Interactions Between the Renin-Angiotensin System and Dyslipidemia

Relevance in the Therapy of Hypertension and Coronary Heart Disease

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Dyslipidemia and hypertension are frequently observed in patients with ischemic heart disease. Studies from a number of laboratories suggest up-regulation of different components of the renin-angiotensin system (RAS) in patients with hypertension and atherosclerosis. Lipid accumulation in the blood vessels enhances the expression of RAS components; on the other hand, activation of RAS stimulates accumulation of low-density lipoproteins, particularly the oxidatively modified form, in the blood vessels. This concept of cross-talk between dyslipidemia and RAS activation has been proven in laboratory-based studies. Clinical trials also suggest that blockade of dyslipidemia and RAS may have a synergistic salutary effect on the outcome of patients with hypertension and/or manifestations of atherosclerosis. This concept needs to be evaluated in large clinical studies.

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Hypercholesterolemia and hypertension are major risk factors for coronary heart disease, and both are often present in the same patient. It is thought that the interactions between dyslipidemia and activation of neurohumoral systems, such as the renin-angiotensin system (RAS), may not only explain the frequent coexistence of hypertension and dyslipidemia but also play an important role in the pathogenesis of atherosclerosis. Experimental data suggest that the effects of angiotensin II and lipoproteins on atherogenic risk are not independent. Accumulating data from recent experimental and clinical studies suggest that the pathways by which angiotensin II and low-density lipoprotein cholesterol (LDL-C) lead to vascular disease may frequently overlap. Interventions directed at lowering total cholesterol, LDL-C, and triglyceride levels and raising high-density lipoprotein cholesterol (HDL-C) levels result in a reduction in cardiovascular events. Control of blood pressure similarly results in a decrease in cardiovascular events. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor (AT1R) blockers modulate RAS and are beneficial in reducing cardiovascular events in patients with vascular disease. There is a suggestion that the combined use of cholesterol-lowering drugs along with agents that modulate RAS may have additive benefit in the prevention and treatment of coronary artery disease (CAD), hypertension, and heart failure. In this review article, we discuss the results of experimental and clinical studies on the interaction between RAS and dyslipidemia in reference to atherogenesis, hypertension, and left ventricular remodeling. These observations may affect the therapy of patients with coronary heart disease, hypertension, and heart failure.

RAS AND CHOLESTEROL BIOSYNTHESIS

Cholesterol accumulation in the macrophages and their transformation into foam cell formations are major events in the development of atherosclerosis. Cellular cholesterol accumulation can result from increased uptake of LDL or oxidatively modified forms of LDL and enhanced macrophage cholesterol synthesis. Using macrophages harvested from the peritoneum after injection of angiotensin II,
Keidar et al² were able to demonstrate that angiotensin II dramatically increases macrophage cellular cholesterol biosynthesis with no significant effect on blood pressure or plasma cholesterol levels. The ACE inhibitor fosinopril sodium and the AT,R blocker losartan potassium decreased cholesterol biosynthesis in response to angiotensin II. Furthermore, in cells that lack the AT,R, such as RAW macrophages, angiotensin II did not increase cellular cholesterol synthesis. These observations confirm the role of the AT,R in the angiotensin II–mediated cholesterol synthesis in the macrophages. Nickenberg et al³ have shown accumulation of LDL-C in cultured vascular smooth muscle cells, and this effect is mediated via AT,R activation.

Angiotensin II–mediated increase in macrophage cholesterol influx has been demonstrated and has been attributed to the oxidant stress that contributes to and facilitates LDL oxidation by arterial wall components.⁴ Angiotensin II can bind to LDL and form modified lipoprotein, which is taken up at an enhanced rate by the scavenger receptors on macrophages. This leads to cellular cholesterol accumulation.⁵ Li et al⁶ have studied the kinetics of oxidized LDL (ox-LDL) uptake in endothelial cells and observed that angiotensin II, in a concentration-dependent fashion, enhanced the uptake of ox-LDL labeled with iodine 125 in these cells. The AT,R blocker losartan but not the angiotensin II type 2 receptor (AT,R) blocker PD 123319 blocked the enhanced uptake of ox-LDL.

