Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

Lipid Management to Reduce Cardiovascular Risk

A New Strategy Is Required

H. Robert Superko, MD; Spencer King III, MD

“...it is not good to settle into a set of opinions. At first putting forth great effort to be sure that you have grasped the basics, then practicing so that they may come to fruition is something that will never stop for your whole lifetime. Do not rely on following the degree of understanding that you have discovered, but simply think. . .This is not enough.”

Hagakure, Yamamoto Tsunetomo, September 10, 1716 (a Samurai)1

For the past 22 years, substantial national efforts have been directed toward reducing the average blood low-density lipoprotein cholesterol (LDL-C) level of the American population. This initiative was initially prompted by the successful results of the Lipid Research Clinic–Coronary Primary Prevention Trial (LRC-CPPT), which first proved that reducing LDL-C resulted in a statistically significant reduction in cardiovascular events.2 The intent of these efforts has been to reduce the human suffering and economic cost of cardiovascular disease. In the subsequent 2 decades, a plethora of monotherapy cholesterol-lowering drug trials has consistently reported a statistically significant 25% relative risk reduction for cardiovascular events. These findings form the basis for the current Adult Treatment Panel (ATP) III guidelines and the recent call to adjust the LDL-C goal even lower.3

Response by Grundy p 568

Although this level of success in the fight against heart disease is laudable, a great danger for our patients’ future health lies in the assumption that cholesterol reduction alone will stem the tide of coronary heart disease (CHD). It is wise and prudent to remember the words of Yamamoto Tsunetomo that “this is not enough.” The purpose of this article is to challenge healthcare workers to consider the possibility that the cholesterol-lowering program has in large part failed to stem the epidemic of CHD and that the well-meaning focus on LDL-C reduction has deflected interest in other therapeutic aspects of lipoprotein treatment that provide equal or greater benefit. This myopic focus on LDL alone is not surprising because, so far, guidelines have not adequately addressed other evidence. This article reviews the knowledge supporting this concept that has been acquired since 1996.4 At that time, it was noted that despite significant LDL-C reduction, large numbers of subjects in the treatment groups continued to have cardiovascular events despite achieving significant LDL-C reduction. In the subsequent 10 years, important advances have been made in the understanding of lipoproteins that have clinical relevance for patient management and improved clinical outcomes beyond LDL-C reduction alone.
Blood Cholesterol-Lowering History

In the 21st century, atherosclerosis is well established as the leading cause of death in most industrialized nations. Large population-based studies have identified several risk factors as targets of intervention that may reduce cardiovascular disease. This approach for identifying “high-risk” populations was used to focus efforts on a population subset that could derive the most benefit from a treatment targeted to disorders such as hypertension or elevated blood cholesterol. The continuation to be true even with the substantially greater absolute LDL-C reduction achieved in recent trials. At this point in the history of cholesterol reduction, it is important to pause and discuss the possibility that statistical (mathematical) significance does not necessarily equate to clinical relevance.

Relative Risk Reduction and Professional/Public Confusion

Clinical trials using monotherapy have consistently reported an 25% relative risk reduction in cardiovascular events regardless of the lipid-lowering medication class (statin, fibrate, niacin) used. This 25% reduction in risk is the “relative risk,” i.e., the difference between the number of events in the treated group relative to the number of events in the control group. To achieve this degree of relative risk reduction, in cholesterol-lowering studies, it is necessary to treat 30 individuals to prevent 1 event. This amount of “success” requires that a huge number of individuals be treated yet leaves a large number of patients in the treatment group experiencing a myocardial infarction or CHD death even with aggressive LDL-C reduction (Figure 1).

It is not uncommon for the public to interpret this 25% risk reduction as meaning that 25% of the entire population was saved from an event as a result of the treatment. In fact, if there were 1000 subjects in the treatment group and 1000 subjects in the placebo group and if 100 events were experienced in the placebo group and 75 events in the treatment group, the difference between 100 and 75 is the 25% relative risk reduction in events. What clinicians must now consider is the possibility that LDL-C reduction alone is not adequate to
statin the epidemic of CHD events when LDL-C values are below “hypercholesterolemic” levels. Although laudable, a 25% relative risk reduction is insufficient to treat this disease; rather, relative risk reductions of 90% should be the goal and have been achieved in some NIH combination lipid drug trials.

Statistical Significance Does Not Necessarily Mean Clinical Relevance

Statistical, or mathematical, significance is a tool useful in calculating how likely it is that the results of an experiment are due to chance alone and not really due to the intervention. Achieving statistical significance generally means that the results observed probably were not due to chance alone and probably were the result of the intervention used in the clinical trial. A value of $P=0.05$ indicates that there is still a 1 in 20 chance that the results were due to chance alone and not the intervention. Thus, statistical significance is a mathematical tool to test the hypothesis that the results observed were probably due to the intervention, but it does not necessarily mean the results are clinically significant or even meaningful.

Small absolute change can be mathematically (statistically) significant and indicate that the intervention achieved some result. In blood cholesterol–lowering trials, however, large numbers of people achieving statistically significantly lower LDL-C did not benefit from the intervention; thus, clinical relevance may be weak despite an impressive probability value. In a meta-analysis of 5 statin clinical trials, in 30,817 men and women, a 27% relative risk reduction in CHD events was reported. However, this represents the difference between 2042 events in the placebo group and 1490 events continuing to occur in the statin treatment group. To achieve this degree of event reduction, $\approx 30$ subjects had to be treated to prevent 1 event.

Another example of debatable clinical relevance is the argument to reduce LDL-C goals even further, which has been based in part on the results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVEIT) trial. In PROVEIT, 40 mg/d pravastatin was tested against 80 mg/d atorvastatin for 2 years in subjects who had been hospitalized for the acute coronary syndrome. The group randomized to atorvastatin achieved a mean LDL-C of 62 mg/dL; the pravastatin group achieved 95 mg/dL. A statistically significant 16% relative risk reduction in clinical events ($P=0.005$) was reported, and it was concluded that in acute coronary syndrome patients, an intensive lipid-lowering statin regimen provided greater protection than a standard statin regimen and indicated that such patients benefit from lowering of LDL-C to levels substantially below current target levels. This statistically significant 16% relative risk reduction represents a primary event rate of 26.3% in the pravastatin group compared with 22.4% in the atorvastatin group (Figure 2). However, the conclusion that the data are evidence that intensive lipid lowering will provide protection against early recurrent cardiovascular events, although true for a small group, ignores the 22.4% of subjects in the intensively treated group who achieved a low LDL-C yet experienced a clinical event. Thus, intensive lipid lowering with a statin only did not successfully prevent an event in a large group of acute coronary syndrome patients.

The potential harm in the assumption that mathematical significance is equivalent to clinical significance is that many public and professional individuals have the misleading impression that if they just get their LDL-C low enough, they will be free of CHD risk. The results of 5 large statin trials show that this is a dangerous misconception in that it leaves large numbers of patients still at risk for cardiovascular events.

