The renin-angiotensin system plays a central role in the pathogenesis of cardiovascular disease. At the molecular and cellular levels, angiotensin II, the main effector peptide of the system, stimulates key components of atherosclerosis. Trials in animals and humans indicate that blocking renin-angiotensin system pathways decreases atherosclerotic plaque progression and ischemic events. This review provides a broad overview of the entire role of the renin-angiotensin system in atherothrombotic disease, ranging from molecular pathways to human genetics to the latest clinical trials.

Cardiovascular disease is the leading cause of mortality for men and women in the United States and worldwide, with 1 of every 2.5 deaths in the United States attributable to cardiovascular disease. The important role of the renin-angiotensin system (RAS) has become increasingly established in many types of cardiovascular disease. Established indications for pharmacologic inhibition of the RAS include hypertension, left ventricular dysfunction, acute myocardial infarction (MI), diabetic nephropathy, and atherosclerosis.

During the past decade, the pathophysiologic understanding of the impact of the RAS has expanded and shifted. Initially, the RAS was conceptualized as a circulating hormonal system, affecting cardiovascular disease through hemodynamic and endocrine factors. The RAS induces vasoconstriction and increases intravascular volume, both of which increase myocardial workload. More recent understanding of the mechanism of the RAS has focused on tissue-based cellular effects occurring in the coronary arteries and myocardium that are reparative responses to tissue injury. In the tissue-based cellular model, the RAS directly contributes to coronary ischemic events via atherosclerosis, altered postinfarct remodeling, and reduced fibrinolysis. Inhibition of the RAS has antiatherosclerotic activity that has been demonstrated in animal models of atherosclerosis and suggested in clinical trials in humans.

This review briefly describes members of the RAS and then uses their genetic and molecular links to disease to explore the results of recent clinical trials and therapeutic trends in atherothrombotic disease.

**OVERVIEW OF THE RAS**

Many of the effects of the RAS are mediated by angiotensin II, an oligopeptide produced by 2 enzymatic cleavages of angiotensinogen, a 452–amino acid protein produced by the liver (Figure 1). Two similar, yet distinct, systems generate angiotensin II: the circulating and tissue RASs. Whereas the circulating RAS may be responsible for short-term regulation, the tissue RAS serves a role in long-term changes.

In the circulating RAS, renin, which is released into circulation by the juxtaglomerular apparatus of the kidney in response to decreased glomerular perfusion, catalyzes the first cleavage-producing angiotensin I. Angiotensin I, a decapptide, is cleaved by lung angiotensin-converting enzyme (ACE), which also degrades brady-
kinin, into the circulating octapeptide angiotensin II.

In contrast to the endocrine function of circulating angiotensin II, the tissue RAS produces local angiotensin II that is involved in autocrine and paracrine signaling within organs and tissues. The tissue RAS is present in all of the major body organs, including the heart, blood vessels, and kidneys. The tissue RAS may operate similarly to the circulating RAS, except that all the components necessary to generate angiotensin II are present within the tissue, such as an isolated blood vessel. Thus, tissue renin generates tissue angiotensin I, subsequently catalyzed by tissue ACE into tissue angiotensin II. Plasma ACE represents a small proportion of total body ACE, which exists on endothelial cells, throughout atherosclerotic plaques, and in the parenchymal cells of certain tissues.

Alternative enzyme pathways also generate angiotensin II in the tissue RAS. Chymase catalyzes conversion of angiotensin I to angiotensin II. Cathepsin G and a chymostatin-sensitive angiotensin II–generating system directly cleave angiotensinogen into angiotensin II. The relative importance of alternate pathways is uncertain. Although chymase in hypercholesterolemic patients provides 95% of the angiotensin II–generating ability in the internal thoracic artery, most vascular chymase is located in the adventitia, so that the presence of angiotensin II in the intima of plaques co-localizes with ACE, not chymase.

