Stroke Prevention Therapy Beyond Antithrombotics: Unifying Mechanisms in Ischemic Stroke Pathogenesis and Implications for Therapy
An Invited Review

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Background—It is estimated that about half of cardiovascular disease risk is explained by conventional risk factors. The realization that atherosclerosis is an inflammatory disease has led to a search for new stroke and cardiovascular disease risk factors and treatments. As such, the vulnerable atherosclerotic plaque has become the main focus for new medical strategies for plaque stabilization and stroke prevention.

Summary of Review—In this invited review, I discuss inflammation as a possible risk factor for stroke, unifying mechanisms in ischemic stroke pathogenesis, and new avenues for stroke prevention—statin agents, angiotensin-converting enzyme inhibitors, and vitamins. These new stroke prevention therapies may help to reduce inflammation, serve to stabilize the atherosclerotic plaque, or act by other protective mechanisms.

Conclusion—Beyond the traditional antithrombotic agents, statin agents, angiotensin-converting enzyme inhibitors, and vitamins may prove to be important additions to our armamentarium for stroke prevention. (Stroke. 2002;33:862-875.)

Key Words: angiotensin-converting enzyme inhibitors (ACE-I) ■ homocysteine ■ infection ■ inflammation ■ statin agents ■ stroke prevention

Stroke is the second leading cause of mortality worldwide. It is estimated to be responsible for 9.5% of all deaths and 5.1 million of the 16.7 million cardiovascular disease deaths. In China and Japan, stroke is the leading cause of mortality. The absolute numbers of stroke in China are estimated to be almost as many as in the entire developed world. Overall, about two thirds or more of stroke deaths occur in the developing world. Throughout the world, unfavorable trends in stroke risk factor profile, lack of prevention programs, lack of awareness of stroke risk factors and warning signs by the public, misapplication or underutilization of stroke preventatives, and lack of emphasis on preventive training in medical school and postgraduate programs portend high stroke rates and serve to widen the stroke prevention gap. This is unfortunate because stroke is well suited for prevention since it has a high prevalence, high burden of illness and economic cost, well-defined modifiable risk factors, and effective prevention measures.

It is estimated that only one half of cardiovascular disease risk is explained by conventional risk factors. The realization that atherosclerosis is an inflammatory disease has led to a search for new stroke and cardiovascular disease risk factors and treatments. The atherosclerotic process consists of a highly specific cellular and molecular inflammatory response. The earliest atherosclerotic lesion, the fatty streak, consists of monocyte-derived macrophages and T lymphocytes. We have advanced our understanding of the development of atherosclerosis from the response-to-injury hypothesis of endothelial denudation to the hypothesis of endothelial dysfunction. The endothelium is an important regulatory barrier that is constantly being challenged by factors such as elevated and modified low-density lipoprotein cholesterol (LDL-C), free radicals generated by cigarette smoking, hypertension, and diabetes mellitus, and genetic modifiers, elevated homocysteine, and infectious microorganisms. If the endothelial barrier succumbs to injury, important surface changes occur: increased adhesiveness to leukocytes or platelets, increased permeability, and procoagulant tendency with formation of vasoactive molecules, cytokines, and growth factors. These changes eventually lead to the full-blown atherosclerotic lesion. During the course of development of the atherosclerotic lesion, there is an intermediate stage characterized by smooth-muscle cell proliferation, thickening of the arterial wall, and gradual dilation of the wall so that the blood vessel lumen remains unaltered (“remodeling”). With continued inflammation and increase in the numbers of macrophages, lymphocytes, and lipids, the release of hydrolytic enzymes, cytokines, chemokines, and growth factors facilitates intraplaque necrosis and rupture of the lipid core beyond the surrounding fibrous tissue cap and smooth muscle cells.
TABLE 1. Novel Risk Factor Candidates for Atherosclerosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Proposed Mechanism of Injury</th>
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<tbody>
<tr>
<td><strong>Markers of inflammation</strong></td>
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<tr>
<td>1. C-reactive protein (CRP)</td>
<td>1. Prothrombotic effects by increasing tissue factor; activation of complement</td>
</tr>
<tr>
<td>2. Intercellular adhesion molecule 1 (ICAM-1)</td>
<td>2. Mediates adhesion and transmigration of monocytes to the vessel wall; may indicate endothelial cell activation and inflammation</td>
</tr>
<tr>
<td>3. Lipoprotein-associated phospholipase A2</td>
<td>3. Generation of lyssolecithin, a proinflammatory agent, or by hydrolyzing oxidized phospholipids into atherogenic fragments</td>
</tr>
<tr>
<td>4. Elevated white blood cell count</td>
<td>4. Associated with chronic subclinical infection or inflammation</td>
</tr>
<tr>
<td>5. Interleukins (IL)</td>
<td>5. Proinflammatory cytokines</td>
</tr>
<tr>
<td><strong>Infectious agents</strong></td>
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<tr>
<td></td>
<td>Production of proinflammatory mediators (cytokines, free radicals), stimulation of vascular smooth muscle cell proliferation, mononuclear cell and T lymphocyte proliferation, and endothelial dysfunction with associated procoagulant and proadhesive state; activation of plaque by infectious agent to destabilize it</td>
</tr>
<tr>
<td><strong>Homocysteine</strong></td>
<td></td>
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<tr>
<td></td>
<td>Endothelial dysfunction and damage, mitogenic effect on vascular smooth muscle cells, activation of factor V, inhibition of protein C, tPA activation, and enhanced platelet aggregation</td>
</tr>
<tr>
<td>Renin angiotensin system (RAS)</td>
<td>Amplification of inflammation via effects on adhesion molecules, growth factors, and chemotaxicant molecules which modulate inflammatory cell migration; oxidative stress</td>
</tr>
<tr>
<td><strong>Coagulation/platelet-related factors</strong></td>
<td></td>
</tr>
<tr>
<td>1. Tissue factor (TF)</td>
<td>1. Binds to factor Vlla and activates coagulation cascade (also interacts with factor X); TF induction at sites of plaque inflammation</td>
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<tr>
<td>2. Fibrinogen</td>
<td>2. Increase in plasma viscosity, promote platelet aggregation, stimulate smooth muscle proliferation; elevated in conjunction with ongoing inflammatory changes</td>
</tr>
<tr>
<td>3. TPA/Plasminogen activator inhibitor type 1 (PAI-1)</td>
<td>3. Impaired fibrinolysis</td>
</tr>
<tr>
<td>4. Platelet reactivity</td>
<td>4. Trigger for thrombosis</td>
</tr>
<tr>
<td>5. Hypercoagulability</td>
<td>5. Predispose to thrombosis</td>
</tr>
<tr>
<td><strong>Lipoproteins</strong></td>
<td></td>
</tr>
<tr>
<td>1. Lipoprotein (a) [Lp (a)]</td>
<td>1. Stimulate growth of vascular smooth muscle cells, enhance expression of ICAM-1, increased expression of PAI-1, inhibit activation of plasminogen by tPA</td>
</tr>
<tr>
<td>2. Small dense LDL</td>
<td>2. Susceptibility to oxidation, increased binding to intimal proteoglycans</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cytokine transforming growth factor (TGF-β)</td>
<td>1. Low levels of TGF-β result in loss of inhibition of proliferation and migration of vascular smooth muscle cells and endothelial cells</td>
</tr>
<tr>
<td>2. Troponin T or I</td>
<td>2. Associated with a larger number of coronary thrombi, complex coronary artery lesions, impaired coronary flow and greater activation of the coagulation system acutely in unstable coronary syndromes</td>
</tr>
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</table>

