopeptidases

Neutral endopeptidase (NEP) is an endothelial, membrane-bound metalloproteinase with zinc at its active site that cleaves endogenous peptides at the amino side of hydrophilic residues (Figure 1). The membrane-bound metalloproteinase has a catalytic unit similar to that of ACE. NEP is widely distributed in endothelial cells, smooth muscle cells, cardiac myocytes, renal epithelial cells, and fibroblasts. NEP is also found in the lung, gut, adrenal glands, brain, and heart. It catalyzes the degradation of vasodilator peptides, including ANP, BNP, CNP, substance P, and Bradykinin, as well as vasoconstrictor peptides, including endothelin-1 and Ang II. It was recently shown that the potent vasodilating natriuretic peptide adrenomedulin is also a substrate for NEP.

Selective NEP inhibitors prevent, in vitro and in vivo, the degradation of natriuretic peptides and increase their biological activity. In addition to degrading vasoactive peptides to inactive products, NEP is also involved in the enzymatic conversion of big endothelin to its active form, the vasoconstrictor peptide endothelin-1. Hence, the balance of effects of NEP inhibition on vascular tone will depend on whether the predominant substrates degraded are vasodilators or vasoconstrictors and on the extent of NEP involvement in the processing of big endothelin-1 (Figure 1). Indeed, in the human forearm circulation, certain NEP inhibitors cause vasoconstriction rather than vasodilatation, indicating that vasoconstrictor peptides, such as Ang II and endothelin-1, can be substrates for NEP. This explains why NEP inhibitors, such as candesartan, thiorphan, and phosphoramidon, increase circulating ANP concentrations in humans and induce natriuresis (Figure 2) but do not lower or may even increase blood pressure in normotensives. In essential hypertension, certain NEP inhibitors lower blood pressure. Long-term treatment with NEP inhibitors augments the effects of ANP and lowers blood pressure in hypertension. The antihypertensive effects may be offset, however, by an increased activity of the RAAS and sympathetic nervous system (SNS), RAAS, ANP, and local mediators. ET-1 indicates endothelin; AT II, Ang II.
system and/or by downregulation of ANP receptors. The blood pressure response to endopeptidase inhibition in hypertension depends on the relative effects on vasodilator (including ANP) and vasoconstrictor (including the RAAS and sympathetic) systems.

NEP is also involved in the metabolism of kinins. In most tissues, NEP accounts for only a small portion of the metabolism of kinins, but in human cardiac tissue, NEP accounts for nearly half of the metabolism of bradykinin.26 When ACE is inhibited, however, NEP becomes a major pathway for bradykinin metabolism. In experimental studies, the reduction of ischemia and reperfusion damage after NEP inhibition is kinin-mediated.27 Interestingly, in hypertension, the selective NEP inhibitor candoxatril led to only minimal blood pressure reduction, whereas its combination with an ACE inhibitor caused a marked decrease in blood pressure.28 In patients with CHF, NEP inhibitors do not reduce afterload, although they do reduce pulmonary capillary wedge pressure, presumably because of their natriuretic effect and vasodilating properties. In moderate to severe CHF, short-term NEP inhibition induces dose-dependent diuresis.29 whereas long-term treatment does not provide this benefit. In dogs with evolving CHF, long-term NEP inhibition causes modest improvement in sodium excretion and enhances the renal response to exogenous ANP, suggesting upregulation of NEP in CHF. Thus, the enzymatic degradation by NEP limits renal responses to increased ANP in chronic CHF, independently of changes in systemic hemodynamic and augmented plasma concentrations of ANP.22 Other possible explanations for the insufficiency of NEP inhibitors in CHF are tolerance to ANP, most likely due to downregulation of ANP receptors, and/or activation of the RAAS.

### Combined ACE and NEP Inhibition

In many cardiovascular diseases, an array of regulatory mechanisms are involved, making drugs with multiple modes of action promising. Because ACE inhibition leads to normalization of the physiological effect of ANP and NEP inhibitors lower blood pressure more effectively in salt- and volume-dependent than in renin-dependent forms of hypertension, the combination of ACE and NEP inhibition may be especially useful in hypertension and CHF.

Indeed, in hypertension and CHF, the hemodynamic and renal effects (ie, urine volume and sodium excretion) achieved after simultaneous inhibition of ACE and NEP are more pronounced than after selective inhibition of both enzymes.

The synergistic effect of combined NEP and ACE inhibition is based on similar modes of action (Figure 1), including blockade of angiotensin synthesis and simultaneous unmasking and potentiation of the effects of peptides, such as ANP, BNP, and bradykinin (by preventing their degradation), in turn inducing vasodilatation and diuresis and improving myocardial function. The earliest dual metalloproteinase inhibitors had limitations because of low potency, short duration of action, or limited oral bioavailability. The new vasopeptidase inhibitors (Figure 3) exhibit long-lasting and potent effects in the cardiovascular system.