Angiotensin II functions through 2 receptors, type 1 (AT1) and type 2 (AT2). The AT1 is ubiquitously and abundantly distributed in adult tissues, including blood vessels, heart, kidney, adrenal gland, liver, brain, and lungs. The effects mediated by the AT1 are currently well understood and include promoting cell growth and regulating the expression of bioactive substances such as vasoconstrictive hormones, growth factors, cytokines, aldosterone, and extracellular matrix components. The AT1 also initiates several autoregulatory feedback loops of the RAS. Through one positive loop, angiotensin II stimulates expression of its precursor, angiotensinogen. This feedback occurs via a multihormone-responsive enhancer, called the acute phase response element, in the promoter of angiotensinogen. Angiotensin II type 1 receptor pathways may similarly result in enhanced ACE activity. However, via the AT1, angiotensin II also engages in a negative feedback loop by inhibiting the secretion of renin.

The AT2 in the adult is limited mainly to the myocardium, vascular epithelium, uterus, ovary, brain, pancreas, and adrenal medulla. It is up-regulated with atherosclerosis, vascular injury, MI, and heart failure. In the human heart, the AT2 is predominantly located in interstitial fibroblasts, suggesting that it may be involved in the progression of inflammation and fibrosis. Although the AT2 often counterbalances the effects of the AT1 by favoring apoptosis and inhibiting the growth of vascular smooth muscle and cardiac myocytes, it may also have a role in cell growth. Ultimately, the ratio of AT1:AT2 expression may mediate the effects of angiotensin II.

Although angiotensin II seems to be the ligand responsible for most signal transduction through the AT1 and the AT2, newly described components of the RAS indicate that it is not the only ligand, and the AT1 and the AT2 are not its only receptors. Angiotensin II may be cleaved into angiotensin III, which stimulates aldosterone synthesis and inflammation, and angiotensin IV, which binds to the AT1, resulting in vasoconstriction, and to the AT4, promoting plasminogen activator inhibitor production. Furthermore, in the heart, kidneys, and testes, an ACE-related carboxypeptidase

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**Figure 1.** Key members of the renin-angiotensin system cascade.

**Figure 2.** Mechanisms by which angiotensin II promotes atherosclerosis. Most effects result from signaling through the angiotensin II type 1 receptor. IL-6 indicates interleukin 6; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; LOX-1, lectin-like oxidized low-density lipoprotein receptor; VCAM, vascular cellular adhesion molecule; ICAM, intracellular adhesion molecule; TGF-β, transforming growth factor β; PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; and NO, nitric oxide.
Angiotensin II, via the AT1, activates intracellular signaling pathways that promote atherothrombosis through inflammation, endothelial dysfunction, growth, altered fibrolysis, and potentiation of low-density lipoprotein (LDL) oxidation (Figure 2).  

Inflammation  
Atherosclerosis is a chronic inflammatory disorder, with inflammation key to all stages of plaque formation and growth.  

The RAS serves an important role in promoting inflammation. Angiotensin II activates the proinflammatory transcription factor nuclear factor kappa B (NF-κB) in human monocytes, human vascular smooth muscle cells (VSMCs), and human endothelial cells. Activated NF-κB leads to increased production of cellular adhesion molecules such as intercellular adhesion molecule and vascular cellular adhesion molecule and proinflammatory cytokines such as monocyte chemoattractant protein-1 and interleukin 6. In addition, human endothelial cells also up-regulate expression of E-selectin in response to angiotensin II. Although the inflammatory effects of angiotensin II rely in part on signal transduction from the AT1, as evidenced by decreased inflammatory activation with AT1 blockers, AT2 signal transduction also activates NF-κB. In contrast to angiotensin II, which signals through both receptors, angiotensin III predominantly stimulates NF-κB through the AT2. Because the AT2 in the human heart is mainly located in interstitial fibroblasts, it may ultimately serve a role in inflammation and fibrosis.

