Expanding Indications for Statins in Cerebral Ischemia

A Quantitative Study

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Background: New US Food and Drug Administration labeling in 2003 recognizes stroke and evidence of cerebrovascular disease as indicator conditions for initiating statin (simvastatin) therapy, based on results of the Heart Protection Study, thereby extending the indications for statins in stroke beyond current US and European guidelines.

Objective: To assess the impact on clinical practice of broadening indications for statins in patients with stroke.

Design: Observational study.

Setting: University hospital stroke service.

Patients: One hundred consecutive patients with ischemic stroke and transient ischemic attack.

Interventions: Development and application of algorithms for initiating statin therapy in patients with stroke and transient ischemia abstracted from recent national and international guidelines (National Cholesterol Education Program Adult Treatment Panel III, European Joint Task Force II), Heart Protection Study entry criteria, and Heart Protection Study–based US Food and Drug Administration labeling.

Main Outcome Measures: Percentages of patients who met clinical trial–validated and US Food and Drug Administration–approved criteria for initiation of statin therapy.

Results: Patient age averaged 74 years (range, 35-96 years); 64% were female, and 74% were white. Stroke subtype was large-vessel atherosclerosis in 24%, cardioembolic in 44%, small-vessel atherosclerosis in 22%, and other in 10%. Twenty of 100 patients were already taking statins on admission. Guidelines for definite initiation of statin treatment were met by 48% of patients for the National Cholesterol Education Program III, 38% for the European Joint Task Force II, 92% for the Heart Protection Study, and 100% for the Food and Drug Administration.

Conclusions: Most clinically encountered patients with ischemic stroke meet clinical trial–validated criteria for initiation of statin therapy. Rigidly applying current national and international guidelines may deprive up to one half of these patients of advantages of statin therapy.

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There is growing evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may play an important role in ischemic stroke prevention, through cholesterol-lowering, anti-inflammatory, and antithrombotic mechanisms.1 Numerous landmark lipid-lowering trials have shown that treatment with statins is associated with a substantial decrease in the risk of stroke and transient ischemic attack (TIA) in patients with symptomatic coronary artery disease or multiple risk factors for atherosclerosis.2-5 Other clinical trials using serial ultrasound measurements have shown that statins retard the progression of, or actually reverse, asymptomatic carotid atherosclerosis in individuals with moderately elevated levels of low-density lipoprotein cholesterol.6 These observations have further been supported by various meta-analyses demonstrating a substantial benefit of statins in the primary prevention of ischemic stroke in patients with a history of, or risk factors for, coronary artery disease, both with and without elevations of serum cholesterol level.7,9

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Few patients with a history of stroke or TIA were enrolled in early trials of statin therapy, leaving uncertain the benefits of statins in the secondary prevention of vascular events after an ischemic stroke or
TIA. Recently, however, the Heart Protection Study (HPS) provided strong evidence of the efficacy of statins as secondary prevention agents in patients with cerebral ischemia.10,11 Overall, the HPS enrolled 20,536 individuals with a variety of vascular risk factors and average cholesterol levels and demonstrated a substantial overall benefit. The HPS cohort included 3280 patients with a history of stroke or TIA. Of these, 55% had no history of coronary artery disease. In these patients, major vascular event rates were reduced from 29.8% to 24.7% (P < .001). Incidence rates of stroke in the entire study cohort were reduced from 5.7% to 4.3% (P < .001).

In the entire HPS population, benefits of statin therapy were observed irrespective of baseline cholesterol levels. The trial also demonstrated the safety of statins in patients with low entry cholesterol levels (minimum permitted total cholesterol level, 135 mg/dL [3.5 mmol/L]), with no evidence of increased hemorrhagic stroke with further cholesterol reduction.

Current recommendations issued to guide medical practice in statin initiation include the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III12 and the European Joint Task Force (EJTF) II for the detection, evaluation, and treatment of high blood cholesterol levels in adults.13

The HPS results suggest additional indications for 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in patients with ischemic stroke beyond current national and international guidelines. Recent systematic reviews have concluded that statins should be initiated in all patients with ischemic stroke.14 On the basis of the HPS, new labeling was approved by the US Food and Drug Administration (FDA) in April 2003, recognizing the occurrence of a stroke and evidence of cerebrovascular disease as indicator conditions for initiation of treatment with simvastatin.15 A recent systematic review similarly concluded that statins should be initiated in all patients with ischemic stroke.16

The objective of this study was to evaluate the impact on clinical practice of applying the new FDA labeling and HPS criteria for statin initiation in stroke, compared with current national and international guidelines.

