Reducing the Risk for Stroke in Patients With Myocardial Infarction
A Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACI) Substudy

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Morbidity and mortality from cerebrovascular disease remain a major public health problem in the United States. Despite an encouraging decline in case fatality rates between 1989 and 1999, the actual number of stroke-related deaths increased during this period.1 Approximately 600,000 people in the United States suffer an initial or recurrent stroke each year. Beyond the risk of death, the complications arising from cerebrovascular disease present a major personal and economic burden. Further therapies are needed both to reduce the incidence of initial stroke and to improve clinical outcomes after a cerebrovascular accident.

Lipids and Cerebrovascular Disease
Risk factors for the development of symptomatic cerebrovascular disease are multifactorial and at least partially related to age. They include the classical risk factors for coronary atherosclerosis.2 The role of dyslipidemia as a risk factor for stroke, however, has been controversial.

The Prospective Studies Collaboration evaluated the association of both circulating cholesterol and diastolic blood pressure with the incidence of cerebrovascular disease.3 This meta-analysis of 45 prospective observational cohorts included 450,000 individuals who were followed over a 5- to 30-year period (mean duration of 16 years). Although stroke occurred in 13,397 participants, a definite statistical association between baseline cholesterol and stroke could not be determined after multivariate adjustment for sex, documented coronary atherosclerosis, ethnicity (Asian or non-Asian), and diastolic blood pressure. However, information on the pathogenesis of stroke was not available. This may compromise the statistical analysis because the lack of an overall correlation does not mean that there is no correlation between cholesterol levels and specific types of stroke.

Evidence about the potentially adverse relationship between low serum cholesterol and increased risk for intracranial hemorrhage has been conflicting. The Honolulu Heart Program (HHP), which evaluated 7850 male subjects of Japanese-American descent over a period of 18 years, found a significant inverse correlation between cholesterol levels and the risk for intracerebral, but not subarachnoid, hemorrhage. The inverse relation was nonlinear, with a higher incidence only for men whose serum cholesterol levels were in the lowest quintile (<189 mg/dL).4 Data from the Multiple Risk Factor Intervention Trial (MRFIT) also revealed an adverse relationship between low serum cholesterol levels and the risk for intracerebral hemorrhage in 350,977 men over a 6-year period.5 However, not all epidemiological studies confirm this relation. The Korean Medical Insurance Corporation Study evaluated 114,793 Korean men (mean age of 45 years) over a 6-year period.6 Low serum cholesterol stratified by quintiles was not associated with an increased risk for intracerebral or subarachnoid bleeds, although smoking was a significant risk factor for subarachnoid hemorrhage, and hypertension was a significant risk factor for both types of hemorrhagic stroke.

A positive association seems to exist between serum cholesterol and the risk for ischemic stroke. This may be related to the atherosclerotic process, which frequently coexists in the cerebral and coronary vasculature. Further analysis of the HHP showed that elevated serum cholesterol was an independent risk factor both for coronary heart disease and thromboembolic stroke. The association between dyslipidemia and cerebrovascular disease may be underestimated because of the competing or shared risk with coronary heart disease, which generally occurs more frequently than stroke.7

In the past, therapy for dyslipidemia was considered ineffective in reducing the risk for cerebrovascular disease. In a meta-analysis of 13 large-scale studies, cholesterol lowering with diet or pharmacological therapy (a fibrate or a bile acid sequestrant) produced no benefit, and a nonsignificant increase in the risk for fatal strokes was associated with intervention.8 Regression analysis was unable to demonstrate a statistical association between the degree of cholesterol reduction and fatal stroke, and it was concluded that alteration of cholesterol by either pharmacological therapy or dietary interventions would be futile in reducing cerebrovascular morbidity and mortality in middle-aged men.

The advent of therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins,” has revolutionized and further defined the role of lipid
management in the prevention of coronary atherosclerosis. In addition, the realization that statins may have nonlipid (pleiotropic) effects has expanded their potential role in preventing and treating vascular disease. Statins have been shown to lessen inflammation, alter coagulation parameters, decrease platelet aggregation, and improve endothelial function.

