Statins for Stroke
The Second Story?
Jorge Plutzky, MD; Paul M. Ridker, MD, MPH

In the 100 years since Ignatovski demonstrated that high-fat diets promote atherosclerosis in rabbits, cardiologists have witnessed an extraordinary evolution in our understanding of atherothrombosis and lipid reduction, culminating in the publication of 5 landmark trials of HMG-CoA reductase inhibition within the past 6 years. In each of these trials, statin therapy was shown to significantly reduce the risks of coronary heart disease in populations with progressively lower degrees of overall risk. These data have had profound effects on preventive medicine and established the first clear success story for this class of therapy.

Despite these triumphs, questions remain in our understanding of statins, how they work, and in what settings. As a result, clinical paradigms regarding cholesterol reduction continue to shift. In this sense, the large meta-analysis from the Prospective Pravastatin Pooling Project, which was published in this issue of Circulation, addresses a question that may represent a second success story for the statins. Does statin therapy lower the risk of stroke and, if so, why, given the controversy over the role of LDL cholesterol as a risk factor for stroke?

These are some of the issues that Byington and colleagues’ address in their analysis of cerebrovascular events in the Prospective Pravastatin Pooling Project, a carefully performed systematic overview including 19 768 patients enrolled in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, the Cholesterol and Recurrent Events (CARE) study, and West of Scotland Coronary Prevention Study (WOSCOPS), each of which randomly allocated study participants between 40 mg of pravastatin or placebo. As outlined in their article, a reduction in stroke events was observed in all 3 of these major trials, which, when pooled, demonstrate a statistically significant 22% reduction in total stroke and a 25% reduction in nonfatal stroke attributable to pravastatin. The prevented events were almost entirely atherothrombotic in origin; pravastatin had no effect on the rates of hemorrhagic stroke.

On initial review, these data are not surprising: prior publications from the CARE® and LIPID® investigators have already shown stroke reductions in those trials, and a benefit on stroke was also observed in the Scandinavian Simvastatin Survival Study (4S), which was performed among postinfarction patients with hyperlipidemia. However, the pooled data for pravastatin command attention for several reasons. Foremost is the size of the study group, which accrued 102 559 person-years of follow-up and almost 600 incident stroke events. Thus, these data provide definitive evidence that pravastatin reduces stroke risk and convincingly suggest that these effects are consistent across all major subgroups analyzed, including those on prophylactic aspirin. Evidence on this issue is important because as recently as 1995, a meta-analysis of nonstatin forms of lipid-lowering therapy showed no statistically significant impact on stroke.

Why do statins seem to decrease cerebrovascular risk when other forms of cholesterol-lowering have not? Although the answer to this question is uncertain, several pathophysiological issues may provide insight into this apparent paradox. First, stroke has many causes, and benefit might be seen only after segregating ischemic from hemorrhagic events. In this regard, the Prospective Pravastatin Pooling Project showed no effect on hemorrhagic stroke; these data are reassuring given the results from the Multiple Risk Factor Intervention Trial, which suggested an increase in hemorrhagic cerebrovascular events at LDL cholesterol levels <70 mg/dL. LDL cholesterol lowering to this extent was unlikely in the Prospective Pravastatin Pooling Project given the fixed dose of drug used and the above-average baseline cholesterol levels among most study participants. This issue will be of interest as statin trials comparing “moderate LDL lowering” with “aggressive LDL lowering” are completed in coming years.