Angiotensin II up-regulates macrophage messenger RNA (mRNA) for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and fluvastatin, a competitive inhibitor of HMG-CoA reductase, blocks the stimulatory effect of angiotensin II on macrophage cholesterol biosynthesis.² The biochemical site for angiotensin II action along the cholesterol biosynthesis pathway is probably HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.⁷ Thus, it seems that the stimulation of cholesterol biosynthesis in macrophages and uptake of LDL in smooth muscle cells and of ox-LDL in macrophages and endothelial cells requires, or is at least facilitated by, AT,R activation. In this process, alteration in the expression of HMG-CoA reductase may play an important role.

**RAS, DYSLIPIDEMIA, AND REACTIVE OXYGEN SPECIES**

Griendling et al⁸ first documented that angiotensin II via AT,R activation increases NADH (nicotinamide adenine dinucleotide hydrogenase)/NADPH (nicotinamide adenine dinucleotide phosphate hydrogenase) oxidase activity in macrophages. Increased oxidative stress is now regarded as an important feature of hypercholesterolemic atherosclerosis. In this context, antioxidants have been shown to reduce the extent of progression of atherosclerosis in experimental animals and in some studies in humans as well.

Warmholtz et al⁹ studied superoxide production in the aortas of rabbits fed a diet containing 0.5% cholesterol. In their first study, they looked at the effects of endothelium removal on vascular superoxide production in control and Watanabe rabbits (hypercholesterolemia secondary to an LDL receptor defect). The rate of superoxide production was increased approximately 2-fold in aortic segments from Watanabe rabbits compared with controls. This increase in superoxide production was abolished by removal of the endothelium from the arterial segments. NADH oxidase but not the NADPH activity was significantly increased in these vascular segments. These findings suggest that hypercholesterolemia is associated with increased superoxide production secondary to activation of vascular NADH oxidase. These authors then measured the effects of an AT,R blocker, Bay 10-6734, on superoxide production and NADH oxidase activity in aortas from rabbits fed a normal diet (controls) or a high-cholesterol diet. Concurrent administration of AT,R blocker reduced superoxide production and inhibited NADH oxidase activity in the animals fed a high-cholesterol diet. The investigators concluded that in hypercholesterolemic animals, NADH oxidase represents a major vascular source of superoxide and that increased vascular levels of angiotensin II may cause increased NADH oxidase activity. Hypercholesterolemia is associated with AT,R up-regulation, endothelial dysfunction, and increased NADH-dependent vascular superoxide production. The improvement of endothelial dysfunction, inhibition of the oxidase, and reduction of early plaque formation by AT,R antagonists suggest a crucial role of angiotensin II–mediated superoxide production in the early stage of atherosclerosis. Clinical and experimental studies have identified a marked attenuation in endothelium-dependent vasodilation as one of the early stages of atherosclerosis.¹⁰¹¹ In some cases, this is related to enhanced inactivation of endothelium-derived nitric oxide (NO) by superoxide¹² rather than a consequence of decreased NO production.¹³ It is known that the activation of AT,Rs leads to membrane-associated, NADH-dependent oxidase.⁹ In addition, LDL enhances AT,R expression in cultured smooth muscle cells,¹⁴ and atherosclerotic lesions are associated with increased ACE expression,¹⁵ which may serve as a source of local production of angiotensin II and ultimately increased production of vascular superoxide.

An experimental study has shown that the blockade of AT,Rs normalizes the activity of NADH oxidase, reduces plaque area and macrophage infiltration, and in parallel improves endothelial studies in animals fed a high-cholesterol diet.¹⁶ These findings suggest a pathogenic role for RAS in both the initiation and acceleration of the hypercholesterolemic atherosclerotic process and that inhibition of RAS may have benefit in the treatment of this malady.

