Reduction of Stroke Incidence After Myocardial Infarction With Pravastatin

The Cholesterol and Recurrent Events (CARE) Study

Jonathan F. Plehn, MD; Barry R. Davis, MD, PhD; Frank M. Sacks, MD; Jean L. Rouleau, MD; Marc A. Pfeffer, MD, PhD; Victoria Bernstein, MD; T. Edward Cuddy, MD; Lemuel A. Moyé, MD; Linda B. Piller, MD; John Rutherford, MB, ChB; Lara M. Simpson, MS; Eugene Braunwald, MD; for the CARE Investigators

Background—The role of lipid modification in stroke prevention is controversial, although increasing evidence suggests that HMG-CoA reductase inhibition may reduce cerebrovascular events in patients with prevalent coronary artery disease.

Methods and Results—To test the hypothesis that cholesterol reduction with pravastatin may reduce stroke incidence after myocardial infarction, we followed 4159 subjects with average total and LDL serum cholesterol levels (mean, 209 and 139 mg/dL, respectively) who had sustained an infarction an average of 10 months before study entry and who were randomized to pravastatin 40 mg/d or placebo in the Cholesterol and Recurrent Events (CARE) trial. Using prospectively defined criteria, we assessed the incidence of stroke, a prespecified secondary end point, and transient ischemic attack (TIA) over a median 5-year follow-up period. Patients were well matched for stroke risk factors and the use of antiplatelet agents (85% of subjects in each group). Compared with placebo, pravastatin lowered total serum cholesterol by 20%, LDL cholesterol by 32%, and triglycerides by 14% and raised HDL cholesterol by 5% over the course of the trial. A total of 128 strokes (52 on pravastatin, 76 on placebo) and 216 strokes or TIAs (92 on pravastatin, 124 on placebo) were observed, representing a 32% reduction (95% CI, 4% to 52%, \( P = 0.03 \)) in all-cause stroke and 27% reduction in stroke or TIA (95% CI, 4% to 44%, \( P = 0.02 \)). All categories of strokes were reduced, and treatment effect was similar when adjusted for age, sex, history of hypertension, cigarette smoking, diabetes, left ventricular ejection fraction, and baseline total, HDL, and LDL cholesterol and triglyceride levels. There was no increase in hemorrhagic stroke in patients on pravastatin compared with placebo (2 versus 6, respectively).

Conclusions—Pravastatin significantly reduced stroke and stroke or TIA incidence after myocardial infarction in patients with average serum cholesterol levels despite the high concurrent use of antiplatelet therapy. (Circulation. 1999;99:216-223.)

Key Words: stroke ■ cholesterol ■ myocardial infarction ■ arteriosclerosis ■ lipids

The relationship between serum cholesterol, its modification, and stroke incidence has been controversial. Although serum cholesterol is a strong risk factor for coronary artery disease, its predictive power for incident stroke in population-based studies is weak or nonexistent.1-7 Furthermore, until recently, even meta-analysis had failed to convincingly demonstrate a significant benefit of cholesterol reduction in the primary prevention of stroke.8 Thus, there may be a disparate effect of hyperlipidemia on various vascular beds.

See p 185

Despite the tenuous epidemiological relationship between serum cholesterol and stroke, it is possible that populations with prevalent atherosclerotic disease, who are at high risk for cerebrovascular events, may benefit from cholesterol modification. The availability of more potent cholesterol-lowering agents, in the form of \( \beta \)-hydroxy-\( \beta \)-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins,” has led investigators to examine this possibility in multicenter cho-
Plehn et al January 19, 1999 217

Lesterol treatment trials aimed primarily at modification of coronary artery disease outcomes.9–11 Although a reduction in stroke incidence with statins has been suggested,9,11,12 these results have been observed in post hoc analyses and are therefore subject to statistical concern.

The Cholesterol and Recurrent Events (CARE) trial was the first large-scale secondary prevention trial of cholesterol reduction with an HMG-CoA reductase inhibitor after myocardial infarction in which stroke was a prespecified end point.13,14 In 4159 patients with average cholesterol levels (mean total cholesterol of 209 mg/dL and LDL cholesterol of 139 mg/dL), the primary end point of the study, coronary artery disease–related death or nonfatal myocardial infarction, was reduced by 24% in pravastatin-treated patients compared with those on placebo. In addition, investigator-reported stroke incidence declined by 31% (3% to 52%, compared with those on placebo. In addition, investigator-reported stroke incidence declined by 31% (3% to 52%, compared with those on placebo.

