Effects of High-Dose Atorvastatin on Cerebrovascular Events in Patients With Stable Coronary Disease in the TNT (Treating to New Targets) Study

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OBJECTIVE

We sought to assess the effects on cerebrovascular events of treating patients with stable coronary disease with low-density lipoprotein cholesterol (LDL-C) levels substantially below 100 mg/dl.

BACKGROUND

Lowering LDL-C with statins has been shown to reduce the risk of stroke in patients with stable coronary disease. In observational studies, naturally low cholesterol levels have been associated with an increased risk of hemorrhagic stroke. The cerebrovascular benefits of treating patients with stable coronary disease to LDL-C levels substantially below 100 mg/dl have not been previously investigated.

METHODS

We describe an analysis of cerebrovascular events in the Treating to New Targets study, a trial where 10,001 patients with documented coronary disease were randomized to treatment with atorvastatin at 10 mg/day or 80 mg/day and followed for a median of 4.9 years.

RESULTS

Mean LDL-C levels were 101 mg/dl on 10 mg atorvastatin and 77 mg/dl on 80 mg. In addition to the reduction in major cardiovascular events (hazard ratio 0.77, 95% confidence interval [CI] 0.69 to 0.89; p = 0.0002), the primary end point of the trial, patients in the 80-mg arm experienced a reduction in cerebrovascular events (hazard ratio 0.77, 95% CI 0.64 to 0.93; p = 0.007) and stroke (hazard ratio 0.75, 95% CI 0.59 to 0.96; p = 0.02). Each 1-mg/dl reduction in LDL-C with treatment was associated with a 0.6% relative risk reduction in cerebrovascular events (p = 0.002) and a 0.5% relative risk reduction in stroke (p = 0.041). The incidence of hemorrhagic stroke was similar in the 80-mg and 10-mg groups, 16 and 18 respectively, and the hemorrhagic strokes were distributed evenly across quintiles of achieved LDL-C during treatment.

CONCLUSIONS

Among patients with established coronary disease, treating to an LDL-cholesterol substantially below 100 mg/dl with 80 mg/day atorvastatin reduces both stroke and cerebrovascular events by an additional 20% to 25% compared with the 10 mg/day dose. An increase in hemorrhagic stroke was not seen at low LDL-C levels. (Treating to New Targets; http://www.clinicaltrials.gov; NCT00327691). (J Am Coll Cardiol 2006;48:1793–9) © 2006 by the American College of Cardiology Foundation

The incidence of cerebrovascular events in Western countries appears to be at least as high as the incidence of coronary events (1). Furthermore, the long-term outcome after even a minor ischemic stroke or transient ischemic attack (TIA) is bleak; for example, in a recent report of a large cohort study from the Netherlands, 60% of patients died and 54% had had at least one other vascular event over a mean follow-up period of 10 years (2).

The relationship between blood cholesterol levels and stroke is not as clear as the relationship between cholesterol and coronary events; in fact, in a meta-analysis of 45 prospective observational studies involving 450,000 individuals, no association was found between cholesterol and stroke rate (3).

Differences emerge when strokes are classified as to type. An increased rate of hemorrhagic stroke has been reported in subjects with naturally low cholesterol levels (4–7), but the incidence of ischemic stroke is increased at higher cholesterol levels in the same populations (7,8).

Although earlier clinical trials did not show a reduction in stroke with cholesterol lowering (9), statins have reduced stroke or
cerebrovascular events in randomized placebo-controlled trials in a variety of different patient populations (10–16). Whether statins reduce stroke by LDL-C reduction or primarily through other mechanisms is controversial (17–19).

The TNT (Treating to New Targets) study randomized 10,001 patients with documented coronary disease to atorvastatin at 10 mg/day or 80 mg/day and followed them for a median of 4.9 years (20). The primary end point of TNT, a composite of coronary death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, and fatal or nonfatal stroke, was reduced in the 80-mg compared with the 10-mg arm (hazard ratio 0.78, 95% confidence interval [CI] 0.69 to 0.89; p = 0.0002). In addition to fatal or nonfatal stroke being a component of the predefined primary end point of the trial, a cerebrovascular event, defined as fatal or nonfatal stroke or TIA, was a predefined secondary end point. Herein we report in detail the results of TNT with respect to stroke and cerebrovascular events.