Investigations using coronary arteriography as an end point also have been revealing in regard to possible misinterpretation of statistical significance and clinical relevance. Multiple LDL-C–lowering only arteriographic trials have documented a statistically significant reduction in the rate of arteriographic progression but no mean regression. This supports the concept that LDL-C reduction alone can slow the rate of progression but that mean arteriographic regression is difficult to achieve. In comparison, arteriographic investigations using combination drug therapy that both lowers LDL-C and raises HDL-C have frequently achieved evidence of arteriographically defined “regression” (Table 1). The Reversal of Atherosclerosis With Lipitor (REVERSAL) trial and A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound–Derived Coronary Atheroma Burden (ASTEROID) are the LDL-C-lowering only exceptions that used intravascular ultrasound and achieved some degree of intravascular ultrasound–determined regression: $-0.4\%$ in REVERSAL and $-1.0\%$ in ASTEROID for percent atheroma volume.

The trial design for ASTEROID used each subject as his or her own control, not a control group as in previous investigations. In ASTEROID, the 53% reduction in LDL-C also was associated with a 15% increase in HDL-C.
raising drug therapy intravascular ultrasound trial reported greater intravascular ultrasound regression (−19.9%) but in a small population.21

Number Needed to Treat

The number needed to treat (NNT) represents the number of patients who need to be treated to prevent 1 cardiovascular event and reflects the efficiency of the treatment modality.22 The smaller the number is, the more efficient the treatment is.

Table 2 lists a number of clinical end-point and arteriographic investigations that used LDL-C–lowering only therapy or LDL-C–lowering plus HDL-C–raising drug therapy. The results of these trials must be interpreted in light of the different types of patient populations and duration of treatment, so a 1-to-1 comparison is difficult. Nevertheless, NNT can be used to assess relative differences in efficiency. The duration of the studies also varies, and to adjust for the duration variable, the NNT per year of treatment was calculated.

Some LDL-C–lowering clinical end-point studies achieved a low NNT per year such as the Scandinavian Simvastatin Survival Study (SSSS), which achieved an NNT of 11.7 and an NNT per year of 2.2.23 This efficiency was achieved in part by treating a high-risk population with very elevated LDL-C (baseline mean, 188 mg/dL) with a relatively powerful drug designed to reduce LDL-C. However, the 6 clinical end-point LDL-C–lowering statin studies (Table 2) achieved an average NNT of 41.0 and an average NNT per year of 8.5, reflecting an overall less efficient therapeutic approach. Three recent trials have compared 1 statin brand or dose against another.18,24,25 In these “statin versus statin” trials, the average NNT was 64.6, and the average NNT per year was 19.1. Arteriographic LDL-C–lowering statin studies achieved an average NNT of 64.3 and an average NNT per year of 28.7. In comparison, LDL-C–lowering plus HDL-C–raising drug studies have been more efficient, achieving an average NNT of 9.6 and an average NNT per year of 3.4. The LDL-C–lowering plus HDL-C–raising studies have primarily used arteriographic outcomes as primary end points. The rather inefficient results of the LDL-C–lowering only trials compared with LDL-C–lowering combined with HDL-C–raising trials should be considered in view of the recent call to lower LDL-C goals even further because this may detract attention from the beneficial aspects of lipoprotein metabolism not directly linked to LDL-C reduction. This is relevant because the combination drug therapy used in the NIH trials is readily available and relatively inexpensive.

The Need To Go Beyond LDL-C Reduction and Incorporate Aspects of Reverse Cholesterol Transport

It is important for clinicians to appreciate the need for additional treatment other than simple LDL-C reduction for 3 important reasons. First, an LDL-C central focus allows many patients to experience a CHD event even with adequately controlled LDL-C values. Second, disorders that contribute to CHD risk other than LDL-C are common in the coronary artery disease population even with LDL-C <100 mg/dL (Table 3). Third, effective therapies currently exist to treat these other disorders, and new therapies under development will greatly expand the armamentarium. A key component of

Table 1. Arteriographic Investigations Using LDL-C–Lowering or LDL-C–Lowering Plus HDL-C–Raising Therapy, Arteriographic Outcomes in the Control and Treatment Groups, and Average Progression or Regression

<table>
<thead>
<tr>
<th>Name</th>
<th>Rx</th>
<th>Duration, y</th>
<th>Control</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C–lowering trials</td>
<td>Lovastatin</td>
<td>2</td>
<td>2.20%</td>
<td>1.60%</td>
</tr>
<tr>
<td>MARS52</td>
<td>MAAS53</td>
<td>REGRESS (MOD)54</td>
<td>Pravastatin</td>
<td>2</td>
</tr>
<tr>
<td>PLAC-I55</td>
<td>Pravastatin</td>
<td>3</td>
<td>3.40%</td>
<td>2.10%</td>
</tr>
<tr>
<td>LCAS (MLD)56</td>
<td>Fluvastatin</td>
<td>2.5</td>
<td>0.10 mm</td>
<td>0.03 mm</td>
</tr>
<tr>
<td>CCAIT57</td>
<td>Lovastatin</td>
<td>2</td>
<td>2.90%</td>
<td>1.70%</td>
</tr>
<tr>
<td>LDL-C–lowering plus HDL-C–raising trials</td>
<td>Nicotinic acid, lovastatin, colestipol</td>
<td>2.5</td>
<td>2.30%</td>
<td>−1.50%</td>
</tr>
<tr>
<td>FATS (&lt;90%ile LDLC)44</td>
<td>Nicotinic acid, colestipol</td>
<td>4</td>
<td>Progression</td>
<td>Stability</td>
</tr>
<tr>
<td>CLAS41</td>
<td>Multifactorial</td>
<td>4</td>
<td>4.40%</td>
<td>1.20%</td>
</tr>
<tr>
<td>SCOR58</td>
<td>Nicotinic acid, lovastatin, colestipol</td>
<td>2.1</td>
<td>0.8</td>
<td>−1.53</td>
</tr>
</tbody>
</table>

Rx indicates treatment; MARS, Monitored Atherosclerosis Regression Study; MAAS, Multicenter Anti-Atheroma Study; PLAC-I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; REGRESS, Regression Growth Evaluation Statin Study; and LCAS, Lipoprotein and Coronary Atherosclerosis Study. Change in arteriographic status was evaluated by different methods, so a direct 1-to-1 comparison is not possible. Percent change in lumen diameter was used when reported. HATS used mean change in percent stenosis for placebo vs the simvastatin plus niacin groups. Stanford Coronary Risk Intervention Project (SCRIP) data are reported for patients with predominantly dense LDL. CLAS reported a "global change score." FATS data represent the population with LDLC <90th percentile (mean LDLC, 152 mg/dL).
the most successful arteriographic “regression” trials has been the combination of LDL-C reduction with enhanced reverse cholesterol transport as reflected by substantially increased HDL-C and HDL2 levels. Understanding the reverse cholesterol transport process is a clinically important topic because current and future pharma-

