Should Angiotensin II Receptor Blockers and Statins Be Combined?

Georg Nickenig, MD

Coronary heart disease (CHD) resulting from atherosclerosis is the single largest killer in the Western world. Approximately 40% of patients with hypertension have hypercholesterolemia, which is central to the pathogenesis of atherosclerosis and cardiovascular disease (CVD). Conversely, hypertension is a significant risk factor in patients with elevated cholesterol. There is strong synergy between hypertension and hypercholesterolemia in terms of risk factors for the development of CVD. Both hypertension and hypercholesterolemia result in endothelial dysfunction and consequently the development of atherosclerosis. The recent definition of the metabolic syndrome, characterized by hypertension, elevated cholesterol and triglyceride levels, insulin resistance/dyslipidemia, and central obesity, has brought together these conditions with the notion that they are linked and represent a cluster of factors that are synergistic for CVD.

The renin-angiotensin system (RAS) contributes importantly to a variety of CVDs and is the target of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs; Figure 1). RAS is an enzymatic cascade that starts with the cleavage of angiotensinogen by renin to form the inactive peptide angiotensin I. ACE is responsible for converting the inactive angiotensin I to the active moiety angiotensin II, which is the principle effector hormone of the RAS and, through its action on angiotensin II receptors, plays a critical role in maintaining arterial blood pressure (BP) and fluid and electrolyte homeostasis. Although angiotensin II binds to both type I (AT1) and type II (AT2) receptor subtypes, the AT1 receptor mediates most of the cardiovascular effects of angiotensin II, including oxidative stress, vasoconstriction, aldosterone secretion, renal sodium resorption, sympathetic stimulation, vasopressin release, cardiac and vascular cell hypertrophy, and cell proliferation. ARBs act by blocking the AT1 receptors with concomitant stimulation of AT2 and thus, prevent the pathophysiological effects mediated by the binding of angiotensin II to the AT1 receptor. In addition to the crucial blockade of the AT1 receptor, facilitated stimulation of AT2 receptors during ARB treatment could exert additional benefit. Several experiments in animals have shown that some of the vascular and myocardial improvements seen during ARB treatment could be blocked by additional application of an AT2 receptor inhibitor. Admittedly, the relevance of these findings was never confirmed in humans, because no AT2 receptor blocker is available that could be administered in humans. The selective and potent inhibition of angiotensin II by ARBs can prevent end-organ damage from hypertension-associated diseases such as CHD, atherosclerosis, and renal disease, and these effects appear to be potentially independent of their BP-lowering effects (VALsartan HEart Failure Trial [Val-HeFT] study group). Reduction in Endpoints in patients with Non–insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan [RENAAL], Irbesartan in Diabetic Nephropathy Trial [IDNT], Losartan Intervention For Endpoint reduction in hypertension [LIFE] study group, Candesartan cilextil in Heart failure Assessment of Reduction Mortality and morbidity [CHARM] study group, and VALsartan In Acute myocardial infarction Trial [VALIANT]. ARBs have increasingly become part of the first line of treatment against hypertensive diseases, with the more selective mode of action of ARBs resulting in a better side-effect profile compared with the ACE inhibitors. In addition, most of the cited trials have revealed that ARB treatment decreases new-onset diabetes. Besides other potential mechanisms (eg, reduced gluconeogenesis, reduced catecholamine levels, and increased muscle perfusion), direct, presumably AT1 receptor–independent effects of ARBs leading to intracellular activation of peroxisome proliferator–activated receptor-γ (PPAR-γ), which is directly linked to an increase in insulin sensitivity, could account for this well-established clinical finding.

Hypercholesterolemia is recognized as a major risk factor for the development and progression of CVDs. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) exert both direct and indirect (cholesterol-lowering) effects on the vasculature. Statins have been shown to significantly reduce cardiovascular mortality and morbidity in patients at risk for CVD. Recent data also suggest that statins may have direct effects on plaque stability, nitric oxide (NO) metabolism, inflammation, endothelial function, oxidative stress (Figure 2), thrombosis, and stroke. Statins are increasingly prescribed as preventive medicine for various cardiovascular risk factors, and more...
recently, the metabolic syndrome has been identified as a secondary target for lipid-lowering therapy by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines in the United States.