METHODS

The design of the TNT study has been previously described in detail (20,21). Eligible patients were men and women 35 to 75 years of age who had clinical evidence of coronary disease, either previous MI or coronary revascularization, or previous or current angina with objective evidence of coronary disease. Patients with LDL-C levels between 130 and 250 mg/dl and triglycerides \( \leq 600 \text{ mg/dl} \) off lipid-lowering treatment were eligible to enter an 8-week run-in period where they received 10 mg/day atorvastatin. Those with an LDL-C level <130 mg/dl were randomly assigned to double-blind therapy with either 10 mg or 80 mg atorvastatin per day. Follow-up visits occurred at week 12 and at months 6, 9, and 12, then every 6 months thereafter. Patients were questioned at each visit about interim events or hospitalizations, and hospital records were obtained.

**Study end points.** The primary predefined outcome was the occurrence of a major cardiovascular event, defined as death from coronary heart disease, nonfatal nonprocedure-related MI, resuscitated cardiac arrest, or fatal or nonfatal stroke. Secondary outcomes were a major coronary event (the primary end point without stroke), a cerebrovascular event, hospitalization for congestive heart failure, peripheral artery disease, death from any cause, any cardiovascular event, and any coronary event.

An independent end points committee consisting of 5 cardiologists adjudicated all potential end points in a blinded fashion. They defined stroke as the rapid onset of a persistent brain deficit thought to be due to obstruction or rupture in the arterial system and not secondary to brain trauma, tumor, or infection. The deficit must have lasted longer than 24 h unless death intervened or unless there was a persistently demonstrable lesion that was consistent with the deficit. Patients admitted with symptoms of developing stroke who were given tissue plasminogen activator (TPA) with subsequent resolution of symptoms were also classified as stroke. Strokes occurring during surgery were also included.

Stroke were categorized as ischemic, hemorrhagic, embolic, or unknown, using the criteria developed for the Systolic Hypertension in the Elderly Program (22). Strokes were classified as ischemic when one of the following criteria was met: 1) a focal brain deficit without evidence by computerized tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture of blood, with the exception of a mottled cerebral pattern, either decreased density by CT in a compatible location, or a negative CT or MRI, or none done; 2) surgical or autopsy evidence of ischemic infarction; 3) symptoms of stroke followed by TPA with resolution of symptoms; or 4) symptoms lasting <24 h but with a CT or MRI showing an infarct or hemorrhage in a location to explain the findings.

Strokes were classified as hemorrhagic when there was: 1) blood in the subarachnoid space or intraparenchymal hemorrhage by CT or MRI scan; 2) bloody spinal fluid by lumbar puncture; or 3) surgical or autopsy evidence of hemorrhage as the cause of the clinical syndrome. Strokes were classified as embolic when that was the likely diagnosis (e.g., in the presence of atrial fibrillation). Strokes were classified as unknown when the available data were insufficient for classification into one of the other categories. A TIA was defined as an event that persisted for <24 h with a documented focal neurologic deficit; the symptoms had to be typical, such as transient unilateral blindness, a speech deficit, or transient hemiparesis.

**Statistical analyses.** Cholesterol inclusion/exclusion criteria were selected to achieve an average level of 100 mg/dl in the 10 mg/day atorvastatin arm. To reach an average LDL-C level in the comparator group of approximately 75 mg/dl, 80 mg/day atorvastatin was chosen. All analyses were performed on an intention-to-treat basis. End points were analyzed from the time of the first dose of study drug to the first event according to the Kaplan-Meier method. Differences between the 80-mg and 10-mg treatment groups were based on log rank analyses of the first occurrence of an end point during the 4.9-year follow-up period in each group. Relative risks, hazard ratios, and their 95% CIs were calculated in univariate and multivariate models using the Cox regression with one or more predictors in the same model. Note that Cox regression models allow for the predictor to be continuous variables (like on-treatment LDL-C) or dichotomous. Proportions were compared using the Fisher exact test.