### METHODS

**CASE IDENTIFICATION**

Subjects were 100 consecutively encountered patients with ischemic stroke or transient ischemic attack admitted to a university-based stroke service from April 1, 2002, to September 24, 2002. History of hypertension, diabetes, tobacco use, peripheral vascular disease, coronary artery disease, atrial fibrillation, and other risk factors was documented at the time of admission. All patients had fasting lipid panels and fasting serum glucose levels drawn the day after admission. For blood pressure determination, 2 separate measurements 48 to 72 hours after admission were averaged. Stroke and TIA subtype diagnoses were rendered with the use of modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.16

**STATIN ELIGIBILITY DETERMINATIONS**

Algorithms for initiating statin therapy were abstracted from HPS trial entry criteria, NCEP III and EJTF II recommendations, FDA labeling, and a stroke mechanism–based decision tree used by the Stroke Service at the University of California, Los Angeles (Table 1).

**Framingham Risk Assessment**

The NCEP III and EJTF II use the Framingham coronary heart disease (CHD) risk model,17-20 mandating statin therapy when the 10-year absolute CHD risk exceeds 20%. To calculate absolute CHD risk in our cohort, we collected the following data corresponding to the CHD risk factors in the Framingham profile: age, sex, systolic blood pressure determination, 2 separate measurements 48 to 72 hours after admission were averaged. Stroke and TIA subtype diagnoses were rendered with the use of modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.16

### Table 1. Criteria for Initiation of Statin Therapy*

<table>
<thead>
<tr>
<th>NCEP-ATP III</th>
<th>EJTF II</th>
<th>HPS</th>
<th>New FDA Labeling</th>
<th>ASMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indications (at least 1 of the following)</td>
<td></td>
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</tr>
<tr>
<td>1. Previous CHD</td>
<td>1. Established CHD</td>
<td>1. CHD</td>
<td>1. CHD</td>
<td>1. Ischemic stroke likely due to large/small-vessel atherosclerosis</td>
</tr>
<tr>
<td>2. 10-y CHD risk ≥20% based on FRA</td>
<td>2. 10-y CHD risk ≥20% based on FRA</td>
<td>2. PAD</td>
<td>2. PAD</td>
<td>2. TIA likely due to large/small-vessel atherosclerosis</td>
</tr>
<tr>
<td>Serum lipid indication (at least 1 of the following)</td>
<td>5. PAD</td>
<td>4. Treated HTN + male sex + age &gt;65 y</td>
<td>5. Nondisabling ischemic stroke</td>
<td>4. Evidence of stroke or other cerebrovascular disease</td>
</tr>
<tr>
<td>1. LDL-C &gt;130 mg/dL (optional for LDL-C = 100-129 mg/dL)</td>
<td>6. AAA</td>
<td>6. TIA</td>
<td>6. TIA</td>
<td>6. TIA</td>
</tr>
<tr>
<td>Total cholesterol ≥135 mg/dL</td>
<td>7. History of CEA or carotid angioplasty</td>
<td>None</td>
<td>7. History of CEA or carotid angioplasty</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, abdominal aortic aneurysm; ASMA, atherosclerotic stroke mechanism algorithm; CEA, carotid endarterectomy; CHD, coronary heart disease; DM, diabetes mellitus; EJTF II, European Joint Task Force II; FDA, Food and Drug Administration; FRA, Framingham risk assessment; HPS, Heart Protection Study; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; NCEP-ATP III, National Cholesterol Education Program–Adult Treatment Panel III; PAD, peripheral arterial disease; TIA, transient ischemic attack.

SI conversion factors: To convert LDL-C and total cholesterol to millimoles per liter, multiply by 0.0259.
NSTEMI patients with 2 or more of these characteristics were considered to have metabolic syndrome if they had 3 or more of these characteristics.

### METABOLIC SYNDROME

The metabolic syndrome is a cluster of metabolic conditions that together increase an individual’s risk of atherosclerotic vascular disease. The NCEP III mandates statin therapy when the metabolic syndrome is present. Four elements used in NCEP III diagnostic criteria metabolic syndrome were obtained in our cohort: blood pressure (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg), glucose (fasting glucose level >110 mg/dL [6.1 mmol/L]), high-density lipoprotein cholesterol level (male, <40 mg/dL [<1.0 mmol/L]; female, <50 mg/dL [<1.3 mmol/L]), and triglyceride level (>150 mg/dL [>1.7 mmol/L]). Patients were considered to have metabolic syndrome if they had 3 or more of these characteristics.

### RESULTS

Demographic and clinical characteristics of the study cohort are delineated in **Table 2** and **Table 3**.