Endothelial Dysfunction  
Endothelial function is crucial in preventing the development of atherosclerosis, with endothelial dysfunction serving as one of the earliest detectable functional abnormalities of the coronary circulation during the initiation of atherosclerosis. Endothelial antithrombogenicity and inhibition of cellular growth occur in part through the secretion of endothelium-derived factors such as nitric oxide (NO) and prostacyclins. Nitric oxide, which is stimulated by bradykinin, inhibits platelet and leukocyte adhesion to endothelium and works with prostacyclin to inhibit platelet aggregation. It also inhibits the growth of VSMCs. These effects occur in part through inhibition of NF-κB. The RAS impairs NO release and activity through inhibition of NF-κB degradation by ACE and oxidative stress. Angiotensin II impairs NO activity by creating oxidative stress through the stimulation of NADH/NADPH (nicotinamide adenine dinucleotide phosphate) oxidae in VSMCs and endothelial cells. This impact on NO may be partially counterbalanced by AT2 pathways increasing bradykinin production and stimulating NO synthase activity.

Angiotensin II–induced endothelial dysfunction and inflammation result in a self-perpetuating feedback loop. Just as angiotensin II–induced inflammation leads to endothelial dysfunction, similarly, endothelial dysfunction stimulates adhesion molecules (vascular cellular adhesion molecule-1), chemoattractants (monocyte chemoattractant protein-1), and cytokines that are proinflammatory.

Growth Factors  
In addition to activating inflammatory cytokines and inducing endothelial dysfunction, angiotensin II also activates several growth-associated kinase pathways, such as Janus kinase/signal transducers and activators of transcription and mitogen-activated protein pathways. Several proto-oncogenes are induced within minutes, including c-fos, c-jun, and c-myc. Within hours, angiotensin II leads to the increased production of autocrine growth factors, including transforming growth factor β1 and platelet-derived growth factor. In VSMCs, transforming growth factor β1 promotes fibrosis, stimulating cellular hypertrophy rather than proliferation by modulating the impact of growth factors such as platelet-derived growth factor. Imbalances in these growth factors, possibly created by vascular injury, may lead to angiotensin II–mediated proliferation. Although the previously mentioned growth effects all depend on AT1 signal transduction, with complete growth inhibition by AT1 blockade, the impact of angiotensin II on growth may be mediated in part by the AT2. The AT2 generally counteracts the growth effects of the AT1, activating phosphatases instead of kinases and thereby inhibiting growth of VSMCs and cardiac myocytes. However, AT2 blockade inhibits medial smooth muscle hypertrophy and fibrosis in vivo in hypertensive rats and angiotensin II–infused rats. These growth stimulatory effects are not reported in smooth muscle cell cultures, and the potential impact of the AT2 on angiotensin II growth regulation is not yet understood.

Thrombosis  
The RAS regulates fibrinolytic balance, inhibiting the fibrinolytic system and enhancing thrombosis by altering the coagulation cascade and platelet activity. The RAS increases the production and release of plasminogen activator inhibitor-1 from endothelial cells and VSMCs. Plasminogen activator inhibitor-1 inhibits the endogenous fibrinolytic system, serving as the most important inhibitor of the tissue plasminogen activator. Bradykinin, which increases tissue plasminogen activator release, is degraded by ACE, further attenuating thrombolysis. The RAS also increases platelet activation and aggregation. Human platelets possess angiotensin II receptors, which sensitize platelets to the effects of other platelet agonists and may stimulate release of vasoconstrictive agents such as thromboxane A2 and proliferative agents such as platelet-derived growth factor. The endogenous platelet inhibitor NO is decreased by the RAS through ACE and superoxide production. Finally, the RAS in-
creases levels of tissue factor, a member of the coagulation cascade that serves as an essential cofactor for factor VII and is increased in atherosclerotic plaques and acute coronary syndromes.30

**LDL Oxidation**

Just as angiotensin II mediates many of the atherothrombotic consequences of the RAS, oxidized LDL plays an important role in the atherothrombotic contribution of hypercholesterolemia. Similar to angiotensin II, oxidized LDL impairs NO formation, promotes superoxide anion formation, and induces endothelial adhesion molecule-1 (E-selectin, vascular cellular adhesion molecule-1, and intercellular adhesion molecule-1), chemokines (monocyte chemotactic protein-1), and smooth muscle growth factors. Angiotensin II enhances the oxidation of LDL via stimulation of lipoxygenase and NADH in macrophages.17,31 Furthermore, angiotensin II, via the AT1, serves a crucial role in mediating the uptake of oxidized LDL by up-regulating its receptor LOX-1 (lectin-like oxidized LDL receptor) on endothelial cells and macrophages.32 Oxidized LDL and hypercholesterolemia increase expression of the AT1 on human endothelial cells and VSMCs.33