Long-term treatment with ACE inhibitors has been shown to improve endothelial vasomotor function in patients with CAD,¹⁷ possibly because of decreased superoxide-mediated inactivation of NO. Importantly, the benefits of ACE inhibitor therapy are more pronounced in patients with hypercholesterolemia.
HYPERCHOLESTEROLEMIA AND RAS ACTIVATION

Experimental studies have shown that hyperlipidemia enhances RAS activity. All components of increased RAS activation have been identified in atherosclerotic lesions. These include, in particular, increased expression of ACE and AT\(_1\)Rs.\(^{18,19}\) A number of recent studies\(^{20,21}\) in human atherosclerotic tissues have confirmed the up-regulation of ACE and AT\(_1\)Rs, particularly in the regions that are prone to plaque rupture. Importantly, these same areas show extensive inflammatory cell deposits, macrophage accumulation, and apoptosis.

In vitro studies have shown that incubation of vascular smooth muscle cells with LDL increases expression of the AT\(_1\)Rs.\(^{22}\) Li et al\(^{23}\) examined the expression of angiotensin II receptors in human coronary artery endothelial cells and observed that ox-LDL increases the mRNA and protein for AT\(_1\)Rs but not AT\(_2\)Rs, implying that ox-LDL increases AT\(_1\) expression at the transcriptional level. In this process, activation of the redox-sensitive transcription factor NF-\(\kappa\)B (nuclear factor kappa B) plays a critical role.

To define the relationship of RAS and lipids in humans, Nickenig et al\(^{24}\) administered angiotensin II in normcholesterolemic and hypercholesterolemic men and found that increase in blood pressure was exaggerated in the hypercholesterolemic group and that this response could be blunted by LDL-C-lowering agents. Furthermore, these investigators found that there was a linear relationship between AT\(_1\)R density on platelets and LDL-C concentration in plasma. Treatment with statins decreased AT\(_1\)R expression in this study. Statin-mediated down-regulation of AT\(_1\)R expression has also been shown in vascular smooth muscle cells.\(^{24}\) Another study\(^{25}\) has indeed shown that statins directly decrease AT\(_1\)R expression in endothelial cells.

The expression of genes for chymases, enzymes by which angiotensin II can be formed independently of ACE activation, has been shown to be increased in atherosclerotic lesions of the aorta from mononuclear cells following a high-cholesterol diet.\(^{26}\) The functional significance of chymase in the development of atherosclerosis, however, remains uncertain. These observations, which are based on laboratory evidence and some clinical data, suggest a close interaction of dyslipidemia and RAS.

ANGIOTENSIN II IN HYPERCHOLESTEROLEMIC ATHEROSCLEROSIS

Activation of RAS with formation of angiotensin II and activation of angiotensin II, particularly the AT\(_1\)Rs, has been implicated in the pathobiology of atherosclerosis, plaque rupture, myocardial ischemic dysfunction, and congestive heart failure.\(^{27}\) Several studies\(^{28,29}\) have shown that ACE inhibitors decrease progression of atherosclerosis in a variety of animal species. Because numerous different ACE inhibitors exert similar antiatherosclerotic effects, one can assume that this represents a class effect. In concurrence with the slowing of progression of atherosclerosis, ACE inhibitors decrease markers of inflammation and LDL oxidation in the atherosclerotic regions.

The AT\(_1\)R blockers have also been shown to reduce the progression of atherosclerosis.\(^{29,30}\) The effects are particularly evident at high doses of AT\(_1\)R blockers, which suggests that either high doses block AT\(_1\)R expression or that these doses reduce atherosclerosis by a nonspecific effect. We recently reported on the antiatherosclerotic effect of losartan potassium \((25 \text{ mg/kg})\) in rabbits fed a high-cholesterol diet and showed that losartan therapy suppressed the expression of adhesion molecules and NF-\(\kappa\)B by activating its regulatory protein IkB\(_\alpha\).\(^{30}\) To determine the specificity of the role of RAS inhibitors (vs the blood pressure–lowering effect), Leif et al\(^{30}\) conducted a study with low doses of fosinopril sodium \((5 \text{ mg/kg daily})\) or losartan potassium \((5 \text{ mg/kg daily})\) that did not lower blood pressure. Control animals were given either placebo or a dose of hydralazine hydrochloride that lowered blood pressure. The LDL oxidation was measured by levels of thiobarbituric acid reactive substances or by formation of conjugated dienes was suppressed by low-dose fosinopril, suppressed only modestly by losartan, and unaffected by placebo or hydralazine. Atherosclerosis was inhibited by fosinopril and losartan, suggesting that the antiatherosclerotic effects of RAS inhibitors may be due, at least in part, to direct inhibition of LDL oxidation and other actions of angiotensin II in the vessel wall.

