High-Dose Statins in Acute Coronary Syndromes Not Just Lipid Levels

Steven E. Nissen, MD

For more than a decade, statin drugs have accumulated a remarkable record of successful clinical trials, demonstrating robust evidence for reduction in clinical events, including myocardial infarction, stroke, and cardiovascular death in primary and secondary prevention populations.1-4 Recent trials have shown that intensive statin therapy is superior to moderate therapy for reducing morbidity following an acute coronary syndrome (ACS) event5,6 and for slowing the progression of coronary atherosclerosis.7 Statin trials have also demonstrated a favorable safety profile with only rare and isolated cases of serious toxicity.8 Given the spectacular success of this class of drugs, the failure of a statin clinical trial to meet its predefined objective and evidence of an adverse safety profile are unusual and mandate careful analysis of potential responsible factors.

Phase Z of the A to Z trial,8 published in this issue of JAMA, is to date the largest trial testing the effects of aggressive statin therapy in ACS. The investigators randomized approximately 4500 patients following an ACS event to receive either high-dose simvastatin (40 mg/d for 1 month and then 80 mg/d thereafter) or to a regimen of placebo for 4 months and then a 20-mg/d dose of simvastatin thereafter. The high-dose regimen failed to show a statistically significant benefit for reducing the primary composite end point of cardiovascular death, myocardial infarction, readmission for ACS, or stroke (absolute risk reduction, 2.3%; hazard ratio, 0.89 [95% confidence interval, 0.76-1.04] \(P=0.14\)). In addition, the high-dose simvastatin regimen was associated with an unusually high rate of myopathy. Ten patients (9 in the high-dose treatment group) experienced elevated creatine kinase levels greater than 10 times the upper limit of normal with accompanying muscle symptoms and 3 patients developed frank rhabdomyolysis (creatine kinase levels >10,000 units/L). Because 32 clinical events were avoided, approximately 1 adverse myopathic event occurred for every 3 patients protected.

Both the lack of efficacy and the unfavorable adverse event profile would seem improbable to those familiar with the statin clinical trial literature. Two other trials in ACS patients showed safety and efficacy (TABLE). The Myocardial Infarction Reduction with Aggressive Cholesterol Lowering (MIRACL) trial compared 80 mg/d of atorvastatin with placebo for 4 months in 3086 patients and showed a 16% reduction in events.9 The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE IT) compared outcomes of 4162 patients receiving 80 mg/d of atorvastatin or 40 mg/d of pravastatin and also showed a significant 16% event reduction.9 Both studies demonstrated a rapid onset of clinical benefit. In MIRACL, the study duration was only 4 months, whereas in PROVE IT the event curves separated within the first 30 days, reaching statistical significance by 6 months. In contrast, post hoc analysis of the A to Z trial showed no effect during the first 4 months (hazard ratio, 1.01), but there did appear to be some later benefit from aggressive treatment.

Explaining the lack of efficacy for high-dose simvastatin in the A to Z trial is difficult. The authors emphasize that fewer events occurred than anticipated by power calculations. While correct, this observation only partially explains the lack of statistical efficacy. Consider the following comparison between the A to Z trial and the MIRACL trial. Both studies showed large low-density lipoprotein (LDL) cholesterol differences between the group receiving active treatment and the group receiving placebo during the first 4 months (62 mg/dL [1.61 mmol/L] in the A to Z trial and 63 mg/dL [1.63 mmol/L] in the MIRACL trial). Despite nearly identical lipid level effects, the A to Z trial showed no risk reduction during the first 4 months, whereas MIRACL showed a 16% reduction in similar end points (Table).

How can identical lipid level lowering with 2 drugs yield such different outcomes? The authors propose that improved concomitant therapies “competed” for risk reduction in the A to Z trial, thereby reducing drug efficacy. However, PROVE IT used similar contemporary therapies and

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showed a 16% reduction in events, which was evident by 30 days and was virtually constant for the trial duration. Even more surprisingly, PROVE IT achieved statistical significance while comparing intensive statin therapy with moderate statin therapy, not placebo, achieving only 33 mg/dL (0.85 mmol/L) greater LDL cholesterol reduction in the intensive treatment group (Table).

Taken together, MIRACL, PROVE IT, and A to Z demonstrate that the beneficial effects of statin therapy in ACS cannot be predicted entirely from the degree of LDL cholesterol reduction. What other explanations are possible? All statins exhibit a variety of anti-inflammatory and anti-proliferative effects commonly described as “pleiotropic” effects.10-13 The most widely examined inflammatory biomarker—high sensitivity C-reactive protein—is commonly measured in statin clinical trials. In the 2 successful ACS trials (MIRACL and PROVE IT), the difference in C-reactive protein between treatment subgroups was 34% and 38%, respectively, at trial completion. In the A to Z trial, the between-group reduction was much smaller (16.7%; Table). This finding suggests an intriguing hypothesis, specifically, that the early benefits of statin therapy are derived largely from the anti-inflammatory effects of the drugs, whereas the delayed benefits are lipid-modulated.