The potential role of statins in reducing morbidity and mortality from cerebrovascular disease recently has been elucidated in a series of elegant basic science studies. For example, statin therapy in wild-type mice was shown to protect against cerebral injury by selectively upregulating endothelial nitric oxide synthase, resulting in increased cerebral blood flow, decreased cerebral infarct size, and improved neurological function, independent of a lipid effect.9 The neuroprotective activity of statin therapy was completely absent in endothelial nitric oxide synthase–deficient mice, indicating that upregulation of this key enzyme is the predominant mechanism. Although epidemiological, observational, and experimental studies are important, they should be regarded as hypotheses generating until the results are confirmed by properly designed and well-controlled clinical trials.

Statins and Stroke: Clinical Trials
Because the HHP and MRFIT results showed an association between low cholesterol levels and hemorrhagic stroke, there was some concern that lipid lowering with statins might have a similar effect. This concern has not been substantiated. In fact, the most compelling evidence for the cerebrovascular benefits of lipid-lowering therapy is found in several major secondary-prevention trials comparing HMG-CoA reductase inhibitors with placebo controls. These studies required either prior myocardial infarction or unstable angina as the major entry criteria. Although cerebrovascular disease was not a primary end point, the results provide a robust database for analyzing the potential benefits of statin therapy in reducing the risk for stroke across a spectrum of clinical risk and cholesterol values. Additionally, the recent Heart Protection Study provides a large database in a high-risk but mixed primary- and secondary-prevention population.

Scandinavian Simvastatin Survival Study
The Scandinavian Simvastatin Survival Study (4S) randomized 4444 men and women with prior myocardial infarction or unstable angina to simvastatin 20 to 40 mg/d or placebo over a median follow-up period of 5.4 years.10 It was the first major study to demonstrate a definite improvement in total mortality, the primary end point, with the use of statin therapy. Total mortality was reduced by 30%, primarily driven by a 42% reduction in coronary death. In a post hoc analysis, simvastatin was associated with a 28% reduction in the incidence of fatal plus nonfatal cerebrovascular events, such as stroke or transient ischemic attack (TIA).11 The signs of cerebrovascular disease were also analyzed, and a reduction in the incidence of carotid bruits was found with simvastatin therapy.

Cholesterol and Recurrent Events
The Cholesterol And Recurrent Events (CARE) trial was a large-scale (4159 subjects) study of individuals who had suffered an acute myocardial infarction and had relatively normal total and low-density lipoprotein (LDL) cholesterol levels.12 The average total and LDL cholesterol levels were 209 mg/dL and 139 mg/dL, respectively. Pravastatin 40 mg/d was compared with control therapy, and the incidence of stroke and TIA was analyzed as a prespecified outcome variable over a median follow-up period of 5 years. A total of 128 strokes and 88 cases of TIA fit the established diagnostic criteria.

Pravastatin therapy was associated with a 32% reduction in relative risk for stroke and a 29% reduction in the risk for stroke or TIA. There was no increase in hemorrhagic stroke with pravastatin. The benefit of therapy was evident despite the concomitant use of platelet inhibitors in 85% of the participants, indicating an additive effect. The relative reduction in the risk for stroke or TIA, although similar to the coronary benefit, was temporally delayed and became appreciable at ≈3.5 years into the study, compared with an earlier separation in the coronary event curves.