This article reviews the available evidence that pharmacotherapies targeting several risk factors can simultaneously improve cardiovascular outcomes. The combination of ARBs and statins as primary treatment may therefore provide a greater degree of protection and control of these risk factors, improving the vascular and general health of the patient.

The Link Between Hypercholesterolemia and Hypertension

Recent evidence points to the interplay between hypercholesterolemia and hypertension, acting through the RAS, to increase cardiovascular risk. Both hypertension and hypercholesterolemia result in endothelial dysfunction and the development of atherosclerosis. Increased levels of angiotensin II are correlated with hypertension, which is a major trigger for endothelial dysfunction. ACE expression and activity have been demonstrated to increase during atherosclerosis and hyperlipidemia. Oxidative stress has been implicated in many pathophysiological conditions in the cardiovascular system, including hypercholesterolemia, hypertension, diabetes, and heart failure. Angiotensin II and AT1 receptor activation stimulate NADPH oxidase, resulting in the generation of reactive oxygen species in vascular cells and eventually, endothelial dysfunction. Oxidative stress results in activation of redox-sensitive genes that are proinflammatory and play a critical role in initiation and progression of atherosclerosis, as well as reduced bioavailability of NO in vascular wall, which appears to result from increased oxygen free-radical generation and decreased NO production.

Hypercholesterolemia and elevated plasma concentrations of LDL cholesterol are involved in the pathogenesis of atherosclerosis. Blockade of AT1 receptors by ARBs results in reduced oxidative stress and decreased breakdown of NO, and conversely, increased bioavailability of NO (see Figure 3). ARBs increase basal NO production and release, independent of BP reduction, in essential hypertension, suggesting that they can have favorable effects on endothelial dysfunction, and have been shown to inhibit the development of atherosclerotic lesions.

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Recent studies have also suggested that angiotensin II may act as a proinflammatory stimulus in addition to its vasoconstrictive action. Angiotensin II has been shown to induce profound inflammation in animal models, and this influence is independent of the effect on BP. Angiotensin II and the resulting oxidative stress activate stress genes and enzyme pathways in vascular smooth muscle cells and monocytes. These result in an increase in the expression of adhesion molecules, which in turn are involved in the movement of inflammatory cells into atheromatous areas. Inflammation appears to play an important role in the pathogenesis of hypertension and atherosclerosis via angiotensin II. Therefore, the benefits seen in recent trials with ARBs may, at least in part, be the result of their effect on arterial inflammation, and the reduction in CVD morbidity and mortality may also be the result of decreasing proinflammatory processes present in patients with hypertension, atherosclerosis, or heart failure.

**Clinical Evidence for Combining ARBs and Statins**

**Benefits of ARBs**

Because angiotensin II is also synthesized in some tissues via alternative pathways that do not involve ACE, inhibition of the actions of the AT1 receptor by ARBs may result in a more complete RAS blockade than by ACE inhibitors: Because “ACE escape” is not allowed, there is a slow return of angiotensin II to pretreatment levels seen with long-term use of ACE inhibitors. The pharmacology of the ARBs has demonstrated that they are highly selective, orally active AT1 receptor antagonists. The sartans are as effective as other antihypertensive agents, such as diuretics, calcium channel blockers, β-blockers, and ACE inhibitors, but have a superior side-effect profile compared with these other drugs. Numerous clinical trials with ARBs have shown their effectiveness, not only in BP control but also across the entire cardiovascular continuum (see the summary [Table 1] of the major trials). Losartan was shown to improve cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. In that study, losartan was compared with atenolol and was shown to have better efficacy as well as tolerability (LIFE study group) and a decrease in the onset of diabetes in losartan-treated individuals compared with the atenolol-treated group also was demonstrated. The superiority of the ARB was especially evident in patients with isolated systolic hypertension or diabetes. The heart
failure trials (Val-HeFT and CHARM) demonstrated a reduction in the combined end point of mortality and morbidity in patients with heart failure when an ARB was added to their conventional therapy. Sartans have been shown to have positive effects on left ventricular hypertrophy, endothelial dysfunction, and atherosclerosis, suggesting that ARBs not only protect target organs but also are very effective in other areas of the cardiovascular system, such as in blood vessels. ARBs have been shown to have protective effects on the kidney (Microalbuminuria Reduction with VALsartan [MARVAL], RENAAL, and IDNT). These findings have led to the recommendation that ARBs should be included in first-line therapy for the treatment of hypertension in patients with type 2 diabetes and renal insufficiency. Thus, ARBs have been demonstrated to be highly effective in slowing the progression of renal disease and importantly, in preventing new-onset diabetes.