**HUMAN GENETIC POLYMORPHISM STUDIES SUPPORTING THE ROLE OF THE RAS IN ATHEROSCLEROSIS**

Genetic components are important in the development of vascular disease, as evidenced by the clustering of premature atherosclerosis in families.34 Naturally occurring variations in DNA sequences, or polymorphisms, that have small effects on vascular disease are common, with gene-gene and gene-environment interactions making an important contribution to the risk. Numerous polymorphisms have been identified in genes of the RAS. Associating these polymorphisms with atherothrombotic disease is helpful in clarifying the role of the RAS in cardiovascular events and offers potential clinical applications in risk stratification and therapeutics.

The most widely studied polymorphism in the RAS is an insertion (I)/deletion (D) polymorphism in ACE. The ACE DD genotype is associated with higher circulating and tissue levels of ACE.35,36 Multiple studies have associated the DD genotype with a higher incidence of atherosclerosis and MI.37-50 but many other studies have failed to confirm the association with atherothrombotic disease.47-53 A meta-analysis50 of 15 published studies with 3394 patients and 5479 controls demonstrated an association between DD and MI, with an odds ratio of 1.26 (95% confidence interval, 1.15-1.39; P < .001). Although the I/D polymorphism is not associated with restenosis after angioplasty in most studies, it has been associated with restenosis after coronary stents are placed.45,54 It has also been associated with cardiac allograft vascular disease after heart transplantation.55 Furthermore, supporting the interaction between the molecular mechanisms of the RAS and cholesterol in promoting atherosclerosis, the DD genotype has been associated with a greater reduction in LDL, a higher rate of regression, and a lower rate of progression of coronary artery disease (CAD) in patients treated with fluvastatin sodium in the Lipoprotein and Coronary Atherosclerosis Study Population.56,57 A declining prevalence of the DD genotype with increasing age is consistent with increased cardiovascular risk and decreased survival of this genotype.58,59

Studies of other polymorphisms in the RAS similarly report conflicting associations with CAD. A case-control study60 of 301 white males showed that homozygotes for the T allele of the angiotensinogen M235T polymorphism have increased angiotensinogen plasma levels, an increased history of MI, and an increased risk of CAD (odds ratio, 1.5; 95% confidence interval, 1.1-2.2; P = .03). Although some studies support these results,46,51-53,61 others have failed to show an association.38 Associations with CAD have been reported in the AT1-1166A/C polymorphism.62 The AT1-810T/A polymorphism also may have an association with CAD and MI.62,63 In a G protein used by the AT1, the G protein β3 subunit C825T polymorphism associates with CAD and MI but not with restenosis.64

Beyond single polymorphisms, gene-gene interactions may have a synergistic impact on cardiovascular risk. Three studies show a synergistic interaction between increased risk associated with the D allele of the ACE I/D polymorphism and the C allele of the AT1-1166A/C polymorphism.65-68 Although patients with ACE DD and AT1 CC alleles in the prospectively defined subsyudy68 of the REGRESS (Regression Growth Evaluation Statin Study) lipid-lowering regression trial had increased ischemic events over 2 years, there was no difference in the progression of angiographically defined atherosclerosis. In contrast, other studies67,69 did not show any synergistic interactions. Results of a recent study70 indicate a synergistic effect between AGT M235T and apolipoprotein E4, with increased risk of MI observed in AGT TT and apolipoprotein E4 carriers.