Destabilization of the atheromatous plaque is a forerunner of ischemic stroke and myocardial infarction. Vessel wall substrates (eg, degree of plaque disruption, vessel wall inflammation) are an important component of Virchow’s triad, which also includes rheology (eg, high shear stress, local stasis), and systemic factors of the circulating blood (eg, dyslipoproteinemias, renin-angiotensin system [RAS], tissue factor, tissue plasminogen activator, leukocytosis, activation of blood particles). Typically, the at-risk or vulnerable asymptomatic atherosclerotic coronary artery plaque is not associated with high-grade stenosis. Instead, it is characterized by a large lipid-rich core, thin fibrous cap, reduced collagen content, and an active chronic inflammatory component. This may or may not be the case in the extracranial carotid circulation because cerebral ischemic symptoms may be more likely with higher degrees of stenosis. In the clinical setting it remains uncertain whether the prothrombotic endothelial surface can lead to thrombosis or embolism independent of plaque rupture.

The vulnerable atherosclerotic plaque has become the main focus for new directions in the prevention and treatment of stroke and coronary atherosclerosis. Beyond traditional antithrombotic agents, medical therapy for plaque stabilization promises to reduce the risk of thrombosis associated with atherosclerosis. In this article, I review the evidence for statin agents, angiotensin-converting enzyme inhibitors (ACE-I), and vitamins in stroke risk reduction. Because inflammation is central to the atherosclerotic process, I begin the discussion with an overview of inflammation as a possible risk factor for stroke.

Inflammation and Stroke Risk

Inflammation ranks as one of the important novel risk factor candidates for atherosclerosis. Table 1 lists key novel candidate risk factors or markers for atherosclerosis and their proposed mechanism of atherosclerotic injury. Many of these factors have overlapping mechanisms, important synergistic actions with the atherosclerotic process, or comple-
Inflammatory actions in the development of arterial thrombosis. Inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, originate in the liver. They are stimulated by systemic cytokines such as interleukin 1β, interleukin 6, and tumor necrosis factor-α. Cytokines are intercellular signaling polypeptides, produced at extrahepatic sites, such as the heart, vessel walls, macrophages, and adipose tissue, and are produced during and serve in the inflammatory process as stimulators of acute-phase proteins that accompany both acute and chronic inflammatory disorders. Acute-phase proteins are believed to be involved in the waxing and waning of the inflammatory response. Many of the factors listed in Table 1 are human acute-phase proteins (eg, fibrinogen, tissue-type plasminogen activator, CRP, angiotensinogen, phospholipase A₂).

The atherosclerotic vessel wall is also the source of soluble adhesion molecules that mark inflammation. These include factors such as intercellular adhesion molecule-1 (ICAM-1), vascular-cell adhesion molecule-1, E-selectin, and P-selectin. Macrophages participate in the inflammatory process and secrete phospholipases when there is injury. Systemic factors independent of traditional cardiovascular disease and stroke risk factors have been implicated in the development of atherosclerotic plaque irregularity and rupture. In human specimens of thrombosed coronary arteries, macrophages and T lymphocytes have been found at the immediate site of rupture or superficial erosion in conjunction with abundant expression of HLA-DR antigen markers suggestive of active inflammation. Human atherosclerotic coronary artery specimens may also express antifibrinolytic potential. Furthermore, the allele T(-260) promoter of the CD14 receptor gene, which is an important mediator for the activation of monocytes and macrophages by infection (endotoxin related), may be found more commonly in myocardial infarction survivors than controls. Carotid endarterectomy specimens have shown an elevation of ICAM-1 expression in symptomatic versus asymptomatic plaques and a greater expression of this marker in high-grade versus low-grade regions of the plaque specimens. Activation of matrix-degrading metalloproteinases by activated mast cells (protease secretors) may be an important mechanism in carotid artery and other atherosclerotic plaque destabilization.

C-reactive protein

Elevated concentrations of CRP are predictive of cardiovascular disease in men and women. Measurement of CRP may be an important means for identifying persons at risk of cardiovascular disease. The use of anti-inflammatory drugs such as aspirin may be useful for reducing the risk of cardiovascular events in persons with elevated CRP.

CRP may be a predictor of stroke risk. Baseline CRP concentrations were higher (1.38 versus 1.13 mg/L) among a subset of men who went on to have ischemic stroke than among those without vascular events in the Physician’s Health Study clinical trial. In addition, those men in the highest quartile of CRP values had about 2 times the risk of ischemic stroke (relative risk 1.9, P = 0.02) compared with men in the lowest quartile. Data on 193 ischemic stroke patients enrolled in the Villa Pini Stroke Data Bank suggest that CRP may be a marker of increased ischemic stroke risk at 1 year. Furthermore, among 228 consecutive ischemic stroke admissions from an acute stroke unit serving a population of 360,000, CRP was shown to be an independent predictor of survival after ischemic stroke. These studies support the role of CRP in the prediction of ischemic stroke risk and outcome, as well as the possible role of inflammation before and after stroke. Additional well-designed epidemiological studies are needed to validate the findings.