Table 2.  Clinical Event Reduction (Fatal and Nonfatal Myocardial Infarction) in Investigations Using LDL-C Reduction Alone Versus LDL-C Reduction Plus HDL-C Elevation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration, y</th>
<th>Patient Type</th>
<th>Baseline Mean LDL-C, mg/dL</th>
<th>Control, n</th>
<th>Treatment, n</th>
<th>Events Control Group, n</th>
<th>Events Treatment Group, n</th>
<th>RRR, %</th>
<th>Absolute, %</th>
<th>NNT</th>
<th>NNT/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S^23</td>
<td>Simvastatin</td>
<td>5.4</td>
<td>High Chol, CHD</td>
<td>186</td>
<td>2223</td>
<td>2221</td>
<td>622</td>
<td>431</td>
<td>−30.7</td>
<td>−8.6</td>
<td>11.7</td>
</tr>
<tr>
<td>LIPID^24</td>
<td>Pravastatin</td>
<td>6.1</td>
<td>CHD</td>
<td>150</td>
<td>4502</td>
<td>4512</td>
<td>715</td>
<td>557</td>
<td>−22.1</td>
<td>−3.5</td>
<td>28.3</td>
</tr>
<tr>
<td>CARE^46</td>
<td>Pravastatin</td>
<td>5</td>
<td>CHD</td>
<td>139</td>
<td>2078</td>
<td>2081</td>
<td>207</td>
<td>157</td>
<td>−24.2</td>
<td>−2.4</td>
<td>41.4</td>
</tr>
<tr>
<td>WOSCOP^48</td>
<td>Pravastatin</td>
<td>4.9</td>
<td>Asympto</td>
<td>192</td>
<td>3293</td>
<td>3302</td>
<td>248</td>
<td>174</td>
<td>−29.8</td>
<td>−2.3</td>
<td>44.2</td>
</tr>
<tr>
<td>AFTexCAPS^49</td>
<td>Lovastatin</td>
<td>5.2</td>
<td>Asympto</td>
<td>156</td>
<td>3301</td>
<td>3304</td>
<td>215</td>
<td>163</td>
<td>−24.2</td>
<td>−1.6</td>
<td>63.3</td>
</tr>
<tr>
<td>CARDS^20</td>
<td>Atorvastatin</td>
<td>3.9</td>
<td>Diabetes</td>
<td>118</td>
<td>1410</td>
<td>1428</td>
<td>74</td>
<td>50</td>
<td>−32.4</td>
<td>−1.8</td>
<td>57.3</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−27.2</td>
<td>−3.4</td>
<td>41</td>
<td>8.5</td>
</tr>
<tr>
<td>Statin vs statin trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−16.0</td>
<td>−1.6</td>
<td>64.6</td>
<td>19.1</td>
</tr>
<tr>
<td>IDEAL^24</td>
<td>Simvastatin 20 vs 80 (mg/d)</td>
<td>4.8</td>
<td>CHD</td>
<td>121</td>
<td>4449</td>
<td>4439</td>
<td>499</td>
<td>442</td>
<td>−11.4</td>
<td>−1.3</td>
<td>79.4</td>
</tr>
<tr>
<td>TNT^25</td>
<td>Atorvastatin 10 vs 80 mg/d</td>
<td>4.9</td>
<td>CHD</td>
<td>98</td>
<td>5006</td>
<td>4995</td>
<td>435</td>
<td>344</td>
<td>−20.9</td>
<td>−1.8</td>
<td>55.5</td>
</tr>
<tr>
<td>PROVEIT^18</td>
<td>Pravastatin 40 vs atorvastatin 80 mg/d</td>
<td>2</td>
<td>ACS</td>
<td>106</td>
<td>2063</td>
<td>2099</td>
<td>206</td>
<td>174</td>
<td>−15.6</td>
<td>−1.7</td>
<td>58.8</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−29.6</td>
<td>−3.4</td>
<td>64.3</td>
<td>28.7</td>
</tr>
<tr>
<td>Arteriographic LDL-C trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−16.0</td>
<td>−1.6</td>
<td>64.6</td>
<td>19.1</td>
</tr>
<tr>
<td>MARS^22</td>
<td>Lovastatin</td>
<td>2</td>
<td>CHD</td>
<td>157</td>
<td>124</td>
<td>123</td>
<td>31</td>
<td>22</td>
<td>−29.0</td>
<td>−7.1</td>
<td>14.1</td>
</tr>
<tr>
<td>MAAS^31</td>
<td>Simvastatin</td>
<td>4</td>
<td>CHD</td>
<td>170</td>
<td>167</td>
<td>178</td>
<td>16</td>
<td>14</td>
<td>−12.5</td>
<td>−1.7</td>
<td>58.3</td>
</tr>
<tr>
<td>REGRESS^14</td>
<td>Pravastatin</td>
<td>2</td>
<td>CHD</td>
<td>166</td>
<td>434</td>
<td>450</td>
<td>13</td>
<td>8</td>
<td>−41.2</td>
<td>−1.7</td>
<td>59</td>
</tr>
<tr>
<td>PLAC-25</td>
<td>Pravastatin</td>
<td>3</td>
<td>CHD</td>
<td>164</td>
<td>157</td>
<td>163</td>
<td>17</td>
<td>8</td>
<td>−52.9</td>
<td>−5.9</td>
<td>16.9</td>
</tr>
<tr>
<td>CCAIT^27</td>
<td>Lovastatin</td>
<td>2</td>
<td>CHD</td>
<td>180</td>
<td>166</td>
<td>165</td>
<td>8</td>
<td>7</td>
<td>−12.5</td>
<td>−0.6</td>
<td>173.4</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−29.6</td>
<td>−3.4</td>
<td>64.3</td>
<td>28.7</td>
</tr>
<tr>
<td>LDL-C+HDL-C therapy arteriographic trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−16.0</td>
<td>−1.6</td>
<td>64.6</td>
<td>19.1</td>
</tr>
<tr>
<td>FATS^44</td>
<td>Nicotinic acid, lovastatin, colestipol</td>
<td>2.5</td>
<td>HyperapoB</td>
<td>193</td>
<td>52</td>
<td>48</td>
<td>10</td>
<td>2</td>
<td>−80.0</td>
<td>−15.1</td>
<td>6.6</td>
</tr>
<tr>
<td>FATS^41</td>
<td>Nicotinic acid, lovastatin, colestipol</td>
<td>8</td>
<td>HFC</td>
<td>193</td>
<td>101</td>
<td>75</td>
<td>19</td>
<td>4</td>
<td>−78.9</td>
<td>−13.5</td>
<td>7.4</td>
</tr>
<tr>
<td>CLAS^54</td>
<td>Nicotinic acid, colestipol</td>
<td>9</td>
<td>CABG</td>
<td>170</td>
<td>71</td>
<td>76</td>
<td>21</td>
<td>8</td>
<td>−61.9</td>
<td>−19.1</td>
<td>5.3</td>
</tr>
<tr>
<td>CLAS 2.5^31</td>
<td>Nicotinic acid, colestipol</td>
<td>2</td>
<td>CABG</td>
<td>170</td>
<td>94</td>
<td>94</td>
<td>5</td>
<td>1</td>
<td>−80.0</td>
<td>−4.3</td>
<td>23.5</td>
</tr>
<tr>
<td>HATS^56</td>
<td>Nicotinic acid, simvastatin</td>
<td>3</td>
<td>Low HDL</td>
<td>130</td>
<td>34</td>
<td>33</td>
<td>7</td>
<td>1</td>
<td>−85.7</td>
<td>−17.6</td>
<td>5.7</td>
</tr>
<tr>
<td>SCRIP^46</td>
<td>Multifactor</td>
<td>4</td>
<td>CHD</td>
<td>157</td>
<td>154</td>
<td>145</td>
<td>44</td>
<td>25</td>
<td>−43.2</td>
<td>−11.2</td>
<td>9</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−71.6</td>
<td>−13.4</td>
<td>9.6</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Chol indicates cholesterol; Asympto, asymptomatic; ACS, acute coronary syndrome; HyperapoB, hyperapolipoprotein B; HFC, familial heterozygous hypercholesterolemia; and CABG, coronary artery bypass graft surgery. Other abbreviations as in Table 1. Relative risk reduction (RRR) is presented with the absolute risk reduction. The NNT to prevent 1 event is listed, as well as the NNT per year of study. LOCAT revealed no clinical event difference between groups, and the NNT is represented as not applicable. Clinical events were selected to be fatal and nonfatal myocardial infarction when reported in the appropriate article. PROVIT data were calculated from the percentages because no raw data were in the article. MARS reported combined events, including myocardial infarction, percutaneous transluminal coronary angiography, cardiovascular death, coronary artery bypass graft surgery, and unstable angina pectoris. Events were determined as accurately as possible to be fatal and nonfatal myocardial infarction for purposes of comparison. To convert cholesterol from milligrams per deciliter to millimoles per liter, multiply millimoles per liter by 0.0259.