**Benefits of Statins**

Statins reduce cholesterol synthesis by competitively inhibiting the enzyme HMG-CoA reductase, which is responsible for converting HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. These lipid-lowering drugs are most effective at decreasing LDL levels but also provide some improvements in HDL cholesterol values. The statins are usually used to treat hypercholesterolemia and to manage patients with ischemic heart disease (IHD), although with the advent of many large clinical trials during the past 10 years, their use has been extended to preventive treatment for a variety of CVDs.

Results from the major clinical trials on statins are summarized in Table 2. The megatrials on hypolipidemic therapy demonstrated instances wherein there was an ~30% reduction in major coronary events, reduced coronary mortality, and reduced total mortality, thus establishing without a doubt that hypolipidemic therapy is safe and reduces morbidity and mortality in hypercholesterolemic patients. These studies also demonstrated that statin treatment could be used as secondary preventive therapy in patients at risk of myocardial infarction but with normal cholesterol levels. These 3 trials demonstrated that statin therapy, besides showing excellent safety profile, are associated with significant reductions in major coronary events, reduced coronary mortality, and reduced total mortality. These 3 trials demonstrated that statin therapy, besides showing excellent safety profile, are associated with significant reductions in major coronary events, reduced coronary mortality, and reduced total mortality.

**TABLE 2. Summary of Major Clinical Trials With Statins**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Name of Trial</th>
<th>No. of Subjects</th>
<th>Cholesterol Level, mmol/L</th>
<th>Duration of Trial</th>
<th>Reduction in LDL</th>
<th>Primary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>4S</td>
<td>4444</td>
<td>5.5–8.0</td>
<td>5.4 years</td>
<td>35%</td>
<td>Major coronary events, coronary mortality, and total mortality</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>WOSCOPS</td>
<td>6595</td>
<td>7.03</td>
<td>4.9 years</td>
<td>26%</td>
<td>Coronary events leading to hospitalization and cardiovascular mortality</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>CARE</td>
<td>4159</td>
<td>5.4</td>
<td>5 years</td>
<td>28%</td>
<td>Coronary death or nonfatal myocardial infarction</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>LIPID</td>
<td>9014</td>
<td>4.0–7.0</td>
<td>6.1 years</td>
<td>25%</td>
<td>Mortality from coronary heart disease, overall mortality, myocardial infarction, stroke (LIPID study group)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>AFCAPS/TexCAPS</td>
<td>6605</td>
<td>5.71</td>
<td>5.2 years</td>
<td>25%</td>
<td>Major coronary event: myocardial infarction, unstable angina, or sudden death</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>MIRACL</td>
<td>3086</td>
<td>3.2</td>
<td>16 weeks</td>
<td>40%</td>
<td>Death, nonfatal myocardial infarction, cardiac arrest, or recurrent symptomatic myocardial ischemia</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HPS</td>
<td>20 536</td>
<td>3–5</td>
<td>5.5 years</td>
<td>29%</td>
<td>Mortality and fatal or nonfatal vascular events</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>ASCOT</td>
<td>10 297</td>
<td>5.5</td>
<td>5 years</td>
<td>36%</td>
<td>Nonfatal myocardial infarction and fatal coronary heart disease</td>
</tr>
</tbody>
</table>