Infection

Generalized or local inflammation may be associated with infection. This observation has bolstered the infectious hypothesis of atherosclerosis. Recently, 3 infectious agents, Chlamydia pneumoniae, Helicobacter pylori, and cytomegalovirus have been implicated in the atherosclerotic process. Subtle defects in the immune regulation system may be responsible for the occurrence of more routine infections in some persons than in others. The occurrence of periodontal disease, one of the most common human infections, illustrates an epidemiological link between infection and stroke. In the first National Health and Nutrition Examination Survey (NHANES), periodontal disease was found to be an important risk factor for nonhemorrhagic stroke. These findings highlight the potential importance of chronic infection/inflammation as a risk factor for stroke and the possibility of remediation, because periodontal disease is treatable.

Recent Infection

Certain infectious agents are capable of invading the endothelium, arterial smooth muscle cells, and monocytes. Both recent and chronic infection have been linked to stroke. Most of the studies are case-control designs. For example, in 37 adults with acute brain infarction, 47 community controls, and 34 hospitalized non-stroke neurological patient controls, Macko et al reported that febrile or nonfebrile infections or inflammatory syndromes were significantly more common in stroke patients within the 7 days preceding stroke. In a case-control study of 197 acute ischemic stroke patients and 197 randomly selected controls, Grau et al reported that recent infection, primarily of bacterial origin, was a risk factor for ischemic cerebrovascular disease (odds ratio 4.6, 95% confidence interval 1.9, 11.3) in older and younger patients. In another study of 166 consecutive acute ischemic stroke patients and 166 patients hospitalized for nonvascular and noninflammatory neurological diseases, recent (within 1 week) bacterial and viral infection was associated with acute ischemic stroke (odds ratio 2.9, 95% confidence interval 1.31, 6.4). These findings were more important in younger patients and were independent of common coagulation parameter abnormalities and inflammatory markers. Finally, recent infection has been associated with cervical artery dissection.

C Pneumoniae, Atherosclerosis, and Stroke

C pneumoniae is a common respiratory pathogen that has been found in atheromatous lesions of coronary arteries, the aorta, and carotid and peripheral arteries. There is evidence that C pneumoniae can infect macrophages, endothelial cells,
and vascular smooth muscle cells and induce formation of foam cells by dysregulating native LDL uptake or metabolism. Thus, *C. pneumoniae* may enhance atherogenesis by causing inflammation and inciting immune responses and therefore has been a target for antibiotic therapy trials to reduce cardiovascular disease risk. *C. pneumoniae* is generally susceptible to macrolide, tetracycline, and quinolone antibiotics. Results of observational studies linking *C. pneumoniae* to incident coronary heart disease (CHD) have been mixed. Overall, the evidence in animal and human studies has been inconclusive. Furthermore, in 1 coronary artery disease trial of 302 patients treated with azithromycin for 3 months, global tests of inflammatory markers improved at 6 months, but there were no differences in antibody titers or clinical outcome events. Therefore, uncertainty exists in this area regarding what types of infection should be treated, which patients might be appropriate for treatment, and how long patients should be treated. Large, well-designed studies are needed to determine whether antibiotic eradication is useful.

Key studies of the association of *C. pneumoniae* and stroke risk are summarized in Table 2. Overall, the weight of the evidence suggests that acute or chronic infection with *C. pneumoniae* may increase the risk of stroke. However, the precise pathophysiological mechanism remains to be elucidated because pathological and immunologic studies of *C. pneumoniae* in the carotid atheromatous plaque raise doubt about the role of this agent in determining future cerebrovascular events. It is possible that *C. pneumoniae* is involved in the atherosclerotic process but does not trigger plaque rupture. Rather, it promotes acute cardiovascular disease or stroke events by procoagulant mechanisms when there is reinfection. Additional well-designed studies are needed to clarify the relationship of stroke and *C. pneumoniae*.

**H pylori and Cytomegalovirus**

*H pylori* is a Gram-negative infectious organism that causes chronic gastric inflammation that may be eradicated by antibiotic therapy. *H pylori* seropositivity has been identified in the atherosclerotic carotid plaque by morphological and immunohistochemical techniques. It has been associated with carotid atherosclerotic lesions and features of inflammatory cell response such as ICAM-1. *H pylori* seropositivity has been reported in association with ischemic cerebrovascular disease and degree of carotid stenosis. Cytomegalovirus has also been associated with atherosclerosis. Additional study of these microorganisms is needed to further clarify their role in the atherosclerotic process.

**Statin Agents**

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are generically classified as “statins.” Drugs of this class are similar to HMG-CoA, a precursor of cholesterol, and competitively inhibit HMG-CoA reductase, the last regulated reaction in the synthesis of cholesterol. The drugs act by upregulating LDL receptor activity and reducing the entry of LDL into the circulation. The statins may be subdivided into natural or fermentation-derived (eg, lovastatin, pravastatin, and simvastatin) and synthetic statins (eg, atorvastatin, cerivastatin, and fluvastatin). These agents vary in the degree of hydrophilic and lipophilic properties and vary in their potency, which has been a focus of debate concerning clinical relevance. The statins are generally well...