### ACE/NEP Inhibition in Hypertension


drug inhibition on aortic eNOS expression (A), endothelium-dependent relaxations to acetylcholine (B), and plasma levels of ANP (C) in salt-sensitive hypertensive Dahl rats. Although the 2 drugs increased eNOS similarly, only omapatrilat elevated ANP and normalized endothelium-dependent relaxations. Results are shown as mean±SEM. *P<0.05 vs control rats and vs treatment groups. †P<0.05 vs control. ‡P<0.05 vs salt-treated group. #P<0.05 vs salt-plus-omapatrilat (Omap) group. Capt indicates captopril. 

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[Figure 3. Dual vasopeptidase inhibitors: In animal models, various molecules displayed different selective inhibitory activity against NEP and ACE. Dual metalloproteinase inhibitors are more potent in hypertension or treatment of CHF than selective inhibition of ACE or NEP alone.]

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Omapatrilat IC50 (nM)</th>
<th>Fasidotrilat IC50 (nM)</th>
<th>Sampatrilat IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral endopeptidase</td>
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<td>5.1</td>
<td>8.0</td>
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<tr>
<td>Angiotensin-converting enzyme</td>
<td>0.5</td>
<td>9.8</td>
<td>1.2</td>
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Omapatrilat increased ANF levels and normalized endothelial function of resistance arteries in this model.32 Unaltered, suggesting that omapatrilat improves structure and function of small arteries.31 In stroke-prone spontaneously hypertensive rats, a greater decrease in pulmonary capillary wedge pressure.40 The pronounced effects of omapatrilat on systolic pressure are intriguing and suggest that large-artery compliance and structure may be favorably affected. Because systolic hypertension is difficult to treat, these new drugs may address unmet needs in the management of hypertension.

Sampatrilat, another ACE/NEP inhibitor, has been tested in hypertensives. Increasing dosages of sampatrilat (50, 100, and 200 mg) administered for 10 days lowered clinic and ambulatory blood pressure, with a trend toward a dose response for systolic ambulatory blood pressure. Sampatrilat inhibited plasma ACE in a dose-dependent fashion but less so than lisinopril (20 mg/d).36 Lisinopril but not sampatrilat increased plasma renin activity, whereas sampatrilat but not lisinopril increased urinary cGMP excretion. A study performed in 58 black hypertensive subjects, who are known to be poorly responsive to ACE monotherapy, confirmed these results.37

ACE/NEP Inhibition in CHF

In cardiomyopathic hamsters with CHF, short-term administration of omapatrilat reduces left ventricular systolic and end-diastolic pressure. These changes were associated with a 40% increase in cardiac output and a 47% decrease in peripheral vascular resistance and were significantly greater after administration of omapatrilat than with SQ-28603 (a selective NEP inhibitor) or the ACE inhibitor enalapril.38 In cardiomyopathic hamsters, long-term vasopeptidase inhibition with omapatrilat improves cardiac geometry and survival more than captopril.39

In an experimental canine model of CHF, omapatrilat was superior to ACE inhibition alone in inducing an increase in sodium excretion and glomerular filtration rate, in addition to a greater decrease in pulmonary capillary wedge pressure.40 Most importantly, these cardiorenal actions were markedly attenuated by a natriuretic peptide receptor antagonist, underscoring that the endogenous natriuretic peptides in part mediate the actions of omapatrilat.

In 48 patients with CHF (NYHA class II to IV), treatment with omapatrilat for 3 months reduced afterload and improved cardiac function and in turn clinical status. Ejection fraction increased from 24% to 28%, whereas myocardial wall stress and heart rate decreased. Moreover, natriuresis increased and norepinephrine levels decreased.41 In a randomized, double-blind study in 369 patients with CHF, omapatrilat decreased blood pressure in a dose-dependent manner.

Omapatrilat administered once daily to spontaneously hypertensive rats on low sodium (high-renin model of hypertension) or deoxycorticosterone acetate salt hypertensive rats (low-renin model) markedly reduced blood pressure up to 24 hours.31 In stroke-prone spontaneously hypertensive rats, a model of malignant hypertension, long-term treatment with omapatrilat decreased systolic blood pressure, whereas endothelium-dependent relaxation of resistance arteries improved. Media width and media/lumen ratio decreased and lumen diameter tended to increase, whereas vascular stiffness was unaltered, suggesting that omapatrilat improves structure and endothelial function of resistance arteries in this model.32

Similar observations were made in salt-induced hypertension of the rat, in which omapatrilat was more effective to reverse structural changes and endothelial dysfunction than captopril.33 In the aorta of the same model, both omapatrilat and captopril increased eNOS expression similarly, whereas only omapatrilat increased ANF levels and normalized endothelium-dependent relaxations to acetylcholine (Figure 4).6,33

In normotensives, oral administration of omapatrilat leads to long-lasting (>24 hours) and dose-dependent ACE inhibition and increases in urinary ANP levels. In a randomized, double-blind, placebo-controlled study on 36 normotensives, omapatrilat potently lowered blood pressure in a dose-dependent manner. The peak effect was registered in the first 3 to 8 hours and was sustained for 24 hours. Comparison with other antihypertensive agents, such as lisinopril, losartan, and amlopidine, revealed more pronounced antihypertensive effects of omapatrilat, particularly in the systolic range (Figure 5).34,35

Figure 5. Comparison of antihypertensive effect of omapatrilat vs lisinopril or amlodipine. At 10 weeks, omapatrilat 80 mg had produced greater reductions in ambulatory blood pressure (BP) than did lisinopril 40 mg (top) or amlodipine 10 mg (bottom).