WOSCOPS indicates West of Scotland COronary Prevention Study; CARE, Cholesterol And Recurrent Events; and LIPID, Long-term Intervention with Pravastatin in Ischemic Disease. Other acronyms as in text.
Aggressive Cholesterol Lowering (MIRACL) trial demonstrated a decrease in death, nonfatal myocardial infarction, cardiac arrest, or recurrent symptomatic ischemia. The recently conducted Heart Protection Study (HPS) demonstrated reduced (by 18%) coronary mortality and a highly significant reduction in total mortality. The ongoing trials such as the Treating to New Targets (TNT) trial, Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) trial, and Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) (see below) will test the hypothesis that lowering LDL to <2.6 mmol/L, which is the current guideline value for low risk, will provide additional benefits for CHD risk reduction.

Evidence for Combination Therapy

There is a strong rationale for combining an ARB with a statin from the preclinical studies discussed earlier in this article. More recently, Horiiuchi et al tested whether statins may enhance the effect of an ARB to improve vascular remodeling in a mouse vascular injury model. They demonstrated that a combination of low-dose valsartan and low-dose fluvastatin acted synergistically to attenuate neointimal formation at doses that were without effect when administered alone and were devoid of any effects on BP or cholesterol levels. There is also a limited clinical study demonstrating an increase in AT1 receptor expression in hypercholesterolemic men. In a comparison of 20 hypercholesterolemic versus 19 normcholesterolemic men, angiotensin II infusion produced a 2-fold increase in BP and a concomitant increase in AT1 receptor expression. Both of these effects could be blocked with statin therapy. Hussein et al also reported a synergistic antioxidative effect of valsartan and fluvastatin against LDL oxidation in a small group (n=21) of hypercholesterolemic and hypertensive men. Statins have been demonstrated to directly downregulate AT1 receptor expression in isolated vascular smooth muscle cells and animal models. This mechanism may explain some of the cholesterol-independent beneficial effects of statins and also answer why giving a statin and an ARB could produce synergistic effects against CVDs.

Nazzaro and coworkers studied 30 hypercholesterolemic hypertensive subjects at rest and during stress to investigate the effects of statins and ACE inhibition on vascular reactivity and vasodilative capacity. Simvastatin reduced total and LDL cholesterol as expected. The ACE inhibitor enalapril also reduced total cholesterol and LDL cholesterol, but there was a greater lowering with combination therapy in both cases. Thus, combination of a statin with antihypertensive therapy demonstrated a significant additive effect on hypercholesterolemia, structural vascular damage, BP, and vascular resistance. These findings also suggest that ACE inhibitors improve vascular reactivity and reduce structural damage in hypercholesterolemic hypertensive subjects. Additional information has been derived from a subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study, indicating that the beneficial effect of ACE inhibition was also evident in patients with concomitant statin therapy. On the other hand, a subgroup analysis from the HPS suggested that the end-point reduction by statin therapy was equally detectable in patients treated with ACE inhibitors or not.

At present, no trials have tested a combination of ARBs with statins. However, post hoc analysis of the OPTIMAL Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), in which patients after myocardial infarction were treated with either captopril or losartan, revealed that additional treatment with a statin resulted in a marked reduction of death and subsequent myocardial infarction. One ongoing trial is testing the hypothesis that reducing cholesterol (with statins) and BP (with ACE inhibitors plus calcium channel blockers vs β-blocker plus a diuretic) may have a CVD preventive effect, regardless of cholesterol diagnosis (ASCOT). The ASCOT is a multicenter international trial that involves 2 treatment comparisons in a factorial design: a prospective, randomized, open, blinded end-point design comparing 2 antihypertensive regimens and a double-blind, placebo-controlled trial of a lipid-lowering agent in a subsample of those hypertensive patients (the lipid-lowering arm). The results from the lipid-lowering arm of the ASCOT demonstrated that patients with high BP but moderate cholesterol levels who were taking atorvastatin had 36% fewer nonfatal myocardial infarction and fatal CHD events compared with the placebo group. The benefit of this treatment emerged almost immediately, and other clinical end points that were significantly reduced were fatal and nonfatal stroke (27%), total coronary events (29%), and total cardiovascular events (38%).

