Abstract—In addition to their primary mode of action, statins and blockers of the renin-angiotensin system possess common additional properties that are under active investigation. The inhibition of cellular proliferation, the restoration of endothelial activity, the inhibition of platelet reactivity, and an antioxidant potential are only a few examples of shared effects that target the arterial wall. These and other properties may eventually become exploited for the improved treatment of cardiovascular diseases and of other diseases apparently unrelated to the cardiovascular field, including inflammation and cancer. This review analyzes the current knowledge on the pleiotropic properties of these classes of drugs. Direct comparison indicates that study of the associations among these drugs may eventually disclose additive or synergistic effects that, perhaps even at lower dosages, may provide improved vascular protection and a strong alliance against several atherogenic mechanisms. (Hypertension. 1999;34[part 2]:987-996.)

Key Words: statins ■ renin-angiotensin system ■ receptors, angiotensin II ■ angiotensin-converting enzyme inhibitors ■ atherosclerosis ■ coronary disease ■ pleiotropy

Emerging data at the molecular, cellular, and biological levels are disclosing an increasing number of relevant properties of the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) and of angiotensin-converting enzyme inhibitors (ACE-I) that seem strongly connected to the vascular protection documented by several clinical trials.

Hyperlipidemia is a major player in atherogenesis: Its relative contribution to cardiovascular risk has been proven beyond doubt and measured by many, either alone or as part of a group of risk factors.1 Hypertension is also 1 of the primary risk factors for atherosclerosis. When non–insulin-dependent diabetes mellitus (NIDDM) or dyslipidemia is associated with high blood pressure, the risk (and incidence) of major cardiovascular events rises dramatically.2 Eventually, atherosclerotic lesions become clinically symptomatic in the form of myocardial infarction (MI), stroke, or claudication; at this later stage, pharmacological intervention alone may no longer be sufficient to control the atherosclerotic burden.

The significant reduction of fatal and nonfatal events observed in trials of primary and secondary prevention has confirmed that HMG-CoA reductase inhibitors reduce the risk of cardiovascular events well beyond the expected hypolipidemic effect.3,4 Likewise, ACE-I are valuable anti-hypertensive drugs that possess additional advantages in the pharmacological management of MI and congestive heart failure (CHF).5 The analysis and comparison of the pharmacological profiles of these 2 classes of drugs reveal that, to a variable degree, statins and ACE-I share some accessory (or pleiotropic) properties and that through different mechanisms, both have common targets of action. It is speculated that combinations of these drugs may provide an improved approach to the therapy of atherosclerosis and that new indications may extend their activity to other diseases, including inflammation and cancer.

Statins
HMG-CoA reductase inhibitors (statins) block the rate-limiting step of cholesterol biosynthesis (Figure 1). The lipid-related effects of this growing class of drugs are well established: Statins stimulate the uptake and degradation of LDL and inhibit LDL oxidation, cholesterol accumulation and esterification, scavenger receptor expression, lipoprotein secretion, and cholesterol synthesis. Trials of primary and secondary prevention have proven that all statins reduce the incidence of coronary syndromes, not only in patients with variable degrees of risk but also in subjects with relatively “normal” cholesterol levels.6,7 In this respect, the large trials like the West Of Scotland CORonary Prevention Study (WOSCOPS),3 the Cholesterol And Recurrent Events (CARE) trial,6 and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),7 have demonstrated significant reductions in the incidence of cardiovascular events in a 1- to 2-year time frame. The WOSCOPS study demonstrated a 31% risk reduction at 6 years with pravastatin, but because the survival curves separated early, it was suggested that acute effects had to be considered as well.3
The improved myocardial perfusion monitored with positron emission tomography observed after a 3-month-long, aggressive lipid-lowering therapy (American Heart Association step II diet, lovastatin 40 mg, and cholestyramine 8 g) supports the issue of early benefit. To confirm the presence of an acute effect, the observed improvements returned to baseline 2 months after the suspension of therapy. In addition, when the predicted curves for the event rate of coronary heart disease (CHD) derived from the Framingham study were used to analyze the incidence of events in the patients of the WOSCOPS study at 4.5 years, a clear discrepancy between expected and observed results became apparent.