Understanding the reverse cholesterol transport process is a clinically important topic because current and future pharma-

ological treatments can have a beneficial effect on reverse cholesterol transport and play an important therapeutic role that amplifies the benefit of LDL-C reduction. There are 5 components of reverse cholesterol transport that are useful for the clinician to understand: enzyme activity, transfer proteins, membrane modulators, apoproteins, and HDL subclasses.
HDL-C–Raising Therapy

On the eve of new treatments designed to increase HDL-C, it is important to emphasize that an effective HDL-C–raising medication has been used clinically for >50 years. Nicotinic acid has been the lipidologists’ drug of choice for increasing HDL-C since the first demonstration that it improves lipid profiles in 1955, followed by successful clinical trial results in 1964. This time-proven medication can achieve substantial elevations in HDL-C and HDL2; reductions in LDL-C, high-sensitivity C-reactive protein, and fibrinogen; and reductions in clinical events and all-cause mortality. It also can help induce arteriographic regression.

The mechanism of action of nicotinic acid has been clarified with the elucidation of the nicotinic acid receptor, which is a G protein–coupled receptor called HM74, and the gene that codes for the protein has been cloned. The mechanism of action of nicotinic acid has been clarified with the elucidation of the nicotinic acid receptor, which is a G protein–coupled receptor called HM74, and the gene that codes for the protein has been cloned.38

Nicotinic acid promotes transfer of cholesterol out of macrophages for uptake by HDL and is stimulated by nicotinic acid. This attribute of nicotinic acid helps drive cholesterol out of fatty plaque and onto HDL3 for eventual removal. This nicotinic acid–induced promotion of cholesterol efflux out of plaque helps to explain the success of atherosclerosis regression trials that used nicotinic acid as 1 component of combination drug therapy.39 Contrary to popular belief, with appropriate clinical support, high compliance rates can be achieved with nicotinic acid.

LDL-C–Lowering Only Therapy Versus LDL-C–Lowering Plus HDL-C–Raising Therapy Trials

For purposes of this discussion, combination therapy is defined as ≥2 pharmacological treatments designed to affect lipoprotein metabolism in 2 different directions. The most common example is 1 drug to reduce LDL-C and another to increase HDL-C.

Studies using such a combination of lipid medications have consistently demonstrated better clinical and arteriographic results compared with LDL-C–lowering only studies. Most combination lipoprotein drug studies have used arteriographic end points and consequently smaller groups compared with clinical end-point trials. However, in addition to arteriographic change, the HDL Atherosclerosis Treatment Study (HATS) investigated the effect of combination treatment on clinical events as a primary hypothesis. The results of the combination drug studies are informative and clinically important to achieve the best clinical outcome for CHD patients. Table 2 compares clinical event reduction in LDL-C–lowering only versus LDL-C–lowering plus HDL-C–raising trials. In Table 2, combination therapy trials have achieved an average 71.6% relative risk reduction compared with 27.2% in monotherapy clinical end-point trials and 29.6% in monotherapy arteriographic trials. It is also helpful to appreciate that long-term follow-up of combination drug
trials has revealed dramatic reduction in events and mortality. A 10-year follow-up of Familial Atherosclerosis Treatment Study (FATS) and a 7-year follow-up of the Cholesterol Lowering and Atherosclerosis Study (CLAS) have reported 93% and 62% reductions in death and myocardial infarction. \(^1\)\(^,\)\(^2\) Table 1 compares arteriographic outcomes from LDL-C–lowering only versus LDL-C–lowering plus HDL-C–raising trials. It is noteworthy that although LDL-C–lowering only drug studies have slowed the rate of arteriographic progression, arteriographic regression is uncommon. In contrast, 3 of the 5 LDL-C–lowering plus HDL-C–raising combination drug therapy arteriographic trials have demonstrated mean arteriographic regression.

The NNT reflects the improved efficiency of combination LDL-C–lowering and HDL-C–raising drug therapy compared with LDL-C–lowering drug therapy alone. In general, LDL-C–lowering only trials require that 20 to 60 subjects be treated to prevent 1 event, and this has been argued to be “cost-effective.” \(^3\) However, in NIH-funded combination LDL-C–lowering plus HDL-C–raising studies, the NNT was on average 9.6. \(^4\)\(^–\)\(^6\) This illustrates the greatly enhanced efficiency in reducing clinical events of LDL-C–lowering plus HDL-C–raising therapy compared with LDL-C–lowering therapy alone.

**Conclusions**

It is clear that although a focus on LDL-C reduction has benefited some patients by reducing CHD risk, large numbers of patients remain at elevated risk despite substantial reductions in LDL-C. The well-intentioned focus on LDL-C reduction alone ignores the multiple other lipoprotein disorders contributing to CHD risk and the better clinical and arteriographic outcomes when combination LDL-C–lowering plus HDL-C–raising therapy is used compared with LDL-C lowering alone. Combination LDL-C–lowering and HDL-C–raising lipid treatment drug studies have been shown to be more efficacious than LDL-C lowering alone in reducing CHD events, inducing arteriographic regression, and improving efficiency, as noted by the substantially lower NNT. On the eve of new therapies designed to increase HDL-C, it is important to appreciate that currently available LDL-C–lowering and HDL-C–raising lipid drug therapy has convincingly demonstrated a superior clinical benefit compared with LDL-C lowering alone in NIH-funded clinical trials. Furthermore, clinicians can use this approach at the present time and not delay treatment of reverse cholesterol transport in appropriate patient populations.

**Source of Funding**

The final aspects of this article were in part accomplished with support from the Federal FEMA grant #EMW-2006-FP-01744.

**Disclosures**

Dr Superko received a research grant from Agilent Technologies and has served on the speakers’ bureau for KOS Pharmaceuticals. Dr King reports no conflicts.

