The Burden of Stroke

In the United States, \(600,000\) persons experience a clinical stroke (first or recurrent) annually.\(^1\) Although the case-fatality rate has declined over the past decades, it is still high. The annual death toll is \(150,000\), which qualifies stroke as the third leading cause of death, behind coronary heart disease (CHD) and cancer. The clinical sequelae of a stroke are often devastating. Among the more than \(3,000,000\) stroke survivors, approximately one half have hemiparesis, one third are clinically depressed, one quarter cannot walk, and one sixth are aphasic.\(^2\) Stroke is the leading cause of serious disability in the United States.\(^3\) Thus, evidence of promising preventive therapies that can reduce the human and societal costs of stroke is welcome news.

### Risk Factors of Incident Stroke

The predictors of clinically recognized incident stroke are numerous and vary with age.\(^4\) The risk factors among older adults, who suffer the highest rates of strokes, were recently examined in the Cardiovascular Health Study cohort.\(^5\) In both men and women \(65\) years old, age was a strong independent risk factor for incident stroke. In subjects \(80\) years old, the annual risk was \(>2.0%\). History of hypertension, use of antihypertensive drugs, and systolic (but not diastolic) blood pressure were, as expected, associated with the risk of stroke. History of diabetes and impaired glucose tolerance were also independent risk factors. Hypertension and diabetes are also strong predictors of acute myocardial infarction in older adults. Several measures of subclinical disease—abnormal left ventricular wall motion and increased left ventricular mass on echocardiography, ultrasound-defined carotid stenosis, and atrial fibrillation—also predicted stroke risk. In middle-aged populations, smoking, decreased physical activity, increased alcohol intake, high fibrinogen levels, and previous heart disease have also been shown to predict incident strokes.

The absence of a consistent and strong association between serum cholesterol and stroke risk is puzzling.\(^6\) However, stroke is not a single disease. A positive relationship of serum cholesterol with atherothrombotic stroke has been reported.\(^6\) Conversely, there may be a negative association between serum cholesterol and hemorrhagic stroke, fatal hemorrhagic stroke in particular.\(^6\)

### Stroke Prevention

Pharmacological treatment of hypertension clearly reduces the risk of stroke.\(^7\) Although scientific documentation is lacking, it seems prudent to recommend a healthy diet, smoking cessation, and regular exercise as a general approach to cardiovascular health, including stroke prevention. Despite widespread use of hypoglycemic agents in type 2 diabetic patients, we still do not know whether these agents reduce the macrovascular complications of diabetes. In patients with atrial fibrillation, warfarin especially, but also aspirin, reduces the risk of embolic stroke.\(^8\) However, the role of aspirin in the primary prevention of ischemic stroke is controversial.\(^4\) Epidemiological studies suggest that prevention of CHD and its progression might be associated with a lower risk of incident stroke.\(^9\)

In this issue of Circulation, Plehn and coworkers\(^10\) report on the favorable effect of pravastatin on stroke incidence, a predefined secondary outcome in the CARE study. In a large group of patients with a recent history of myocardial infarction and moderately elevated LDL cholesterol, pravastatin in a fixed dose of \(40\) mg/d reduced the relative risk of stroke significantly, by \(32\%), over a median follow-up period of 5 years. In absolute terms, the stroke risk was reduced from \(7.3/1000\) person-years to \(5.0/1000\) person-years. This translates into a number-needed-to-treat for 1 year to prevent 1 stroke of 435. The stroke findings were supported by a similar
and parallel reduction in the incidence of transient ischemic attacks. Although the statistical power was limited for subgroup analyses, the reductions in stroke were similar in subgroups defined by sex and history of hypertension, diabetes, or previous stroke. In an exploratory analysis, a trend toward greater benefit was noted for those with the highest baseline LDL cholesterol.

The CARE findings are similar to those reported from the Scandinavian Simvastatin Survival Study (4S). In this trial of coronary patients with elevated levels of serum cholesterol, simvastatin 20 to 40 mg/d reduced the combined incidence of stroke by 29%. The incidence of stroke in the placebo group was 7.7/1000 person-years, similar to that in CARE. The observations from these 2 large secondary prevention trials are supported by data from a pooled analysis of 4 regression studies of pravastatin and a small trial of lovastatin.