By comparison, the Lipid Research Clinics study, which explored the effect of cholestyramine on cardiovascular risk, demonstrated a direct relationship between cholesterolemia and cardiovascular events; however, the effect became statistically significant after 4 to 5 years. Likewise, the Program On the Surgical Control of the Hyperlipidemias (POSCH study) explored the effect of cholestyramine on cardiovascular risk, and nonfatal MI in hypercholesterolemic patients. The surgical procedure had an isolated effect on cholesterol absorption and consequently, on cholesterolemia. With this approach, the survival curves between treated and untreated patients separated after 5 years.

In contrast, the AFCAPS/TexCAPS study confirmed that additional mechanisms, other than lipid lowering, play a relevant part in the action of statins. The therapeutic goal was to bring LDL cholesterol to <110 mg/dL by using lovastatin at 20 or 40 mg/d, and the primary end point was to reach a 30% risk reduction in the development of a major coronary event. Surprisingly, the study was terminated before schedule, because the statistical significance planned at the start was reached within the sixth year. The efficacy of lovastatin therapy was already apparent from the first year of treatment and continued to increase throughout the study. The overall risk reduction was equal to 37%. In the single-risk groups, there was a 40% reduction in the incidence of MI, a 32% reduction of unstable angina, and a 25% reduction of all cardiovascular diseases. The benefit was apparent for all of the LDL cholesterol tertiles (90 to 235 mg/dL) and was consistent for all subgroups considered (women, elderly, diabetics, hypertensives, and smokers). The results of the AFCAPS/TexCAPS study suggested that healthy people with "average" cholesterol values are at significant risk of developing CHD and that broad implications can be inferred from the study, especially on how people should be screened and treated for the prevention of CHD.

### Pleiotropic Effects of Statins

Table 1 provides a synopsis summary of the pleiotropic effects of statins compared with similar targets of activity of ACE-I. The inhibition of HMG-CoA reductase limits the synthesis of cholesterol and of several other proteins that are part of the same biochemical pathway (Figure 1). Besides cholesterol, the mevalonate pathway leads to the formation of dolichols, with a key role in lipoprotein synthesis; ubiquinone, which has a role in electron transport; and isoprenoids, involved in the lipid modification of many proteins, including those needed for cell proliferation.

Several properties are common to all statins, while at least in vitro, others seem to be molecule-specific. For instance, in vitro simvastatin and fluvastatin inhibit smooth muscle cell proliferation, whereas pravastatin is devoid of any such effect, as the hydrophilic nature of pravastatin limits its free diffusion through membranes. The addition of mevalonate abolishes this inhibition, whereas the presence of ubiquinone, squalene, or cis-trans-geranylgeraniol does not restore cell replication. Only the presence of geranylgeraniol or farnesol in the medium containing statins leads to an almost-complete restoration of the mitogenic response.

Farnesol and geranylgeraniol interact with the hydrophilic Ras protein family and become covalently linked. The acquisition of lipophilicity by the complex allows the interaction of Ras proteins with cellular membranes. The proteins that undergo prenylation and thus, are converted to a more lipophilic state are numerous: It has been calculated that 0.5% to 1.0% of the total cellular protein content becomes geranylgeranylated. Prenylated proteins can be subdivided into 3 major groups on the basis of their molecular weight. The high-molecular-weight proteins such as the laminin family of the nuclear envelope need to be farnesylated to become active. There are ~110 low-molecular-weight proteins that can become either farnesylated or geranylgeranylated. For instance, the Ras family, necessary for cellular differentiation and proliferation (and cancer growth, as well), becomes farnesylated, whereas the Rho family, important for cytoskeleton formation, superoxide generation, and cell growth progression, is geranylgeranylated. Other proteins that become geranylgeranylated include the Rab proteins, necessary for vesicle transport within the cell; the Rap family, which plays a role in cell replication, platelet activation, and the generation of oxygen radicals; and the G proteins, necessary in the processes of signal transduction. The study of the interaction of statins with these proteins may provide a better understanding of the direct activity of this class of drugs on the arterial wall. As listed in Table 1, statins can influence a number of cellular functions that ultimately may have an impact on cardiovascular pathophysiology.

