Reducing Residual Risk in Secondary Prevention of Cardiovascular Disease

Neil J. Stone, MD

Prevention of cardiovascular disease (CVD) spans the human lifespan, including primordial, primary, and secondary prevention efforts. Extensive evidence from epidemiological, genetic, and animal studies confirms the central importance of elevated low-density lipoprotein (LDL) cholesterol (LDL-C) in atherosclerotic CVD events. The Cholesterol Treatment Trialists Collaboration provides per-person documentation from large-scale randomized clinical trials of the striking reduction in CVD events per 1 mmol (38.8 mg/dL) of LDL-C lowering with statins over a wide range of baseline LDL-C values. It is worth recalling that the major statin trials were not designed to determine the effectiveness of titration to LDL-C or even to non–high-density lipoprotein cholesterol goals by statins but were fixed-dose comparisons of various statins against placebo and then, more recently, large-dose statin therapy versus moderate-dose statin therapy. What is not so clear is whether we can intervene to reduce so-called residual risk further in secondary prevention patients optimally treated with statin therapy. A promising short list of proposed potential targets other than LDL includes efforts to promote smoking cessation and therapies to improve the prothrombotic and inflammatory state of the metabolic syndrome and to control elevated blood pressure.

The article by Mora et al in this issue of Circulation is helpful in shedding light on this unresolved but important clinical problem. The investigators used data from a large-scale clinical trial of secondary prevention patients called Treating to New Targets (TNT). They evaluated risk factors for recurrent CVD events in those treated with intensive statin therapy (atorvastatin 80 mg/d) to address the challenges inherent in further risk reduction for those who had major cardiovascular events despite high-dose (atorvastatin 80 mg/d) statin therapy.

The trial design of TNT included enrollment of participants with chronic coronary artery disease and LDL-C <130 mg/dL who were randomized to either atorvastatin 80 mg daily or atorvastatin 10 mg daily and then followed up in double-blind fashion for a median of 4.9 years. The primary end point was the occurrence of a major cardiovascular event such as coronary death, nonfatal myocardial infarction, and resuscitation after cardiac arrest, or fatal or nonfatal stroke. The group assigned atorvastatin 80 mg/d, had a major cardiovascular events rate of 8.7% over 5 years, but had significantly fewer major cardiovascular events than the group assigned atorvastatin 10 mg/d. The absolute reduction in the rate of major cardiovascular events was 2.2% with a 22% relative reduction in risk (hazard ratio, 0.78; 95% confidence interval, 0.69–0.89; P<0.001). The high-dose atorvastatin group had a low frequency of but more liver transaminase abnormalities than the low-dose group. In addition, the additional LDL-C lowering did not produce a significant change in total mortality.

In the present article from TNT, the authors examined those in the high atorvastatin group who had no major cardiovascular events or death in the first year and had complete lipid and apolipoprotein measurements. They found various multivariable predictors of increased or decreased risk that are summarized in Table 1. The list seemed to include all the “usual suspects” except that on-treatment 1-year levels of lipids and apolipoproteins were not selected into the multivariable model because they were not associated with risk after baseline apolipoproteins and clinical risk factors were taken into account.

On the basis of their analysis, the authors appropriately suggested a multifaceted prevention approach to address residual risk. This approach would be consistent with the approach recommended in the most recent American College of Cardiology/American Heart Association secondary guidelines statement. A provocative finding was their observation that on-treatment lipid and apolipoproteins measurements dropped out of the multivariate equation. This differs from the predictive value of on-trial apolipoprotein B in a prespecified analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial data. This finding could prompt some clinicians to be less interested in posttreatment lipid measurements because, after the 3-month lipid determination, the LDL-C remained stable. Clinicians should realize that there is much to be gleaned by periodic lipid evaluation.

First, it is important to consider whether an expected response to the statin dose is seen. In TNT, LDL-C values fell 35% with 10 mg/d atorvastatin during the first 8-week open-label phase and then fell 14% more (a total of ∼49% from baseline) in those for whom the dose was increased (in a blinded fashion) to atorvastatin 80 mg/d. These values can be useful benchmarks in those on a maximal statin dose (see package insert for data on the other statins) because the most...
high-dose statin use. The FDA reviewed meta-analyses that showed little increase in diabetes risk. From clinical trial meta-analyses and epidemiological data from the published literature, information concerning an effect of statins on incident diabetes mellitus and increases in hemoglobin A1c and/or fasting plasma glucose was added to statin labels.

**Warnings** Healthcare professionals should follow the recommendations in the lovastatin label regarding drugs that may increase the risk of myopathy/rhabdomyolysis when used with lovastatin.

**FDA** indicates Food and Drug Administration.


way in which a “polypill” of secondary prevention therapies is used to see whether it proves beneficial in improving adherence to evidence-based regimens.14

Second, an unsatisfactory lipid response to statin therapy could be a clue to associated secondary causes such as hypothyroidism, nephrosis, or obstructive liver disease.15 Although checking a liver panel, urine for protein, and thyroid-stimulating hormone is recommended before statin therapy is started, these tests may be useful when a reduced response to the statin is seen after an intervening period of successful therapy.