**ANIMAL STUDIES OF RAS INHIBITION AND REDUCTION OF ATHEROSCLEROSIS**

If the RAS promotes atherosclerosis, then inhibition of the RAS should reduce atherosclerosis. Inhibition of the RAS, through either ACE inhibition or AT1 blockade, decreases the extent of vascular lesions in several animal models of atherosclerosis. In the normotensive Watanabe heritable hyperlipidemic rabbit, use of captopril reduced aortic atherosclerosis, with a reduced area of involvement and reduced cholesterol content. Similar results were obtained in the high-cholesterol–fed rabbit, hamster, mini-pig, cynomolgus monkey, and diabetic and non-diabetic apolipoprotein E-deficient mice using different ACE inhibitors at doses comparable to those used clinically.52,71-73 These results are not dependent on blood pressure because other antihypertensive agents do not produce similar results6,74 and because some studies show decreased atherosclerosis...
at doses that do not alter blood pressure. Although most studies have reported positive results, some have not demonstrated decreased atherosclerosis. For example, low-dose trandolapril did not affect blood pressure or atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. However, it potentiated the efficacy of AT1 blockade, which does not alter bradykinin levels.

HUMAN CLINICAL TRIALS OF RAS INHIBITION WITH SURROGATE END POINTS

The results of clinical trials using surrogate outcomes to measure the impact of RAS inhibition support a role for the RAS in inflammation and endothelial dysfunction but offer conflicting results on atherosclerosis and postprocedure restenosis. A small randomized controlled trial (RCT) comparing treatment with the AT1 blocker eprosartan with hydrochlorothiazide in 38 hypertensive patients showed a statistically significant reduction in the inflammatory markers monocyte chemoattractant protein-1 and vascular cellular adhesion molecule and increased LDL oxidation lag time, while achieving comparable blood pressure control. In the TREND (Trial on Reversing Endothelial Dysfunction), an RCT of 129 patients using vasoconstriction responses to acetylcholine during human cardiac angiography, 6 months of treatment with quinapril improved endothelial dysfunction. The results of TREND are supported by the BANFF study, which was the first human study of the impact of AT1 blockade on endothelial function. In this multidrug crossover study comparing quinapril, enalapril, losartan, and amloidipine therapy, only quinapril use led to improved flow-mediated vasodilation, indicating improved coronary endothelium-dependent vasodilation. In a similar comparison of quinapril and enalapril therapy in patients with heart failure, only quinapril improved radial artery blood flow, indicating enhanced endothelial function. One explanation for the efficacy of quinapril therapy over enalapril therapy may be the 15-fold increase in potency for tissue ACE of quinapril compared with enalapril. Although losartan therapy improved endothelial function in the BANFF study, the improvement was not statistically significant and was not as marked as that seen with quinapril use. The greater efficacy of quinapril over losartan may indicate a role of increased bradykinin levels in enhancing endothelial function, since ACE inhibition increases bradykinin levels but AT1 blockade does not. An additional flow-mediated dilation study supports a bradykinin-dependent efficacy of quinapril. Alternatively, the efficacy of quinapril therapy may indicate a need for higher dosing of losartan and may reflect different potencies between AT1 blockers. Another study similarly shows a small improvement in endothelial function with losartan therapy.

Beyond adding insight into the role of the RAS in endothelial function, and the importance of tissue ACE, the BANFF study also supports the clinical significance of polymorphisms. Specifically, quinapril therapy improved endothelial function in patients with the ACE II or I/D genotypes only. Potentially, the higher levels of ACE in patients with the DD genotype would have required substantially higher doses of quinapril to enhance endothelial function.

Although RAS inhibition seems to promote endothelial function, measures of atherosclerosis have produced conflicting results. In a substudy of the HOPE (Heart Outcomes Prevention Evaluation) study known as SECURE (Effects of Ramipril and Vitamin E on Atherosclerosis: The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E), 693 patients with vascular disease or diabetes mellitus and 1 additional risk factor were randomized to receive ramipril (2.5-10.0 mg/d) or placebo for 5 years. Carotid intimal medial thickness (IMT), which reflects early atherosclerosis, was assessed by ultrasound measurement. There was a significant reduction in the progression slope of mean maximal IMT by 0.04 mm (P = .046). These results conflict with those of a similarly designed study, the PART-2 (Prevention of Atherosclerosis With Ramipril Trial), an RCT of the ACE inhibitor ramipril in which 617 patients with coronary or other occlusive disease (CAD, transient ischemic attacks, or intermittent claudication) were randomized to receive ramipril.
ramipril (5-10 mg/d) or placebo for 4 years. Carotid IMT was assessed by ultrasound. After 4 years, this trial did not find any significant change in the mean IMT between the ramipril and placebo groups, with an 80% power to detect changes of 0.05 mm. A smaller randomized trial of 69 hypertensive patients demonstrated regression of mean IMT after 1 year of therapy with either lisinopril or amlopidine, with amlopidine use leading to greater regression. Two other studies, the atherosclerosis substudy of the QUIET (Quinapril Ischemic Event Trial) and the SCAT (Simvastatin/Enalapril Coronary Atherosclerosis Trial), did not demonstrate an angiographically apparent effect on coronary atherosclerosis over 3 and 4 years, respectively.