### NCEP III RESULTS

Sixty-two patients exhibited at least 1 of the NCEP III clinical condition criteria. Among these, 38 also exceeded the NCEP III low-density lipoprotein cholesterol threshold of 130 mg/dL (3.4 mmol/L), indicating definite initiation of statin treatment, and an additional 18 patients had low-density lipoprotein cholesterol levels in the range of 100 to 129 mg/dL (2.6-3.3 mmol/L), indicating possible initiation of statin therapy and/or lifestyle changes at the discretion of the clinician. Among the 34 patients with 1 or more NCEP III indicator clinical conditions who had fasting low-density lipoprotein cholesterol levels less than 160 mg/dL (4.1 mmol/L), 10 were already taking statins. When these patients were added to those who met full NCEP III criteria, 48 patients met NCEP III indications for definite initiation or continuation of statin therapy.

### EJTF II RESULTS

Thirty patients had indications for EJTF II statin initiation. Among the 24 patients with 1 or more EJTF II indicator clinical conditions who had lipid levels below treatment initiation thresholds, 8 were already taking statins. Altogether, 38 patients met EJTF II indications for initiation or continuation of statin therapy.

### HEART PROTECTION STUDY

All patients had TIA or ischemic stroke, indicator clinical conditions in the HPS. Of these, 86 had fasting total chole-

### Abbreviations

- CHD: coronary heart disease
- CLM: cholesterol-lowering medication
- DBP: diastolic blood pressure
- HDL-C: high-density lipoprotein cholesterol
- LDL-C: low-density lipoprotein cholesterol
- NIH Stroke Scale score
- SBP: systolic blood pressure
- TIA: transient ischemic attack
terol levels of 135 mg/dL (3.5 mmol/L) or greater, meeting inclusion criteria for initiation of statin therapy, and another 6 were already taking statins. Altogether, 92 patients met HPS indications for initiation or continuation of statin therapy.

**FDA LABELING**

All patients in the cohort had either an ischemic stroke or evidence of a cerebrovascular condition (TIA), indicator clinical conditions in FDA labeling. With no lipid level cutoff under the new FDA labeling, 100% of the cohort met indications for initiation or continuation of statin therapy.

**STROKE MECHANISM ALGORITHM**

Twenty-four patients in the cohort had evidence of large-vessel aortocervical atherosclerosis and 22 patients had lacunar stroke, suggesting intracranial branch atheromatosis. Nonatherosclerotic mechanisms of stroke included cardioembolism in 44 patients, arterial dissection in 4, hypercoagulable state in 5, and vasculitis in 1. Among these patients, an additional 28 had CHD or systemic indication for statins, yielding a total of 74 patients who met indications of the stroke mechanism algorithm for initiation or continuation of statins.

The Figure displays the frequency of indications for statin therapy in the cohort per the HPS and the various panel recommendations.

**STATIN UTILIZATION RATES**

Eighty-six patients, including the 6 individuals who were taking statins before admission, were actually discharged on a statin regimen. Patients not treated with statins included 8 patients who did not meet HPS criteria, 2 patients with formal contraindication to therapy due to significantly elevated liver enzyme levels (>4 times normal), and 4 patients with solely nonatherosclerotic stroke mechanisms.

Our study demonstrated that many patients with stroke and TIA consecutively encountered in routine clinical practice meet clinical trial–validated criteria for initiation of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy. In our cohort, 92% met HPS criteria, 100% met FDA labeling criteria based on the HPS, and 74% met stroke mechanism criteria. In contrast, practice according to current EJTF II and NCEP III guidelines mandated statin initiation in a much lower proportion of patients, only 38% to 48%, depriving up to about one half of all encountered patients of the potential benefits of reduction in vascular events evident in the HPS trial.

During the past decade, researchers, clinicians, and writers of guidelines have increasingly recognized atherosclerosis as a systemic disease, meriting aggressive, multimodal treatment irrespective of the particular vascular bed in which it first becomes manifest. Coronal artery atherosclerotic disease and cerebrovascular atherosclerotic artery disease share common risk factors, and patients with one condition are at high risk of developing the other. The NCEP III recognizes a variety of CHD equivalents, including the cerebrovascular condition of symptomatic carotid disease. However, the NCEP III criteria reflect a very limited view of how atherosclerotic disease affects the cerebral vasculature, confining indications for statin therapy to carotid disease alone. Atherosclerosis develops in many sites within the aortocervicocephalic circulation other than the carotid artery. Patients with cerebral ischemia due to atherosclerotic disease in the aortic arch, the vertebral arteries, the basilar artery, the middle cerebral arteries, and intracranial branch atheromatosis do not qualify per se for statin therapy under NCEP III.