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wimmer</td>
<td>Case-control</td>
<td>58 cerebral ischemia cases and 52 hospital controls; elevated IgA titers, immune complexes or both to <em>C. pneumoniae</em>; evidence of chronic infection was associated with increased risk of stroke and TIA</td>
</tr>
<tr>
<td>Cook</td>
<td>Case-control</td>
<td>176 stroke or TIA patients and 1518 hospital controls; based on increase in IgG, IgM, or IgA <em>C. pneumoniae</em> titers, stroke and TIA were associated with previous infection or recrudescence infection</td>
</tr>
<tr>
<td>Glader</td>
<td>Nested case-control</td>
<td>101 incident cases and 201 matched controls; no evidence that <em>C. pneumoniae</em> IgG or IgA titers were associated with future ischemic stroke events</td>
</tr>
<tr>
<td>Eikind</td>
<td>Nested case-control</td>
<td>89 cases and 89 controls; IgA titers were more strongly associated with risk of ischemic stroke than IgG titers; chronic infection with <em>C. pneumoniae</em> increased the risk of ischemic stroke</td>
</tr>
<tr>
<td>Fagerberg</td>
<td>Risk factor intervention study</td>
<td>130 men at baseline; based on high titers to IgA or IgG to <em>C. pneumoniae</em> at entry or after 3.5 years, in 6.5 years time there was increased risk of stroke; <em>C. pneumoniae</em> but not cytomegalovirus seropositivity increased the risk of future stroke</td>
</tr>
<tr>
<td>Markus</td>
<td>Series of health insurance enrollees</td>
<td>No serological evidence for association of <em>C. pneumoniae</em> infection and early atherosclerosis of carotid arteries by ultrasound determination of intima-media thickness and the thickness of atheromatous plaques among 938 normal persons</td>
</tr>
<tr>
<td>Gibbs</td>
<td>Surgical case series</td>
<td>Carotid endarterectomy specimens from 98 symptomatic patients; <em>C. pneumoniae</em> was detected in 25.5% but had little detectable impact on plaque instability when measured by clinical markers</td>
</tr>
<tr>
<td>Schmidt</td>
<td>Risk factor intervention study</td>
<td>Seropositivity for <em>C. pneumoniae</em> associated with increased intima-media thickness in the common carotid artery but no plaque status in hypertensive men after ultrasound examination</td>
</tr>
<tr>
<td>LaBiche</td>
<td>Surgical case series</td>
<td>Plaques from 37 symptomatic and 57 asymptomatic patients; presence of <em>C. pneumoniae</em> in about 15% of plaques; no association between <em>C. pneumoniae</em> presence and symptomatic disease or severity of carotid stenosis; high serum IgA titers to <em>C. pneumoniae</em> associated with symptomatic disease</td>
</tr>
<tr>
<td>Yamashita</td>
<td>Surgical case series</td>
<td>20 carotid endarterectomy specimens with <em>C. pneumoniae</em> immunoreactivity in 55% and wide infection of endothelial cells, macrophages, and smooth muscle cells of the atherosclerotic artery</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
TABLE 3. Non–Lipid-Lowering Beneficial Effects of Statins69,71,72

<table>
<thead>
<tr>
<th>Effect on</th>
<th>Proposed Mechanism(s) of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Endothelial function</td>
<td>1. Endothelial dilatation by limiting acetylcholine-induced vasoconstriction, improving endothelial nitric oxide-mediated vascular relaxation, diminished cardiovascular reactivity to angiotensin II and norepinephrine, reduction in synthesis of endothelin (a potent vasoconstrictor and growth promoter)</td>
</tr>
<tr>
<td>2. Inflammation</td>
<td>2. Suppress inflammatory response (eg, decrease in natural killer T-cell cytotoxicity and synergistic inhibition of cytotoxic T-lymphocyte activity), decrease in leukocyte adhesion responsiveness, decrease in chemotaxis of neutrophils and monocytes</td>
</tr>
<tr>
<td>3. Macrophages</td>
<td>3. Inhibit cholesterol ester accumulation in monocyte-derived macrophages</td>
</tr>
<tr>
<td>4. LDL oxidation resistance and tissue capacity</td>
<td>4. Increase in total antioxidant capacity of plasma and increase in LDL oxidation resistance</td>
</tr>
<tr>
<td>5. Smooth muscle cell proliferation</td>
<td>5. Inhibition of smooth muscle cell proliferation and migration induced by platelet-derived growth factor and fibrinogen, decrease in expression of major components of the extracellular matrix that relate to plaque stability and decrease in matrix metalloproteinases</td>
</tr>
<tr>
<td>6. Thrombosis</td>
<td>A. Decrease in tissue factor expression by reducing synthesis of geranyl-geranylated protein involved in tissue factor synthesis</td>
</tr>
<tr>
<td></td>
<td>B. TEPI (counterbalances extrinsic coagulation cascade)</td>
</tr>
<tr>
<td></td>
<td>C. Platelet aggregation and decrease in deposition</td>
</tr>
<tr>
<td></td>
<td>D. Fibrinogen and blood viscosity</td>
</tr>
<tr>
<td></td>
<td>E. Fibrinolytic balance</td>
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</table>

TEPI indicates tissue factor pathway inhibitor; PAI-1, plasminogen activator inhibitor type 1.

tolerated.62 The most common adverse events include gastrointestinal upset, muscle aches, and hepatitis or hepatotoxicity (<1%). Rarer problems include myopathy, rash, peripheral neuropathy, insomnia, bad or vivid dreams, difficulty sleeping, or difficulty concentrating. Statins with hydrophilic properties are prone to cause hepatotoxicity, and those with greater lipid solubility may be limited by myopathy. Recently, cerivastatin was withdrawn from the market in the US because it was associated with rhabdomyolysis and death, especially among those taking gemfibrozil.

Statins have non–lipid-lowering effects.65–72 For example, these agents may upgrade endothelial nitric oxide synthase (eNOS), inhibit inducible NOS, attenuate the inflammatory cytokine responses that accompany cerebral ischemia, and possess antioxidant properties that ameliorate ischemic oxidative stress of the brain.66 Preservation of eNOS is believed to preserve blood flow and therefore limit neurological damage in acute stroke. This has been verified in an animal model. Prophylactic administration of mevastatin to mice in a middle cerebral artery occlusion model was associated with upregulated eNOS, augmented cerebral blood flow, reduction in infarct size, and improved neurological deficits in the absence of changes in serum cholesterol levels.67