Clinical trials always raise questions about the interpretation and extrapolation of the findings, and CARE is no exception.

**What Are the Postulated Mechanisms Behind Stroke Reduction With Statins?**

The reduction in stroke observed in CARE and 4S might be a direct result of retardation of atherosclerosis progression, plaque stabilization, or improved endothelial function. Another intriguing explanation is about to be reported (Marco Pahor, MD, July 25, 1998, written personal communication). In a placebo-controlled crossover trial designed to assess treatment effect on blood pressure in patients with hypertension, pravastatin significantly reduced both systolic and diastolic blood pressure and blunted the hypertensive response to a cold pressor test. Pravastatin may cause vasodilation and a fall in blood pressure by modulating the sympathetic and endothelial regulation of vasomotor tone.

Statins may reduce stroke risk indirectly. Because coronary events and revascularizations are both related to increased stroke risk, one would predict that reductions in such events/procedures might lead to a decreased incidence of stroke.

**Do the Findings From CARE and 4S Extend to Non-CHD Patients?**

In our recent review, we reported a highly statistically significant reduction in stroke risk of 30% in pooled analysis of published secondary prevention trials of statin use in CHD patients. These trials evaluated pravastatin, simvastatin, or lovastatin. The experience from primary prevention and mixed trials was more limited, and the pooled estimates of overall stroke reduction did not reach statistical significance. The point estimates were 11% (95% CI, −31% to 40%) for the primary prevention trials and 30% (−132% to 79%) for the mixed trials. Thus, available clinical trial data do not support a recommendation for the general use of statins for prevention of incident stroke in subjects with no manifest CHD.

**Do All Lipid-Lowering Agents Reduce Stroke Risk?**

Meta-analyses of published trials have not shown a consistent lowering of the risk of stroke. Most trials reported a small number of events. Two of the agents examined, clofibrate and high doses of estrogen, may even be associated with an excess risk of stroke. Reductions in serum cholesterol level with the nonstatins were modest or 50% to 33% of the reductions obtained with statins. The reasons for the difference between early lipid-lowering trials and the recent trials of statins are unclear and may include offsetting secondary drug actions (clofibrate, estrogen), inadequate reductions in serum cholesterol, insufficient statistical power, and/or favorable nonlipid actions of the evaluated statins. It should be noted that niacin treatment in the Coronary Drug Project was associated with a significant reduction in stroke risk.

**How Much of the Benefit of Statins Is Mediated Through Cholesterol Reduction?**

In our recent meta-analysis, we reported that adding the results from the statin trials strengthened the relationship (slope) between lowering of cholesterol and reduction in CHD/total mortality, with the standard error of the estimated slopes decreasing by ∼50%. Despite this stronger association, it would be improper to infer that the entire or even the majority of the overall or net clinical benefit of lipid-lowering agents is mediated through cholesterol reduction, because the variability around the slope is still substantial. The proportion of variability of the observed mortality benefit that statistically can be attributed to reductions in total (and LDL) cholesterol is influenced by multiple factors, including other drug-related mechanisms of action. We know that certain cholesterol-lowering drugs (fibates and hormones) increase non-CHD mortality, offsetting the decrease in CHD mortality attributed to a reduction in serum cholesterol. The variability is likely to decrease further if individual data on initial cholesterol level, concomitant medications, and medical history and trial data on treatment duration are considered. However, a proportion of the variance will remain, and nonlipid effects are probably among the sources of unexplained variation, even for the statins. A recent report from the CARE trial raised questions about the role of an anti-inflammatory effect of pravastatin.

**Are All Statins Created Equal?**

Two subtypes of statins are currently on the US market: the fermentation-derived, or natural, statins (lovastatin, pravastatin, and simvastatin) and the synthetic statins (atorvastatin, cerivastatin, and fluvastatin). The chemical structures of the 3 natural statins are very similar. However, the structures of the 3 synthetic statins are dissimilar, and all 3 are very different from the natural ones (Figure).