For instance, the combined analysis of 450 000 individuals with a mean follow-up of 16 years and with 13 397 recorded strokes confirmed the lack of relationship between chole-
terol and stroke. In this respect, whereas studies with cholestyramine, niacin, diet, and fibrates had no effect on cerebrovascular accidents, stroke events were significantly reduced in the Scandinavian Simvastatin Survival Study (4S; 28%),4 the CARE trial (231%), 6 and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID; 19%) study. 52

With the exception of hydrophilic pravastatin, the proliferation of cultured smooth muscle cells is also negatively influenced by the presence of statins.11 The potential clinical relevance of these observations is suggested by the study on sera from hypercholesterolemic patients treated with multiple doses of fluvastatin or pravastatin. Sera collected at different time points after the administration of fluvastatin inhibited cholesterol synthesis by up to 50% at the 1-hour peak, and smooth muscle cell proliferation was reduced to ~45% at 6 hours. The sera of patients receiving pravastatin did not inhibit cellular growth, although the lipid-lowering effect was the same in both sets of patients.53 The comparison of experimental and clinical data concerning pravastatin provides a good example of drug profile discrepancies and indicates that differences in the activity profile of single statins studied in vitro cannot be directly extrapolated to the clinical situation. HMG-CoA reductase inhibitors can also reduce the secretion of matrix metalloproteinase 9 by macrophages that play a role in the degradation of the extracellular matrix. The inhibition of this function may contribute to the stabilization of the plaque.42

In addition, in the rat, statins stimulated a 3-fold increase in tissue plasminogen activator activity and a reduction of plasminogen activator inhibitor-1 activity.19 Furthermore, fluvastatin and simvastatin reduced tissue factor activity in

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**TABLE 1. Pleiotropic Effects of Statins and ACE Inhibitors (ACE-I) on the Vascular System**

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism Influenced</th>
<th>Statins</th>
<th>ACE-I</th>
<th>Statins</th>
<th>ACE-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelium</td>
<td>eNOS</td>
<td>Stimulation11,12-14</td>
<td>Stimulation15,16</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PG12 synthesis</td>
<td>Inert12</td>
<td></td>
<td>Stimulation17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EDHF</td>
<td>Stimulation19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tPA</td>
<td>Stimulation19</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>uPA</td>
<td>Stimulation19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAI-1</td>
<td>Inhibition19,20</td>
<td>Inhibition21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tissue factor</td>
<td>Inhibition22</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Endothelin</td>
<td>Inhibition14</td>
<td>Inhibition23</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>p-Selectin expression</td>
<td>Inhibition24</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Smooth muscle cells</td>
<td>Proliferation</td>
<td>Inhibition19,25</td>
<td>Inhibition26</td>
<td></td>
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<tr>
<td></td>
<td>Migration</td>
<td>Inhibition19,25</td>
<td>Inhibition26</td>
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<tr>
<td></td>
<td>c-fos–c-jun Expression</td>
<td>Inhibition20,27</td>
<td>Inhibition28</td>
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<tr>
<td></td>
<td>PDGF</td>
<td>Inhibition19,20,25</td>
<td>Inhibition28</td>
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</tr>
<tr>
<td></td>
<td>TGF-β1</td>
<td>Inhibition20</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Apoptosis</td>
<td>Stimulation29-31</td>
<td>Inhibition23</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ras and rho proteins</td>
<td>Inhibition20,33</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>ACE activity</td>
<td>Reduced14,35</td>
<td>Reduced46</td>
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<tr>
<td>B lymphocytes</td>
<td>Activation</td>
<td>Inhibition27,38</td>
<td></td>
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<tr>
<td>T lymphocytes</td>
<td>Proliferation</td>
<td>Inhibition38,39</td>
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<tr>
<td>Natural killer lymphocytes</td>
<td>Cytotoxicity</td>
<td>Inhibition38,39</td>
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<td>Macrophages</td>
<td>Monocyte chemoattractant protein-1</td>
<td>Inhibition40</td>
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<td>Oxidative burst</td>
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<tr>
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<td>Chemotaxis</td>
<td>Inhibition41</td>
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<tr>
<td>Matrix</td>
<td>Matrix metalloproteinase</td>
<td>Inhibition42</td>
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<tr>
<td></td>
<td>Fibronectin</td>
<td>Inhibition43</td>
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</tr>
<tr>
<td>Oxidation</td>
<td>LDL oxidation</td>
<td>Inhibition39,44-46</td>
<td>Inhibition15,47</td>
<td></td>
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<tr>
<td>Blood</td>
<td>RBC deformability</td>
<td>Restoration48</td>
<td></td>
<td></td>
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<td></td>
<td>Fibrinogen concentration</td>
<td>Reduced49</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Viscosity</td>
<td>Reduced49</td>
<td></td>
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<tr>
<td></td>
<td>Cholesterolmia</td>
<td>Reduced4-4,6,7</td>
<td>Inert16</td>
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<tr>
<td>Platelets</td>
<td>Adhesion</td>
<td>Inhibition50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Aggregation</td>
<td>Inhibition50</td>
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</tr>
<tr>
<td>Blood pressure</td>
<td>VOC dependent</td>
<td>Reduced (SHR)34</td>
<td>Reduced16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td>Reduced (SHR)34</td>
<td>No reflex tachycardia36</td>
<td></td>
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</tr>
</tbody>
</table>