Response to Superko and King

Scott M. Grundy, MD, PhD

Superko and King argue that lowering of low-density lipoprotein (LDL) is inadequate to stem the cardiovascular epidemic and that other lipid targets (eg, high-density lipoprotein [HDL]) could provide additional risk reduction. First, the authors underestimate the benefit of LDL lowering in secondary prevention. When clinical trial data are combined, including the Treating to New Targets (TNT) and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) studies, maximal LDL lowering can be calculated to reduce cardiovascular events by 45% to 50%. Moreover, epidemiological studies imply that prolonged LDL lowering in primary prevention will reduce risk even more. Of course, modifying other lipid targets (eg, other apolipoprotein B–containing lipoproteins or HDL) might produce more benefit. In particular, lowering of atherogenic triglyceride-rich lipoproteins likely will be efficacious. Whether raising HDL by pharmacological intervention that directly targets HDL will reduce cardiovascular risk remains to be proven. This idea is attractive to many investigators because of the known association between low HDL levels and cardiovascular risk. On the other hand, it is possible that a low HDL is primarily a marker of risk caused by other factors (eg, metabolic syndrome) and that direct HDL raising will not substantially modify risk. To resolve this question, 2 things are needed: development of a drug that will effectively raise HDL (without a confounding lowering of apolipoprotein B–containing lipoproteins) and demonstration of the efficacy of such a drug in a morbidity/mortality outcome trial. Until these have been accomplished, the benefit of raising HDL per se remains in the arena of speculation. See article p 569.
Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

Promise of Low-Density Lipoprotein–Lowering Therapy for Primary and Secondary Prevention

Scott M. Grundy, MD, PhD

One of the foremost medical advances of the past 2 decades has been proof that elevated low-density lipoprotein (LDL) is a cause of atherosclerotic cardiovascular disease (ASCVD) and that lowering of LDL levels will reduce risk for ASCVD.1,2 The application of this knowledge in clinical and public health arenas offers the opportunity to greatly reduce morbidity and mortality from ASCVD. This article outlines the rationale underlying this opportunity.

Response by Superko and King p 573

LDL: The Driving Force of Atherogenesis

Although several major risk factors for ASCVD exist, the realization that elevated plasma LDL is the driving force of atherogenesis highlights the possibilities for prevention. Many studies in laboratory animals have shown that high serum cholesterol levels induce atherosclerotic lesions resembling those found in humans.1 Similarly, humans with severe forms of hypercholesterolemia commonly exhibit premature atherosclerotic disease. Epidemiological studies reveal a strong association between serum cholesterol levels and ASCVD prevalence1; moreover, in populations in which cholesterol levels are low, ASCVD is correspondingly low even when other risk factors are common.4 The latter observation has recently been confirmed through genetic epidemiology; in those persons who carry a mutation causing low cholesterol levels over a lifetime, ASCVD is virtually absent even in the presence of other risk factors.5 Finally, many recent clinical trials have documented that LDL-lowering therapy reduces risk for ASCVD.6 All told, these several lines of evidence indicate that a lifetime of low LDL levels lowers risk for ASCVD by up to 80% to 90% compared with the general population of the United States,5 whereas intensive LDL-lowering therapy even in the presence of advanced atherosclerotic disease reduces risk for major ASCVD events by 40% to 50%.6–8 However, the latter response leaves 50% to 60% of risk untouched; this has called been residual risk.

Residual Risk Beyond LDL Lowering

Because of the success of LDL-lowering therapy, hopes have been raised that the residual risk remaining after LDL reduction can be attacked through other means. Several potential targets for residual risk exist and are worthy of brief attention.

Cigarette Smoking

Ample evidence indicates that cigarette smoking accelerates atherosclerosis and predisposes people to ASCVD syndromes. Continued smoking represents a major cause of residual risk. Fortunately, smoking cessation can reduce ASCVD risk by up to one third.9
Metabolic Syndrome
A major portion of residual risk in many persons can be attributed to the metabolic syndrome. This condition contains several risk factors of metabolic origin. They include high triglycerides, low HDL, elevated blood pressure, hyperglycemia (diabetes), and prothrombotic and proinflammatory states. Each is a potential target of therapy.

Although many investigators believed for a long time that LDL is the unique atherogenic lipoprotein, strong evidence points to an atherogenic potential of triglyceride-rich lipoproteins that contain apolipoprotein B. Support for this concept comes from studies showing that either serum total apolipoprotein B or cholesterol in LDL plus triglyceride-rich lipoproteins (called non–high-density lipoproteins [HDL]) predicts risk for ASCVD better than LDL does alone. Thus, the cholesterol in apolipoprotein B–containing triglyceride-rich lipoproteins probably should be combined with LDL as the preferred target of cholesterol-lowering therapy.

Low serum levels of HDL are associated with increased risk for ASCVD. The association seemingly can be explained through 3 mechanisms. First, a low HDL commonly reflects an increase in atherogenic lipoproteins (eg, triglyceride-rich lipoproteins and small LDL particles). Second, a low HDL level is associated with other risk factors of the metabolic syndrome (eg, insulin resistance, elevated blood pressure, and prothrombotic and proinflammatory states). Third, a low HDL per se may directly promote atherogenesis; if this is true, HDL could be a direct target of therapy. To date, however, the efficacy of HDL-raising therapy to reduce ASCVD risk has not been proved.

Elevations of blood pressure unquestionably predispose to ASCVD and add to residual risk beyond LDL. Treatment of hypertension is a critical part of a risk-reduction strategy.

Hyperglycemia may accelerate atherogenesis, but in addition, it predisposes to complications once ASCVD develops (eg, myocardial dysfunction and heart failure, renal impairment, and stroke). When diabetes is present, control of hyperglycemia is mandated to reduce microvascular disease and the complications of ASCVD.

Arterial Wall Factors
The development of atherosclerosis appears to be driven largely by elevated LDL and the other major risk factors. However, once significant atherosclerosis develops, instabilities in plaque structure can lead to rupture or erosions, causing acute ASCVD syndromes. In advanced plaques, instabilities can be mitigated somewhat by control of the major risk factors, but removing all instability by risk factor control undoubtedly will prove difficult. For this reason, arterial wall factors will continue to play a role in the residual risk of persons with advanced atherosclerosis.

LDL Lowering in Secondary Prevention
The proven efficacy of LDL-lowering therapy in patients with established ASCVD makes it a mainstay in clinical management. Recent clinical trials have demonstrated that risk reduction continues down to an LDL cholesterol level near 70 mg/dL. Through use of high-dose statins or LDL-lowering drugs in combination, LDL concentrations can be reduced to these safer levels in most patients. In particular, for patients at very high risk who have established coronary heart disease plus other high-risk conditions (eg, metabolic syndrome, diabetes, or persistent cigarette smoking), reducing LDL cholesterol to near or below 70 mg/dL is a reasonable option. In addition, intensive management of other risk targets beyond LDL, as discussed above, is clearly indicated.

Primary Prevention of ASCVD
A remaining challenge of great importance is how to apply our understanding of the role of LDL in atherogenesis to management in those at risk who do not yet have established ASCVD. Because a high proportion of the population will eventually develop ASCVD, it makes sense to intervene widely with LDL-lowering therapy. However, before almost universal intervention can be advocated, several issues must be addressed and resolved.

Balancing the Therapeutic Triad: Efficacy, Cost, and Safety
The efficacy of maintaining a low LDL level throughout life through healthy life habits or intervention with drugs later in life has been amply demonstrated. Although LDL-lowering efficacy in primary prevention has not been documented through clinical trials in all subgroups of the population (eg, women and the elderly), the massive evidence of efficacy in both epidemiology and multiple clinical trials makes the assumption of universal benefit reasonable. Nonetheless, some debate likely will persist on the issue of extrapolation, even though the general efficacy of LDL-lowering to reduce risk is widely accepted.

Since the advent of statins, their high cost has been a barrier to their widespread use. The same holds true for other cholesterol-lowering drugs. Recently, however, since several statins have come off patent, their costs have fallen dramatically. The cost barrier thus has been largely removed and is no longer a significant issue.