Long-Term Intervention With Pravastatin in Ischaemic Disease
The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial evaluated the effects of pravastatin on coronary heart disease mortality as the primary end point in a large-scale, placebo-controlled trial of 9014 subjects with documented myocardial infarction or unstable angina.13 The lipid entry criteria were wide ranging, with total cholesterol values from 155 to 271 mg/dL. Stroke was a predefined secondary end point and included all-cause cerebrovascular disease and nonhemorrhagic stroke as subgroups. A total of 419 strokes over the 6-year follow-up period were subdivided into 309 ischemic, 31 hemorrhagic, and 79 of unknown type. In this study, there was a statistically significant (P=0.05) reduction of 19% in the relative risk for stroke (4.5% in the placebo group compared with 3.7% in subjects randomized to pravastatin). Pravastatin therapy was not associated with an increase in hemorrhagic stroke. The LIPID study demonstrated the safety and moderate benefit of pravastatin in reducing the risk for strokes in subjects with coronary disease and a broad range of lipid values.

Prospective Pravastatin Pooling Project
The Prospective Pravastatin Pooling (PPP) Project14 was a combined analysis of 3 clinical trials that provided 102 559 person-years of evaluation in a population of 19 768 subjects. In the CARE and LIPID studies together, pravastatin reduced the risk for all stroke events by 22%. It was estimated that 588 patients per year would require pravastatin therapy to prevent one stroke. Additionally, there was a reduction in the absolute risk for stroke with pravastatin. Benefit was seen in patients receiving aspirin co-therapy and in those receiving or not receiving blood pressure medications. However, results in patients not taking antihypertensive medication lacked statistical significance. The combined CARE/LIPID results are comparable to the reduction in stroke rates reported with antiplatelet therapy administered to post–myocardial infarction patients.14 Hemorrhagic stroke was not increased with pravastatin therapy.
Heart Protection Study
The Heart Protection Study (HPS) was a large trial involving 20,536 patients whose eligibility was guided primarily by the uncertainty principle. Using a 2×2 factorial design, this study evaluated the role of simvastatin 40 mg/d and antioxidant vitamins vs placebo in individuals considered to be at high risk for a coronary event, but for whom adequate clinical trial support for pharmacological therapy was lacking. Participant recruitment was based on the presence of myocardial infarction or known coronary heart disease, noncoronary atherosclerosis, diabetes, or hypertension. The minimum total cholesterol level before randomization was ≥135 mg/dL, and the subjects could not be definite candidates for antioxidant or hypolipidemic therapy on the basis of currently available clinical evidence. During the trial, the randomized participants were allowed to begin nonstudy statin therapy if clinical data from other studies emerged to indicate a potential benefit. However, the combination of study regimen plus nonstudy statin was not to exceed the lipid-lowering potency of 40 mg of simvastatin.

Stroke was a predefined end point, and simvastatin therapy significantly reduced the incidence rate of cerebrovascular disease. A total of 585 placebo patients experienced a first stroke after randomization, compared with 444 statin patients, a significant 25% risk reduction. Definite ischemic strokes occurred in 409 placebo subjects versus 290 simvastatin subjects. Hemorrhagic cerebral infarctions or subarachnoid bleeds were not increased, although the absolute numbers were small. A total of 53 hemorrhagic strokes occurred in the placebo group versus 51 in the simvastatin group. In absolute terms, 5.7% of the 10,267 individuals randomized to placebo suffered a cerebrovascular accident, compared with 4.3% of the 10,269 individuals receiving simvastatin. The large database provided by the HPS, and the fact that almost 40% of control patients were also receiving statin therapy by the end of the study, emphasize the beneficial role of HMG-CoA reductase inhibitors as a means of preventing cerebrovascular events in high-risk individuals. Antioxidant therapy had no impact on the risk for a stroke, although an adverse effect was not documented.

Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering
The 6 major primary- and secondary-prevention statin trials have revolutionized the treatment of patients with dyslipidemia by providing an extremely robust database of 51,353 subjects. However, the secondary-prevention trials—CARE, LIPID, and 4S—delayed the initiation of statin therapy for a period of 3 to 36 months after the defining event. Thus, the effect of statin therapy begun during an acute coronary syndrome had not been explored in prospective randomized clinical trials. The Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) study randomized 3086 adults with unstable angina or non-Q–wave acute myocardial infarction to atorvastatin 80 mg/d or placebo initiated between 24 and 96 hours after hospital admission. Conducted over a 16-week period, MIRACL was of relatively short duration because previous studies had shown the clinical benefit of statin therapy beyond this time period.

