Vasopeptidase Inhibition
A Double-Edged Sword?

Duncan John Campbell

Abstract—The enormous benefits of inhibition of ACE demonstrate that manipulation of the metabolism of peptide hormones is a valuable therapeutic strategy for cardiovascular disease. Recent attempts to expand these benefits have combined ACE inhibition with inhibition of other peptidases such as neutral endopeptidase (NEP) in a single molecule, a strategy known as vasopeptidase inhibition. NEP metabolizes natriuretic peptides, and NEP inhibition offers the prospect of combining the benefits of increased natriuretic peptide levels with those of ACE inhibition. However, peptidases such as ACE and NEP have many different substrates, and there are complex interactions between ACE inhibition and NEP inhibition. Both ACE and NEP metabolize the kinin peptides bradykinin and kallidin, and NEP also converts angiotensin (Ang) I to Ang-(1-7) and metabolizes Ang II and endothelin. Addition of NEP inhibition to ACE inhibition potentiates the ACE inhibitor–induced increase in kinin levels, increases Ang II levels, reduces Ang-(1-7) levels, and may increase endothelin levels. These additional consequences of combined ACE/NEP inhibition increase the risk of angioedema and may counteract any benefit of ACE inhibition that depends on reduced Ang II levels and increased Ang-(1-7) levels. Further considerations are that the ratio of ACE and NEP inhibition is fixed for vasopeptidase inhibitors, and there is uncertainty how these drugs should be compared with ACE inhibitors. Vasopeptidase inhibitors will therefore require careful evaluation before they are introduced to patient care. (Hypertension. 2003;41:1011–1017.)

Key Words: angiotensin converting enzyme ■ neutral endopeptidase ■ angiotensin ■ bradykinin ■ natriuretic peptides

The importance of neurohormonal mechanisms in cardiovascular disease is well illustrated by the beneficial effects of ACE inhibition and β-blockade in hypertension, ischemic heart disease, heart failure, and renal disease. Despite the success of these therapies, blood pressure is not adequately controlled in a large proportion of hypertensive patients. In addition, heart failure and renal disease continue to present a therapeutic challenge. The limitations of current therapies serve to stimulate research and development of new therapies. The success of ACE inhibition for the treatment of many conditions has led to the development of strategies that build on this success. One strategy that has received considerable attention is the development of vasopeptidase inhibitors.1–3 These are single molecules that simultaneously inhibit the activity of ACE and neutral endopeptidase (NEP). Previous reviews of vasopeptidase inhibitors have concentrated on the potential therapeutic advantages of these new drugs.1–3 There are, however, complex interactions between ACE and NEP inhibition. The purpose of this brief review is to discuss the effects of ACE and NEP inhibitors when administered separately and in combination, and to draw attention to those consequences of their combination that indicate a need for caution in the introduction of vasopeptidase inhibitors to the clinic. In this review the effects of addition of NEP inhibition to ACE inhibition, when the two can be titrated individually, are discussed separately from dual ACE/NEP inhibition by a single molecule, where the relative ACE and NEP inhibitory activities of the medication are fixed.

ACE and NEP
ACE and NEP are 2 membrane-bound zinc-containing metallopeptidases involved in the metabolism of a variety of biological peptides.4–6 Both ACE and NEP have a widespread tissue distribution, including the vascular endothelium and smooth muscle cells, cardiac myocytes and fibroblasts, the brush border of proximal tubule cells of the kidney, and the brain.5,6 ACE metabolizes many peptides, including angiotensin (Ang) I, Ang-(1-7), the kinin peptides bradykinin and kallidin, chemotactic peptide, enkephalins, neurotensin, substance P, luteinizing hormone–releasing hormone, and the hemoregulatory peptide N-acetyl-Ser-Asp-Lys-Pro.5,7,8 NEP also has many substrates, including natriuretic peptides, Ang I, Ang II, kinin peptides, substance P, adrenomedullin, endothelin, chemotactic peptide, enkephalins, and the amyloid β peptide.4,6,9–11 NEP may also contribute to the formation of endothelin from its precursor big endothelin,3 although

