Working on new antibiotic candidates, Akira Endo found in 1976 that statins could strongly inhibit HMG-CoA reductase. It turned out that his discovery was the most important advance in cardiovascular prevention since aspirin and blood pressure-lowering. Contradicting most epidemiological studies which failed to find a link between cholesterol levels and stroke, statins strongly reduce stroke incidence. This prompted an investigation of the non–cholesterol-dependent effects of statins, so called pleiotropic effects, on biologic actions related to plaque instability, inflammation, endothelial function, fibrinolytic activity, platelet function, as well as cerebral blood flow and NO-enhancing pathways leading to neuroprotection.

Low-Density Lipoprotein Reduction as an Essential Biological Marker of Stroke Risk
Since the publication of the Scandinavian Simvastatin Survival Study (4S), the majority of statin trials found a significant reduction in stroke events in patients with coronary heart disease, or with a history of vascular disease, high blood pressure or diabetes. The meta-analysis of over 90,000 patients showed a significant 21% stroke reduction with no statistical heterogeneity between trials and no increase in hemorrhagic stroke. Indeed, from the meta-analysis, low-density lipoprotein (LDL) reduction could be related to 35% to 80% of the statin benefit. New results from randomized trials confirmed that LDL-lowering was associated with a decreased risk of stroke by 48% in diabetics with “normal” LDL cholesterol at baseline, and 25% in patients with coronary artery disease. In the Treat to New Target trial, the benefit was observed in patients with a mean LDL cholesterol of 70 mg/dL as compared with the group of patients with a mean LDL level of 1.02 mg/dL. These results suggest that LDL cholesterol provides a useful biological marker to target the efficacy of statin therapy and reduce the risk of stroke. An important next step is to test the hypothesis that aggressive LDL-lowering is associated with a decreased risk of recurrent stroke in patients after a recent stroke or transient ischemic attack.

Contradicting previous epidemiologic observations, the incidence of strokes has now been associated with increasing LDL cholesterol in 787,442 people, the largest cohort study ever studied. Presented at the 2005 European Stroke Conference, the subjects from Korea were aged 30 to 64 years and followed for 11 years. There were 6328 incident ischemic strokes, 3947 incident hemorrhagic strokes, and 4417 myocardial infarctions. Both ischemic stroke and myocardial infarction were strongly associated with serum cholesterol levels.

The most recent Anglo Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed that treatment of hypertensive and normocholesterolemic patients with calcium-channel blockers plus statins reduced the risk of stroke by almost half compared with a similar group of patients treated with beta-blocker–based treatment alone (4.6% versus 8.2%, respectively).

Low C-Reactive Protein Together With Low LDL Levels Predict Better Cardiovascular Outcomes
Decreased progression of carotid intima-media thickness was also strongly associated with LDL reduction in the meta-analysis. Reduced progression of atherosclerosis was also observed in coronary arteries in a randomized trial testing aggressive cholesterol-lowering versus usual LDL cholesterol treatment (40 mg pravastatin). In this trial, the volume of coronary atherosclerosis increased in the usual care arm and was stable in the aggressive arm. This effect was even greater in patients who had both low LDL and low C-reactive protein levels. The benefits of lowering LDL and C-reactive protein was also noted in the PROVE-IT-TIMI-22 trial in which fewer cardiovascular events were reported in the aggressive LDL-lowering group compared with the usual care arm.

Neuroprotective Effects of Statins
Several laboratories have now shown that chronic statin administration reduces infarct size in rats and mice after transient middle cerebral artery occlusion and also improve behavioral deficits. The protection is dose-dependent and...
obtained using 5 different statins, indicative of a class effect. Acute administration also protects against stroke damage when tested after permanent occlusion. 

The explanations for stroke protection in normocholesterolemic animal models are multiple and probably attributable to cholesterol-independent pleiotropic actions dependent on HMGCoA reductase inhibition. Large doses given chronically for 2 weeks raise cerebral blood flow in both the ischemic core and penumbra but do not lower cholesterol at this treatment duration. As one mechanism, these drugs increase endothelium-derived nitric oxide synthase (eNOS) and do so by increasing the amount and activity of the generating enzyme nitric oxide synthase within the vascular endothelium. eNOS converts the guanidino nitrogen of the semiessential amino acid L-arginine to NO. Vascular NO regulates cerebral perfusion in part by relaxing vascular smooth muscle, and statins improve relaxation in peripheral vessels within 2 weeks of initiating therapy. In genetically engineered mice lacking endothelial nitric oxide synthase gene expression, blood flow is more significantly reduced within the ischemic territory as compared with the wild-type strain, and these mice are susceptible to developing larger infarcts after middle cerebral artery occlusion. Administering an eNOS enzyme inhibitor as an alternative approach significantly increases infarct volume in experimental models, presumably because of blood flow–dependent mechanisms.

Consistent with these observations, manipulations that increase rather than decrease NO availability dilate cerebral vessels and increase cerebral blood flow. The effects are greatly amplified after eNOS upregulation by statin treatment. Enhancing NO generation by L-arginine significantly increases flow in the ischemic penumbra. Infusion is followed shortly thereafter by increased electrophysiological activity within the perifocal zone, indicative of tissue recovery, and stroke damage is reduced. Although the statin and L-arginine data emphasize the importance of nitric oxide–induced flow effects, nitric oxide also exhibits antithrombic, anti-inflammatory actions on endothelial progenitor cells and neovascularization, and these are relevant to reducing stroke risk and recovery. However, the extent to which the NO- or cholesterol-dependent mechanisms explain statin actions in humans remains to be determined by future studies.

In addition to effects on cholesterol, chronic statin administration impacts the synthesis of isoprenoids, intermediates in the cholesterol pathway. Decreasing the availability of isoprenoids inhibits the function of a small GTP-binding protein, whose membrane localization and function are dependent on isoprenylation. Statins down-regulate Rho and Rho-kinase, its downstream effector. Rho-kinase is a serine-threonine kinase that regulates stress fiber formation, smooth muscle contraction and cell migration. Rho-kinase is important in a number of pathological conditions including vascular inflammation and remodeling, hypertension and vasospasm, as well as atherosclerosis. Rho-kinase inhibition both in vivo and in vitro up-regulate eNOS and increase cerebral blood flow, as well as protect in models of stroke in a dose-dependent manner. Protective effects by Rho-kinase inhibitors are absent in eNOS-deficient mice implicating NO and eNOS up-regulation once again. In the clinical arena, Rho-kinase inhibitors reportedly improve patients with subarachnoid hemorrhage, and recent preliminary data show that statins improve clinical outcome after subarachnoid hemorrhage as well. Acute statin effects, by contrast, depend on eNOS phosphorylation by phosphoinositide 3-kinase (PI3K) and PKB/Akt(3,4)-dependent pathways.

The mechanisms of statin stroke protection are complex and difficult to dissect in part because of multiple stroke-related pathways downstream from HMGCoA reductase inhibition in liver as well as within the endothelium. However, with complexity comes opportunity based on diversity of actions and vectors targeting the inflammatory process and the dynamic mechanisms that place the blood vessel at center stage in the evolution of ischemic stroke. Attempts to clarify and build on the mechanisms most relevant to stroke protection in man are a major challenge for the future.

References


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