The main activity of each drug class is listed in bold-faced type.
unstimulated and lipopolysaccharide-stimulated macrophages. Pravastatin was devoid of effects in these experimental settings as well. The ability of macrophages to oxidize LDL was proportionally inhibited by increasing concentrations of simvastatin and was completely restored on the addition of mevalonate. Also, the propensity of LDL to oxidation in hypercholesterolemic patients receiving fluvastatin or lovastatin was reduced by >30%. By comparison, specific antioxidants, including vitamin E (200 IU) and probucol (500 mg), reduced LDL oxidizability by almost 50%.

A reduction of fibrinogen in plasma and a reduced viscosity of blood have been documented in type 2 hyperlipidemic patients treated with pravastatin, but not with simvastatin. Interestingly, in the WOSCOPS study, patients receiving pravastatin showed a reduction of blood viscosity. Pravastatin also corrected the increased deformability of red blood cells in hypercholesterolemic patients, and the effect was proportional to the LDL cholesterol reduction. Other in vivo effects common to lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin include a reduction of platelet aggregation ex vivo and in vitro.

Statins promote a positive effect on survival and reduced rejection after cardiac transplantation. In this regard, pravastatin administered with prednisone and corticotropin improved the survival of patients in the first year after cardiac transplantation. The living population was 94% for the patients receiving pravastatin and 78% for the controls. In addition, pravastatin inhibited the chemotaxis of U937 macrophages, and this effect was reversed by the addition of mevalonate. Furthermore, the inhibition of nonkiller T lymphocytes by pravastatin, such as the cytotoxicity of natural killer cells occurring after kidney transplantation, may provide an explanation, at least in part, for the beneficial effects observed in patients undergoing cardiac transplantation.

Additional relevant effects relate to the stimulation of endothelial relaxation. Atorvastatin and simvastatin upregulated nitric oxide (NO) synthase (NOS), and simvastatin reversed the decrease in NOS activity generated by the incubation of veins with oxidized LDL. Furthermore, statins possess properties that seem unrelated to the cardiovascular system. The recent reports on the inhibition of osteoclast formation by lovastatin suggest that inhibition of the mevalonate pathway may have beneficial effects on the progression of osteoporosis as well. The presence of geranylgeraniol prevents the inhibition of bone function by lovastatin: The prenylation of G proteins controls a series of mechanisms that participate in the activation of osteoclasts, including reorganization of the cytoskeleton, vesicular fusion, and apoptosis. Adipogenesis and steroid-induced osteonecrosis are also processes that can be influenced by inhibition of the mevalonate pathway.

Finally, exciting observations have been made on the influence of statins on cancer growth, and the antineoplastic potential of statins is being explored actively. The influence of statins on cellular proliferation has been extended to inhibition of the growth of an experimental tumor in the rat treated with a combination of carmustine and simvastatin. This combined treatment significantly reduced the percentage of cells undergoing mitosis. Furthermore, micromolar concentrations of lovastatin can effectively inhibit the growth of ovarian cancer cells: Additive effects have been demonstrated when the statin was coadministered with phenylacetate, phenylbutyrate, and cisplatin, and apoptotic reactions to lovastatin have been observed in neuroblastoma and leukemic cells. The first data on clinical trials exploring the antineoplastic potential of statins have been recently reported.