Received November 10, 2002; first decision November 13, 2002; accepted December 10, 2002.
From the St. Vincent’s Institute of Medical Research and Department of Medicine, University of Melbourne, Fitzroy, Victoria, Australia.
Correspondence to Dr D.J. Campbell, St. Vincent’s Institute of Medical Research, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. E-mail J.Campbell@medicine.unimelb.edu.au

Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000054215.71691.16
ACE inhibition produces changes in the levels of several peptides that may contribute to the beneficial and adverse effects of this therapy (Figure, Table 1). ACE is the major pathway of conversion of Ang I to Ang II by serine protease activity and is also shown. BK-(1-4) indicates bradykinin-(1-4); BK-(1-5), bradykinin-(1-5); BK-(1-7) bradykinin-(1-7); Ang-(1-2), angiotensin-(1-2); Ang-(1-4), angiotensin-(1-4); Ang-(1-5), angiotensin-(1-5); Ang-(1-7), angiotensin-(1-7).

ACE inhibition also increases kinin peptide levels. Kinins are potent vasodilators, promote diuresis and natriuresis, and have cardioprotective actions. Many studies demonstrate a role for kinins in mediating the cardiac effects of ACE inhibitors, including the prevention of cardiac hypertrophy and the reduction in infarct size. Kinin peptides also participate in the regulation of coronary vascular tone and blood pressure in humans, and contribute to the vasodilator effects of ACE inhibition in heart failure. However, high levels of kinin peptides produce inflammation, and uncommonly, ACE inhibitors produce marked elevation of kinin peptide levels, resulting in angioedema.

ACE inhibition causes a marked increase in Ang-(1-7) levels. This is due in part to increased renin secretion producing increased Ang I levels that are converted to Ang-(1-7) by endopeptidases such as NEP. Another mechanism by which ACE inhibition increases Ang-(1-7) levels is by preventing Ang-(1-7) metabolism by ACE (Figure). Ang-(1-7) has actions that counteract many of the actions of Ang II. These include vasodilatation, reduction of blood pressure, and potentiation of the hypotensive effects of kinin peptides. Ang-(1-7) also improves cardiac and endothelial function in rats with heart failure due to myocardial infarction. The increased levels of Ang-(1-7) that accompany ACE inhibition may contribute to the therapeutic actions of ACE inhibitors by both the direct vasodilator actions of this peptide and by its potentiation of the actions of the increased kinin levels that result from ACE inhibition.

### NEP Inhibition

The effects of NEP inhibition are attributed in most part to the increased biological activity of natriuretic peptides that result from their reduced metabolism. Natriuretic peptides include the atrial (ANP) and brain-derived (or B-type [BNP]) natriuretic peptides that are produced principally in the cardiac atria and myocardium, respectively. Secretion of ANP and BNP is increased in response to mechanical strain of heart muscle. C-type natriuretic peptide, found in the kidney, heart, lung, and vascular endothelium, is released in response to shear stress. Natriuretic peptides have direct vasodilator effects; inhibit renin, aldosterone, and endothelin secretion; reduce sympathetic activity; and may also reduce smooth muscle proliferation and reduce cardiac fibrosis. In heart failure patients, ANP infusion increases cardiac index by reducing systemic vascular resistance, and more recent studies show a similar benefit from BNP infusion.

NEP inhibition potentiates plasma levels and effects of administered natriuretic peptide but has variable effects on plasma levels of endogenous natriuretic peptide because any tendency of NEP inhibition to increase peptide levels by inhibiting metabolism may be negated by reduced natriuretic peptide secretion caused by a diuresis- and natriuresis-induced reduction in cardiac filling pressures. However, NEP inhibition produces consistent increases in urine sodium and cyclic GMP excretion. This is likely because renal tubular NEP is a major site of natriuretic peptide metabolism, and NEP inhibition may increase natriuretic peptide levels in urine without detectable change in circulating levels.