The question of safety remains, however. As a general rule, statins have proved to be remarkably safe, even with long-term use. In secondary prevention in which any side effects are more than outweighed by benefits, the use of statins is
rarely questioned. Occasionally, serious side effects such as severe myopathy can occur. For this reason, statins should be used judiciously in all patients, particularly those at risk for myopathy.25 The safety-to-benefit ratio becomes a greater issue when lower-risk persons are prescribed a cholesterol-lowering drug for a lifetime. Unfortunately, even when side effects cannot be documented, perceived side effects of statins too commonly stand in the way of their long-term use. Limited adherence thus is a barrier to effective primary prevention.

**Therapeutic Selection Based on Short-Term Risk**

Current treatment algorithms for use of cholesterol-lowering drugs are designed to balance efficacy and cost. Most guidelines use 10-year risk as the deciding metric for drug initiation. For example, the National Cholesterol Education Program identified a 10-year risk for hard coronary heart disease (myocardial infarction plus coronary heart disease death) of 10% as a threshold for drug consideration.¹ This threshold was based on cost-effectiveness calculations assuming a drug price that was 20 times the current costs of generic statins. Therefore, using the 10-year threshold of 10% as a means to control drug costs is no longer necessary. A new metric is needed. If costs of therapy are to remain in the prescribing equation, costs of implementing and monitoring drug therapy must be considered in the context of current clinical practice; the costs of drugs per se are no longer the critical issue. Drug safety can be another factor to consider for initiation of drug therapy, but drug safety is a more nebulous issue than drug costs for policy makers. Safety of therapy depends more on the judgment of the practicing physician than on policy.

**Changing the Focus to Lifetime Risk**

Considering the large fraction of the population that will eventually develop ASCVD, investigators are more and more shifting their attention away from 10-year risk to lifetime risk. Most authorities believe that adoption of a healthy lifestyle is the foundation of lifetime prevention. A healthy lifestyle includes smoking cessation, an LDL-lowering diet, weight control, and regular physical activity. A healthy lifestyle can be promoted through both public health and clinical strategies.¹ However, the possibility of using LDL-lowering drugs as an adjunct to lifestyle is becoming increasingly attractive²⁶; even so, any public health policy using drugs for prevention carries its devils in the details, as indicated below.

One proposal is to use a polypill containing a statin, a blood pressure–lowering drug, and aspirin. The concept as a public health strategy is superficially attractive, but several perplexing questions arise: Who are candidates for the polypill? Who will pay? How will patients be monitored? Will the public agree? Will individuals adhere to therapy over a lifetime? An alternative approach would be for the medical profession to take responsibility for implementing widespread drug therapy for primary prevention. Many of the same questions as above could be asked. Moreover, if intervention of this type is not made profitable to the medical profession, healthcare providers might be reluctant to embrace the concept and to become implementers of the strategy. What appears to be needed is a new practice model for primary prevention that is both financially rewarding to providers and financially acceptable and effective for a large segment of the population.

**Conundrum of Population Subgroups**

Because drug therapy is strongly driven by clinical trial evidence, there is reluctance on the part of many to extrapolate results from some tested subgroups to other untested ones.²⁷ The benefits of cholesterol-lowering therapy have been demonstrated mainly in middle-aged men. Before these findings in men can be applied to women, some would demand that comparable trials be carried out in women. Other population subgroups such as the elderly have not been studied as extensively either. Unfortunately, cholesterol-lowering trials are expensive, and there seems to be little incentive to carry out the requested trials now that statins have become generic. Thus, universal extrapolation of existing data could present a conceptual barrier. This is particularly the case for primary prevention with drug therapy in persons at uncertain risk.

**The Promise of Imaging**

Matching the intensity of preventive therapy with absolute risk, even lifetime risk, is a sound principle. Risk factors undoubtedly carry predictive power for ASCVD. Current treatment strategies are based on estimates of 10-year risk using algorithms that use major risk factors.¹ These algorithms, however, are dominated by age as a risk factor; other risk factors provide considerably less predictive power. Risk factors are even less reliable for long-term prediction for individuals. A possible solution to this dilemma lies in atherosclerosis imaging. The power of imaging for detecting subclinical atherosclerosis to predict future ASCVD events is increasingly being recognized.²⁸–³⁰ Imaging has at least 3 virtues. It individualizes risk assessment beyond use of age, which is a less reliable surrogate for atherosclerosis burden; it provides an integrated assessment of the lifetime exposure to risk factors; and it identifies individuals who are susceptible to developing atherosclerosis beyond established risk factors. Also of importance, in the absence of detectable atherosclerosis, short-term risk appears to be very low. Thus, for primary prevention, a recommendation could be established that detection of significant plaque burden is a preferred strategy for initiation of LDL-lowering drugs. With such a recommendation, major risk factors and emerging risk factors could be used as a guide for selecting subjects for imaging more than as a primary guide for therapy. Once subclinical atherosclerosis is detected, intensity of drug therapy could be adjusted for plaque burden. This 2-step approach to risk assessment could provide a solution to the dilemma of patient selection for cholesterol-lowering drugs in primary prevention. In addition, it could be applied to all population
subgroups. It could also be useful as a guide to low-dose aspirin prophylaxis and cholesterol-lowering therapy.

Conclusions

Elevated serum LDL is a major risk factor for ASCVD and appears to initiate atherogenesis, promote atherosclerosis, and play a role in plaque destabilization and rupture. Without some elevation of LDL, atherosclerosis is slow to develop even when other risk factors are present. The longer the LDL level is kept low, the better for risk reduction.\(^3\) The lower the level that is achieved, the greater the risk reduction will be, particularly in people with advanced atherosclerotic disease.\(^2\)

The major challenge for the medical community is how best to achieve LDL lowering in the general population. This likely will require a rethinking of the medical and public health models of prevention. New models almost certainly will include a broader use of inexpensive LDL-lowering drugs but with improved selection of individuals who are likely to benefit.

Disclosures

In the area of LDL-lowering therapy, Dr Grundy has been an investigator on a grant from Merck and has been a consultant to Pfizer, Merck Schering Plough, and AstraZeneca.

References


25. Pasternak RC, Smith SC Jr, Mairbayer-Merz CN, Grundy SM, Cleeman JJ, Lenfant C, for the American College of Cardiology, American

Response to Grundy

H. Robert Superko, MD; Spencer King III, MD

Dr Grundy’s article, paired with ours, presents an eloquent and cogent rationale for the cardiovascular benefits of low-density lipoprotein cholesterol (LDL-C) reduction. We could not agree more with the statement that a healthy lifestyle is the foundation for lifelong cardiovascular disease prevention. Despite our widespread agreement with the benefits of LDL-C reduction, there are several subtle but clinically important differences that were emphasized in our article. First, the abundance of publicity surrounding the cardiovascular benefits of LDL-C reduction has served to alert the public and medical community to the need for appropriate attention to this issue. However, it also has provided a false sense of security to many patients who eventually have a cardiovascular event despite reduced LDL-C and/or statin therapy. This is explained in part by the common misunderstanding of the difference between relative risk and absolute risk reduction. As noted in our article, a 25% “relative risk” reduction is inadequate as a universal therapy because it leaves many patients at elevated risk for cardiovascular events. We suggest that the number-needed-to-treat calculation may be a better reflection of treatment efficiency. Second, the concept that “lower is better” needs to be challenged on the basis of the existing evidence. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVEIT) study, there was a 16% reduction in the hazard ratio, which was statistically significant (P< 0.005). However, this reflects 26.3% events in the 40 mg pravastatin group versus 22.4% in the 80 mg atorvastatin group, a difference of 3.9 percentage points, and a large number of the atorvastatin group still had a clinical event. The danger of completely focusing on the “lower is better” approach is that many patients will experience a nonfatal or fatal event even with substantially reduced LDL-C. The metabolic syndrome exemplifies the potential for public and medical profession confusion because atherosclerosis in metabolic syndrome patients is primarily a result of metabolic disturbances unrelated to elevated LDL-C. Our position and Dr Grundy’s article are in agreement on many points, with a healthy lifestyle being the foundation of prevention in both our approaches. However, it is wise to recall the 1716 quote from the Hagakure that opened our article, “It is not good to settle into a set of opinions. . . .This is not enough.” See article p 560.
Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk?