Thus, there are several observations on statins in support of the existence of pleiotropic effects in vivo. The relative importance of each of these effects has not yet been precisely determined, and only specific clinical trials will provide a definitive answer on the contribution of such diversity of activity to the preservation or restoration of vascular integrity.

### Angiotensin-Converting Enzyme Inhibitors

Several clinical studies of ACE-I have been carried out in patients with impaired cardiac function of different degrees of severity. Tables 2 and 3 summarize the data of the main trials of ACE-I in patients with either left ventricular (LV) dysfunction alone or after MI. Taken together, the data suggest that ACE-I are more effective at later stages of CHF.

After MI, the heart must cope with tissue damage and repair. Inevitably, the scarring process of damaged myocardial tissue occurs while the heart continues its vital pumping action. Often, a variable portion of the injured myocardium no longer contributing to active ejection starts to dilate, and through “remodeling,” the inexorable process that leads to CHF begins. At the structural level, ACE-I delay remodeling of the heart, while at the cellular level, ACE-I possess a series of desirable vasoprotective properties that do not depend merely on the hypotensive effect obtained with the inhibition of angiotensin II (Ang II) production. Many of the effects observed with ACE-I relate to the inhibition of bradykinin breakdown, as described later, and could thus be referred to as accessory.

<table>
<thead>
<tr>
<th>Study</th>
<th>NYHA Class</th>
<th>ACE Inhibitor</th>
<th>Mortality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS I</td>
<td>IV</td>
<td>Enalapril vs placebo</td>
<td>-40%</td>
<td>63</td>
</tr>
<tr>
<td>SOLVD (treatment)</td>
<td>II and III</td>
<td>Enalapril vs placebo</td>
<td>-16%</td>
<td>64</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>II and III</td>
<td>Enalapril vs hydralazine, isosorbide dinitrate</td>
<td>-18%</td>
<td>65</td>
</tr>
<tr>
<td>SOLVD (prevention)</td>
<td>I</td>
<td>Enalapril vs placebo</td>
<td>-8%,NS</td>
<td>66</td>
</tr>
</tbody>
</table>
Angiotensin-Converting Enzyme

ACE, or kininase II, is a bivalent dipeptidyl carboxyl metallopeptidase present as a membrane-bound form in endothelial, epithelial, or neuroepithelial cells, including the heart, kidney, and brain (90% to 99%), and as a soluble form in blood and numerous body fluids (1% to 10%). ACE cleaves the C-terminal dipeptide from Ang I and bradykinin and a number of small peptides that lack a penultimate proline residue. Thus, as shown in Figure 2, ACE strategically regulates the balance between the RAS and the kallikrein-kinin system.75

The circulating RAS has evolved to provide short-term regulation of the cardiovascular system that becomes activated in acute conditions, including hypotension, hypovolemia, hemorrhage, and severe heart failure. This mechanism aims to promptly restore blood pressure and cardiac homeostasis, after which time any further renin release and circulating RAS activity are suppressed.36

In the case of CHD, hypertension, and CHF, activation of the RAS causes long-term regulation of cardiovascular homeostasis via sustained activation of focal angiotensin and degradation of bradykinin, resulting in the secondary, permanent structural changes that are peculiar to these chronic pathological conditions. Locally generated Ang II can produce autocrine-paracrine tissue responses independently and often complementary to the circulating RAS activity.36,65

Ang II is a potent vasoconstrictor acting directly on vascular smooth muscle cells, mainly via the more abundant Ang II type 1 (AT-1) receptors. In addition, Ang II interacts with the sympathetic nervous system, peripherally and centrally, to increase vascular tone. Ang II causes volume expansion through sodium retention (via aldosterone and renal vasoconstriction) and fluid retention (via the antidiuretic hormone).36

Responses to ACE Inhibition

As shown in Table 1, several cardiovascular effects of ACE-I are shared with statins. The inhibition of Ang II formation and the increased availability of bradykinin obtainable with ACE-I typically produce coronary and peripheral vasodilatation without reflex tachycardia. The inhibitory effect on proliferation becomes apparent even at low dosages, as seen in humans by the reduction in LV mass and afterload. Notably, these effects have been observed in patients with or without CAD.65