A recent article published by Wald and Law suggested that taking a single combination pill (statin, thiazide, β-blocker, ACE inhibitor, folic acid, and aspirin) could reduce the risk of CVD and the risk of stroke by >80%. They suggested that such a pill should be given to people with vascular disease and all people older than 55 years, which is a very bold claim, but their conclusion was based on a systematic review and meta-analysis of 750 trials and 400 000 participants. Lowering cholesterol concentrations that are >4.0 mmol/L and of BP values that are >140/90 mm Hg will provide significant benefit as shown in the ASCOT. Thus, these exciting conclusions suggest that the combination of an ARB and a statin would potentially have profound beneficial effects against CVD.

Who Would Benefit From Combined Therapy of ARBs and Statins?

Accumulating evidence suggests that preventive medications are a future trend in a growing population in whom longevity is increasing. Thus, one can envisage that combination therapy of an ARB and a statin would find utilization in people with cardiovascular risk factors and provocatively, also in people without symptomatic disease but who are >55 years old, as age also becomes a risk factor for CVDs. Patients presenting with 2 or more linked risk factors for CVD would benefit from the combination of cholesterol lowering and antihypertensive drug therapy (ie, patients with hypertension, moderate cholesterol levels, the metabolic syndrome, type 2 diabetes, and a previous cardiovascular event such as stroke or myocardial infarction). The patients in the

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lipid-lowering arm of the ASCOT all had hypertension and ≥3 other risk factors for CHD. Therefore, one could speculate that the combination of an ARB and a statin could be given to any patient at risk of developing CVD. Some of the important patient groups who may benefit from this therapy are summarized below.

The Metabolic Syndrome
Type 2 diabetes and CVD have many risk factors in common, and many of these risk factors are highly correlated with 1 another. The clustering of several of the metabolic and CVD risk factors has been termed the metabolic syndrome. Metabolic syndrome arises from a number of causes, including predetermined genetic factors such as insulin resistance, as well as acquired or lifestyle characteristics such as obesity, physical inactivity, and high-carbohydrate diets (>60% total calories). Dyslipidemia, which includes hypercholesterolemia and hypertriglyceridemia, is associated with hypertension and central obesity, all of which, together with insulin resistance, constitute the metabolic syndrome. The components of the metabolic syndrome are associated with insulin resistance, disturbances of coagulation and fibrinolysis, endothelial dysfunction, and elevated markers of subclinical inflammation. This syndrome is presumably a powerful determinant of diabetes and CVD. The end product of the metabolic syndrome is atherosclerosis leading to CVD, myocardial infarction, stroke, peripheral arterial disease, and endothelial dysfunction. The prevalence of the metabolic syndrome is increasing worldwide, with an estimated 20% to 25% of American adults being affected. Their identification warrants aggressive intervention to prevent type 2 diabetes, progression of atherosclerosis, and CVD. Recently, the NCEP ATP III recommended that statins be first-line therapy for patients with high LDL levels, but this group also recognized the need for combination therapy to treat total lipid profiles. They also recommended aggressive treatment of any hypertension present. The Joint National Committee VII recommended appropriate drug therapy for each of the constituents of the metabolic syndrome, including cholesterol-lowering drugs and antihypertensive agents. Thus, combination of an ARB and a statin would have great potential for use in the metabolic syndrome.