Bavry et al\(^{31}\) from our laboratory showed that the ACE inhibitor quinapril hydrochloride decreased intra-arterial thrombus formation, whereas the AT\(_1\)R blocker losartan had a minimal effect. The inhibitory effect of ACE inhibitors on the generation of plasminogen activator inhibitor 1 may be relevant in this differential effect of ACE inhibitors and AT\(_1\)R blockers. This is especially relevant since thrombosis is intimately involved in atherogenesis.\(^{32}\)

The role of angiotensin II in promoting atherosclerotic lesions and aneurysms in apolipoprotein E–deficient mice has been recently examined by Daugherty et al.\(^{33}\) These investigators showed that 1-month infusion of angiotensin II enhanced the severity of aortic atherosclerotic lesions compared with placebo. There was extensive formation of abdominal aortic aneurysms in apolipoprotein E–deficient mice infused with angiotensin II. Furthermore, the presence of hyperlipidemia was necessary for the development of atherosclerosis. These observations suggest that increased plasma concentrations of angiotensin II when combined with hyperlipidemia have profound effects on vascular biology.

ENDOTHELIAL FUNCTION, RAS, AND DYSLIPIDEMIA

Endothelial dysfunction in hypercholesterolemic animals has been shown to be improved by ACE inhibitors.\(^{34}\) Bradykinin antagonists can diminish some of this benefit, suggesting that inhibition of bradykinin breakdown rather than the inhibition of angiotensin II formation may be important in this effect.\(^{35}\) Mancini et al\(^{37}\) showed that
treatment of patients with CAD with the ACE inhibitor quinapril improved coronary vasomotion. Quinapril had greater efficacy in improving endothelial function in patients with serum LDL-C levels greater than or equal to 130 mg/dL (3.36 mmol/L) than in patients with serum LDL-C levels less than 130 mg/dL (3.36 mmol/L).

Acetylcholine stimulates release of the potent vasodilator species NO, which is broken down by the reactive oxygen species. One of the mechanisms responsible for the improvement of acetylcholine-mediated vasodilation may be inhibition of angiotensin II–sensitive, NADH-dependent, superoxide-producing enzymes, resulting in a reduction of NO inactivation. Warnholtz et al36 showed that AT1R blockade inhibited NADH oxidase activity and in parallel improved endothelial dysfunction in cholesterol-fed animals. These findings cannot be attributed to the lowering of serum cholesterol levels, because treatment with the AT1R blocker has no effect on total cholesterol or LDL-C levels. Nonetheless, cellular levels of cholesterol may decrease and not be reflected in the serum.

INTERACTION BETWEEN Ox-LDL AND RAS

The atherosclerotic plaques, particularly those prone to rupture, reveal accumulation of large amounts of ox-LDL, and the plasma levels of ox-LDL are increased in patients with acute coronary syndromes; however, the serum cholesterol levels are not significantly different from those in control subjects.36 Steinberg et al37 underlined the significance of oxidation of LDL beyond absolute cholesterol values in the pathogenesis of atherosclerosis. We have recently identified high-affinity lectinlike receptors for reverse transcriptase–polymerase chain reaction, Western blot testing, and radioligand binding.38 Native LDL does not bind to this receptor. Vascular endothelial cells in culture39 and in vivo40 internalize and degrade ox-LDL through this putative receptor–mediated pathway that does not seem to involve the classic macrophage scavenger receptor. Recent studies show that the cytokine tumor necrosis factor α41 and fluid shear stress42 markedly up-regulate LOX-1 gene expression. LOX-1 activation is involved in apoptosis (programmed cell death) in response to ox-LDL.43,44 MAPK-1 (mitogen-activated protein kinase 1) activation, and expression of adhesion molecules and attachment of monocytes to activated endothelial cells.45 The redox-sensitive transcription factor NF-κB plays a critical role in the effects of ox-LDL on endothelial cells.46 The proapoptotic effect of angiotensin II in human coronary artery endothelial cells and the role of AT1R and protein kinase C activation have also been shown by our group.47