Methods

Study Design

The design of the CARE trial has been described previously.13,14 In brief, CARE enrolled patients 21 to 75 years old who had experienced a myocardial infarction within the past 3 to 20 months and whose total serum cholesterol was <240 mg/dL, LDL cholesterol between 115 and 174 mg/dL, and fasting triglycerides <350 mg/dL during 4 weeks of treatment with the National Cholesterol Education Panel Step 1 diet. For inclusion, subjects were required to have a fasting glucose level of ≤220 mg/dL, left ventricular ejection fraction of ≥25%, and absence of symptomatic congestive heart failure. The qualifying myocardial infarction was centrally confirmed at an EC core laboratory. Plasma lipid levels were obtained on at least 2 occasions a minimum of 8 weeks after myocardial infarction and averaged to determine patient eligibility. Lipids were measured at a reference core laboratory standardized by the Centers for Disease Control and Prevention. Recruitment for CARE took place at 80 centers (67 in the United States and 13 in Canada) between December 4, 1989, and December 31, 1991.

Neurological events were included in the standard adverse event reporting protocol and were collected and stored at a central data coordinating center. Attempts were made to obtain office and hospital notes, consultation reports, discharge summaries, autopsy results, and reports of duplex ultrasound, angiographic, CT, and MRI studies. Data on all reported cases of possible cerebrovascular events were provided to the CARE Endpoints Committee, which was blinded to lipid data and treatment group. Cases were randomly distributed to the 8 committee members for event categorization, and each event was independently reviewed by 2 committee members. Disagreements were resolved by investigator consensus or, failing this, by the committee as a whole.

Definitions

On the basis of the following classifications defined at the outset of the study, events were categorized as either stroke or transient ischemic attack (TIA), and strokes were further subcategorized as to pathogenesis. The diagnosis of stroke included patients with an acute disturbance of focal neurological or monocular function resulting in either death or signs and/or symptoms of presumed vascular origin that persisted for ≥24 hours, whereas TIA was diagnosed when such a neurological disturbance lasted <24 hours. Only a single event was counted per subject, with stroke taking precedence over TIA.

Strokes were categorized as follows.

**Ischemic:** Infarction due to large-artery atherosclerosis with angiographic or duplex scan evidence of stenosis (≥70%) or total occlusion of the internal carotid artery or siphon, basilar artery, or major cerebral artery stem in a distribution consistent with the patient’s signs and symptoms and without strong evidence of a separate cardioembolic source. In the absence of confirmatory laboratory results, an ipsilateral or preferential TIA also resulted in this diagnosis. A high-convexity infarction on CT or MRI also served as evidence of large-artery infarction if there had been no TIA within the preceding 30 days.

**Lacunar:** Stroke with consciousness and higher cerebral function maintained in the setting of one of the typical lacunar syndromes: pure motor, pure sensory, pure sensorimotor, pure hemiballism, or pure hemichorea. The patient had to have had a CT and/or MRI scan within 1 week after the stroke that was normal or that demonstrated a small, deep infarct in the basal ganglia, internal capsule, or brain stem. If angiography was performed, the major ipsilateral cerebral artery must not have demonstrated severe disease, defined as ≥90% stenosis.

**Embolic:** Stroke with a recognized cardiac source without definite evidence of large-artery occlusive disease. This included atrial fibrillation or flutter, endocarditis, myocardial infarction within the previous 6 weeks, presence of a prosthetic heart valve, atrial myxoma, right-to-left intracardiac shunt with right-sided source of embolus, and pulmonary venous thrombosis.

**Tandem arterial pathology:** When an extracranial lesion was insufficient in itself to account for stroke on a hemodynamic basis but might have served as a source of embolism, this diagnosis was made. Supportive findings included a hemispheric surface infarct, a stenosis of ≥70%, a single ulcer of ≥2 mm in depth or multiple craters in the internal carotid artery, and a >50% stenosis of any major cerebral stem or the basilar artery.

**Endarterectomy-related:** An embolic stroke occurring at the time of carotid endarterectomy.

**Procedure-related:** A stroke occurring in close temporal relationship to an invasive catheter or surgical procedure other than endarterectomy.