These findings emphasize a critical principal of appropriate, evidence-based interpretation of clinical trials. It is hazardous to assume that similar agents always yield identical results. While a class effect for statins is likely, each agent requires careful testing in clinical trials to establish the extent of benefit and risk. These observations are even more important when applied to nonstatin LDL–cholesterol-lowering therapies. Because these agents, such as ezetimibe, have not demonstrated anti-inflammatory effects in the absence of concomitant statin administration,14 their value in reducing events cannot be assumed and must be tested in well-designed clinical outcome trials.

The myopathy rate in the A to Z trial, while low, is higher than observed in most other clinical statin trials. In trials using submaximal doses of pravastatin, lovastatin, fluvastatin, or simvastatin, myopathy has occurred rarely.8 Six studies treated patients with the highest dose of atorvastatin (80 mg/d), randomizing more than 10,000 patients, with no reported cases of myopathy (defined as 10 times the upper limit of normal creatine kinase levels with muscle symptoms) or frank rhabdomyolysis.5-7,15-17 The myopathy rate of 0.4% observed in the A to Z trial occurred despite patient selection criteria that sought to specifically exclude patients at greater risk.5 However, this rate is consistent with the reported 0.6% myopathy rate reported in a meta-analysis of the efficacy and safety of the 80-mg/d dose of simvastatin.18

The myopathy rate of the 80-mg/d dose of simvastatin observed in the A to Z trial and the previously reported meta-analysis are not particularly surprising. For many years following its introduction, the maximum dose of simvastatin approved by the Food and Drug Administration (FDA) was 40 mg/d. However, in 1997 the manufacturer undertook a development program to study 2 higher doses of simvastatin (80 mg/d and 160 mg/d).8,19-20 Although a favorable report appeared in the medical literature,20 development of the 160-mg/d dose was abandoned due to high muscle toxicity.8,19 Although never reported in the scientific literature, the financial community was informed that the rate of muscle-related symptoms was 5.7% for the 160 mg/d dose.19 The dose of 80 mg/d of simvastatin was eventually approved, but in 2002, the FDA product label was modified to include warnings about concomitant medications than inhibit cytochrome P450 3A4, the major metabolic pathway for simvastatin elimination.21 This warning was provoked by cases of rhabdomyolysis when simvastatin was administered with 3A4 inhibitors.21

There are several lessons to be learned from these events. The failure of the 160-mg/d dose of simvastatin and the enhanced toxicity that occurred with 3A4 inhibitors should probably have served as a warning that the 80-mg/d dose of simvastatin might border on a toxic threshold. Relatively minor differences in the rate of elimination, a low body mass index, mild renal insufficiency, or other unknown factors appear capable of pushing simvastatin blood levels into the toxic range. The failure to publish the actual results of studies using the 160-mg/d dose (negative publication bias) arguably prevented the medical and scientific community from fully appreciating the myopathic potential of high-dose simvastatin. In addition, the voluntary nature of the US postmarketing surveillance system may have compromised the ability of the FDA to recognize increased risk of the 80-mg/d dose. Indeed, it took several years to recognize that cerivastatin was associated with a 16- to 80-fold increase in risk of myopathy prior to its withdrawal.22

It must be emphasized that the cluster of myopathy events in the A to Z trial may be partially explained by chance alone.

### Table: Intensive Statin Therapy in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th></th>
<th>A to Z</th>
<th>MIRACL</th>
<th>PROVE IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>4497</td>
<td>3086</td>
<td>4162</td>
</tr>
<tr>
<td>LDL cholesterol differential, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>62</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>Late</td>
<td>15</td>
<td>NA</td>
<td>28</td>
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<tr>
<td>C-reactive protein differential, %</td>
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<td>38</td>
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<tr>
<td>Event reduction, %</td>
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<tr>
<td>Early</td>
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<tr>
<td>Late</td>
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<tr>
<td>Myopathic event§</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: LDL, low-density lipoprotein; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; NA, data not available; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy.

SI conversion factor: To convert LDL cholesterol to mmol/L, multiply by 0.0259.
Although potentially alarming, 9 myopathic events in 2250 treated patients are insufficient to recommend withdrawal of the 80-mg/d dose of simvastatin. Fortunately, there is a larger ongoing trial randomizing 12,000 patients to either 80 mg/d or 20 mg/d of simvastatin. In addition, the FDA maintains a high degree of vigilance in this area and undoubtedly will subject high-dose simvastatin to additional scrutiny. If either FDA monitoring or ongoing clinical trials confirm that a regimen of 80 mg/d of simvastatin constitutes an unacceptable risk, this dosage level should be withdrawn by its manufacturer.

It is important to reassure practicing physicians and patients that the unfavorable risk-benefit relationship observed in the A to Z trial does not in any way diminish the value of intensive statin treatment in secondary prevention, including ACS patients. There was a trend toward reduced events in the A to Z trial, a finding that supports the lower is better concept. The increased myopathy rate applies only to a specific dose of a single agent and should not tarnish this remarkable class of drugs. It must also be emphasized that simvastatin in doses of up to 40 mg/d has shown excellent safety and efficacy in a series of clinical trials. For now, though, the 80-mg/d dose of simvastatin should be used with caution, particularly because other effective agents are available. Finally, in an era when criticism of selective reporting of positive trial results is common, the A to Z investigators are to be commended for their prompt and thorough reporting of a critically important major trial that did not meet its original objectives.

REFERENCES