NEP inhibition has quite variable effects on blood pressure. There may be no change, a decrease, or an increase in blood pressure of normotensive and hypertensive human subjects in response to NEP inhibition. Moreover, NEP inhibition increased systemic vascular resistance during the first few

### TABLE 1. Effects of ACE Inhibition Alone and the Addition of NEP Inhibition to ACE Inhibition on Peptide Levels

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Effects of ACE Inhibition</th>
<th>Effects of Addition of NEP Inhibition to ACE Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang II</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Ang-(1–7)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td>→</td>
<td>↑</td>
</tr>
<tr>
<td>Endothelin</td>
<td>→</td>
<td>↑</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; NEP, neutral endopeptidase. The arrows indicate an increase (↑), decrease (↓), or no change (→) in the peptide levels, with a double arrow indicating a greater change.
tions of ACE and NEP inhibitors on angiotensin and kinin peptide levels during simultaneous ACE and NEP inhibition (Figure 1). Addition of NEP inhibition to ACE inhibition produced greater inhibition of bradykinin metabolism and higher bradykinin levels than those seen with ACE or NEP inhibition alone.40,48 Furthermore, addition of NEP inhibition to ACE inhibition increased Ang II levels in plasma and lung of control rats40 and in plasma, lung, aorta, and kidney of rats with myocardial infarction.48 Moreover, NEP inhibition markedly reduced Ang-(1-7) levels in ACE inhibitor–treated rats.40 The increased kinin peptide levels may contribute to the natriuretic, hypotensive, and cardioprotective effects of addition of NEP inhibition to ACE inhibition. However, given the role of kinin peptides in ACE inhibitor–induced angioedema,20,21 the additional impairment of kinin metabolism by NEP inhibition would be predicted to increase the occurrence of angioedema. In addition, by increasing Ang II levels and reducing Ang-(1-7) levels NEP inhibition may counteract any benefit of ACE inhibition that depends on reduced Ang II levels and increased Ang-(1-7) levels.

Many studies in animal models demonstrate improved therapeutic efficacy from addition of NEP inhibition to ACE inhibition in hypertension and heart failure.49–51 Addition of NEP inhibition to a moderate dose of ACE inhibition produced greater reduction of cardiac hypertrophy in a rat model of myocardial infarction than either drug alone, in association with higher levels of bradykinin in the heart.46 It is of note, however, that the effect of the combination of ACE and NEP inhibition was equivalent to the reduction in cardiac hypertrophy seen with a higher dose of ACE inhibitor alone.52

Addition of NEP inhibition to ACE inhibition reduces blood pressure more effectively in hypertensive patients than does ACE or NEP inhibition alone.34 However, for patients with heart failure, addition of the NEP inhibitor ecaadotril to standard therapy, including ACE inhibition, produced no evidence of improvement in signs or symptoms.53,54 Of particular concern was the occurrence of aplastic anemia in several patients, which was attributed to the thrombocyte group on the ecaadotril molecule.53

Vasopeptidase Inhibitors: Dual ACE/NEP Inhibition by a Single Molecule

Several dual ACE/NEP inhibitors have been developed (Table 2).51,55–57 When NEP inhibition is added to ACE inhibition, the doses of the 2 inhibitors can be titrated to obtain optimal efficacy and thus to demonstrate superiority over ACE inhibition alone. This separate titration of ACE and
NEP inhibition is not possible when both are mediated by a single molecule because the ratio of ACE to NEP inhibition is fixed. It is therefore important to assess whether dual ACE/NEP inhibitors have therapeutic effects different from ACE inhibition alone. There are no established criteria for how one should match the ACE inhibition produced by an ACE inhibitor with that produced by a dual ACE/NEP inhibitor. Many published studies compare a single dose of ACE inhibitor with 1 or 2 doses of dual ACE/NEP inhibitor, and it is difficult to determine whether any difference in efficacy is owing to failure to match the ACE inhibition produced by the 2 therapies.