HUMAN CLINICAL TRIALS OF RAS INHIBITION WITH CLINICAL OUTCOMES

Patients With Decreased Ejection Fractions

In numerous trials, ACE inhibition has been shown to decrease the risk of coronary events and cardiovascular death in patients with heart failure or left ventricular dysfunction (Table). Combined results from the SOLVD (Studies of Left Ventricular Dysfunction) Treatment trial, the SOLVD Prevention trial, the SAVE (Survival and Ventricular Enlargement) trial, the AIRE (Acute Infarction Ramipril Efﬁcacy) study, and the TRACE (Trandolapril Cardiac Evaluation) study showed a 21% relative risk (RR) reduction for MI (P = .001). Trials have extended this efﬁcacy to AT1 blockade, with the ELITE (Evaluation of Losartan in the Elderly), ELITE II, and OPTIMAAL (Optimal Therapy in Myocardial Infarction With the Angiotensin II Antagonist Losartan) trials failing to show a signiﬁcant difference between captopril and losartan therapy. However, the presence of a nonsigniﬁcant trend favoring captopril indicates that further investigation comparing ACE inhibition and AT1 blockade is needed. In these trials, the magnitude of the reduction in events was larger than expected from the modest decreases in blood pressure. Because the trials of RAS inhibition in heart failure indicated a reduction in ischemic events, subsequent trials have examined RAS inhibition in patients with normal ejection fractions.

Patients With Normal Ejection Fractions

The HOPE study demonstrated that ACE inhibition with ramipril therapy decreased rates of death and MI in high-risk patients without left ventricular dysfunction or heart failure. This RCT included 9297 patients with a history of CAD, peripheral vascular disease, stroke, or 2 or more cardiovascular risk factors, one of which had to include diabetes mellitus. The patients were followed for 5 years for a primary outcome composite of MI, stroke, or death from cardiovascular causes. Inhibition of ACE signiﬁcantly decreased MI, stroke, and death from cardiovascular causes separately and as the primary outcome composite (RR, 0.78; P < .001). In addition, death from any cause was signiﬁcantly reduced, and many clinical events, for example, worsening angina, were also signiﬁcantly reduced. Inhibition of ACE was beneﬁcial in each of the subgroups in the study and was independent of other medications the patients were taking. Thus, ACE inhibition in high-risk patients without known heart failure or ventricular dysfunction signiﬁcantly decreased clinical events associated with atherosclerosis and ischemia. The decrease in clinical events is supported by the PART-2. Although the trial was not designed or powered to assess clinical end points, it observed trends toward decreased cardiovascular deaths and events (RR, 0.43 and 0.66, respectively). Further support comes from the ACE inhibition revascularization study, a 3-year RCT of 159 patients randomized to receive ramipril (5 mg/d) after revascularization by percutaneous transluminal coronary angioplasty or coronary artery bypass graft, which showed a signiﬁcant decrease in the primary end point of cardiac death, acute MI, or clinical heart failure (RR, 0.58; P = .03). Although this study accepted patients with and without heart failure, the results were consistent across subgroups, including patients with normal ejection fractions. Finally, the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) found that ACE inhibition in 6105 patients with a history of cardiovascular accidents or transient ischemic attacks reduced the secondary outcome of cardiac death or acute MI (RR, 0.74; P < .05).