RESULTS

**Patient population.** A total of 18,469 patients were screened at 256 sites in 14 countries; of these, 15,464 patients entered
the open-label run-in period and 10,001 were randomized to double-blind treatment with either 10 or 80 mg/day atorvastatin, as previously described (20,21). Of the 8,468 patients who did not enter the randomized phase of the study, 7,639 had exclusion criteria, including 96 with elevated hepatic enzymes >1.5 times the upper limit of normal while taking 10 mg/day atorvastatin and 727 with LDL-C levels >130 mg/dl or triglycerides >600 mg/dl. Among the other 827 patients who were screened but not randomized, 16 died and 195 had ischemic events during the run-in period; 197 had other adverse events, including myalgia in 35. The remaining 419 patients either did not comply with treatment or were eliminated for a variety of administrative reasons. Two patients who were randomized but never given drug were also excluded.

Patients were followed for a median of 4.9 years after randomization, during which time 38 patients in the 10-mg group and 130 mg/dl in the 80-mg arm. Mean triglyceride levels were 156 mg/dl in the 10-mg arm and 132 mg/dl in the 80-mg arm.

At baseline, mean systolic and diastolic blood pressures were identical in the 2 treatment groups: systolic 131 ± 17 mm Hg and diastolic 78 ± 10 mm Hg. At last follow-up, systolic blood pressure had decreased by 1.2 ± 15.4 mm Hg in the 10-mg arm and by 1.2 ± 15.1 mm Hg in the 80-mg arm; diastolic pressure decreases were 0.7 ± 9.3 mm Hg in both groups. Blood pressures were very similar in the 2 treatment groups throughout the study.

**Cerebrovascular events.** During the follow-up period, 272 patients (2.7%) experienced a stroke, including 30 who experienced a fatal stroke. A TIA occurred in 197 patients, and a total of 448 (4.5%) experienced a cerebrovascular event (stroke or TIA). As shown in Table 2, stroke was reduced in the 80-mg compared with the 10-mg group (hazard ratio 0.75, 95% CI 0.59 to 0.86; p = 0.021). Cerebrovascular events were also reduced in the 80-mg arm (hazard ratio 0.77, 95% CI 0.64 to 0.93; p = 0.007). The Kaplan-Meier curves for these end points are depicted in Figure 1. Among patients without a history of cerebrovascular disease (who comprised 95% of the study population), fewer strokes occurred in the 80-mg compared with the 10-mg group: 101 versus 128 (2.1% vs. 2.8%)

### Table 1. Baseline Features of the Study Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Atorvastatin 10 mg/day (n = 5,006)</th>
<th>Atorvastatin 80 mg/day (n = 4,995)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>4,321 (86.3%)</td>
<td>4,332 (86.7%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,675 (53.4%)</td>
<td>2,702 (54.1%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1,362 (27.2%)</td>
<td>1,352 (27.1%)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>275 (5.5%)</td>
<td>252 (5.0%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>742 (14.8%)</td>
<td>695 (13.9%)</td>
</tr>
<tr>
<td>Lipid levels (mg/dl)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>175 ± 24</td>
<td>175 ± 25</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>98 ± 18</td>
<td>97 ± 18</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>47 ± 11</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>151 ± 72</td>
<td>151 ± 70</td>
</tr>
</tbody>
</table>

*Lipid levels at baseline at the end of the run-in period with patients receiving atorvastatin 10 mg/day.*

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention.
Myalgia was reported in 241 patients in the 80-mg arm and in 234 patients in the 10-mg arm (4.8% vs. 4.7%; p = 0.72). Consecutive ALT and/or AST elevations >3 times the upper limit of normal were seen in 60 patients in the 80-mg arm and in 9 patients in the 10-mg arm (1.2% vs. 0.2%; p < 0.001). No patient experienced consecutive creatine kinase elevations >10 times the upper limit of normal.

**DISCUSSION**

This study provides evidence that reducing LDL-C levels with 80 mg/day atorvastatin to levels well below 100 mg/dl in patients with stable coronary disease reduces the incidence of stroke and all cerebrovascular events. The relative risk reductions in cerebrovascular events and coronary events are similar. An increase in the incidence of hemorrhagic stroke was not seen either at the high dose of atorvastatin or at the lowest achieved LDL-C levels during treatment.

**Previous studies.** Randomized, placebo-controlled statin trials have shown a reduction in cerebrovascular events as well as coronary events in patients with stable coronary disease (10–12) as well as in patients with unstable coronary disease (13), hypertension (14), high coronary risk (15), and diabetes (16). The Cholesterol Treatment Trial collaborators have recently reported a prospective meta-analysis of 90,056 patients from 14 randomized statin trials (23). Overall, fatal or nonfatal stroke was reduced by 17% (95% CI 12% to 22%). There was a trend toward greater proportional reductions in stroke with greater LDL-C reduction (p = 0.009).