Pharmacokinetically, the statins differ, but these differences do not always follow the subtypes. All statins are metabolized by the liver. Lovastatin, simvastatin, atorvastatin, and cerivastatin have a common metabolic pathway through cytochrome P-450 3A4. The metabolic enzyme for fluvastatin is cytochrome P-450 2C9. Pravastatin has multiple metabolic pathways. These differences could have clinical relevance because the metabolic pathways define the potential interactions with other drugs that are metabolized through
the same pathways, as illustrated by the mibefradil experience. However, clinical practice suggests that these drugs are not often involved with drug interactions. The plasma half-life is 2 to 3 hours for all statins except atorvastatin, which has a half-life of 14 to 20 hours. Pravastatin is the most hydrophilic and simvastatin the most lipophilic, although the clinical relevance of the differences in solubility among the statins is unknown.

The statins also vary in their potency, the clinical relevance of which is debated. With proper dose titration, reductions of 33% to 55% in LDL cholesterol are often achieved with the natural statins and atorvastatin. Fluvastatin and cerivastatin are less effective. The optimal goal of LDL cholesterol reduction has not been scientifically established. Whether additional health benefits result from lowering LDL cholesterol to 130 mg/dL via a higher dose or a different statin is unknown. One study found that atorvastatin is more effective in reducing triglycerides than the other statins. Recent data have shown that the triglyceride-lowering capacity of statins parallels the lowering of LDL cholesterol and that the magnitude of the triglyceride reduction is strongly associated with pretreatment triglyceride levels. Emerging comparative clinical trial data confirm the observation that atorvastatin, in a dose-dependent manner, unfavorably influences HDL cholesterol. Atorvastatin 80 mg/d does not appear to increase HDL cholesterol, in contrast to the natural statins.

Rosenson and Tangney recently suggested that 4 nonlipid mechanisms may contribute to the beneficial effects of statins on clinical events. These include modification of (1) endothelial function, (2) inflammatory responses, (3) plaque stability, and (4) thrombus formation. Endothelial dysfunction may be ameliorated by statins. Suppression of the inflammatory response, illustrated by a reduction of inflammatory cells in the atherosclerotic plaque, has been demonstrated for some but not all statins. Differences between statins in their ability to inhibit cholesterol accumulation in macrophages have also been reported. This represents a drug effect that may influence plaque stability. Similarly, the inhibition of smooth muscle cell proliferation varies among the statins. Lipophilic, but not hydrophilic, statins suppress tissue factor expression, an important initiator of coagulation. The natural statins may influence platelet aggregation through different mechanisms of action. PAI-1 antigen levels are reduced by pravastatin and lovastatin and are increased by atorvastatin.

The effect of atorvastatin on fibrinogen levels is under debate. In a small subset of patients, Sinzinger (Helmut Sinzinger, MD, August 4, 1998, written personal communication) observed reproducible atorvastatin-induced increases in fibrinogen levels of >50%, as well as changes in the...
molecular structure of fibrinogen. The relevance of these observations, if confirmed, needs to be examined.

What Are the Clinical Implications?
The practice of medicine should be based primarily on meaningful clinical evidence from properly designed randomized, controlled clinical trials. Substantial documentation of clinical benefit—reductions in stroke and coronary events—and long-term safety is available only for the natural statins. The strongest evidence relates to patients with CHD. Highly statistically significant reductions have been reported for stroke, cardiovascular mortality, nonfatal myocardial infarction, all-cause mortality, and need for cardiovascular procedures. The only event data on synthetic statins originate from a small angiographic study of fluvastatin.

It is unknown whether and to what extent differences in pharmacokinetics, half-life, solubility, potency, lipid and nonlipid mechanisms, and effects on other risk factors influence the clinical benefits. These critical and urgent questions can only be answered by large, long-term clinical trials comparing different statins. It is not appropriate to assume that the untested drugs will be as effective as the proven drugs.

The potential fallacy of relying on surrogates, such as reductions in LDL cholesterol, in clinical decision-making and regulatory approval is well documented from multiple fields of medicine. Prescribing an unproven drug in place of a proven drug may expose patients to the unnecessary risk of not benefitting from the documented treatment. The natural statins should be used as first-line drugs in the prevention of stroke and coronary events. Until they are proved to be superior or equivalent, synthetic statins and other cholesterol-lowering agents should be reserved for patients who do not respond to natural statins.

References
Natural Statins and Stroke Risk
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