Improving Lipid Goal Attainment
Is It Enough?

Antonio M. Gotto, Jr, MD, DPhil

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Lowering elevated levels of low-density lipoprotein cholesterol (LDL-C) is a surefire way to reduce cardiovascular risk. On the basis of a wealth of clinical trial evidence, guidelines from the National Cholesterol Education Program Adult Treatment Panel (ATP) have established progressively lower LDL-C targets, with the most recent iteration recommending an optional treatment goal of <70 mg/dL for very-high-risk patients. Increased attention has focused on addressing global cardiovascular risk, although LDL-C remains the primary target of lipid-lowering therapy.

In this issue of Circulation, Waters et al. present results from the Lipid Treatment Assessment Project (L-TAP) 2, a survey to determine the percentage of dyslipidemic patients receiving lipid-lowering therapy (which includes diet and exercise) and also achieving their LDL-C goals. The first L-TAP survey was conducted in 1996 to 1997 in the United States with approximately 5000 patients. L-TAP 2 assessed nearly twice as many patients in 9 countries, including the United States, Canada, Mexico, Brazil, Spain, the Netherlands, France, Taiwan, and Korea, in 2006 to 2007. The overall LDL-C goal achievement rate in L-TAP 2 was 73%, as compared with 38% in the original L-TAP. As in the last survey, low-risk patients were the most likely to attain their LDL-C goals (86%), whereas high-risk patients experienced more difficulty in reaching their correspondingly lower targets (67%). In the United States, only 35% of patients with coronary heart disease (CHD) and at least 2 risk factors attained the optional LDL-C goal of <70 mg/dL. Success rates ranged from 47% to 84% across countries, with the highest rates seen in Korea and the United States. L-TAP 2 also assessed high-density lipoprotein cholesterol (HDL-C) levels and found that the prevalence of low HDL-C varied widely among countries.

The expansion of L-TAP 2 to encompass 9 countries provides additional information on rates of LDL-C goal attainment worldwide, but it makes a direct comparison with the first L-TAP somewhat difficult, because the 2 study populations are very different. As Waters et al note, the variations in outcomes across countries are likely due to differences in guidelines, patient characteristics, and healthcare systems. These factors may also be expected to complicate the comparison with the original L-TAP, so that the exact magnitude of improvement in LDL-C success rates between studies may be indeterminable. Nevertheless, it is clear that there has been a considerable increase in rates of LDL-C goal attainment across all risk groups in L-TAP 2 (Table). In addition, a rough comparison between the 2 studies suggests that not only did more patients achieve their LDL-C targets in L-TAP 2, but also among those who did, mean LDL-C levels decreased substantially, particularly for individuals in the low- and moderate-risk groups. The change in mean LDL-C levels among patients who did not achieve their targets does not appear as dramatic in comparison.

The trend in improved control of LDL-C levels in L-TAP 2 accords with the recently published results of European Action on Secondary and Primary Prevention through Intervention to Reduce Events (EUROASPIRE) III, a similar survey conducted in patients with CHD in Europe. A subset analysis compared results from 8 countries (Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, and Slovenia) that had participated in all 3 EUROASPIRE surveys. EU-ROASPIRE I took place in 1995 to 1996, EUROASPIRE II in 1999 to 2000, and EUROASPIRE III in 2006 to 2007. EU-ROASPIRE III assessed adherence to the Joint European Societies’ recommendation of total cholesterol \(<4.5\) mmol/L (\(\approx175\) mg/dL) in patients with CHD, among other parameters. The proportion of patients achieving this goal increased significantly across studies, from 5.5% in EUROASPIRE I, to 23.3% in II, to 53.8% in EUROASPIRE III (\(P<0.0001\)). The proportion of patients who smoked or who had high blood pressure remained nearly constant, however, and the frequency of obesity and self-reported diabetes increased.

In combination with the results from the EUROASPIRE studies, the article from Waters et al indicates that LDL-C goal attainment has improved over the past decade, whereas control of hypertension and lifestyle risk factors has remained the same or worsened. These results suggest that the beneficial shift in LDL-C success rates is most likely not due to sizable improvements in patient compliance or physician awareness of national guidelines. The more likely explanation of the observed improvement in control of LDL-C levels is the introduction of more effective lipid-lowering therapies.

In both L-TAP studies, roughly 75% of participants were taking a statin, and 16% received nondrug therapy. During the time that the original L-TAP was conducted, atorvastatin, rosuvastatin, and the cholesterol absorption inhibitor ezetimibe had not yet been introduced. More than half of all participants in L-TAP 2 were taking one of these newer drugs: 33% for atorvastatin, 12% for rosuvastatin, and 10%...
for ezetimibe either as combination or monotherapy. The availability and widespread use of these high-intensity agents may account in large part for the increase in LDL-C goal attainment. At a maximal dose of 80 mg, atorvastatin decreases LDL-C by 60%. Rosuvastatin has an expected 52% LDL-C reduction at the starting dose, up to a maximum reduction of 65%. As monotherapy, ezetimibe at 10 mg reduces LDL-C by approximately 17%, but when added to any dose of statin, it reduces LDL-C by an additional 25%. Given the well-established log-linear relationship between LDL-C and relative risk for CHD, these greater degrees of LDL-C reduction can be expected to result in improved clinical outcomes, although this has not yet been proven in the case of ezetimibe.