A further consideration in the assessment of dual ACE/NEP inhibitors is that although ACE and NEP inhibition are mediated by the same molecule, it cannot be assumed that ACE inhibition will parallel NEP inhibition in vivo. There are differences in the relative abundance of ACE and NEP in different tissues. The biological effects of the dual inhibitor may be owing to inhibition of ACE at tissue sites different from those in which NEP inhibition produces biological effects, and these different tissue sites may have different accessibility to the drug. Moreover, modification of the drug in vivo may differentially alter its ability to inhibit ACE and NEP. For example, the dual ACE/NEP inhibitor S 21402 is a potent inhibitor of both ACE and NEP in vitro (Table 2). However, studies in rats showed that inhibition of ACE in vivo requires doses of S 21402 at least 1000-fold higher than those required to inhibit NEP, indicating that in vivo modification may have differential effects on the ability of the compound to inhibit ACE and NEP. This discrepancy between relative inhibition of ACE and NEP by S 21402 in vitro and in vivo was confirmed in human studies.

Animal Studies of Vasopeptidase Inhibitors
The most extensively investigated dual ACE/NEP inhibitor is omapatrilat, also known as BMS-186716. Omapatrilat is an effective hypotensive agent in experimental hypertension and was shown to be more effective than the ACE inhibitor fosinopril in reducing blood pressure and improving hemodynamics. Omapatrilat also has beneficial hemodynamic and renal effects in experimental heart failure, and is reported to be equivalent to, or superior to, ACE inhibition. However, failure to perform dose-response studies creates uncertainty whether the apparent superiority was owing to the doses of omapatrilat and ACE inhibitor chosen for study.

One approach to investigation of the relative contribution of ACE and NEP inhibition to the effects of dual ACE/NEP inhibition was to administer a natriuretic peptide receptor antagonist. In a study of anesthetized dogs with pacing-induced heart failure, the natriuretic peptide receptor antagonist HS-142-1 attenuated the increase in urine sodium and cyclic GMP excretion, glomerular filtration rate (GFR), and plasma renin and cyclic GMP level, thereby demonstrating a contribution of natriuretic peptides to the changes in renin, cyclic GMP, GFR, and urine sodium caused by dual ACE/NEP inhibition.

Evaluation of Vasopeptidase Inhibitors in Humans

Normotensive Subjects
Comparison of 10 mg omapatrilat with 20 mg fosinopril in mildly sodium-depleted normotensive subjects showed that at these doses the 2 drugs had similar potencies for ACE inhibition, producing similar suppression of plasma ACE activity and Ang II levels, and similar increases in plasma renin and Ang I levels that persisted for 24 hours. However, 10 mg omapatrilat had only a transient hypotensive effect, whereas the hypotensive effect of 20 mg fosinopril lasted 24 hours. Thus, it would appear that when the ACE inhibition produced by omapatrilat and fosinopril was matched, omapatrilat offered no advantage and appeared to be inferior to fosinopril.

In a subsequent study of sodium-depleted and sodium-supplemented normotensive subjects, much higher doses of omapatrilat (40 mg and 80 mg) were compared with 20 mg fosinopril. These higher doses of omapatrilat produced greater suppression of plasma ACE activity and greater stimulation of plasma renin levels than did fosinopril. At 24 hours after drug dosing, in comparison with fosinopril, these 2 doses of omapatrilat produced similar decreases in blood pressure in sodium-depleted subjects and greater decreases in blood pressure in sodium-supplemented subjects. The change in urinary ANP excretion showed that the duration of NEP inhibition was shorter than the duration of ACE inhibition produced by omapatrilat, with a mild and transient natriuretic effect that was no different from that of fosinopril. Omapatrilat, but not fosinopril, also produced increases in plasma levels of big endothelin, but no change in endothelin level.

Omapatrilat (40 mg and 80 mg) was also compared with fosinopril/hydrochlorothiazide combination (20 mg and 12.5 mg) in normotensive subjects. Although the acute natriuretic effects of the fosinopril/hydrochlorothiazide combination were higher, the cumulative sodium excretion was similar for omapatrilat and the fosinopril/hydrochlorothiazide combination over 7 days. Omapatrilat, but not the fosinopril/hydrochlorothiazide combination, produced a marked increase in renal plasma flow, indicative of renal vasodilatation, without change in GFR.