Other major beneficial pleiotropic effects of statins include modification of endothelial function, inflammatory responses, plaque vulnerability, and thrombus formation. These effects, which are beyond lipid lowering, and their proposed mechanism are reviewed in Table 3. The precise mechanism underlying the benefit of statins remains controversial69 and may be a combination of lipid-lowering and pleiotropic effects. Furthermore, certain statin agents among this class of medications may not share all of the same non–lipid-lowering antiatherosclerotic or antithrombotic properties. For a detailed discussion of specific antiatherosclerotic and anti-thrombotic mechanisms of specific statin agents, the reader is referred to reviews by Farmer,69 Rosenson and Tangney,71 and Rosenson and Lowe.72 Newer statin agents such as the pure enantiomers, rosuvastatin and itavastatin, are in clinical development, in a search for more effective drugs.73

Clinical Observations: CRP and Statins

Acute-phase reactants such as CRP may have positive or negative effects on the inflammatory process.74 On the one hand, these proteins may be anti-inflammatory, neutralizing proinflammatory cytokines, proteases, and oxidants in the blood that originate from inflammatory local tissue sites. CRP and ICAM-1, for example, can reduce the adherence of leukocytes to the vascular endothelium thereby permitting margined neutrophils to migrate to infected sites and preventing them from accumulating in uninflamed tissues. On the other hand, the release of CRP from macrophages and smooth muscle cells within active atheromas may induce production by the liver of CRP and other acute phase reactants, involved in the waxing and waning of the inflammatory response. In addition, chronic, low-level activators of acute-phase response such as smoking, smoldering infections like bronchitis, gastritis, or periodontal infection, or proinflammatory conditions (eg, obesity) may contribute to atherosclerosis via CRP effects.

Several clinical studies have shown that with the administration of statin therapy (eg, pravastatin) CRP levels may be reduced independently of LDL-C.75,76 These findings suggest that statins have anti-inflammatory effects in addition to lipid-lowering effects. Furthermore, administration of statin therapy may be beneficial in the primary prevention of coronary events in persons with relatively low lipid levels but...
lowering.CRQ Also, these agents may be useful in lowering the risk of type 2 diabetes mellitus by lowering triglycerides or by anti-inflammatory mechanisms.

**Statins and Stroke**

Hypercholesterolemia is an important modifiable risk factor for CHD but is not considered a well-established risk factor for stroke. Much debate has occurred about cholesterol as a risk factor for stroke. Although blood lipids have been linked to carotid artery intima-media thickness, observational cohort studies have shown only a weak positive association between cholesterol level and risk of ischemic stroke or no clear association between plasma cholesterol and total stroke. Also, there has been a weak inverse association of cholesterol level with hemorrhagic stroke risk, and 1 major cohort study suggested that intake of fat, saturated fat, and monounsaturated fat may be associated with reduced risk of ischemic stroke in men. The observational epidemiological studies of plasma lipids and stroke have limitations that I have reviewed previously. Most of the criticism centers around studies that have been carried out in CHD patients rather than in stroke patients, and the heterogeneity of stroke and cholesterol subtypes have not been carefully taken into account.

Evidence from individual statin trials in patients with CHD, and meta-analyses of these trials, show that stroke risk is reduced by statin agents. Stroke risk reduction may be predominantly for nonfatal stroke with the effect on fatal stroke being less clear. The results led to the US FDA approval of pravastatin and simvastatin for stroke prevention in patients with CHD. Overall, the studies show no major hemorrhagic stroke risk with use of these agents. It is unclear, however, whether the stroke risk reduction is related predominantly to reduction in heart disease and subsequent cardioembolic stroke events or to some other mechanism.

For persons who do not have CHD, I recommend following the guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). An advance in the updated guidelines includes a target LDL goal of <100 mg/dL in persons with CHD and CHD risk equivalents. CHD risk equivalents include other clinical forms of atherosclerotic disease such as symptomatic carotid artery disease; diabetes mellitus; and multiple risk factors that confer a 10-year risk for CHD >20%. Therefore, patients with symptomatic atherosclerotic stroke are candidates for lipid-lowering therapy. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) group is assessing aggressive lipid-lowering therapy with atorvastatin in patients with previous stroke or transient ischemic attack (TIA) to determine the efficacy of this agent in the reduction of the primary end point fatal or nonfatal stroke. The results of the SPARCL group will add important information on the efficacy and safety of atorvastatin in recurrent stroke prevention.

**Angiotensin-Converting Enzyme Inhibitors**

Hypertension is the most important modifiable risk factor for stroke. Up to 50% of strokes may be attributable to hypertension. Hypertensives are at about 3 to 4 times greater risk of stroke than nonhypertensives, and borderline hypertensives are at about 1.5 times the risk of nonhypertensives. Hypertension, whether systolic, diastolic, or combined, increases stroke risk. It is estimated that lowering usual diastolic blood pressure for a prolonged period of time by 5 to 6 mm Hg could lower the risk of a first stroke by 35% to 40%, and lowering diastolic blood pressure 5 to 6 mm Hg and systolic blood pressure 10 to 12 mm Hg for 2 to 3 years in stroke and TIA patients could reduce the annual risk of stroke from 7.0% to 4.8%. The risk of stroke increases proportionately with increasing blood pressure. However, persons with high-normal blood pressure or mild hypertension are at risk of stroke. In the past it was estimated that up to 75% of strokes occurred in nonhypertensives.

Unfortunately, hypertension is poorly controlled in the United States and elsewhere. However, the risk of stroke may be reduced when specific blood pressure treatment goals are attained in hypertensives with a reduction of stroke within 1 year for hemorrhagic strokes and within the second year for ischemic strokes.

**Renin-Angiotensin System and Stroke**

Hypertension may predispose to stroke by potentiating atherosclerosis of the aorta and large cerebral arteries, causing arteriosclerosis and lipohyalinosis of small-diameter penetrating arteries, and promoting heart disease. The RAS has been implicated in hypertension, as well as a number of genetic, humoral, and cellular mechanisms that may be involved in atherogenesis or related phenomena in hypertensives. These factors and their proposed mechanisms of action, beyond the direct endocrine effects of this system to raise blood pressure, that link the RAS to stroke and cardiovascular disease are listed in Table 4 according to reviews by Rossi et al., and Farmer and Torre-Amione. As one notes, the RAS is involved in vascular remodeling, modulation of left ventricular hypertrophy, generation of oxidative stress, and inflammation in the atherosclerotic process by effects on adhesion molecules, growth factors, and chemotraactive molecules that modulate inflammation in the subendothelial compartment. In clinical-genetic studies, the ACE I/D genotype has been associated with ischemic stroke in hypertensives, the DD genotype with lacunar stroke, and low ACE activity at stroke presentation and the D allele with increased risk of early death from acute cerebral infarction. There has been inconsistent results for angiotensinogen mutations M235T and T174M for ischemic stroke, and there is an association with the B haplotype of the angiotensinogen promoter gene in absence of the wild-type A haplotype as a susceptibility factor for microangiopathy-related cerebral damage.