ACE-I have also been tested in the field of atherosclerosis (mainly in animal models), and a series of direct and indirect effects have been reported. The protection of the endothelium and antimitogenic and antithrombotic effects were observed, and a general antiatherosclerotic effect has been documented.26 The additional antioxidant properties of the ACE-I are restricted to those containing a sulfhydryl group.28 Patients with CAD receiving ACE-I improve their endogenous fibrinolytic function, which has become unbalanced by the Ang II–dependent increase in plasminogen activator inhibitor-1 synthesis and secretion.76 Indirect ACE-I effects include a reduction of oncogene expression (eg, c-fos, c-myc, and c-jun), reduction of growth factor gene expression, and reduction of polymorphonuclear cell chemoattractant release.28

AT-1 and AT-2 Receptor–Mediated Activities

Ang II binds to at least 2 specific receptors: the Ang II type 1 and type 2 receptors (AT-1 and AT-2). AT-1 and AT-2 receptors belong to the 7-transmembrane, G protein–coupled receptor family.23 However, accumulating evidence demonstrates that the function and signaling mechanisms of these receptor subtypes are quite different and tissue-specific, and these differing characteristics explain their opposite effects in terms of cell growth and blood pressure regulation.77

AT-1 receptors are widely distributed in the body and mediate most of the Ang II effects through several signal transduction systems, including activation of phospholipases C and A2, the inhibition of adenylate cyclase, the opening of calcium channels, and the activation of tyrosine kinases. The AT-1 receptors are predominant in the adult. AT-1 gene expression and receptor protein seem to be under the regulation of ambient norepinephrine (NE) levels, as NE-induced downregulation of AT-1 mRNA and receptor protein is mediated, at least in part, by activated α1-adrenoceptors.78

Activation of endothelial AT-1 receptors results in the production of vasodilatory agents, including NO and prosta-
cyclopentane (PGI₂), which counteract the direct vasoconstrictor effects of Ang II on the adjacent smooth muscle cells.⁷⁹ AT-1 receptors are involved in cell growth and fibrosis of mesangial cells, smooth muscle cells, and fibroblasts. Fibrosis relates to the increase in synthesis and to the decrease in degradation of the main components of the extracellular matrix. The AT-1 receptor–dependent effects are, for the most part, indirect and mediated by growth factors, cytokines, and other peptides, including endothelin, transforming growth factor-β1, and platelet-derived growth factor.⁷⁹ Thus, blocking of the AT-1 receptors seems to influence the pathophysiology of several systems, hopefully all in favor of the heart at risk.

AT-2 receptors are predominant in the fetus. In the adult, AT-2 receptors seem mainly localized in the adrenal glands, ovaries, uterus, and brain and become reexpressed in mesenchymal cells in the event of tissue injury and subsequent wound healing. Apart from its involvement in development, the role of the AT-2 receptor in physiology is not well known. The AT-2 receptor counteracts the AT-1 receptor–mediated tyrosine kinase activation by activating several tyrosine phosphatases and serine/threonine phosphatases, thereby suppressing the cell growth process stimulated by various growth factors.

The relative importance of AT-1 and AT-2 receptor actions depends on the regional levels of AT-1 and AT-2 receptor expression.⁸⁰ Perhaps if AT-2 receptors were prevalent in the dedifferentiated smooth muscle cells of lesions, AT-1 blockade and the subsequent increase in Ang II availability for AT-2 receptors would truly preferentially target the diseased vessel wall.