**Indeterminate cause or stroke with a normal angiogram:** Definite cerebral infarction not meeting one of the above-described criteria or when there was >1 possible explanation for stroke. A bruit or a history of a TIA ipsilateral to the stroke-affected hemisphere could not have been present. There also could not have been an obvious cardiac source of embolism, a normal CT or MRI scan, or one that demonstrated definite diagnostic findings. Scans in which the interpretation would not allow for reliable classification of a traditional stroke category also fit into this classification.

**Other unusual causes:** Cerebral infarction due to a rare cause, such as arteritis, aortic dissection, fibromuscular hyperplasia, migraine, mycotic aneurysm, or other diagnosed, but rare or unusual, causes of stroke.

**Hemorrhagic:** Intra-axial (cerebral or cerebellar) hemorrhage as diagnosed by CT or MRI scans. The diagnosis of subarachnoid hemorrhage required a typical clinical presentation, including the sudden onset of headache, with or without focal signs, and positive scan or lumbar puncture evidence of bleeding primarily in the subarachnoid space.

Patients

The main results of the CARE study have been reported previously.14 There were 4159 subjects (86% male, 14% female) with a mean age of 59±9 years recruited between December 4, 1989, and December 31, 1991, and randomized to the active (n=2081) or placebo (n=2078) arms of the trial. Randomization into CARE occurred at a mean of 10 months (range, 3 to 20 months) after index myocardial infarction in both groups. Baseline lipids were identical in the placebo and treatment arms, with total serum cholesterol of 209±17 mg/dL, VLDL cholesterol of 27±16 mg/dL, LDL cholesterol of 139±15 mg/dL, HDL cholesterol of 39±9 mg/dL, and...
triglycerides of 155±61 mg/dL. Risk factors for stroke were also similar at baseline. The prevalences of hypertension, diabetes mellitus, current smoking, congestive heart failure, and left ventricular ejection fractions were no different between placebo and treatment groups. In addition, at randomization, 83% of patients in both groups were currently taking aspirin on a regular basis, with an additional 2% taking another form of platelet inhibitor. Warfarin was used by 3.5% and 3.7% of placebo-treated and actively treated patients, respectively (P=NS). There was a history of prior stroke in 2.9% of placebo- and 3.0% of pravastatin-treated patients, with 4.8% and 5.3%, respectively, of subjects having experienced either stroke or TIA in the past (P=NS for both).

Statistical Analysis
All analyses were performed on an intention-to-treat basis, and P values were 2-sided. The effect of therapy on stroke and stroke/TIA and reductions in risk were assessed with a Cox proportional hazards model. Treatment effects were also analyzed as in the prespecified subgroups of the primary end point of this trial. A Cox proportional hazards model was used to assess the relation of lipid measurements to treatment effects.

Results
Effects on Lipids
As previously reported, compared with placebo controls, total serum cholesterol was reduced by 20% (42 mg/dL), LDL cholesterol was reduced by 32% (44 mg/dL), HDL cholesterol was raised by 5% (2 mg/dL), and triglycerides was reduced by 14% (22 mg/dL) in pravastatin-treated patients (P<0.001 for all effects).

Cerebrovascular Events
Based on the Endpoint Committee’s chart review, 14 of the original 132 investigator-reported strokes were reclassified as noncerebrovascular events, and 10 new cases were added, for a total of 128 adjudicated strokes. Of the initial 118 investigator-diagnosed TIAs, the committee rejected 16 cases and added 4, for a total of 106. Of these 106 TIAs, 18 occurred in patients who went on to manifest stroke. Thus, 88 cases of isolated TIAs were confirmed by committee review, for a total of 216 strokes or TIAs (see Appendix).

Over a median 5-year follow-up period (Figure 1), first incident stroke of any type occurred in 52 patients assigned to pravastatin and 76 placebo patients, representing a 32% reduction in relative risk (4% to 52%, P=0.03). Similarly, strokes or TIAs were experienced by 92 patients receiving pravastatin compared with 124 on placebo, for a relative risk reduction of 27% (4% to 44%, P=0.02), as portrayed in Figure 2. There was a treatment-associated reduction in all stroke categories (Table 1), although there was inadequate power to test for significance because of the limited number of outcome events in each class. A 21% (−20% to 48%, P=0.268) risk reduction for ischemic (atherosclerotic or tandem arterial pathology) strokes was observed. There was no increase in intracerebral hemorrhages on pravastatin, with 6 events occurring in placebo-treated patients compared with 2 on active therapy. Only 6 fatal strokes were documented, which included 5 patients on pravastatin versus 1 on placebo.