We have shown that angiotensin II up-regulates LOX-1 expression and the uptake of ox-LDL in human coronary artery endothelial cells via activation of the AT1R.48 The effects of angiotensin II can be blocked by the AT1R blockers losartan and candesartan but not by the AT1R blocker PD 213319.49 Angiotensin II and ox-LDL together exert a cumulative cellular injurious effect. Again, the AT1R blockers can reduce the cumulative injurious effect of angiotensin II and ox-LDL. Importantly, the chain-breaking antioxidant α-tocopherol can also attenuate the injurious effect of ox-LDL and angiotensin II.47

The cross-talk between ox-LDL and angiotensin II is further evident from the work of Chen et al,30 who showed intense immunostaining for and up-regulation of the gene for LOX-1 in the atherosclerotic tissue of rabbits fed a high-cholesterol diet. Losartan therapy not only reduced atherosclerosis but also blocked the up-regulation of LOX-1. Recent studies from our laboratory show marked up-regulation of LOX-1 in concert with apoptosis in human atherosclerotic plaques, particularly in the regions that are prone to rupture. These observations collectively emphasize the importance of redox-sensitive pathways in the cross-talk between ox-LDL and RAS. The Figure depicts the interaction of dyslipidemia and RAS in atherosclerosis, with particular reference to the expression of LOX-1.

DYSLIPIDEMIA AND RAS IN HYPERTENSION

The association of hypertension with hyperlipidemia has been noted in several population studies. The prevalence of hypertension is greater in populations with high levels of serum cholesterol.49 Dyslipidemia may be another metabolic factor that influences blood pressure. However, these studies used older, less rigorous definitions than are currently recommended. Recently, Lloyd-Jones et al50 evaluated 4962 patients from the Framingham Heart Offspring Study and cross-clarified them according to the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Data were collected from patients examined between 1990 and 1993. The prevalence of dyslipidemia (defined as total cholesterol level ≥240 mg/dL [6.22 mmol/L], HDL-C level ≤35 mg/dL [0.91 mmol/L], or patients currently receiving lipido- lowering therapy) increased with increasing blood pressure in men and women. On average, more than 40% of men and 33% of women with blood pressures of 145/90 mm Hg or higher were also dyslipidemic. These data demonstrate that hypertension and hypercholesterolemia are frequently associated, even when current rigorous definitions are used. These observations also suggest that individuals with hypertension may be more likely to become dyslipidemic over time. It is unclear at this time whether an interaction between hyperlipidemia and blood pressure might play a role in the metabolic syndrome of syndrome X, in which hyperlipidemia, hypertension, visceral obesity, and insulin resistance seem to occur in the same patient.

Sung et al51 examined the blood pressure response to a standard mental arithmetic test in 37 healthy, normotensive patients with hypercholesterolemia (mean total cholesterol, 263 mg/dL [6.81 mmol/L]) and 33 normotensive, normocholesterolemic patients. None of the hypercholesterolemic patients was receiving lipid-lowering therapy before study entry. In the first part of the study, the blood pressure response
endothelial cell. Genes for lectinlike ox-LDL receptor (LOX-1) and other scavenger receptors (SRs). EC indicates nitric oxide (NO), and be related to its proinflammatory properties. Angiotensin II promotes expression of the cysteine oxidase (Cox) type 1 receptor (AT1R). The prooxidant effect of angiotensin II may stimulate oxidation of LDL, degrade nitric oxide (NO), and be related to its proinflammatory properties. Angiotensin II promotes expression of genes for lectinlike ox-LDL receptor (LOX-1) and other scavenger receptors (SRs). EC indicates endothelial cell.