Type 2 Diabetes
Type 2 diabetes increases the risk for hypertension and associated CVDs. The worldwide prevalence of type 2 diabetes has exploded in recent years. The frequent association of diabetes with dyslipidemia, hypertension, and endothelial and metabolic abnormalities also aggravates the underlying vascular disease process in patients who possess these comorbid conditions. Diabetes is a predictor of atherosclerosis, and this is the main cause of morbidity and mortality in these patients. Insulin induces AT1 receptor overexpression. Clinical trials have shown that ARBs effectively reduce cardiovascular end points in hypertensive diabetics and preserve renal function in diabetics with nephropathy (LIFE, RENAAL, IDNT, and MARVAL). The American Diabetes Association recommends the use of statins to treat dyslipidemia in patients with type 2 diabetes, as well as the use of antihypertensives to target BP goal of 130/80 mm Hg. Therefore, a combination of an ARB and a statin could have beneficial effects in type 2 diabetes.

Stroke
Stroke is the third leading cause of death in the United States, with ~750,000 new cases and 158,000 deaths each year, and stroke is the leading cause of neurological disability in adults. Hypertension is a major risk factor for stroke, and epidemiological studies have confirmed a relation between hypertension and stroke. A meta-analysis of studies of antihypertensives reported that a modest 5- to 6-mm Hg decrease in BP resulted in a 42% reduction in stroke incidence. There is convincing evidence that ACE inhibitors and especially ARBs can significantly reduce the risk of stroke. The LIFE trial was a primary stroke prevention study of losartan in high-risk patients, and the investigators were able to demonstrate a significant decrease in stroke (Table 1). Recently, another ARB, candesartan, was demonstrated to reduce stroke by 28% in the Study on COgnition and Prognosis in the Elderly (SCOPE). This study focused on elderly patients (70 to 89 years) with mild hypertension: A significant reduction in stroke and a trend toward reduced rates of new-onset diabetes were seen. There is not a strong correlation between the risk of stroke and cholesterol levels. However, clinical trials of statins in patients with coronary artery disease have shown significant stroke-preventive effects. Law et al performed a systematic review and meta-analysis of the statin trials and were able to show that statins can lower LDL cholesterol concentrations by an average of 1.8 mmol/L, which translates into a 60% decrease in the risk of IHD and a 17% reduction in the risk of stroke. Therefore, combination of an ARB and a statin may have tremendous potential for the prevention of first stroke as well as in poststroke patients.

Heart Failure
Recent studies have demonstrated a beneficial effect of ARBs in heart failure. There is also evidence that statins are beneficial in heart failure, as shown in a subgroup analysis from the Scandinavian Simvastatin Survival Study (4S) trial, and further ongoing trials are examining the effects of statins in heart failure. Recent studies have demonstrated direct effects of statins on the myocardium. Therefore, patients at risk from heart failure would probably be ideal candidates for combination therapy with an ARB and a statin. Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) is a long-term, randomized, double-blind, placebo-controlled, multinational study that is evaluating the effects of rosuvastatin on cardiovascular mortality and morbidity and overall survival in 4950 patients aged 60 years or greater with chronic symptomatic systolic heart failure (NYHA class II–IV) of ischemic etiology who are receiving standard treatment.

Conclusions
Treatment of the multiple risk factors associated with elevated BP and cholesterol with therapy that minimizes excessive oxidative stress is critical to the maintenance of normal endothelial cell function and a reduction in cardiovascular morbidity and mortality.
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Statins reduce cholesterol, are atheroprotective, and improve endothelial function. ARBs are effective in controlling hypertension and associated CVD risks beyond BP lowering by blocking the binding of angiotensin II to the AT1 receptor. Therefore, further studies are warranted to confirm the beneficial impact of ARBs and statins through their potentially synergistic mode of action, which could represent a potent and effective combination in a variety of patient populations.

In this light, a combination of statins and ARBs in one pill not only would be appealing with respect to the efficient prevention of cardiovascular end points but also would potentially increase treatment adherence in patients who have been prescribed long-term polymedication therapy.

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**KEY WORDS:** receptors, angiotensin II, statins, heart failure, cardiovascular diseases, syndrome X
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_Circulation_. 2004;110:1013-1020
doi: 10.1161/01.CIR.0000139857.85424.45
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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