Effect of Baseline Characteristics
In univariate analysis, the variables of age >60 years; absence of a history of hypertension, diabetes, prior stroke, or TIA; and a left ventricular ejection fraction <40% were all associated with enhanced reduction of stroke or TIA with pravastatin (Table 2). However, when evaluated by stepwise regression, both stroke and stroke or TIA incidence were reduced independently of potential covariates, including age, sex, history of hypertension, current use of cigarettes, diabetes, left ventricular ejection fraction, history of stroke or TIA, and baseline lipid values.

To detect potential trends in the effect of baseline lipid values on treatment efficacy, subjects were dichotomized by median cutpoints (Tables 3 and 4). Pravastatin reduced both stroke and stroke or TIA incidence in patients with higher lipid levels, including total, LDL, and HDL cholesterol and triglycerides. There was no significant event reduction in patients with lower baseline levels. Further division of baseline LDL cholesterol into quintiles, as portrayed in Figure 3 (lowest quintile at <125 mg/dL, middle 3 quintiles

<table>
<thead>
<tr>
<th>TABLE 1. Stroke Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Atherosclerotic</td>
</tr>
<tr>
<td>Lacunar</td>
</tr>
<tr>
<td>Embolic</td>
</tr>
<tr>
<td>Tandem</td>
</tr>
<tr>
<td>Procedural</td>
</tr>
<tr>
<td>Undetermined</td>
</tr>
<tr>
<td>Other/ unusual</td>
</tr>
<tr>
<td>Intra-axial</td>
</tr>
<tr>
<td>Subarachnoid</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
at 125 to 150 mg/dL inclusive, upper quintile at \( >150 \) mg/dL), revealed a trend toward a greater reduction in stroke and stroke or TIA with increasing LDL cholesterol, which became more evident at levels \( >150 \) mg/dL. Above this cutpoint, patients on pravastatin exhibited a 44% reduction in stroke (\( 2 \) to 73, \( P = 0.05 \) NS) and a 54% reduction in stroke or TIA (17 to 74, \( P = 0.009 \)). However, a test for interaction between the treatment effect in the 3 LDL cholesterol groups was of only borderline significance (\( P = 0.07 \)).

**Discussion**

The weak epidemiological link between serum cholesterol and all-cause stroke\(^{16,18–20}\) has led to considerable doubt regarding the efficacy of lipid modification on the reduction of cerebrovascular events. Until recently, these concerns had been further fueled by the mixed results of interventional trials. Although Dayton and colleagues\(^{21}\) reported a trend toward reduced cerebral infarction in a population of middle-aged and elderly men assigned to a diet high in unsaturated fats, there was no impact on cerebrovascular outcome in the Lipid Research Clinics trial of \( >3800 \) patients randomized to cholestyramine or placebo.\(^{22}\) Secondary prevention trials have also provided variable results. Treatment with clofibrate in patients with previous cerebrovascular events has failed to reduce stroke, with some investigators actually observing an increase in recurrent cerebral infarction.\(^{23}\) In the Coronary Drug Project, clofibrate again failed to reduce stroke or TIA after myocardial infarction.\(^{24}\) In contrast, niacin had a beneficial effect on cerebrovascular outcome of borderline significance. Meta-analysis of the effect of cholesterol reduction with nonstatin agents on all-cause fatal and nonfatal stroke has also failed to demonstrate benefits.\(^{8}\)

The availability of better-tolerated and more powerful lipid-lowering agents in the form of statins has rekindled interest in the possible modification of atherothrombotic cerebrovascular disease outcome. This enthusiasm has been supported by ultrasonic evidence of plaque regression or prevention of plaque propagation associated with lovastatin or pravastatin treatment.\(^{25–28}\) Thus, application of statins to selected populations at increased risk for cerebrovascular events might result in enhanced therapeutic success compared with earlier modalities, and this possibility led to the inclusion of stroke as a prespecified end point in CARE.\(^{13}\)