Second, because LDL cholesterol is not a strong risk factor for stroke, it is possible that nonlipid mechanisms associated with statin use may be more important for cerebrovascular disease than previously appreciated. In this regard, statins have been shown to have several antithrombotic and anti-inflammatory effects. For example, statins reduce inflammatory markers such as C-reactive protein in an LDL-independent fashion, and they may be more effective in terms of event reduction in the presence of elevated C-reactive protein levels. This issue is of clinical interest because epidemiological studies have demonstrated that C-reactive protein is a potent risk factor for thromboembolic stroke, although total and LDL cholesterol are not. Such data support the view that plaque stabilization may be an
important process by which statins reduce vascular event rates. This may be of particular significance in the cerebral vessels, where increasing evidence suggests plaque rupture is a pathogenic mechanism.\textsuperscript{17,18}

Although observations regarding statins and stroke are intriguing, these effects may not be unique. In the secondary prevention Veterans Affairs HDL Intervention Trial (VA-HIT), gemfibrozil led to a 59\% decrease in transient ischemic attacks, a 65\% decrease in carotid endarterectomy (both $P<0.001$), and a 25\% reduction in strokes ($P=0.10$) among patients with baseline low LDL (104 mg/dL) and low HDL (32 mg/dL) levels.\textsuperscript{19} As with statins, a specific vascular drug effect could also be invoked to explain these data, given the fact that gemfibrozil is a possible ligand for the PPAR\textsubscript{a} nuclear receptor, which transcriptionally regulates important vascular and lipid targets.\textsuperscript{20,21} The broader importance of the VA-HIT data may be that, for both coronary heart disease and for stroke, event rates were reduced with a form of lipid-lowering therapy that had very little effect on LDL cholesterol levels.

For the clinician, information regarding statin effects on stroke have several implications. Among patients with a prior history of myocardial infarction, such as those enrolled in the CARE, LIPID, and 4S trials, statins significantly reduce future stroke event rates and, thus, provide yet another reason to place patients on these agents. Stroke stands as a devastating event in the lives of patients and their families, often irrevocably changing independence, productivity, and quality of life. Patients understand this, with clinical experience suggesting perhaps a greater fear of stroke than heart attack. As such, clinicians may be able to use results like those from the Prospective Pravastatin Pooling Project to foster greater patient acceptance and adherence to prescribed statin therapy.

That being said, it is important to put the absolute risk reduction for stroke seen in the Prospective Pravastatin Pooling Project into perspective and to compare this to reductions in risk that can be expected for coronary heart disease. As Byington and colleagues\textsuperscript{7} note, the number of patients who need to be treated (NNT) for 1 year to prevent 1 stroke event is relatively large. Specifically, among patients with a prior history of myocardial infarction who were enrolled in the CARE and LIPID trials, the NNT for 1 year to prevent 1 stroke was 588, whereas the NNT among primary prevention participants enrolled in WOSCOPS was 3333. As shown in the Figure, stroke event rates in each of these trials and the expected risk reductions in stroke attributable to pravastatin are smaller than those observed for coronary heart disease. Thus, from an absolute risk reduction perspective, the principal use of these agents will largely remain in the prevention of coronary heart disease. At the same time, evidence of a stroke benefit with statins underscores the need to broaden our approach to prevention and consider all vascular beds, not just the coronary arteries, as targets for the treatment of atherosclerosis. Through this widened lens, improved patient outcomes may come not only from the cerebrovascular and peripheral arterial systems, but also from the treatment of concomitant occult atherosclerosis lurking in the arteries.

Despite the statin database, clinical questions persist. What is the ideal LDL level after a myocardial infarction? What is the clinical relevance of the non-LDL effects of statins on atherosclerosis? How do we integrate HDL and triglyceride treatment into patient management? If the foundation for the progress in cholesterol was laid in basic science stretching from Ignatovski to Brown and Goldstein\textsuperscript{1,22} and beyond, the first floor was no doubt built from the unequivocal results from the statin trials. With emerging data like that regarding stroke, clearly the “second story” is going up.

References


**Key Words:** Editorials ■ heart diseases ■ statins ■ stroke ■ cholesterol ■ lipids
Statins for Stroke: The Second Story?
Jorge Plutzky and Paul M. Ridker

_Circulation._ 2001;103:348-350
doi: 10.1161/01.CIR.103.3.348
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/3/348

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/