The distributions of Ang II AT-1 and AT-2 receptors have been mapped by in vitro autoradiography throughout most tissues of many mammals, including humans. In addition to confirming that AT-1 receptors occur at sites known to be targets for the physiological actions of angiotensin, such as the adrenal cortex and medulla, renal glomeruli and proximal tubules, vascular and cardiac muscle, and brain circumventricular organs, many new sites of action have been demonstrated. In the kidney, AT-1 receptors occur in high density in renal medullary interstitial cells. The function of these cells, which span the interstitial space between the tubules and the vasa rectae, remains to be determined, as well as the influence of ACE-I and AT-1 receptor antagonists on these structures.⁸¹

In addition to AT-1 receptors, renal medullary interstitial cells possess receptors for a number of vasoactive hormones, suggesting that in concert with their anatomic location, they may be important for the regulation of fluid reabsorption or renal medullary blood flow. In the heart, the highest densities of AT-1 receptors occur in association with the conduction system and vagal ganglia. It seems that only endothelial cells possess similar amounts of both types of receptor. In the central nervous system, high AT-1 receptor densities occur in many regions behind the blood-brain barrier, supporting a role for neurally derived angiotensin as a neuromodulator. The physiological role of angiotensin in the central nervous system remains uncertain.⁸¹

Thus, receptor-binding and localization studies of AT-1 and AT-2 receptors not only outline a number of regions where the actions of angiotensin are known but also provide much possible speculation about novel physiological roles for this peptide.

**AT-1 Receptor Antagonists**

Sartanes represent a new class of antihypertensive drugs that selectively block the AT-1 receptor. In chronological order, the AT-1 receptor antagonists are losartan, valsartan, irbesartan, candesartan, and tasosartan.⁸² Other sartanes are under development and are being actively studied.⁸³,⁸⁴ By inducing a dose-dependent blockade of Ang II effects, blood pressure is reduced, as well as urinary protein and glomerular sclerosis.

Although there are not nearly as much data on sartanes as there are on ACE-I, the accumulating evidence suggests that the effects observed cannot be solely attributed to pure AT-1 receptor blockade. Despite the lack of consensus,⁸⁵ sartanes are thought to elicit accessory activities in many ways similar to those of ACE-I by shifting the balance to AT-2 and B₂ receptor stimulation, prostaglandin release, and NO formation.⁸⁶

There is hope that sartanes will provide end-organ protection by blocking AT-1–dependent Ang II effects and by leaving the AT-2 activation unopposed. Perhaps this class of drugs may also reduce the morbidity and mortality associated with MI and with the structural and functional alterations of the heart, kidney, and arteries that are observed in patients with the clinical manifestations of atherosclerosis.⁸⁷ For instance, insulin is typically elevated in patients with NIDDM and in patients with the plurimetabolic syndrome. Among several other effects, insulin stimulates the upregulation of vascular AT-1 receptor gene expression. Consequently, the arterial tree becomes more sensitive to Ang II stimulation, as reflected by the frequent association between glucose intolerance, hypertension, and atherosclerosis.⁸⁸ Thus, by blocking overexpressed AT-1 receptors, sartanes may provide an improved control of high blood pressure in patients at higher cardiovascular risk.

With mechanisms similar to those of ACE-I, sartanes possess a number of accessory properties, which may add to the benefits observed in the clinical situation. For instance, low-dose candesartan when given to hypertensive rats normalized vascular NOS production and improved vascular morphology.⁸⁹ In addition, it is known that the activation of monocytes to macrophages includes the upregulation of the angiotensin receptors. Since at least in vitro sartanes can suppress the AT-1–dependent oxidative burst of macrophages, perhaps sartanes might be useful to suppress the oxidative reactions of macrophages within atherosclerotic lesions.⁹⁰

It is of interest that candesartan tends to normalize the shift to higher pressures in the autoregulation curve of genetically hypertensive rats and has a profound modulatory role in brain AT-1 receptors, both inside and outside the blood-brain barrier.⁹¹ Finally, it has also been reported that in mice, losartan has potential memory-enhancing properties, as shown by its facilitation of spatial and short-term working memory. The effect has been attributed to increased cholin-
The pleiotropic effector of ACE-I and Sartanes

The delayed breakdown of bradykinin achieved with ACE-I provides a sustained activation of B2 receptors, which, among other effects, promote vasodilatation by stimulating the production of prostaglandins, NO, and endothelium-derived hyperpolarizing factor in the vascular endothelium. In addition, the activation of B2 receptors inhibits platelet adhesion and aggregation and smooth muscle cell mitogenesis, producing an overall effect of plaque stabilization. In the kidney, bradykinin causes natriuresis through direct tubular effects. ACE-I, by inhibiting bradykinin breakdown, enhance all of these activities.