Hypertensive Subjects
In patients with hypertension, omapatrilat produces greater decreases in both systolic, diastolic, and pulse pressure than does ACE inhibition alone. Comparison with other antihypertensive agents, such as lisinopril, losartan, and amlodipine, revealed more pronounced antihypertensive effects of omapatrilat. Omapatrilat (80 mg/d) was a more effective hypotensive agent than was enalapril (40 mg/d) over 12 weeks of therapy in hypertensive subjects studied 24 hours after the last drug administration. Similarly, omapatrilat (40 mg/d) was a more effective hypotensive agent than was lisinopril (20 mg/d) in salt-sensitive hypertensive patients. Although omapatrilat increased plasma and urine ANP levels and urine cyclic GMP excretion, there were no differences in urine sodium excretion between subjects treated with omapatrilat or lisinopril.
The Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study randomized 25,302 hypertensive subjects to either omapatrilat titrated up to 80 mg daily or enalapril titrated up to 40 mg daily for a period of 24 weeks. Compared with enalapril, omapatrilat reduced blood pressure further, by \( \approx 3 \) mm Hg systolic and 2 mm Hg diastolic. Angioedema was reported in 2.17% of patients receiving omapatrilat and in 0.68% of patients receiving enalapril, and the individual episodes with omapatrilat were more severe and their timing was earlier, the majority occurring within the first few hours after the initial dose. Because of these concerns about angioedema, omapatrilat has not been approved for treatment of hypertension.

### Subjects With Heart Failure

Omapatrilat produces an acute dose-related hemodynamic improvement in heart failure patients that is maintained for at least 12 weeks. The Inhibition of Metallo Protease by BMS-186716 in a Randomized Exercise and Symptoms Study in Subjects With Heart Failure (IMPRESS) clinical trial randomized 573 patients with heart failure to a daily regimen of either 40 mg omapatrilat or 20 mg lisinopril. At 24 weeks, patients randomized to omapatrilat had a significant reduction in the combined endpoint of death, hospitalization, or discontinuation of study drug for worsening heart failure, when compared with endpoints for patients randomized to lisinopril. Patients randomized to omapatrilat also had significantly fewer serious adverse cardiac events, including heart failure, myocardial ischemia, and cardiac arrhythmia. These promising findings of the IMPRESS trial led to the subsequent much larger Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study.

The OVERTURE study assigned 5,770 patients with New York Heart Association class II to IV heart failure to treatment with either enalapril (40 mg twice daily [BD]) or omapatrilat (40 mg once daily) for a mean of 14.6 months. Enalapril or omapatrilat were added to conventional therapy that included \( \beta \)-blockers in 50% of patients, but no open-label therapy with ACE inhibitors or angiotensin antagonists was permitted. The primary endpoint of combined risk of death or hospitalization for heart failure requiring intravenous treatment was not different for the 2 treatment groups, although analysis of secondary outcomes showed the omapatrilat group had a 9% lower risk of cardiovascular death or hospitalization \( (P=0.024) \) and a 6% lower risk of death \( (P=0.34) \). Post hoc analysis showed a 11% lower risk for hospitalization for heart failure in patients treated with omapatrilat \( (P=0.012) \). Differences between omapatrilat and enalapril on the primary endpoint were generally similar in direction and magnitude in subgroups defined by baseline variables, including therapy with \( \beta \)-blockers and spironolactone.

The OVERTURE study raises several questions. The study used only 1 dosage regimen for each of the 2 drugs. The authors noted that in the IMPRESS study, 40 mg omapatrilat lowered blood pressure \( >20 \) mg lisinopril at peak, but less than lisinopril at trough. They suggest that “the benefits expected from inhibition of both ACE and NEP may have been largely offset by the failure of once-daily dosing with omapatrilat to maintain continuous ACE inhibition to the same degree as twice-daily dosing with enalapril.” However, a more reasonable explanation for the failure of omapatrilat to produce a sustained hypotensive effect is the short duration of NEP inhibition produced by this compound. Although it may be argued that a higher dosage or BD dosage may increase the benefits obtained with omapatrilat in heart failure, it could also be argued that a higher dosage of enalapril may similarly increase the benefits from ACE inhibition alone.