Third, genetic mechanisms are worth considering and may allow tailoring of statin therapy in the future.13 Although a detailed discussion of clinically relevant polymorphisms that identify subgroups that may have a greater or lesser LDL-C response to statin therapy is beyond the scope of this editorial, it is worthwhile to mention elevated lipoprotein(a) as a potential cause of statin resistance. Although not a recent observation, in patients with elevated lipoprotein(a), a calculated LDL-C may appear to respond less well to statin therapy.

**Table 2.** Statins and Food and Drug Administration Drug Safety Communication

<table>
<thead>
<tr>
<th>Topic</th>
<th>Actions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins and the potential for liver side effects</td>
<td>Healthcare professionals should perform liver enzyme tests before initiating statin therapy in patients and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternative cause is not found, the statin should not be restarted.</td>
</tr>
<tr>
<td>Statins and the data on cognitive impairment</td>
<td>There have been rare postmarketing reports of cognitive impairment (eg, memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and are reversible on statin discontinuation, with variable times to symptom onset (1 d to years) and symptom resolution (median of 3 wk). Data from the observational studies and clinical trials did not suggest that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline.</td>
</tr>
<tr>
<td>Statins and the risk of diabetes mellitus</td>
<td>Increases in glycosylated hemoglobin A1c and fasting serum glucose levels have been reported with statin use. The FDA reviewed meta-analyses that showed little increase in diabetes risk. From clinical trial meta-analyses and epidemiological data from the published literature, information concerning an effect of statins on incident diabetes mellitus and increases in hemoglobin A1c and/or fasting plasma glucose was added to statin labels.</td>
</tr>
<tr>
<td>Statins and drug-drug interactions with lovastatin</td>
<td>Healthcare professionals should follow the recommendations in the lovastatin label regarding drugs that may increase the risk of myopathy/rhabdomyolysis when used with lovastatin.</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Apo, apolipoprotein; BUN, blood urea nitrogen; and CVD, cardiovascular disease.

important nongenetic contributor to a reduced statin response is poor medication adherence.9

Certain groups are potentially more prone than others to discontinue their medications. In a companion article describing the experience of female participants in TNT, women derived as much benefit from atorvastatin 80 mg/d, but they were more likely than men to discontinue this dosage secondary to adverse events (6.5% versus 3.7%). In addition, women assigned 80 mg/d atorvastatin were more likely to discontinue their statin than women assigned to 10 mg/d (6.5% versus 3.0%).10 A cohort study following up patients ≥66 years of age found that whether the patients had acute coronary syndrome or chronic coronary artery disease, 2-year adherence rates were disappointingly low.11 Only 40.1% of the acute coronary syndrome and 36.1% of the chronic coronary artery disease patients still adhered to their statin.

Indeed, nonadherence to statin therapy because of statin intolerance has gained the attention of patients and clinicians alike as a result of a drug safety communication published on its Web site by the Food and Drug Administration (FDA)12 (see Table 2). The FDA communication was appropriately cautious and did not recommend that patients stop their statins without consulting their health professional. This is important because an individual’s CVD risk status must be considered in discussions of the differing impact of a reduction in atherosclerotic CVD events, including stroke, compared with the likelihood, albeit low, of a statin-associated increase in blood sugar and hemoglobin A1c, resulting in more diagnoses of diabetes mellitus.

Recently, a compelling editorial called for a pragmatic clinical trial for statin-intolerant patients.13 The authors emphasized the complexity of statin intolerance, noting that patient characteristics have excluded many groups from randomized clinical trials and that patients and clinicians alike may not recognize that fatigue and weakness are possible statin-related side effects requiring evaluation. To deal with the problems of polypharmacy, studies are under-
than expected and should prompt consideration of lipoprotein(a), especially in patients with a personal or family history of premature CHD.16

Thus, TNT investigators have provided useful insights into the challenges that confront those who seek to reduce residual risk in the patient with chronic coronary disease. To achieve the potential benefits of high-dose statin therapy, the patient and his or her health professional need to focus more strongly on drug adherence, and this should be part of the risk communication when statins are prescribed. To guide prevention efforts, however, we need coordinated research investigations that lead to feasible policies to better recognize and manage those high-risk individuals who develop intolerance to statin therapy. As noted, the research should include those groups that traditionally have not qualified for randomized clinical trials. And to make notable progress against residual risk, a final wish is for a resource commitment (perhaps cofunded by insurance companies and government) so that smoking cessation and improvement in metabolic syndrome risk factor management by lifestyle can occur with higher success rates than are currently attained.8,17

Disclosures
None.

References

Key Words: Editorials cardiovascular diseases risk statins