Promise of Low-Density Lipoprotein–Lowering Therapy for Primary and Secondary Prevention

Scott M. Grundy, MD, PhD

One of the foremost medical advances of the past 2 decades has been proof that elevated low-density lipoprotein (LDL) is a cause of atherosclerotic cardiovascular disease (ASCVD) and that lowering of LDL levels will reduce risk for ASCVD. The application of this knowledge in clinical and public health arenas offers the opportunity to greatly reduce morbidity and mortality from ASCVD. This article outlines the rationale underlying this opportunity.

Response by Superko and King p 573

LDL: The Driving Force of Atherogenesis

Although several major risk factors for ASCVD exist, the realization that elevated plasma LDL is the driving force of atherogenesis highlights the possibilities for prevention. Many studies in laboratory animals have shown that high serum cholesterol levels induce atherosclerotic lesions resembling those found in humans. Similarly, humans with severe forms of hypercholesterolemia commonly exhibit premature atherosclerotic disease. Epidemiological studies reveal a strong association between serum cholesterol levels and ASCVD prevalence; moreover, in populations in which cholesterol levels are low, ASCVD is correspondingly low even when other risk factors are common. The latter observation has recently been confirmed through genetic epidemiology; in those persons who carry a mutation causing low cholesterol levels over a lifetime, ASCVD is virtually absent even in the presence of other risk factors. Finally, many recent clinical trials have documented that LDL-lowering therapy reduces risk for ASCVD. All told, these several lines of evidence indicate that a lifetime of low LDL levels lowers risk for ASCVD by up to 80% to 90% compared with the general population of the United States, whereas intensive LDL-lowering therapy even in the presence of advanced atherosclerotic disease reduces risk for major ASCVD events by 40% to 50%. However, the latter response leaves 50% to 60% of risk untouched; this has called been residual risk.

Residual Risk Beyond LDL Lowering

Because of the success of LDL-lowering therapy, hopes have been raised that the residual risk remaining after LDL reduction can be attacked through other means. Several potential targets for residual risk exist and are worthy of brief attention.

Cigarette Smoking

Ample evidence indicates that cigarette smoking accelerates atherosclerosis and predisposes people to ASCVD syndromes. Continued smoking represents a major cause of residual risk. Fortunately, smoking cessation can reduce ASCVD risk by up to one third.
Metabolic Syndrome
A major portion of residual risk in many persons can be attributed to the metabolic syndrome. This condition contains several risk factors of metabolic origin. They include high triglycerides, low HDL, elevated blood pressure, hyperglycemia (diabetes), and prothrombotic and proinflammatory states. Each is a potential target of therapy.

Although many investigators believed for a long time that LDL is the unique atherogenic lipoprotein, strong evidence points to an atherogenic potential of triglyceride-rich lipoproteins that contain apolipoprotein B. Support for this concept comes from studies showing that either serum total apolipoproteins that contain apolipoprotein B. Support for this concept comes from studies showing that either serum total apolipoproteins that contain apolipoprotein B. Support for this concept comes from studies showing that either serum total apolipoproteins that contain apolipoprotein B.

The development of atherosclerosis appears to be driven largely by elevated LDL and the other major risk factors. However, since significant atherosclerosis develops, instabilities in plaque structure can lead to rupture or erosion, causing acute ASCVD syndromes. In advanced plaques, instabilities can be mitigated somewhat by control of the major risk factors, but removing all instability by risk factor control undoubtedly will prove difficult. For this reason, arterial wall factors will continue to play a role in the residual risk of persons with advanced atherosclerosis.

LDL Lowering in Secondary Prevention
The proven efficacy of LDL-lowering therapy in patients with established ASCVD makes it a mainstay in clinical management. Recent clinical trials have demonstrated that risk reduction continues down to an LDL cholesterol level near 70 mg/dL. Through use of high-dose statins or LDL-lowering drugs in combination, LDL concentrations can be reduced to these safer levels in most patients. In particular, for patients at very high risk who have established coronary heart disease plus other high-risk conditions (eg, metabolic syndrome, diabetes, or persistent cigarette smoking), reducing LDL cholesterol to near or below 70 mg/dL is a reasonable option. In addition, intensive management of other risk targets beyond LDL, as discussed above, is clearly indicated.

Primary Prevention of ASCVD
A remaining challenge of great importance is how to apply our understanding of the role of LDL in atherogenesis to management in those at risk who do not yet have established ASCVD. Because a high proportion of the population will eventually develop ASCVD, it makes sense to intervene widely with LDL-lowering therapy. However, before almost universal intervention can be advocated, several issues must be addressed and resolved.

Balancing the Therapeutic Triad: Efficacy, Cost, and Safety
The efficacy of maintaining a low LDL level throughout life through healthy life habits or intervention with drugs later in life has been amply demonstrated. Although LDL-lowering efficacy in primary prevention has not been documented through clinical trials in all subgroups of the population (eg, women and the elderly), the massive evidence of efficacy in both epidemiology and multiple clinical trials makes the assumption of universal benefit reasonable. Nonetheless, some debate likely will persist on the issue of extrapolation, even though the general efficacy of LDL-lowering to reduce risk is widely accepted.

Since the advent of statins, their high cost has been a barrier to their widespread use. The same holds true for other cholesterol-lowering drugs. Recently, however, since several statins have come off patent, their costs have fallen dramatically. The cost barrier thus has been largely removed and is no longer a significant issue.

The question of safety remains, however. As a general rule, statins have proved to be remarkably safe, even with long-term use. In secondary prevention in which any side effects are more than outweighed by benefits, the use of statins is
rarely questioned. Occasionally, serious side effects such as severe myopathy can occur. For this reason, statins should be used judiciously in all patients, particularly those at risk for myopathy.25 The safety-to-benefit ratio becomes a greater issue when lower-risk persons are prescribed a cholesterol-lowering drug for a lifetime. Unfortunately, even when side effects cannot be documented, perceived side effects of statins too commonly stand in the way of their long-term use. Limited adherence thus is a barrier to effective primary prevention.