The TNT study differs from previous statin trials because 2 doses of the same statin were compared and because a lower LDL-C level, a mean of 77 mg/dl, was maintained over a median of 4.9 years in the 80-mg atorvastatin arm. The TNT study demonstrates that additional benefit for stroke and other important vascular end points can be achieved with the highest dose of...
a potent statin, reducing LDL-C well below the traditional target of 100 mg/dl.

The TNT study does not address the issue of whether statin therapy reduces the risk of cerebrovascular events in patients with previous cerebrovascular events but without known coronary disease. The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, comparing placebo to 80 mg/day atorvastatin in 4,731 patients with a previous stroke or TIA, recently demonstrated that the high dose of atorvastatin significantly reduced both stroke and coronary events in this population (24).

**Mechanism of benefit.** The reductions in stroke and cerebrovascular events in the 80-mg arm were not due to a reduction in blood pressure, because both systolic and diastolic pressures were identical in the treatment arms throughout the study. However, each 1-mg/dl change in on-treatment LDL-C was associated with a 0.6% change in the risk of a cerebrovascular event (p = 0.002) and a 0.5% change in the risk of stroke (p = 0.041). Expressed in terms of treatment groups, LDL-C was 24% lower in the 80-mg arm, stroke was 25% lower, and cerebrovascular events were 23% lower. The relationship of LDL-C changes to stroke is similar to what has been reported in meta-analyses of placebo-controlled statin trials (23).

Cholesterol lowering with statins has been shown to stabilize carotid artery plaques in patients undergoing ca-

**Figure 1.** Kaplan-Meier curves for stroke (A) and cerebrovascular events (B).
rotid endarterectomy (25) and to slow the progression of carotid atherosclerosis as assessed by B-mode ultrasound (26). Most ischemic strokes are caused by thromboemboli from the carotid arteries or the aortic arch. Statins may interfere with the thrombotic component of ischemic stroke by inducing beneficial effects on the coagulation cascade (27) and by correcting the increased thrombogenic potential of platelets that is associated with hyperlipidemia (28).

Statins also induce an impressive variety of beneficial effects that are independent of cholesterol lowering. A limitation of many studies in this area is the difficulty in distinguishing between causation and just a statistical correlation. In the cerebral endothelium and parenchyma, statins regulate nitric oxide synthase to reduce platelet and leukocyte adhesion and activation, increase vasodilation and reduce postischemic permeability (18). Statins also exert antiinflammatory and antioxidant effects that are neuroprotective in cerebral ischemia and stroke (18). In different rodent models statins have been shown to reduce the severity of stroke through these mechanisms (18).

**Low cholesterol and hemorrhagic stroke.** Naturally low blood cholesterol levels have been associated with an increased risk of hemorrhagic stroke in different geographic populations (4–7). In the Multiple Risk Factor Intervention Trial, a study of 350,977 middle-aged men with no history of MI or diabetes at baseline, death from intracranial hemorrhage was 3-fold higher in those middle-aged men with no history of MI or diabetes at baseline (7). Most ischemic strokes are caused by thromboemboli from the carotid arteries or the aortic arch. Statins may interfere with the thrombotic component of ischemic stroke by inducing beneficial effects on the coagulation cascade (27) and by correcting the increased thrombogenic potential of platelets that is associated with hyperlipidemia (28).

The criteria used to define stroke and the categories of stroke selected by the end points committee differ from the generally accepted criteria, and the end points committee did not include a neurologist. The findings of this study apply to patients with stable coronary disease. The study population was overwhelmingly Caucasian, and <20% were women. Extrapolation of these results to other populations should be done with caution. Although the incidence of hemorrhagic stroke was not increased at lower LDL-C levels, the number of these events is not sufficient to detect a small increase in risk.

Despite these limitations, the results of TNT demonstrate that lowering LDL-C considerably below 100 mg/dl using 80 mg/day atorvastatin provides additional clinical benefit, including a reduction in stroke and cerebrovascular events. The reduction in cerebrovascular events and overall stroke, without an observed low-cholesterol high-risk group. An increased risk of hemorrhagic stroke was not seen, however, either in the 80-mg arm or in the lowest quintile of on-treatment LDL-C (<64 mg/dl).