Recently, it has been reported that the activation of the B2 receptors results in vasodilatation via a non-NO/PGI2 mechanism involving the opening of K+ channels, protects against free-radical injury, activates 12(S)-lipoxygenase, and at least in human lung fibroblasts, stimulates the production of interleukin-8. In humans, the contribution of bradykinin to interleukin-8. In humans, the combination of captopril, hydrochlorothiazide, and pravastatin was well tolerated by >600 hypertensive, hypercholesterolemic patients. Finally, vascular reactivity and vasodilative capacity were investigated in 30 hypercholesterolemic, hypertensive patients treated with either enalapril or simvastatin for 14 weeks and then with both medications for an additional 14 weeks. The combination produced a significant additive benefit on hypercholesterolemia, structural vascular damage, blood pressure, and forearm vascular reactivity. Thus, there are already some encouraging indications on the tolerability and efficacy regarding the coadministration of both drugs that deserve further scrutiny.

Conclusions

The pleiotropic effects of statins and ACE-I are undergoing a common process of reevaluation. While new indications are
being explored, new observations are needed to follow closely the timing of action of the 2 classes, as indicated in Table 4.26. The synoptic view of Table 1 suggests that both drug classes may share the potential to stabilize the atherosclerotic plaque.26,28 Indeed, through different mechanisms, both classes interfere with a number of salient atherogenic processes, including smooth muscle cell migration and proliferation, inflammatory reactions, platelet adhesion and aggregation, macrophage activation, the fibrinolytic system, and mediator expression. To date, it is not known whether the effects of the ACE-I–statin association are additive or synergistic. Better understanding of some of the pleiotropic effects of statins should derive from new and original clinical trials. For instance, the Diabetes, Atherosclerosis, Lipid-Lowering, and Antioxidant Study (DALLAS Study) is designed to compare the effects of fluvastatin with those of antioxidant vitamins on coronary vasomotion in NIDDM patients on an American Heart Association step I diet who also have CAD and “normal cholesterol levels.” The primary end point is centered on endothelial function. Other secondary end points include lipid metabolism, LDL oxidizability, fibrinolysis, and platelet function and activation. Thus, for the first time, a study has been planned asking whether a statin can generate early effects on vascular reactivity in a clinical trial that, in relation to the classic long-term studies, is very short and not centered on hypolipidemic effects and coronary events.98

The potential merging of ACE-I use in the field of atherosclerosis is suggested by studies and clinical trials, which have raised the intriguing possibility that the renin-angiotensin-kinin system may play a critical part in the pathophysiology of atherosclerosis and consequently, of an important new therapeutic role for ACE-I. However, only large-scale trials will establish whether laboratory findings and clinical trials on heart failure will apply to patients with ischemic heart disease, irrespective of the presence or absence of LV dysfunction.99 One such study, the Quinapril Ischemic Event Trial Quantitative Coronary Angiography (QCA) Study, involved 1750 patients with normal LV function undergoing coronary angiography and angioplasty. The study was centered on the analysis of angiographic structure and not on changes in vascular function. After 3 years, the comparison between the placebo group and the study group did not provide statistically significant differences in disease progression, minimum lumen diameter, and stenosis. However, the authors cautioned that potential confounders of this trial may have disturbed analysis of the data.100

At present, statins and ACE-I will be tested, though separately, in nearly-healthy populations. In this respect, ACE-I have already been studied in milder forms of hypertension to monitor their pharmacological effects on vascular reactivity.101 As for statins, it seems that hypercholesterolemia does not need to be severe to deserve attention, as even relatively normocholesterolemic patients have already shown significant cardiovascular risk reduction.7 In addition, new indications are being explored, either to investigate the short-term effects of statins or their role in cancer growth.

The extension of use to new indications for both drug classes and the eventual recommendations for combined use will have to wait for clinical trials, as yet to be designed or carried out. The available data seem to indicate that the coadministration of statins and ACE-I may further improve the pharmacological therapy of atherosclerosis. Hopefully, low-dose combinations will add to the safety and efficacy of treatment, and additional benefit may derive from preventive strategies in populations at risk.

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References


Statins and Blockers of the Renin-Angiotensin System: Vascular Protection Beyond Their Primary Mode of Action

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