Two recent randomized trials of hypertensive patients compared ACE inhibition to other antihypertensive agents to assess whether ACE inhibition truly confers cardiovascular beneﬁts beyond blood pressure lowering. In a study by Wing et al., 683 hypertensive patients aged 65 to 84 were randomized to receive an ACE inhibitor or a diuretic. The addition of other agents was used as needed to obtain an equivalently optimized blood pressure control in both groups. After an average follow-up of 5 years, the primary outcome of all cardiovascular events or death from any cause was reduced in the ACE inhibitor group (RR, 0.89; 95% CI, 0.79-1.00; P = .05). The number needed to treat with an ACE inhibitor was 32 participants to prevent 1 cardiovascular event or death. A secondary outcome showed that the rate of MI was reduced (RR, 0.68; 95% CI, 0.47-0.98; P = .04). Thus, this trial supports the conclusions that ACE inhibition provides cardiovascular beneﬁts beyond blood pressure lowering.

In contrast to the results mentioned in the previous paragraph, a similarly designed study, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) trial, found no additional beneﬁt of ACE inhibition. In ALLHAT, 33,357 hypertensive patients were randomized to either chlorthalidone, amlodipine, or lisinopril and were followed for 5 years. At the end of the study, the blood pressure control of the chlorthalidone group was signiﬁcantly better by 2 mm Hg (P < .001). The primary outcome of MI or fatal coronary heart disease was equivalent between chlorthalidone and li-
Multiple small differences between the study by Wing et al\textsuperscript{101} and ALLHAT\textsuperscript{102} may explain the different results. While the study on hypertension in the elderly population\textsuperscript{101} achieved equivalent blood pressure control, ALLHAT patients in the lisinopril group had a slightly higher blood pressure, which may have partially counteracted the additional cardiovascular benefit of RAS inhibition. As with other discussions, the choice of ACE inhibitor may also be significant, since lisinopril has a lower tissue specificity and half-life than some other ACE inhibitors such as ramipril. Finally, different patient populations were studied, raising the possibility of genetic differences affecting results.

Several trials that are currently in progress should continue to expand our understanding of the effects of RAS inhibition. The EUROPA (European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease), which finished recruitment in 1998, is examining the impact of 3 to 5 years of ACE inhibition on mortality, MI, unstable angina, and cardiac arrest in 10,500 patients with proven CAD without clinical heart failure.\textsuperscript{103} Another RCT, the PEACE (Prevention of Events With Angiotensin Converting Enzyme Inhibition) study, will review the 5-year outcome of cardiovascular death, MI, and CVA; no significant change in progression of atherosclerosis, no difference in ischemic events. Upcoming trials will also begin to assess AT1 blockade in patients with normal ejection fraction. The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial will follow approximately 14,400 patients with hypertension and mod-

<table>
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<tr>
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**Randomized Controlled Trials of ACE Inhibition With Cardiovascular Outcomes**

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**Normal EF Trials**

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**Surrogate outcome**

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<tr>
<td>SECURE\textsuperscript{94}</td>
<td>Carotid atherosclerosis (via ultrasound)</td>
<td>History of CAD, CVAs, TIAs, or DM plus 1 cardiovascular risk factor; excluded for heart failure or EF &lt;40%</td>
<td>693/Ramipril/5 y</td>
<td>Progression slope of carotid mean maximal IMT</td>
</tr>
<tr>
<td>PART-2\textsuperscript{95}</td>
<td>Carotid atherosclerosis (via ultrasound), LV mass (via echocardiography)</td>
<td>History of CAD or TIAs or intermittent claudication; excluded for heart failure</td>
<td>617/Ramipril/4 y</td>
<td>No significant change in mean IMT, trend cardiovascular death, trend coronary events</td>
</tr>
<tr>
<td>SCAT\textsuperscript{98}</td>
<td>Coronary atherosclerosis (via angiography)</td>
<td>Normal cholesterol level</td>
<td>460/Enalapril/simvastatin, or both/4 y</td>
<td>Combined death, MI, and CVA; no significant change in progression of atherosclerosis, no difference in ischemic events</td>
</tr>
<tr>
<td>QUIET\textsuperscript{87}</td>
<td>Coronary atherosclerosis (via angiography)</td>
<td>CAD, normal LV function</td>
<td>453/Quinapril/3 y</td>
<td>Revascularization, no significant change in progression of atherosclerosis, no difference in ischemic events</td>
</tr>
</tbody>
</table>