**Angiotensin-Converting Enzyme Inhibitors**

ACE-I were introduced for the treatment of high blood pressure in the United States in the 1970s. They act on the renin-angiotensin-aldosterone system by blocking the conversion of angiotensin I to angiotensin II by inhibiting the
angiotensin-converting enzyme (ACE). Angiotensin II raises blood pressure because it is a potent peripheral vasoconstrictor, a stimulator of aldosterone from the adrenal cortex, and has a negative influence on renin secretion. ACE is identical to Kinnase II, the enzyme that catalyzes the breakdown of bradykinin. Bradykinin is a potent vasodepressor. By identical to Kininase II, the enzyme that catalyzes the breakdown of bradykinin. Bradykinin is a potent vasodepressor. By blocking ACE with ACE-I, there is more bradykinin available.

ACE-I may have less effect in persons with low-renin hypertension. For example, blacks may have low renin levels, and their response to ACE-I of lowering diastolic blood pressure may be only half that observed in nonblacks. ACE-I are generally safe but some may be associated with tent cough (in up to 15%), angioedema (0.1% to 0.2%; more frequent in blacks), and hyperkalemia, persistent cough (in up to 15%), angioedema (0.1% to 0.2%; more common in blacks), and headache, dizziness, or fatigue. Physiological and pathological studies in hypertensives receiving ACE-I have shown that vascular compliance is increased after therapy. There is regression of periarteriolar collagen area, total intimal collagen volume density, and slight reduction in the arteriolar wall area in coronary arteries with improvement of coronary reserve. In addition, there is normalization of resistance artery structure and left ventricular hypertrophy, and normalization of the ratio of media thickness to lumen diameter in resistance vascular tissue. Studies of the cerebrovasculature are limited. In 1 study, carotid territory blood flow was not reduced in persons with cerebral ischemia and carotid territory occlusive disease.

### ACE-I and Stroke

**Heart Outcomes and Prevention Evaluation (HOPE) Study**

HOPE was a double-blind, 2×2 factorial, randomized trial evaluating ramipril and vitamin E in 9297 high-risk patients who had vascular disease (eg, history of coronary artery disease [~80%], stroke or TIA [~11%], peripheral vascular disease [~42%]), or diabetes mellitus (~39%) plus 1 other cardiovascular risk factor (eg, hypertension [~48%], elevated total cholesterol [~65%], low high-density lipoprotein cholesterol [~18%], cigarette smoking [~14%]) but who were not known to have a low ejection fraction or heart failure. Matching placebos were used and patients were followed for a mean of 5 years. The primary outcome was myocardial infarction, stroke, or death from cardiovascular causes. At baseline, patients were receiving medications such as beta-blockers (~39%), aspirin or other antiplatelet agents (~75%), lipid-lowering agents (~28%), diuretics (~15%), and calcium-channel blockers (~46%). Approximately 21% had microalbuminuria at baseline.

Although the effects of vitamin E were not significant, the ramipril treatment group had a significant reduction in the primary composite end point (22%, *P*<0.001), death from cardiovascular causes (26%, *P*<0.001), myocardial infarction (20%, *P*<0.001), stroke (32%, *P*<0.001), death from any cause (16%, *P*<0.005), and a host of other outcomes such as complications related to diabetes (16%, *P*<0.03), heart failure (23%, *P*<0.001), cardiac arrest (38%, *P*<0.02), and new diagnosis of diabetes (34%, *P*<0.001). At the end of the study the blood pressure difference in the ramipril treatment group was about 3 mm Hg systolic and 2 mm Hg diastolic, suggesting the possibility that the beneficial treatment effect of ramipril may not be ascribed solely to blood pressure lowering.

HOPE shows that ACE inhibition with ramipril significantly reduces the risk of many major vascular outcomes or related complications in high-risk patients who do not have low ejection fraction or heart failure. There was predominantly benefit for prevention of recurrent myocardial infarction and first stroke in subgroup analysis. Furthermore, subgroup analysis showed a benefit for diabetics and nondiabetics, women and men, those with or without cardiovascular disease, those <65 years and ≥65 years, those with or without a history of hypertension, those with or without microalbuminuria, those with or without coronary artery disease, and those with or without baseline cardiovascular disease prevention medication. These data add to the burgeoning literature of the benefits of ACE inhibition in
high-risk individuals, especially those with diabetic or non-diabetic renal disease.\textsuperscript{135–138}

**Perindopril Protection Against Recurrent Stroke Study (PROGRESS)**

PROGRESS was a double-blind, placebo-controlled, randomized trial of treatment with the ACE inhibitor perindopril and the diuretic indapamide for those with no definite indication for or contraindication to treatment with a diuretic or matching placebo.\textsuperscript{139} Patients with any type of stroke except subarachnoid hemorrhage and both hypertensives and normotensives were eligible. The study was performed in Europe, Australia and New Zealand, the People’s Republic of China, and Japan at a total of 172 centers. After a run-in phase, 6105 patients were allocated randomly to receive active treatment or placebo.

At baseline, the following key characteristics were noted among the 6105 study enrollees:\textsuperscript{139} mean age 64 years; mean blood pressure 147/86 mm Hg; hypertension 62%; smoking 20%; diabetes 13%; history of acute myocardial infarction 7%; and use of aspirin or other antiplatelet agent 77%, any blood pressure-lowering agent 59%, oral anticoagulant 9%, and HMG-CoA reductase inhibitor 8%. At baseline, 11% had a history of cerebral hemorrhage.