Figure 6. In IMPRESS study, omapatrilat 80 mg in CHF was more effective on composite end points (ie, death, admission, or discontinuation of treatment because of worsening CHF) than lisinopril 20 mg.
manner, increased left ventricular function, and reduced pulmonary capillary wedge pressure. Plasma BNP, an important prognostic factor if increased, was lower after 12 weeks of treatment with 40 mg/d and was reflected by a reduced incidence of death and hospitalization for CHF.42

In the IMPRESS (Inhibition of Metalloproteinase in a Randomized Exercise and Symptoms Study in Heart Failure) trial, 573 patients with CHF (63% NYHA class II and 37% NYHA class III/IV) were randomized to either omapatrilat (40 mg/d) or lisinopril (20 mg/d).43 After 12 weeks, exercise tolerance increased similarly in both groups. Omapatrilat, however, led to a better clinical status and lower incidence of the combined mortality/morbidity end point (ie, hospitalization and discontinuation of study medication for worsening heart failure) compared with lisinopril (Figure 6). Both drugs were well tolerated, but serious adverse events and marked elevations of creatinine were less frequent with omapatrilat. Omapatrilat increased ANP and resulted in lower plasma norepinephrine levels than lisinopril. It also did not increase endothelin-1 levels, suggesting that the combined effects of ACE inhibition and NEP inhibition prevented the rise of endothelin-1 in this setting. In the postinfarction rat model, omapatrilat prevented the expected rise in endothelin-1 (unpublished observations). In the IMPRESS study, omapatrilat also had a positive influence on conduit vessel stiffness compared with lisinopril, reducing pulsatile load on the heart without compromising a potentially tenuous mean arterial pressure.44

Vasopeptidase Inhibition and Angioedema
Angioedema is a serious and potentially fatal complication of ACE inhibitors, which is relatively rare in the general population but more common among blacks/Afro-Caribbeans.45 ACE inhibitor–induced angioedema occurs with an incidence of 0.1% to 0.5%.46 Fewer than 20% of angioedema attacks are potentially life-threatening (ie, affecting the larynx or the upper respiratory tract), but this may reach 50% among patients with hereditary angioedema.47 Surprisingly, Ang II receptor antagonists also have an increased risk of angioedema, particularly in patients with a previous episode of angioedema attributed to ACE inhibitors.48

Symptoms of angioedema range from mild gastrointestinal disturbance (ie, colic, nausea, vomiting, and diarrhea) to severe dyspnea due to larynx edema. The mechanism remains unclear, but bradykinin and its metabolite des-arg9-bradykinin have been implicated in ACE-induced angioedema.48 Plasma bradykinin concentrations can rise >10-fold during acute attacks of angioedema associated with ACE inhibitor therapy.49 Recently, an enzyme defect involved in the des-arg9-bradykinin metabolism, aminopeptidase P, leading to bradykinin and to an even greater extent to des-arg9-bradykinin accumulation, has been reported.48

Vasopeptidase inhibitors acting simultaneously on 2 enzymes that inactivate bradykinin, ie, ACE and NEP, may increase the risk of angioedema. Company statements refer to a rate of angioedema associated with omapatrilat similar to that reported for ACE inhibitors. In data submitted to the New Drug Application, however, the incidence of angioedema was >3 times as common when the starting dose was ≥20 mg than it was with lower doses, which suggests a pharmacodynamic rather than allergic effect.50 In this report, 44 instances of angioedema occurred among >6000 patients, and 4 cases were severe enough to require intubation. A possible explanation for the relatively high incidence could be that the omapatrilat trial program included significant numbers of blacks, who are known to have a higher rate of angioedema than whites. The OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) trial investigates, in 25 000 untreated or poorly controlled hypertensives, whether force titration of omapatrilat from 10 to 20 mg (with elective uptitration up to 80 mg) is or is not associated with a higher incidence of angioedema than enalapril. The results will be crucial for the potential widespread use of this new class of drugs in cardiovascular medicine.

Conclusions
The encouraging experimental and limited clinical results obtained with combined ACE/NEP inhibitors warrant further clinical investigation. In particular, it will be important to know whether combined NEP and ACE inhibition, in addition to its potent antihypertensive and hemodynamic effects as well as vascular protection, indeed confers a clinical advantage over ACE inhibition alone. Therefore, an adequately powered mortality/morbidity trial in CHF is required and under way (OVERTURE). In addition, a trial in isolated systolic hypertension in the elderly (OPERA) is also under way to assess the reduction in complications secondary to hypertension and atherosclerosis. Once these indications are established, similar trials are needed in patients with coronary artery disease with or without myocardial infarction.

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