### Treatment Effect and Relation to Underlying Stroke Risk

Patients who have experienced myocardial infarction are one of the populations at elevated risk for subsequent stroke.
Although a cardioembolic mechanism prevails in the early phase of recovery (<3 months), an increased risk of ischemic stroke has been documented in the postinfarction period, which is probably related to the association between coronary and cerebrovascular atherosclerosis. CARE patients, who were randomized at 3 to 20 months (mean, 10 months) after index myocardial infarction, therefore provided a population in whom a relatively high frequency of ischemic stroke would be expected and in whom pravastatin therapy might be efficacious. This presumption was, in fact, confirmed by the observed ischemic and nonhemorrhagic stroke rates of 1.9% and 3.4%, respectively, in placebo patients over the 5-year follow-up period despite concurrent use of platelet inhibitors by 85% of CARE participants. Although a treatment effect was observed in the CARE population, application of these results to broader populations at lower risk of stroke may be unwarranted, and recent meta-analyses enthusiastically endorsing the general application of statins for stroke reduction should be met with tempered enthusiasm at the present time. These reviews

### TABLE 3. Relationship of Baseline Serum Lipids to Stroke Reduction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>No. (%) of Patients With Stroke</th>
<th>% Risk Reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 2078)</td>
<td>Pravastatin (n = 2081)</td>
<td>Placebo</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥209</td>
<td>1040</td>
<td>1032</td>
<td>33 (3)</td>
<td>25 (2)</td>
</tr>
<tr>
<td>&gt;209</td>
<td>1038</td>
<td>1049</td>
<td>43 (4)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥137</td>
<td>1048</td>
<td>1042</td>
<td>40 (4)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>&gt;137</td>
<td>1030</td>
<td>1039</td>
<td>36 (4)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤37</td>
<td>1025</td>
<td>1033</td>
<td>28 (3)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>&gt;37</td>
<td>1053</td>
<td>1048</td>
<td>48 (5)</td>
<td>22 (2)</td>
</tr>
<tr>
<td>LDL:HDL ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.7</td>
<td>1043</td>
<td>1036</td>
<td>35 (3)</td>
<td>31 (3)</td>
</tr>
<tr>
<td>≥3.7</td>
<td>1035</td>
<td>1045</td>
<td>41 (4)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤144</td>
<td>1049</td>
<td>1031</td>
<td>32 (3)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>≥144</td>
<td>1029</td>
<td>1050</td>
<td>44 (4)</td>
<td>25 (2)</td>
</tr>
</tbody>
</table>

### TABLE 4. Relationship of Baseline Serum Lipids to Stroke or TIA Reduction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>No. (%) of Patients With Stroke</th>
<th>% Risk Reduction (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 2078)</td>
<td>Pravastatin (n = 2081)</td>
<td>Placebo</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥209</td>
<td>1040</td>
<td>1032</td>
<td>55 (5)</td>
<td>46 (5)</td>
</tr>
<tr>
<td>&gt;209</td>
<td>1038</td>
<td>1049</td>
<td>69 (7)</td>
<td>46 (4)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥137</td>
<td>1048</td>
<td>1042</td>
<td>64 (6)</td>
<td>54 (5)</td>
</tr>
<tr>
<td>&gt;137</td>
<td>1030</td>
<td>1039</td>
<td>60 (6)</td>
<td>38 (4)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤37</td>
<td>1025</td>
<td>1033</td>
<td>58 (6)</td>
<td>50 (5)</td>
</tr>
<tr>
<td>&gt;37</td>
<td>1053</td>
<td>1048</td>
<td>66 (6)</td>
<td>42 (4)</td>
</tr>
<tr>
<td>LDL:HDL ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.7</td>
<td>1043</td>
<td>1036</td>
<td>56 (5)</td>
<td>41 (4)</td>
</tr>
<tr>
<td>≥3.7</td>
<td>1035</td>
<td>1045</td>
<td>68 (7)</td>
<td>51 (5)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤144</td>
<td>1049</td>
<td>1031</td>
<td>48 (5)</td>
<td>46 (4)</td>
</tr>
<tr>
<td>≥144</td>
<td>1029</td>
<td>1050</td>
<td>76 (7)</td>
<td>46 (4)</td>
</tr>
</tbody>
</table>
were largely powered by the results of CARE and the Scandinavian Simvastatin Survival Study (4S), trials involving patients with overt cardiovascular disease, and the role of statins in primary stroke prevention has not as yet been established. In fact, when primary and secondary prevention statin trials have been analytically segregated, a nonsignificant, 15% to 20% reduction in stroke events has been observed in the former studies, compared with a 31% to 32% reduction in the latter.\textsuperscript{33,34} The nonsignificant 11% stroke reduction observed in the West of Scotland Coronary Prevention Study (WOSCOPS), an investigation of the effects of pravastatin on cardiovascular outcome in patients with moderate hypercholesterolemia without prior myocardial infarction, would also seem to underscore this uncertainty.\textsuperscript{37}