Existing data have not established a lower threshold beyond which LDL-C reduction ceases to be beneficial. In secondary prevention, the Treating to New Targets (TNT) study in patients with CHD demonstrated that intensive statin therapy to a mean LDL-C of 77 mg/dL, as compared with a mean LDL-C of 101 mg/dL in the standard treatment group, confers a 22% relative reduction in the risk of a first major cardiovascular event, with no clinically significant increase in adverse event rates. Although LDL-C goal attainment has improved greatly over the past decade, there is still much room for improvement in the treatment of high-risk patients, who have the greatest need for large LDL-C reductions, preferably to levels <70 mg/dL. Studies in various populations worldwide suggest that rosuvastatin may be particularly effective in helping high-risk patients to attain their cholesterol goals. In 1 study conducted in the United States, 1632 high-risk patients were randomized to treatment with rosuvastatin, atorvastatin, or simvastatin. After 12 weeks, 76% of patients treated with rosuvastatin had achieved LDL-C levels <100 mg/dL, as compared with 58% of patients treated with atorvastatin and 53% of patients treated with simvastatin (P<0.001).

In primary prevention, results from the recent Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) indicate that low-risk individuals without hyperlipidemia but with elevated levels of C-reactive protein (CRP) can also experience significant risk reductions with treatment to very low LDL-C levels (median 55 mg/dL in the intervention group), with no increase in adverse events. In that trial, the unexpected magnitude of benefit in the treatment group compared with placebo (44% relative reduction in major cardiovascular events) was associated with reductions in CRP as well as LDL-C. Although it remains to be seen how and if CRP levels and targets may be incorporated into future guidelines, full adherence to existing ATP III primary prevention guidelines in the United States could prevent an estimated 20 000 myocardial infarctions and 10 000 CHD deaths per year. A recent study shows that full adherence would be cost effective from a health-policy standpoint and that increased availability of low-cost or generic statins could even result in overall cost savings.

The results from L-TAP 2 indicate that there is still a considerable gap in the treatment of patients at highest risk for cardiovascular events. The introduction of more potent lipid-lowering agents, as well as clinical trial evidence showing increased benefit with intensive statin therapy, should make full adherence to national guidelines a realistic objective. However, therapeutic control of lipids is only part of a successful strategy for prevention. It is interesting to note that in L-TAP 2, one of the reported predictors of LDL-C goal achievement was absence of dietary counseling (P<0.001). This is possibly due to outlier data from Korea, which reported only 1% of patients receiving dietary counseling, despite being the country with the highest rate of LDL-C goal attainment. To reduce cardiovascular risk worldwide, we need to develop and implement more productive ways of addressing lifestyle risk factors such as diet, smoking, and physical inactivity. Rates of obesity and diabetes have worsened over the past decade, and cardioprotective drugs can only do so much to remedy the metabolic complications that often result from poor lifestyle choices. Effectively addressing global cardiovascular risk requires an increased focus on lifestyle, as well as lipids.

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### Table. Comparison Between L-TAP and L-TAP 2

<table>
<thead>
<tr>
<th>LDL-C goal success rates, %</th>
<th>Overall</th>
<th>Low Risk (&lt;1 Risk Factor)</th>
<th>Moderate Risk (≥2 Risk Factors)</th>
<th>High Risk (CHD, Other Atherosclerotic Disease, Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-TAP</td>
<td>38</td>
<td>68</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>L-TAP 2</td>
<td>73</td>
<td>86</td>
<td>74</td>
<td>67</td>
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</table>

**Mean LDL-C in patients achieving goal, mg/dL**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Low Risk (&lt;1 Risk Factor)</th>
<th>Moderate Risk (≥2 Risk Factors)</th>
<th>High Risk (CHD, Other Atherosclerotic Disease, Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-TAP</td>
<td>...</td>
<td>129</td>
<td>109</td>
<td>87</td>
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<tr>
<td>L-TAP 2</td>
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<td>92</td>
<td>73</td>
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</table>

**Mean LDL-C in patients not achieving goal, mg/dL**

<table>
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<tr>
<th></th>
<th>Overall</th>
<th>Low Risk (&lt;1 Risk Factor)</th>
<th>Moderate Risk (≥2 Risk Factors)</th>
<th>High Risk (CHD, Other Atherosclerotic Disease, Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-TAP</td>
<td>...</td>
<td>188</td>
<td>163</td>
<td>140</td>
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<tr>
<td>L-TAP 2</td>
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<td>185</td>
<td>158</td>
<td>127</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; and L-TAP, Lipid Treatment Assessment Project.
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Dr Gotto is a current consultant for Genentech, KOWA, Merck, and Merck-Scheringer-Plough. He is on the Board of Directors of Aegerion and Arisaph Pharmaceuticals, and he serves on advisory boards for DuPont and Novartis.

References

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