**Therapeutic Selection Based on Short-Term Risk**

Current treatment algorithms for use of cholesterol-lowering drugs are designed to balance efficacy and cost. Most guidelines use 10-year risk as the deciding metric for drug initiation. For example, the National Cholesterol Education Program identified a 10-year risk for hard coronary heart disease (myocardial infarction plus coronary heart disease death) of 10% as a threshold for drug consideration.1 This threshold was based on cost-effectiveness calculations assuming a drug price that was 20 times the current costs of generic statins. Therefore, using the 10-year threshold of 10% as a means to control drug costs is no longer necessary. A new metric is needed. If costs of therapy are to remain in the prescribing equation, costs of implementing and monitoring drug therapy must be considered in the context of current clinical practice; the costs of drugs per se are no longer the critical issue. Drug safety can be another factor to consider for initiation of drug therapy, but drug safety is a more nebulous issue than drug costs for policy makers. Safety of therapy depends more on the judgment of the practicing physician than on policy.

**Changing the Focus to Lifetime Risk**

Considering the large fraction of the population that will eventually develop ASCVD, investigators are more and more shifting their attention away from 10-year risk to lifetime risk. Most authorities believe that adoption of a healthy lifestyle is the foundation of lifetime prevention. A healthy lifestyle includes smoking cessation, an LDL-lowering diet, weight control, and regular physical activity. A healthy lifestyle can be promoted through both public health and clinical strategies.1 However, the possibility of using LDL-lowering drugs as an adjunct to lifestyle is becoming increasingly attractive;26 even so, any public health policy using drugs for prevention carries its devils in the details, as indicated below.

One proposal is to use a polypill containing a statin, a blood pressure–lowering drug, and aspirin. The concept as a public health strategy is superficially attractive, but several perplexing questions arise: Who are candidates for the polypill? Who will pay? How will patients be monitored? Will the public agree? Will individuals adhere to therapy over a lifetime? An alternative approach would be for the medical profession to take responsibility for implementing widespread drug therapy for primary prevention. Many of the same questions as above could be asked. Moreover, if intervention of this type is not made profitable to the medical profession, healthcare providers might be reluctant to embrace the concept and to become implementers of the strategy. What appears to be needed is a new practice model for primary prevention that is both financially rewarding to providers and financially acceptable and effective for a large segment of the population.

**Conundrum of Population Subgroups**

Because drug therapy is strongly driven by clinical trial evidence, there is reluctance on the part of many to extrapolate results from some tested subgroups to other untested ones.27 The benefits of cholesterol-lowering therapy have been demonstrated mainly in middle-aged men. Before these findings in men can be applied to women, some would demand that comparable trials be carried out in women. Other population subgroups such as the elderly have not been studied as extensively either. Unfortunately, cholesterol-lowering trials are expensive, and there seems to be little incentive to carry out the requested trials now that statins have become generic. Thus, universal extrapolation of existing data could present a conceptual barrier. This is particularly the case for primary prevention with drug therapy in persons at uncertain risk.

**The Promise of Imaging**

Matching the intensity of preventive therapy with absolute risk, even lifetime risk, is a sound principle. Risk factors undoubtedly carry predictive power for ASCVD. Current treatment strategies are based on estimates of 10-year risk using algorithms that use major risk factors.1 These algorithms, however, are dominated by age as a risk factor; other risk factors provide considerably less predictive power. Risk factors are even less reliable for long-term prediction for individuals. A possible solution to this dilemma lies in atherosclerosis imaging. The power of imaging for detecting subclinical atherosclerosis to predict future ASCVD events is increasingly being recognized.28–30 Imaging has at least 3 virtues. It individualizes risk assessment beyond use of age, which is a less reliable surrogate for atherosclerosis burden; it provides an integrated assessment of the lifetime exposure to risk factors; and it identifies individuals who are susceptible to developing atherosclerosis beyond established risk factors. Also of importance, in the absence of detectable atherosclerosis, short-term risk appears to be very low. Thus, for primary prevention, a recommendation could be established that detection of significant plaque burden is a preferred strategy for initiation of LDL-lowering drugs. With such a recommendation, major risk factors and emerging risk factors could be used as a guide for selecting subjects for imaging more than as a primary guide for therapy. Once subclinical atherosclerosis is detected, intensity of drug therapy could be adjusted for plaque burden. This 2-step approach to risk assessment could provide a solution to the dilemma of patient selection for cholesterol-lowering drugs in primary prevention. In addition, it could be applied to all population
subgroups. It could also be useful as a guide to low-dose aspirin prophylaxis and cholesterol-lowering therapy.

Conclusions
Elevated serum LDL is a major risk factor for ASCVD and appears to initiate atherogenesis, promote atherosclerosis, and play a role in plaque destabilization and rupture. Without some elevation of LDL, atherosclerosis is slow to develop even when other risk factors are present. The longer the LDL level is kept low, the better for risk reduction. The lower the level that is achieved, the greater the risk reduction will be, particularly in people with advanced atherosclerotic disease.

The major challenge for the medical community is how best to achieve LDL lowering in the general population. This likely will require a rethinking of the medical and public health models of prevention. New models almost certainly will include a broader use of inexpensive LDL-lowering drugs but with improved selection of individuals who are likely to benefit.

Disclosures
In the area of LDL-lowering therapy, Dr Grundy has been an investigator on a grant from Merck and has been a consultant to Pfizer, Merck Schering Plough, and AstraZeneca.

References
Dr Grundy’s article, paired with ours, presents an eloquent and cogent rationale for the cardiovascular benefits of low-density lipoprotein cholesterol (LDL-C) reduction. We could not agree more with the statement that a healthy lifestyle is the foundation for lifelong cardiovascular disease prevention. Despite our widespread agreement with the benefits of LDL-C reduction, there are several subtle but clinically important differences that were emphasized in our article. First, the abundance of publicity surrounding the cardiovascular benefits of LDL-C reduction has served to alert the public and medical community to the need for appropriate attention to this issue. However, it also has provided a false sense of security to many patients who eventually have a cardiovascular event despite reduced LDL-C and/or statin therapy. This is explained in part by the common misunderstanding of the difference between relative risk and absolute risk reduction. As noted in our article, a 25% “relative risk” reduction is inadequate as a universal therapy because it leaves many patients at elevated risk for cardiovascular events. We suggest that the number-needed-to-treat calculation may be a better reflection of treatment efficiency. Second, the concept that “lower is better” needs to be challenged on the basis of the existing evidence. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction (PROVEIT) study, there was a 16% reduction in the hazard ratio, which was statistically significant (P < 0.005). However, this reflects 26.3% events in the 40 mg pravastatin group versus 22.4% in the 80 mg atorvastatin group, a difference of 3.9 percentage points, and a large number of the atorvastatin group still had a clinical event. The danger of completely focusing on the “lower is better” approach is that many patients will experience a nonfatal or fatal event even with substantially reduced LDL-C. The metabolic syndrome exemplifies the potential for public and medical profession confusion because atherosclerosis in metabolic syndrome patients is primarily a result of metabolic disturbances unrelated to elevated LDL-C. Our position and Dr Grundy’s article are in agreement on many points, with a healthy lifestyle being the foundation of prevention in both our approaches. However, it is wise to recall the 1716 quote from the Hagakure that opened our article, “It is not good to settle into a set of opinions. . . .This is not enough.” See article p 560.
Promise of Low-Density Lipoprotein–Lowering Therapy for Primary and Secondary Prevention
Scott M. Grundy

Circulation. 2008;117:569-573
doi: 10.1161/CIRCULATIONAHA.107.720300
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/117/4/569

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/