The results were presented as a platform presentation at the 11th European Meeting on Hypertension, Milan, Italy, June 15 to 19, 2001 and more recently as a full length publication.\textsuperscript{140} Perindopril-based therapy proved to be safe and well tolerated. There were reductions in the primary outcome end point total recurrent stroke (28%, \( P<0.0001 \) for all participants and a 43% reduction for those on combination therapy), major vascular events (26%, \( P<0.001 \)), nonfatal myocardial infarction, dementia and cognitive decline among patients with stroke, and stroke-related disability. Furthermore, all age groups, men and women, diabetics and nondiabetics, all entry blood pressure levels including normotensives, and all ethnic groups from all regions benefitted from perindopril-based therapy. The most impressive benefits for stroke reduction occurred among Asians and those taking perindopril plus indapamide combination therapy. The average blood pressure drop was about 9/4 mm Hg overall and 12/5 mm Hg with the combination therapy.

<table>
<thead>
<tr>
<th>TABLE 5. Comparison of Standard and Newer Stroke Preventatives: Number-Needed-to-Treat (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Standard stroke preventatives</strong></td>
</tr>
<tr>
<td>A. Antiplatelet agents vs aspirin*</td>
</tr>
<tr>
<td>1. Aspirin 50 mg/d vs aspirin 50 mg plus extended-release dipyridamole 400 mg/d</td>
</tr>
<tr>
<td>2. Aspirin 1300 mg/d vs ticlopidine 500 mg/d</td>
</tr>
<tr>
<td>3. Aspirin 325 mg/d vs clopidogrel 75 mg/d</td>
</tr>
<tr>
<td>B. Carotid endarterectomy plus medical management vs medical management alone: symptomatic patients\†</td>
</tr>
<tr>
<td>1. 70% to 99% Carotid stenosis</td>
</tr>
<tr>
<td>2. 50% to 69% Carotid stenosis</td>
</tr>
<tr>
<td>3. &lt;50% Carotid stenosis</td>
</tr>
<tr>
<td>C. Carotid endarterectomy plus medical management vs medical management alone: asymptomatic patients\‡</td>
</tr>
<tr>
<td>1. ( \geq 50% ) Carotid stenosis</td>
</tr>
<tr>
<td>2. ( \geq 60% ) Carotid stenosis</td>
</tr>
<tr>
<td>D. Warfarin in symptomatic (prior cerebral ischemic event) atrial fibrillation\‡</td>
</tr>
<tr>
<td>E. Aspirin in acute stroke treatment\‡</td>
</tr>
<tr>
<td><strong>II. Newer stroke preventives</strong></td>
</tr>
<tr>
<td>A. Perindopril-based therapy\textsuperscript{140}</td>
</tr>
<tr>
<td>1. Overall</td>
</tr>
<tr>
<td>2. Combination perindopril plus indapamide therapy</td>
</tr>
<tr>
<td>B. Ramipril-based therapy\textsuperscript{133}</td>
</tr>
<tr>
<td>C. Pravastatin vs placebo after myocardial infarction\§</td>
</tr>
<tr>
<td><strong>III. Antihypertensive agents for first stroke prevention\textsuperscript{110}</strong></td>
</tr>
<tr>
<td>A. 90–110 mm Hg diastolic blood pressure (DBP)</td>
</tr>
<tr>
<td>B. Up to 115 mm Hg DBP</td>
</tr>
<tr>
<td>C. Above 115 mm Hg DBP</td>
</tr>
<tr>
<td><strong>NNT</strong></td>
</tr>
<tr>
<td>33 to save 1 stroke at 2 years</td>
</tr>
<tr>
<td>40 to save 1 stroke at 2 years</td>
</tr>
<tr>
<td>125 to save 1 stroke at 2 years</td>
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<td>8 to save 1 stroke at 2 years</td>
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<td>20 to save 1 stroke at 2 years</td>
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<tr>
<td>67 to save 1 stroke at 2 years</td>
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<tr>
<td>48 to save 1 stroke at 2 years</td>
</tr>
<tr>
<td>83 to save 1 stroke at 2 years</td>
</tr>
<tr>
<td>12 to save 1 stroke at 1 year</td>
</tr>
<tr>
<td>100 to save 1 stroke at 6 months</td>
</tr>
<tr>
<td>23 to prevent 1 stroke at 5 years (( \approx 1% ) reduction per year)</td>
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<tr>
<td>14 to prevent 1 stroke at 5 years</td>
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<tr>
<td>67 to prevent 1 stroke at 5 years</td>
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<tr>
<td>83 to prevent 1 stroke at 5 years</td>
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<td>118 to prevent 1 stroke at 5 years</td>
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<tr>
<td>52 to prevent 1 stroke at 5 years</td>
</tr>
<tr>
<td>29 to prevent 1 stroke at 5 years</td>
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</tbody>
</table>

\*Calculated from data in Albers et al.\textsuperscript{183} 5th ACCP Consensus Conference, Chest 1998; comparisons are indirect and confidence intervals overlap; studies may not be powered to study stroke alone as an outcome endpoint; all NNT favor the nonaspirin agent.

\†From Gorelick 1999.\textsuperscript{184}

\‡From Chaturvedi 1999.\textsuperscript{185}

\§Calculated from Plehn et al 1999.\textsuperscript{186}
PROGRESS highlights the importance of meticulous blood pressure control for recurrent stroke prevention and additional antihypertensive therapy for stroke prevention, and raises the possibility that the beneficial effects of perindopril-based therapy go beyond blood pressure lowering, as the reduction of myocardial infarction went beyond that expected for blood pressure-lowering alone. The PROGRESS results, which show prevention of recurrent stroke and prevention of a first myocardial infarction, complement the HOPE trial in which there was predominantly prevention of recurrent myocardial infarction and prevention of first stroke. In both studies, nonhypertensives benefited from ACE-I therapy.

Vitamins

Diets that are high in fruits and vegetables have been associated with a lower risk of cancer and cardiovascular disease. These foods are sources of the antioxidant nutrients vitamin C, beta-carotene and vitamin E. Total cholesterol, LDL-C, and oxidized LDL-C are important in the atherosclerotic process. For example, in basic studies, oxidized LDL-C accelerates endothelial damage, monocyte/macrophage recruitment, uptake of LDL-C by foam cells, abnormalities in vascular tone, induction of growth factors, and autoantibodies to oxidized LDL-C. Antioxidant vitamins might reduce atheroma formation by inhibiting oxidation of LDL.