Angioedema was reported in similar proportions of omapatrilat-treated (0.8%) and enalapril-treated patients (0.5%) in the OVERTURE study. The lower frequency of angioedema in heart failure than was reported for hypertensive patients in the OCTAVE study was attributed to the possibility that heart failure patients may be resistant to the ability of kinin peptides to produce cutaneous exudation, as shown in dogs with pacing-induced heart failure. It should also be noted that a lower incidence of angioedema was to be expected because all patients received ACE inhibitor therapy before enrollment in the OVERTURE study. Therefore, any patient who experienced angioedema with previous ACE inhibitor therapy would have been excluded from the study. Of the other adverse events reported on the OVERTURE study, hypotension and dizziness were more frequent with omapatrilat (19.5% and 19.4%, respectively) than with enalapril (11.5% and 13.9%), but heart failure and renal impairment were less frequent with omapatrilat (22.6% and 6.8%) than with enalapril (25.6% and 10.1%). The incidence of cough was similar for omapatrilat and enalapril therapy (9.7% and 9.0%, respectively).

When administered to heart failure patients, omapatrilat caused transient increases in plasma ANP and cyclic GMP levels that lasted less than 24 hours. In addition, the first dose of omapatrilat was associated with an acute increase in plasma levels of endothelin, noradrenaline, and adrenomedullin, although the plasma levels of these neurohormones were not elevated when measured 24 hours after dose after 12 weeks of therapy. However, Sheehy et al reported increased plasma endothelin and interleukin-10 levels when measured 24 hours after dose after \( \geq 12 \) weeks of omapatrilat therapy, but not after lisinopril therapy, in the IMPRESS study. These studies suggest that increased plasma endothelin levels may compromise any benefit from omapatrilat therapy.

### Alternative Approaches to Dual ACE/NEP Inhibition

An alternative approach to vasopeptidase inhibition has been to produce molecules that inhibit both ECE and NEP. The rationale of this approach is to combine the benefits of increased natriuretic peptide levels with reduced endothelin levels. Despite the theoretical advantages of such an approach, there is a need for caution in the clinical application of these compounds. ACE inhibition is established therapy for all of the conditions for which dual ECE/NEP inhibitors might be used, and current experience indicates that the combination of a dual ECE/NEP inhibitor with an ACE inhibitor will produce an unacceptable incidence of angioedema.
Conclusion

The many different actions of ACE and NEP inhibitors indicate a need for caution in the combination of these 2 treatments. ACE inhibition reduces Ang II levels and increases Ang-(1-7) and kinin levels. Although Ang-(1-7) and kinin peptides may contribute to the therapeutic benefits of ACE inhibition, kinin peptides also contribute to angioedema. In addition to increase in natriuretic peptide levels, NEP inhibition affects metabolism of angiotensin, kinin, and endothelin peptides. Combination of NEP inhibition with ACE inhibition causes further increase in kinin peptide levels and increases the incidence of angioedema. Moreover, by attenuating the increase in Ang-(1-7) levels and decrease in Ang II levels that accompany ACE inhibition, NEP inhibition may counteract some of the therapeutic benefit of ACE inhibition.

Dual ACE/NEP inhibition by a single molecule has complex pharmacology whereby ACE and NEP inhibition do not operate in parallel. For omapatrilat, the duration of NEP inhibition is shorter than the duration of ACE inhibition. For most clinical trials that compare omapatrilat with an ACE inhibitor in hypertension and in heart failure, it would appear that omapatrilat was used at doses that produce more extensive ACE inhibition than that produced by the comparator ACE inhibitor. Even if the problem of excess angioedema with dual ACE/NEP inhibitors were to be resolved, there is continuing uncertainty about how these drugs should be compared with ACE inhibitors and what advantage they offer for patient management.

References


Vasopeptidase Inhibition. A Double-Edged Sword?
Duncan John Campbell

_Hypertension_. published online February 3, 2003;

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/early/2003/02/03/01.HYP.0000054215.71691.16.citation

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/