to the arithmetic test was determined. The blood pressure response during the arithmetic test was significantly higher in the hypercholesterolemic group compared with the normocholesterolemic group (18 vs 10 mm Hg, respectively, P=0.005). In the second part, the hypercholesterolemic group was divided into 2 subgroups that received either 6 weeks of lovastatin or 6 weeks of placebo in a double-blind, crossover design. There were 26 evaluable patients in this part of the study. Statin treatment resulted in significant reductions in total cholesterol and LDL-C levels and was associated with lower mean systolic blood pressure before (119±11 vs 122±9 mm Hg, P=0.07) and during (133±12 vs 141±10 mm Hg, P=0.05) the arithmetic test. Diastolic blood pressure changes did not significantly correlate with lipid lowering. These observations demonstrate that individuals with hypercholesterolemia have exaggerated systolic blood pressure response to mental stress and that lipid-lowering therapy improves the systolic blood pressure response to stress. Although the effects of elevated cholesterol level on atherosclerosis are well documented, the modest change in the degree of stenosis demonstrated by angiographic studies is not sufficient to explain the benefit of cholesterol reduction. It may well be that cholesterol lowering, particularly by statins, alters the activity of some neurohumoral mediators, such as angiotensin II and ACE expression, and improves vascular tone. It is noteworthy that statins have been shown to stabilize the atherosclerotic plaque, attenuate the reduction in endothelial NO synthase expression, and reduce the expression of leukocyte adhesion molecules, characteristic of the rapidly advancing atherosclerotic regions. Some of the pleiotropic effects of statins include antiplatelet, antithrombotic, antioxidant, antiatherosclerotic, angiogenic, antiapoptotic, antiischemic, anticarcinogenic, antiosseoprotic, and antidiabetic effects.

Interesting observations have been made that may explain some of the benefits seen with lipid-lowering therapy in hypertensive patients. It is known that sodium-lithium countertransport (SLC) activity is increased in essential hy-

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pertension but not necessarily related to blood pressure. Carr et al measured SLC in 17 patients with hyperlipidemia before and after lipid-lowering treatment and observed that the increased SLC activity seen with hyperlipidemia had returned to normal after treatment and the change in SLC activity was related to the change in serum triglyceride levels. Similarly, in a recent study, Saitta et al showed that hypercholesterolemia affects red blood cell sodium transport systems, with an increase in SLC activity, passive sodium permeability, and the internal sodium content.

In some animal models of hypertension, lipid-lowering treatment has been shown to cause prevention or attenuation of hypertension. Shatara et al demonstrated that the use of fenofibrate lowered blood pressure in 2 genetic models of hypertension, such as the stroke-prone, spontaneously hypertensive rats and Dahl salt-sensitive rats. They attributed this to possible natriuretic effect. Wilson et al have also shown the blood pressure-lowering effect of fenofibrate and pravastatin sodium in the Dahl salt-sensitive rats. Similarly, Si et al observed that bezafibrate attenuated vascular hyperresponsiveness and elevated blood pressure in fructose-induced hypertensive rats. In a recent study, Park et al used angiotensin II-dependent models of rats to show that statin prevented angiotensin II–induced renal injury independent of blood pressure and cholesterol-lowering effects. In this model, statin reduced inflammation, cell proliferation, and type II isoenzymes and collagen I in the left ventricle. This effect was also seen with hyperlipidemia before and after treatment and the change in SLC activity was related to the change in serum triglyceride levels.