The relative risk of hemorrhagic stroke for statin–treated versus placebo patients in the Cholesterol Treatment Trialists Collaborators meta-analysis is 1.05 (95% CI 0.78 to 1.41) (23). In the SPARCL study (24), high-dose atorvastatin reduced stroke overall; however, hemorrhagic stroke, albeit uncommon, occurred more frequently in the atorvastatin group (p = 0.02). Taken together, these data suggest that it is unlikely that high-dose statins increase the risk of hemorrhagic stroke in most subsets of patients. Whether some patients with previous stroke are at increased risk for hemorrhagic stroke with statin therapy requires further study.

**Study limitations.** The criteria used to define stroke and the categories of stroke selected by the end points committee differ from the generally accepted criteria, and the end points committee did not include a neurologist. The findings of this study apply to patients with stable coronary disease. The study population was overwhelmingly Caucasian, and <20% were women. Extrapolation of these results to other populations should be done with caution. Although the incidence of hemorrhagic stroke was not increased at lower LDL-C levels, the number of these events is not sufficient to detect a small increase in risk.

Table 3. Types of Stroke in Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin 10 mg/day (n = 5,006)</th>
<th>Atorvastatin 80 mg/day (n = 4,995)</th>
<th>Total Patients (n = 10,001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>155 (3.1%)</td>
<td>117 (2.3%)</td>
<td>272 (2.7%)</td>
</tr>
<tr>
<td>Embolic</td>
<td>44 (0.9%)</td>
<td>29 (0.6%)</td>
<td>73 (0.7%)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>90 (1.8%)</td>
<td>68 (1.4%)</td>
<td>158 (1.6%)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>18 (0.4%)</td>
<td>16 (0.3%)</td>
<td>34 (0.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (0.3%)</td>
<td>11 (0.2%)</td>
<td>26 (0.3%)</td>
</tr>
</tbody>
</table>

Values expressed as number of patients (%).

Table 4. Factors Predictive of Cerebrovascular Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (%)</th>
<th>HR (95% CI), Univariate</th>
<th>p Value</th>
<th>HR (95% CI), Multivariate*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td>517 (5.2)</td>
<td>3.38 (2.60–4.40)</td>
<td>&lt;0.0001</td>
<td>2.60 (1.99–3.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,501 (15)</td>
<td>2.35 (1.91–2.88)</td>
<td>&lt;0.0001</td>
<td>1.94 (1.57–2.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5,412 (54)</td>
<td>1.94 (1.59–2.37)</td>
<td>&lt;0.0001</td>
<td>1.63 (1.32–2.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age older than 65 yrs</td>
<td>3,809 (38)</td>
<td>1.92 (1.59–2.31)</td>
<td>&lt;0.0001</td>
<td>1.70 (1.40–2.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>781 (7.8)</td>
<td>1.72 (1.30–2.29)</td>
<td>0.0002</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDL-C at 3 months†</td>
<td>9,769 (98)</td>
<td>1.006 (1.002–1.01)</td>
<td>0.002</td>
<td>1.006 (1.002–1.01)</td>
<td>0.0014</td>
</tr>
<tr>
<td>LDL-C change‡</td>
<td>9,762 (98)</td>
<td>0.997 (0.993–1.000)</td>
<td>0.043</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1,902 (19)</td>
<td>1.23 (0.98–1.53)</td>
<td>0.07</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Revascularization</td>
<td>4,654 (47)</td>
<td>1.22 (0.92–1.62)</td>
<td>0.18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDL-C at screening‡</td>
<td>9,994 (100)</td>
<td>1.003 (0.998–1.008)</td>
<td>0.25</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDL-C at end of run-in‡</td>
<td>9,993 (100)</td>
<td>1.001 (0.999–1.005)</td>
<td>0.43</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Never smoked</td>
<td>2,338 (23)</td>
<td>1.09 (0.88–1.35)</td>
<td>0.44</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5,833 (58)</td>
<td>1.05 (0.87–1.26)</td>
<td>0.63</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*First all predictors were used in the multivariate model; predictors with p > 0.1 were then removed. † Hazard ratio calculated for each 1 mg/dl difference in LDL-C. ‡Change in LDL-C from screening (off medication) to 3 months of treatment on study drug.

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.
increase in hemorrhagic stroke, provides an additional reason to treat coronary patients more aggressively.

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