The primary end point in the MIRACL study was a composite of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring hospitalization. With atorvastatin, LDL cholesterol was decreased by an adjusted mean of 40% to 72 mg/dL, and there was a statistically significant reduction (P=0.048) in the composite primary end point, driven primarily by a reduction in recurrent symptomatic myocardial ischemia requiring hospitalization.

Nonfatal stroke (hemorrhagic, embolic, thrombotic, or undetermined) was a predefined secondary end point, and the results of this subgroup analysis are presented in the present issue of Circulation. The incidence of fatal and nonfatal stroke was analyzed post hoc. Transient ischemic events were not included because of the inherently subjective nature of the diagnosis.

In the MIRACL trial, 136 placebo and 130 atorvastatin patients had preexisting cerebrovascular disease (8.8% and 8.5%, respectively; P=N.S.). A definite nonfatal stroke occurred in 22 placebo-treated subjects and 9 individuals receiving atorvastatin, which represented a statistically significant relative risk of 0.40. Fatal and nonfatal strokes occurred in 24 placebo patients versus 12 atorvastatin patients, which was also statistically significant. Interestingly, the 3 clinically identified hemorrhagic strokes all occurred in the placebo group, despite the fact that atorvastatin therapy reduced LDL cholesterol to a level hypothesized to increase the relative risk for intracerebral bleeds. There were 6 strokes within 14 days of a coronary intervention.

The MIRACL study adds to the growing body of evidence supporting the benefit of statin therapy in the reduction of cerebrovascular events. Currently the only prospective, large-scale, statin-based intervention trial in acute coronary syndromes, it emphasizes the potential benefit of initiating therapy immediately after an acute ischemic event, irrespective of baseline lipid levels. The temporal occurrence of cerebrovascular benefit with atorvastatin is in contrast to the results of prior secondary-prevention trials. In the CARE study, a definite separation in the curves between statin and placebo groups was not evident until ≈36 months of treatment. Simvastatin therapy in 4S was also associated with a reduction in all-cause stroke and TIA, but the curves between simvastatin and placebo overlapped until ≈42 months of therapy, despite a separation at ≈8 to 12 months in the incidence of carotid bruit. In the LIPID trial, a definite separation of the curves was not evident until ≈2 years of therapy. The time course in the HPS secondary-prevention cohort has not been analyzed.

In the MIRACL study, Kaplan-Meier curves for the cumulative incidence of stroke began to separate at ≈2 weeks and continued to separate during the 16-week period of the trial, perhaps in part because some patients with acute coronary syndromes may have vulnerable plaques in other arterial beds, which may be stabilized by statin therapy. Notably, concurrent medications were allowed, and the control patients in the MIRACL study were treated with agents that reduce the risk for stroke. A total of 92% of MIRACL placebo patients received aspirin, 78% received β-blockers, 50% were
on an ACE inhibitor or an angiotensin II receptor blocker, and 48% were on calcium channel blockers.

Despite the encouraging results of MIRACL, there are several caveats. The atorvastatin dose of 80 mg/d is not commonly used in the United States. Whether less aggressive dosing would produce the same benefit will require the results of current ongoing trials (eg, the Treating to New Targets [TNT] study). Additionally, although statistically significant, the absolute number of cerebrovascular events was small (12 fatal or nonfatal strokes in the atorvastatin group and 24 in the placebo group).

Nevertheless, it is encouraging that hemorrhagic stroke was not increased with atorvastatin, and the overall effects of aggressive lipid-lowering therapy during an acute coronary syndrome are in concert with other secondary-prevention trials. The results of the MIRACL trial support the role of aggressive lipid modification in the early phase of acute myocardial infarction or unstable angina, not only to decrease further myocardial damage, but also to reduce the risk for stroke. As the authors point out, however, randomized placebo-controlled trials must be conducted to determine if these results can be confirmed.2

References
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