Elevated low-density lipoprotein cholesterol (LDL-C) and elevated non-high-density lipoprotein cholesterol (non–HDL-C = total cholesterol minus HDL-C) are recognized as major risk factors for cardiovascular disease (CVD). Most cardiovascular risk reduction strategies for individuals with dyslipidemia focus on controlling LDL-C and non–HDL-C levels, with specific targets based on a person’s global risk. The role of atherogenic particles such as the apolipoprotein B (apoB)-containing lipoproteins (particularly LDL) in development and progression of atherosclerosis is well established. In patients with elevated triglycerides (TG) (200–499 mg/dL), other apoB-containing particles, such as very-low-density lipoprotein (VLDL), become more abundant and may contribute to the atherosclerotic process. Atherosclerosis typically begins in early adulthood and progresses over several decades before symptoms appear. The build-up of atherosclerotic lesions may eventually cause angina or precipitate life-threatening thrombotic events such as myocardial infarction (MI). The relationships between dyslipidemia, atherosclerosis, and CVD risk have become an increasing area of research and were assessed in MESA (titles of clinical trials reported in Appendix I). This prospective evaluation identified dyslipidemia as a powerful CVD risk factor in otherwise healthy adults. In addition, a recent study suggests...
ed that atherosclerosis may be assessed using carotid intima-media thickness (CIMT) and elevated coronary artery calcium in patients with hypercholesterolemia.6

A 15-year study assessing coronary heart disease (CHD) incidence demonstrated that approximately 3% of subjects had an LDL-C-lowering variation in the gene for the proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9).7 PCSK9 affects cholesterol concentrations by degrading LDL receptors, leading to increased circulating concentrations of LDL-C.8,9 Loss-of-function mutations in the gene for PCSK9 diminish this activity, lowering LDL-C levels. Results provide compelling evidence for significant CVD risk reduction associated with lifelong low LDL-C concentrations.7

Given the asymptomatic nature of atherosclerosis progression and the seriousness of potential CVD events, the timely implementation of prevention strategies focused on effective control of LDL-C and non–HDL-C concentrations is now recognized as a critical public health goal. In fact, many individuals with dyslipidemia do not achieve recommended lipid goals, suggesting a lost opportunity for decreasing cardiovascular risk. Cholesterol management is one of the top priorities promoted by Million Hearts, a national initiative to prevent 1 million MIs and strokes over the next 5 years.10 Notably, when the much-anticipated Adult Treatment Panel (ATP) IV guidelines are released in the near future, current recommendations may need to be reconsidered.11 This review discusses recommended CVD risk reduction pharmacotherapies for various patient populations with dyslipidemia in light of recently published clinical data and explores emerging areas of research.

Criteria for Selection and Assessment of Literature

PubMed.gov was searched using the terms dyslipidemias, lipids, lipid-lowering therapy, and hydroxymethylglutaryl-CoA reductase inhibitors or statin. The literature search was limited to articles reporting randomized controlled trials published in English between January 1, 2004, and July 1, 2011. Initial search results were narrowed to include only large, multicenter studies. Separate searches on PubMed and Google were performed to identify large observational studies, recent meta-analyses (published in 2010-2011), US government statistics on disease prevalence, and practice guidelines published since 2004. Additional references were identified through retrieved articles.