The HPS inclusion and exclusion criteria and recent FDA labeling extend greatly the cerebral ischemia indications for statins. First, they recognize all ischemic strokes and TIAs as clinical indicator conditions for therapy. Second, they make atherosclerosis, not cholesterol level, the primary target for statin treatment, with the HPS including for therapy patients with fasting total cholesterol levels as low as 135 mg/dL (3.5 mmol/L) if they have manifestations of atherosclerotic disease. Whether the HPS provides sufficient evidence to alter clinical practice has been questioned. Although HPS showed a substantial reduction in major vascular events in patients with stroke, both with and without a history of CHD, patients with stroke were a subgroup, rather than the sole target population, in the trial. The ongoing Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial will provide more definitive evidence, when completed, of the effects of statin in secondary stroke prevention. However, the FDA found the stroke data from the HPS sufficient to lead to new labeling. The HPS stroke data do meet conventional statistical standards for persuasive evidence of treatment effects in subgroups: the stroke subgroup in the HPS was prespecified and large, and results in the subgroup were homogeneous with results in the overall study population.
A difficulty in applying the HPS results to individual patients is the absence of data on how patients with different subtypes of ischemic stroke fared in the trial. Were the benefits of statin therapy homogeneous across large-vessel and small-vessel atherothrombotic stroke, extracranial and intracranial sites of atherosclerosis, and anterior and posterior circulation sites of atherosclerosis? Were patients with cardioembolic stroke, nonatherosclerotic arteriopathies (migraine, dissection, etc.), hypercoagulable states, and other stroke mechanisms included in the HPS? As is common in megatrials, data on the subtype of index ischemic stroke and TIA were not collected in the HPS (written communication, Louise Bowman, MD, for the HPS Investigators, February 21, 2003). Accordingly, it is not known from the HPS whether there are subtypes of patients with cerebral ischemia who do not experience the benefit from statin therapy evident in patients with ischemic stroke and TIA in general.

In this study, we applied the HPS criteria strictly as stated in the HPS protocol and new FDA labeling, recognizing any ischemic stroke or TIA as a qualifying indication for statin therapy. We also examined the stroke mechanism–based decision approach we use in current practice, a modified version of the HPS criteria, recognizing as cerebrovascular clinical indicator conditions only those ischemic strokes or TIsAs due to large-artery atherosclerosis or intrinsic small-vessel disease (frequently intracranial branch atheromatosis). There are several limitations to this study. Compared with large US registry cohorts, our patient cohort had a greater frequency of cardioembolism and a lesser frequency of large-vessel atherosclerosis as stroke subtypes, which may have influenced the observed frequencies of statin indications under different algorithms. Systolic blood pressure values in our patients used in the Framingham formula for calculating future CHD risk were derived from measurements performed 48 to 72 hours after admission to include patients with TIA and minor, nondisabling strokes, who often do not remain in the hospital longer than 72 hours. This approach may have led to overestimation of baseline blood pressure levels in some patients. Although most of the acute rise in blood pressure at stroke onset resolves by 48 to 72 hours, pressures may not return fully to baseline levels in all patients for another several days. However, our blood pressure measures were obtained in the time frame when clinicians in practice make the key decisions regarding selection of long-term secondary prevention strategies.

The NCEP III guidelines for rendering a diagnosis of the metabolic syndrome are predicated on an individual meeting at least 3 of 5 diagnostic criteria. We obtained measurements for 4 of the criteria, but not waist circumference. Accordingly, we may have failed to identify a few more individuals who had the metabolic syndrome in our cohort and therefore met NCEP III indications for statin initiation. There could not be more than 12 such individuals (12%) in the cohort, as only 12 patients without other indications for statins had 2 of the 4 examined criteria for the metabolic syndrome.

While the HPS results and new FDA labeling suggest a marked expansion of the indications for statin therapy among patients with ischemic stroke and TIA, it is of course one thing to have proved treatments and quite another to implement them in appropriate individuals. Large proportions of high-risk patients are still not even achieving the more conservative goals recommended in the NCEP III and EJTF II guidelines, let alone the newer algorithms. The implementation of effective secondary prevention strategies with appropriate lifestyle interventions and evidence-based statin therapy for patients with cerebral ischemia needs to be strongly encouraged.

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Author Contributions: Study concept and design: Ovbiagele, Kidwell, Saver. Acquisition of data: Ovbiagele, Kidwell, Saver. Analysis and interpretation of data: Ovbiagele, Kidwell, Saver. Drafting of the manuscript: Ovbiagele. Critical revision of the manuscript for important intellectual content: Ovbiagele, Kidwell, Saver. Statistical analysis: Ovbiagele, Saver. Obtained funding: Ovbiagele, Saver. Administrative, technical, and material support: Ovbiagele, Saver. Study supervision: Kidwell, Saver.

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REFERENCES