Table 1. Evidence for Blood Pressure–Lowering Effect of Lipid-Lowering Treatment

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Outline</th>
<th>Drug Used</th>
<th>Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Callaghan et al,14 1994</td>
<td>25 Patients with hypertension and hyperlipidemia</td>
<td>Pravastatin sodium vs placebo for 12 wk</td>
<td>Pravastatin did not lower blood pressure</td>
</tr>
<tr>
<td>Abete et al,15 1998</td>
<td>23 Patients with hypertension and hyperlipidemia</td>
<td>Fluvasatin sodium, 40 mg, for 3 mo</td>
<td>Fluvasatin lowered blood pressure by 8-16 mm Hg</td>
</tr>
<tr>
<td>Glorioso et al,26 2000</td>
<td>25 Patients with hypertension and hyperlipidemia</td>
<td>Pravastatin sodium, 20-40 mg vs placebo for 32 wk</td>
<td>Pravastatin decreased systolic blood pressure by 8 mm Hg</td>
</tr>
<tr>
<td>Sposito et al,67 1999</td>
<td>Patients with hypertension and hyperlipidemia</td>
<td>ACE inhibitor (enalapril maleate or lisinopril) alone or with statin (lovastatin or pravastatin)</td>
<td>Additive blood pressure–lowering effect of the combination compared with ACE inhibitor alone</td>
</tr>
<tr>
<td>Borghi et al,68 2000</td>
<td>Patients with hypertension and hyperlipidemia</td>
<td>Statins (pravastatin or simvastatin) in addition to antihypertensive treatment</td>
<td>Additive benefit of statins in blood pressure lowering shown</td>
</tr>
<tr>
<td>Tonolo et al,69 2000</td>
<td>26 Microalbuminuric hypertensive patients with type 2 diabetes mellitus</td>
<td>Simvastatin in addition to antihypertensive treatment</td>
<td>Simvastatin exerted additional blood pressure–lowering effect and also reduced 24-h urinary albumin excretion</td>
</tr>
<tr>
<td>Jonkers et al,70 2001</td>
<td>17 Patients with hypertriglyceridemia and hypertension</td>
<td>Bezafibrate</td>
<td>Bezafibrate reduced systolic blood pressure by 5 mm Hg</td>
</tr>
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Abbreviation: ACE, angiotensin-converting enzyme.

LEFT VENTRICULAR MASS AND REMODELING

Increased left ventricular mass is common in patients with hypertension and is a powerful predictor of future cardiovascular events. It is interesting that the addition of pravastatin to antihypertensive treatment led to a greater reduction in left ventricular mass in patients with hypertension and hyperlipidemia in one study, suggesting an interaction of RAS and hyperlipidemia. This effect might be related to attenuation of angiotensin II–mediated increase in left ventricular mass.

Recent studies have in fact shown the benefit of statins in ameliorating the angiotensin II–mediated end organ damage. The known effect of statins in attenuating angiotensin II–induced cellular signaling and the involvement of angiotensin II in left ventricular remodeling after myocardial infarction led to a study by Bauersachs et al on the effect of statin in rats with heart failure after myocardial infarction. In this study, the authors were able to demonstrate the benefit of statin therapy in improving left ventricular remodeling and function in rats with heart failure. This effect was associated with attenuation of expression of fetal myosin heavy chain isoenzymes and collagen I in the left ventricular tissue, suggesting that statins may retard the progression of heart failure. Similarly, Dechend et al demonstrated the amelioration of angiotensin II–induced cardiac injury by cerivastatin, using an angiotensin II–dependent model of cardiac fibrosis and heart failure. In this study, the use of cerivastatin ameliorated the angiotensin II–induced hypertrophy, fibrosis, and remodeling independent of cholesterol levels. Although the clinical significance remains uncertain, the results suggest that statins interfere with angiotensin II–induced signaling and transcription factor activation, thereby ameliorating end-organ damage.

MODULATION OF RAS AND DYSLIPIDEMIA IN CAD

Although numerous epidemiologic studies have shown that elevated levels of LDL are associated with the onset of hypertension and atherosclerosis, the underlying mechanisms remain unclear. Angiotensin-converting enzyme inhibition has...
been shown to promote regression and even prevent atherosclerosis, suggesting a link between atherosclerosis and RAS.71

The clinical benefits from simultaneous modulation of RAS and dyslipidemia in patients with CAD are summarized in Table 2. Indirect evidence for an interaction between dyslipidemia and RAS comes from some clinical studies, such as Evaluation of Losartan in the Elderly (ELITE)72 and the Lipoprotein and Coronary Atherosclerosis Study (LCAS).73

The LCAS was conducted in 429 patients with CAD and at least 1 lesion of 30%- to 75%-diameter stenosis. Patients were randomized to fluvastatin sodium or placebo for 2.5 years, and the primary end point was change in minimum lumen diameter as assessed by quantitative coronary angiography. Marian et al73 studied response to statin therapy according to ACE insertion/deletion (I/D) phenotype in the LCAS population. The patients with D/D, I/D, or I/I phenotypes achieved reductions of 31%, 25%, and 21%, respectively. There was a significant genotype-by-treatment interaction (P = .005). A similar result was obtained for reduction in total cholesterol levels. Patients with D/D phenotype also had a higher rate of regression and a lower rate of progression than patients with the other 2 phenotypes.