Recommended Lipid Goals

The 2004 update of the National Cholesterol Education Program (NCEP) ATP III guidelines recommends 4 different sets of lipid goals for individuals at high, moderately high, moderate, and low risk of CHD death and nonfatal MI, with LDL-C as the primary target of therapy (Table 1).2,11,12 Non–HDL-C concentrations are a secondary target of therapy in patients with TG levels 200 mg/dL or higher (Table 1).2 For example, a target of LDL-C less than 130 mg/dL or non–HDL-C less than 160 mg/dL would be recommended for a patient with 2 or more risk factors and a global 10-year risk of less than 10%, whereas an LDL-C goal of less than 100 mg/dL (optional goal <70 mg/dL) would be recommended for a patient with diabetes and established CHD (ie, very high risk). In their 2008 consensus statement, the American Diabetes Association and the American College of Cardiology (ACC) essentially confirmed the ATP III treatment goals for patients at high or very high risk for CVD events. In addition, they proposed specific target values for apoB (Table 1); apoB is the serum lipid parameter that most accurately reflects the total number of atherogenic particles in the circulation.5 In its 2011 clinical guidance for the treatment of patients with familial hypercholesterolemia (FH), the National Lipid Association recommends a 50% or more reduction in LDL-C concentrations for adult and pediatric patients (aged >8 years) with LDL-C greater than 190 mg/dL (Table 1).12 A recent update from the American Heart Association/ACC Foundation guideline on secondary prevention and risk reduction in patients with atherosclerotic vascular disease recommends reducing the LDL-C to less than 100 mg/dL and by 30% or more.11 For patients with CHD who are at highest risk, the American Heart Association/ACC Foundation guideline indicates that an LDL-C goal of reduction to less than 70 mg/dL is reasonable (Table 1).

Treatment of Dyslipidemia

Therapeutic lifestyle changes, including diet,13 exercise,14 and avoidance of sedentary behaviors,15 are essential for reducing cardiovascular risk. However, these measures are often insufficient to achieve the recommended lipid goals in high-risk patients with elevated LDL-C, such as patients with FH as well as dyslipidemic patients with diabetes, and/or established CHD. Lipid goal attainment in these patients often requires drug therapy; these therapies are summarized in Table 2.16-27 Statins are the most potent LDL-C-lowering agents available, have a good safety profile, and are generally well tolerated.28-31 Statins have been shown to reduce CVD risk in diverse patient populations, including primary prevention populations,32-38 diabetics,39,40 and the elderly.38,41 Thus, statin therapy is the primary LDL-C-lowering treatment option for high-risk patients who fail to achieve LDL-C goals with therapeutic lifestyle changes.3 When LDL-C lowering drug therapy is prescribed in high-risk or moderately high-risk patients, it is advised that the intensity of therapy be sufficient to achieve at least a 30–40% reduction in LDL-C levels and, if possible, a greater than 50% reduction in LDL-C in patients with CHD or CHD risk equivalent.3 In addition, a 50% or more reduction in LDL-C is recommended for pa-
patients with FH. Compared with other lipid-lowering agents, rosuvastatin and atorvastatin are potent enough as monotherapy to more often achieve this degree of LDL-C reduction (Table 2).

LACK OF OPTIMAL THERAPY IN CLINICAL PRACTICE

Recent studies suggest that one reason many individuals with dyslipidemia or at high risk for CVD do not achieve or maintain recommended lipid goals is nonoptimal treatment. L-TAP 2, a multinational survey of 9955 adults with dyslipidemia (75% receiving statin therapy), found LDL-C goal attainment rates of 86%, 74%, and 67% for individuals at low (≤1 risk factor), moderate (≥2 risk factors), and high (coronary or other atherosclerotic vascular disease or diabetes mellitus) risk, respectively. Notably, LDL-C less than 70 mg/dL was achieved by only 30% of patients at very high risk. Lipid goal attainment was significantly lower for patients with diabetes and for those with metabolic syndrome compared with patients without these risk factors. The GWTG study, a database analysis of records from 65,396 patients hospitalized in the US for acute coronary syndrome (ACS), found that most patients received inadequate lipid-lowering therapy at discharge. For example, less than 50% of patients with LDL-C higher than 130 mg/dL at hospitalization received intensive lipid-lowering therapy (therapy likely to achieve >50% reduction in LDL-C) at discharge. Data from the Medications Applied and Sustained Over Time registry including patient records from 41 US hospitals showed that of 341 patients with ACS who were prescribed statin therapy on discharge, 71% maintained LDL-C levels of 100 mg/dL or less and only 31% maintained LDL-C of 70 mg/dL or less at 12 months’ follow-up. The median LDL-C concentrations at baseline were 82 mg/dL in patients who received lipid-lowering therapy before hospitalization (n = 314) and 109 mg/dL in patients who did not receive prior lipid-lowering therapy (n = 474). These findings suggest the need for more intensive lipid-lowering statin therapy in high-risk patients.