The ability of pravastatin to lower stroke incidence, a prespecified study end point in CARE, although substantial, was not strongly statistically significant, with values of $P=0.03$ and $P=0.02$ for stroke and stroke or TIA reduction, respectively. However, the CARE findings are consistent with and supported by those previously reported in 4S. In a post hoc analysis of the latter, 30% and 31% reductions in stroke and TIA, respectively, were initially reported in patients treated with simvastatin after myocardial infarction or angina pectoris,\textsuperscript{11,18} although subsequent reanalysis of the data indicated a slightly more modest 28% reduction in fatal and nonfatal cerebrovascular events.\textsuperscript{12} In any event, both CARE and 4S suggest a significant benefit of pravastatin and simvastatin in stroke reduction when selected coronary artery disease populations are targeted. The improvement in cerebrovascular outcome with pravastatin in CARE was particularly notable, because this was observed despite the high background use of platelet inhibitors, which have known cerebrovascular protective effects.

**Mechanisms of Stroke Reduction**

Pravastatin therapy in CARE resulted in a 21% decrease in ischemic stroke events, an effect that did not reach statistical significance, probably because of the inadequate number of outcome events in this category. However, the considerably greater 32% reduction in all-cause stroke suggests that other mechanisms affecting both atherosclerotic and nonatherosclerotic processes could have been operative. Statins have previously demonstrated a variety of properties that might potentially alter the course of cerebrovascular disease.\textsuperscript{39,40}

Their beneficial effects on vascular physiology have been documented in laboratory studies and include plaque stabilization, suppression of inflammation, improvement in endothelial function, and platelet antiaggregant activity. It has even been suggested that statins may reduce lacunar infarction, a condition generally believed to be of hypertensive pathogenesis.\textsuperscript{39} In addition, statins, by limiting recurrent myocardial infarction, may also prevent deterioration of ventricular systolic function, an important mechanism of cardioembolic stroke.\textsuperscript{15} Although pravastatin therapy was associated with a reduction in all categories of incident stroke in CARE, the study was inadequately powered to confirm the possibility of a multimodal pharmacological effect. Future secondary prevention trials involving larger cohorts of well-categorized stroke patients may be more definitive in this regard.

**Comparison of Cerebrovascular and Coronary Outcomes**

The effects of pravastatin on stroke and coronary event reduction in CARE appear to be consistent in a number of ways. First, the 32% reduction in stroke incidence is comparable to the 24% improvement in the primary end point of the study: coronary disease mortality or nonfatal myocardial infarction.\textsuperscript{14} Also, the divergence of the treatment arms, as assessed qualitatively, was delayed for both coronary and stroke events, although to different degrees. The effect of pravastatin on stroke and stroke or TIA reduction (Figures 1 and 2) became appreciable at $\approx 3.5$ years into the study, in contrast to an earlier separation (at $\approx 1$ to 2 years) of the coronary event curves.\textsuperscript{14} Interestingly, a similar delay in stroke treatment effect was observed in 4S.\textsuperscript{12}

Another parallel between cerebrovascular and coronary outcomes in CARE involved the possible predictive value of baseline LDL cholesterol on treatment effect. LDL cholesterol levels in the lowest quintile (<125 mg/dL) of patients assigned to pravastatin were associated with a nonsignificant 3% increase in combined fatal coronary events, nonfatal myocardial infarction, and revascularization procedures ($P=0.85$).\textsuperscript{14} Likewise, a nonsignificant 14% reduction in stroke or TIA incidence ($P=0.631$) was noted at these lipid levels. In contrast, baseline LDL cholesterol levels in the upper quintile (>150 mg/dL) were associated with risk reductions of 35% ($P=0.008$) for the same clustered coronary outcomes and 54% for stroke or TIA ($P=0.0009$), as depicted in Figure 3. Thus, baseline LDL cholesterol may be an important predictor of the efficacy of pravastatin in reducing vascular events, including myocardial infarction and stroke. However, because the test for interaction of baseline cholesterol groups did not quite reach statistical significance ($P=0.07$), these results are at best only hypothesis-generating and will require confirmation in larger, prospective trials.