The effect of ACE inhibition on CAD progression was the subject of the Quinapril Ischemic Events Trial. This study showed that quinapril had only a slight effect on the progression of CAD.74,75 However, in patients with LDL-C levels of 130 mg/dL (3.37 mmol/L) or higher, there was significantly less progression of CAD in the quinapril group. Thus, the rapid disease progression seen in patients receiving placebo with higher LDL-C levels did not occur in quinapril-treated patients. As in the Trial on Reversing Endothelial Dysfunction study,76 the ACE inhibitor seemed to have greater efficacy in patients with elevated LDL-C levels. Observations made from these studies are important in our understanding of the relevance of RAS and hyperlipidemia in atherosclerosis. However, the studies are limited due to the small number of patients enrolled and retrospective nature of data analysis for this purpose.

The ACE inhibitors are beneficial in a variety of clinical situations, such as hypertension, diabetes, and congestive heart failure. Long-term studies with ACE inhibitors in patients with decreased left ventricular function77-79 have shown a decrease in cardiac ischemic events and/or need for revascularization. One pathogenic factor common to both heart failure and ischemic heart disease is endothelial dysfunction or activation, which is improved with ACE inhibitors. Clinical studies, such as the Heart Outcomes Prevention Evaluation (HOPE) trial,80 have confirmed the benefit of ACE inhibitors in reducing vascular events in patients with preexisting vascular or coronary disease, even in patients with normal ventricular function and normal blood pressure. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E trial,81 a substudy of the HOPE trial, demonstrated the beneficial effect of ramipril in preventing carotid atherosclerosis progression. Similarly, the AT1R blocker irbesartan has been shown to reduce markers of inflammation in patients with premature atherosclerosis.82 These findings suggest a potential role of RAS in the progression of atherosclerosis and therapy of related clinical syndromes.

To our knowledge, no large randomized study has examined the hypothesis that treatment with RAS blockers, such as ACE inhibitors or AT1R blockers, combined with lipid-lowering drugs exerts additive or incremental benefit. Some of the ongoing randomized trials may shed light in this direction.

**CONCLUSIONS**

Hypertension and dyslipidemia, 2 major risk factors for atherosclerotic disease, are frequently associated in patients with CAD. Data from clinical studies suggest the existence of lipoprotein-neurohormonal interactions that may adversely affect vascular ultrastructure and function. Data from preclinical studies suggest that RAS is up-regulated by abnormal lipid levels, most likely via production of ox-LDL. On the other hand, activation
of RAS leads to release of reactive oxygen species and transcriptional up-regulation of LDL and increased ox-LDL uptake in macrophages, smooth muscle cells, and endothelial cells. These findings extend our understanding of the interplay among risk factors for atherosclerosis to synergistically increase cardiovascular risk and of the antiatherosclerotic effects of local ACE inhibition to reduce cardiovascular risk. Trials aimed at modifying RAS along with drugs that reduce total cholesterol and LDL-C levels will address the clinical relevance of this biological interaction.

In conclusion, findings from cellular, animal, and human experiments suggest a cross-talk between dyslipidemia and RAS relative to vascular dynamics. The common effects of dyslipidemia and RAS include the following:

- Formation and release of reactive oxygen species
- Apoptosis (programmed cell death)
- Activation of redox-sensitive transcription factor NF-κB
- Expression of adhesion molecules and cytokines
- Up-regulation of the gene for monocyte chemoattractant protein 1
- Monocyte adhesion
- Degradation or decrease of endothelial NO synthase expression
- Decrease of endothelium-dependent vasodilation.

These effects may have a bearing on the pathogenesis of hypertension and atherosclerosis.

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