There has not been consistent evidence that antioxidants reduce coronary or stroke event rates in large-scale clinical trials. It has been hypothesized that inhibition of superoxide production at enzymatic levels (mechanism of ACE-I effect) is a more effective therapy than superoxide scavenging (antioxidant vitamin effect). However, it has been argued that the most potent form of the vitamin E family has not been administered in clinical studies or that adequate doses of vitamin E have not been used in some studies.

Homocysteine

Homocysteine, a sulfur-containing amino acid, is demethylation product of dietary methionine. It is converted to cysteine by cystathionine B-synthase, a vitamin B₆-dependent enzyme, or it can be remethylated by methionine synthase. The latter reaction is vitamin B₁₂ dependent and requires 5-methyl-tetrahydrofolate, a product of folic acid metabolism that uses methylene-tetrahydrofolate reductase (MTHFR). Defects of cystathionine B-synthase and MTHFR and deficiencies in folic acid, B₁₂, and B₆ can lead to raised levels of homocysteine, which have been associated with cardiovascular disease and stroke. After low vitamin concentrations, factors that may be associated with elevations in homocysteine include old age (eg, older than age 70), renal insufficiency, ≥4 cups of coffee per day, and drugs such as methotrexate, 6-azauridine, nicotinic acid, and bile acid sequestrants. Alcohol, smoking, and physical inactivity also may alter homocysteine levels.

Reference ranges for total serum homocysteine concentrations in US residents have been established. Overall, upper reference limits increase with age (eg, 95th percentile for men 60 years or older = 15.3 μmol/L versus 11.4 μmol/L for men 20 to 39 years), are higher for men than women (eg, 95th percentile for men 40 to 59 years = 12.9 μmol/L versus 10.2 μmol/L for women 40 to 59 years), and are associated with low serum vitamin concentrations. The fortification of enriched grain products with folic acid has been associated with a decrease in mean total homocysteine concentration and the prevalence of high homocysteine concentration.

A number of mechanisms have been proposed to link homocysteine to vascular damage, stroke, and cardiovascular disease. These include impairment of endothelial function, endothelial desquamation, oxidation of LDL, increased monocyte adhesion to the vessel wall, impaired vascular response to nitric oxide, and thrombotic tendency mediated by activation of coagulation factors and platelet dysfunction.

A number of epidemiological studies have suggested that elevated homocysteine may be a risk factor for ischemic stroke. For example, in the Physician’s Health Study trial there was a small but nonsignificant association between elevated plasma homocysteine and risk of ischemic stroke. In patients with ischemic cerebrovascular disease, a relationship has been shown between MTHFR genotype and serum homocysteine concentration and an interaction with serum folate concentration. In the Third National Health and Nutrition Examination Survey (1988–1994), homocysteine was associated with risk of nonfatal stroke, and in the Stroke Prevention in Young Women Study, elevated homocysteine was associated with stroke independent of traditional vascular risk factors, vitamin use, and poverty status. In the Framingham Study, nonfasting total homocysteine was an independent factor for incident stroke in elderly persons. In other studies, the MTHFR A677V allele has been associated with severe carotid stenosis, a moderately elevated homocysteine after methionine loading with increased risk of ischemic stroke in young adults, a graded association of increasing plasma homocysteine with ischemic stroke caused by large-artery atherosclerosis and to a lesser extent small-artery disease, an association with risk of silent brain infarction, an association with cervical artery dissection, and microvascular stroke.

Although some observational epidemiological studies confirm an independent risk of vascular disease in patients with increased homocysteine level, when one scrutinizes the rigor of the evidence one finds that in contrast to cross-sectional and case-control studies, prospective studies generally show less or no predictive ability for plasma homocysteine in coronary disease and stroke. Despite the potential relationship, well-designed large randomized trials are needed to determine whether reduction of homocysteine with vitamin therapy is of clinical benefit. Eikelboom and colleagues have summarized randomized clinical trials of vitamin treatment to decrease homocysteine in patients with vascular disease. Three such ongoing studies, the Bergen Vitamin Study, Vitamins in Stroke Prevention (VISP), and Vitamins to Prevent Stroke Study (VITATOPS), primarily focus on stroke outcomes.

Conclusion

In this review I have discussed new avenues for stroke prevention—inflammation and infection, statin agents,
ACE-I, and vitamins. Our armamentarium of potential therapeutic options for first and recurrent stroke prevention is expanding as the treatment and prevention landscape rapidly changes. Physicians and other healthcare professionals who treat stroke patients or stroke-prone persons need to be aware of new guidelines for stroke prevention and effective ways to implement the recommended prevention and treatment measures. Although treatments for lowering inflammatory markers or infection risk and vitamins for reducing stroke risk are undergoing testing and as such are not ready to be incorporated into evidence-based practice guidelines, within the next several years well-designed clinical trial results will be available to substantiate or refute the clinical usefulness of some of these measures. However, for statin agents and ACE-I, the evidence base has been heightened by recent study results. Statin agents are now recommended for prevention of stroke in persons with CHD, and according to the NCEP Adult Treatment Panel III recommendations, symptomatic carotid artery disease is a CHD risk equivalent that merits modifying LDL cholesterol to a goal of <100 mg/dL. Furthermore, ACE-I have been shown to reduce stroke risk in high-risk persons with vascular disease or diabetes mellitus plus other risk factors and in those with ischemic or hemorrhagic stroke and elevated or normal blood pressure. Now, the challenge is to craft clinical practice guidelines to reflect this important information and to develop and monitor quality indicators to make certain that new practice guidelines for stroke prevention are being utilized appropriately in the community.

Table 5 summarizes information on number-needed-to-treat for standard stroke prevention measures and for ACE-I and statin agents, the newer means to reduce stroke risk. Overall, these newer measures compare favorably.

Acknowledgments

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Stroke Prevention Therapy Beyond Antithrombotics: Unifying Mechanisms in Ischemic Stroke Pathogenesis and Implications for Therapy: An Invited Review
Philip B. Gorelick

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