The univariate analyses of the relationship of baseline lipoproteins to treatment effect displayed in Tables 3 and 4 are also of interest. When cutoffs at the mean baseline lipid levels were examined, it appeared that patients with elevated total, LDL, as well as HDL cholesterol derived greater cerebrovascular benefit with pravastatin therapy. Although the enhanced treatment effect found in patients with elevated

![Figure 3. Effect of baseline LDL cholesterol on stroke incidence (top) and stroke or TIA incidence (bottom).](http://circ.ahajournals.org/lookup/fig/10.1161/01.CIR.89.1.211-221)

- LDL-C mg/dL
- Stroke
  - <125
  - 125 - 150
  - 151 - 175
- Stroke/TIA
  - <125
  - 125 - 150
  - 151 - 175
- Risk Reduction (%)
- Benefit
- P Value
total and LDL cholesterol seems logical, it is difficult to hypothesize an explanation for the similar effect noted with elevated HDL cholesterol, and this finding will also need to be reevaluated in future studies.

Safety
The therapeutic benefits of pravastatin in CARE were accompanied by an excellent safety profile. The CARE study was specifically targeted at a population with only average serum cholesterol levels at baseline. Because of previous concerns that hemorrhagic stroke might be increased in patients with low cholesterol levels (the J-shaped curve),1,4,41 lipid modification in populations, like those in CARE, with average lipid values was considered potentially hazardous. Nevertheless, despite reductions of 20% and 32% in total and LDL serum cholesterol, respectively, the hemorrhagic stroke rate was no greater in pravastatin-treated patients (n = 2) than in those assigned to placebo (n = 6). These results are particularly reassuring, considering that the mean cholesterol level of 167 mg/dL achieved by CARE patients on active therapy was close to the 160-mg/dL level, below which an increase in hemorrhagic stroke was observed in MR3F1,42 Conversely, the potential increase in fatal strokes previously associated with clofibrate therapy8 could not be adequately tested in CARE because of the rarity of this outcome (1 on placebo and 5 on active treatment). Although a small trend in this direction has also been observed in WOSCOPS,52 the numbers were similarly small and nonsignificant. Furthermore, previous meta-analysis has also failed to detect an increase in fatal stroke rate related to statin therapy.36

The results of CARE establish the value of lipid modification with pravastatin in reducing stroke or TIA in patients with average LDL cholesterol and a history of myocardial infarction. These data are provocative and suggest that investigation of statin efficacy in other populations at increased risk for cerebrovascular events (eg, patients with stroke or peripheral vascular disease) may also be fruitful.

Appendix
The data presented here vary slightly from those submitted to the United States Food and Drug Administration. The Endpoints Committee concluded that a fatal intracerebral hemorrhage, originally submitted as a stroke, was due to a massive overdose of warfarin, and the cause of death was therefore primarily nonneurological. This adjudication was made after the data had been locked for FDA submission. Therefore, the present data include 216 of the original 217 patients submitted to the FDA, excluding this single pravastatin-assigned patient. In the FDA submission, risk reductions of 26% (3 to 43) for stroke and 31% (2 to 51) for stroke or TIA were reported, in contrast to the 27% and 32% reductions, respectively, described here.

Acknowledgments
The CARE study was supported by an investigator-initiated grant from the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ. The authors are indebted to Alexander Reeves, MD, section of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, who provided neurological consultation in the development of this investigation.

References
10. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dL) plus two additional athero-sclerotic risk factors. Am J Cardiol. 1993;72:1031–1037.


Reduction of Stroke Incidence After Myocardial Infarction With Pravastatin: The Cholesterol and Recurrent Events (CARE) Study
for the CARE Investigators

_Circulation._ 1999;99:216-223
doi: 10.1161/01.CIR.99.2.216

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/99/2/216

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/