**Clinical outcome**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Main Outcome Measures</th>
<th>Inclusion Criteria</th>
<th>Patients, No./Intervention/Treatment Duration</th>
<th>Results: Reduction in</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE\textsuperscript{90}</td>
<td>Composite of MI, stroke, and death from cardiovascular cause</td>
<td>History of AD, CVAs, PVD, or DM plus 1 risk factor; excluded for heart failure or EF &lt;40%</td>
<td>9297/Ramipril/5 y</td>
<td>Mortality from cardiovascular causes, MI, or CVA; death from any cause; worsening angina; cardiac arrest</td>
</tr>
<tr>
<td>PROGRESS\textsuperscript{94}</td>
<td>Secondary outcome of cardiac death or MI</td>
<td>History of CVAs or TIAs</td>
<td>6105/Perindopril/4 y</td>
<td>Mortality from cardiovascular causes, MI</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotension-converting enzyme; CAD, coronary artery disease; CVAs, cardiovascular accident; DM, diabetes mellitus; EF, ejection fraction; IMT, intimal medial thickness; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; TIAs, transient ischemic attack. See the text for full trial names.
erate to high cardiovascular risk for 6 years, comparing cardiovascular events with amiodipine therapy. A comparison between AT1 blockers alone or with an ACE inhibitor will be evaluated in 14 500 patients after an MI by the VALIANT (Valsartan in Acute Myocardial Infarction Trial). The impact of combining an ACE inhibitor and AT1 blocker in 23 400 patients with CAD, cardiovascular accident, peripheral vascular disease, or diabetes mellitus with end-organ damage will occur in the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) trial. Since these trials have clinical events as the end point, the results should complement the HOPE study and may begin to discern any clinical differences between ACE inhibition and AT1 blockade, but they will not be able to comment directly on the mechanism of this impact.

CONCLUSIONS

Atherosclerosis results in 725 000 deaths per year in the United States, making it a leading cause of morbidity and mortality. Current strategies to prevent and slow the progression of atherosclerosis have involved lifestyle modification and pharmacologic intervention to control hyperlipidemia, increasingly through 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Although lipids serve a critical role in atherogenesis, atherosclerosis develops in many people without hypercholesterolemia and continues to progress in people with pharmacologically controlled lipids. Other mechanisms, therefore, must operate along with hyperlipidemia to promote atherosclerosis. During the 1990s, researchers recognized a crucial role for inflammation and endothelial dysfunction in atherogenesis. The RAS, via angiotensin II, directly leads to both of these mechanisms. Inhibition of the RAS reduces plaque development in all animal models of atherosclerosis and in vitro human experiments. Several RCTs have shown decreased cardiovascular ischemic events in high-risk patients receiving ACE inhibitors, with conflicting evidence as to whether this reduction results from decreased plaque progression. These trials have initiated a trend toward routine management of high-risk cardiovascular patients with RAS inhibition, in addition to aspirin, β-adrenergic blocking agents, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Continued research will elucidate new components of the RAS and the impact of AT1:AT2 ratios and ultimately will attempt to clarify the mechanism of reduced ischemic events, with possibilities including decreased plaque formation, enhanced plaque stability, and altered fibrinolytic balance. Understanding this mechanism will become important in evaluating the clinical significance of mechanistic differences between ACE inhibitors and AT1 blockers. Finally, the complex interactions between the RAS and hyperlipidemia and their similar mechanisms in promoting atherosclerosis will continue to be explored with the potential for synergistic pharmacologic therapies, or new therapies targeted at common elements. The answers to these questions will define the appropriate patient populations to receive RAS inhibition, including a role for genetic effects on risk stratification and therapeutic outcomes.

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