Benefits and Risks of Intensive Statin Therapy

Efficacy in Cardiovascular Risk Reduction

Both baseline lipid concentrations and statin doses are highly significant predictors of lipid goal attainment. Results of a recent meta-analysis of data from 170,000 participants of 26 statin trials published by the Cholesterol Treatment Trialists’ Collaboration suggest that more intensive

<table>
<thead>
<tr>
<th>Organization</th>
<th>Lipid Goals, mg/dL</th>
<th>LDL-C</th>
<th>Non–HDL-C</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP ATP III Guidelines (2004)²</td>
<td>High risk: CHD or CHD risk equivalent (eg, diabetes or 10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Moderately high risk: ≥2 risk factors (10-year FRS 10-20%)</td>
<td>&lt;70 (optional)</td>
<td>&lt;100 (optional)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Moderate risk: ≥2 risk factors (10-year FRS &lt;10%)</td>
<td>&lt;130</td>
<td>&lt;160</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Low risk: 1 or no risk factor</td>
<td>&lt;130</td>
<td>&lt;160</td>
<td>NA</td>
</tr>
<tr>
<td>ADA/ACC Consensus Report (2008)³</td>
<td>Highest risk: CVD or diabetes plus additional major CVD risk factors</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td></td>
<td>High risk: No diabetes or known CVD but ≥2 major CVD risk factors, or diabetes but no other major CVD risk factors</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>AHA/ACCF Guideline on Secondary Prevention (2011)⁴</td>
<td>All pts. with coronary or other atherosclerotic vascular disease</td>
<td>≥30% reduction and &lt;100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>In pts. with CHD at very high risk⁵</td>
<td>&lt;70 (reasonable)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NLA Expert Panel on FH, Clinical Guidelines (2011)¹²</td>
<td>Adults (aged ≥20 years) with FH and LDL-C ≥190 mg/dL or non–HDL-C ≥220 mg/dL</td>
<td>≥50% reduction</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Children (aged ≥8 years) with FH and LDL-C ≥190 mg/dL or non–HDL-C ≥220 mg/dL</td>
<td>≥50% reduction or &lt;130</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; ADA/ACC = American Diabetes Association/American College of Cardiology; ADA/ACC = American Heart Association/American College of Cardiology Foundation; ApoB = apolipoprotein B; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; FRS = Framingham risk score; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; NLA = National Lipid Association; TG = triglycerides.

²Factors that favor reducing LDL-C levels to <70 mg/dL also place patients in the category of very high risk. The 2004 update of the ATP III guidelines lists, in addition to the presence of established CVD, risk factors such as (1) multiple major risk factors (especially diabetes); (2) severe and poorly controlled risk factors (especially continued cigarette smoking); (3) multiple risk factors of the metabolic syndrome (especially high TG ≥200 mg/dL plus non–HDL-C ≥130 mg/dL with low HDL-C [≤40 mg/dL]); and (4) the presence of ACS.²

³Patients with CHD plus (1) multiple major risk factors (especially diabetes); (2) severe and poorly controlled risk factors (especially continued smoking); (3) multiple risk factors of the metabolic syndrome (especially triglycerides ≥200 mg/dL plus non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and (4) ACS.

⁴All patients with FH are considered at high risk for CHD.
therapy leading to lower LDL-C concentrations generally is associated with greater reduction in CVD risk, including a 10% reduction in all-cause mortality (rate ratio [RR], 0.90; 95% CI 0.87 to 0.93) for every 38.6 mg/dL reduction in LDL-C.\textsuperscript{47} The 26 analyzed trials included both primary and secondary prevention populations, thus representing patients with different levels of risk and a diversity of risk factors. Subgroup analyses demonstrated that the benefit of intensive therapy in preventing a first major vascular event was similar for men and women and included a highly significant 25% proportional risk reduction (p < 0.0001) for every 38.6 mg/dL reduction in LDL-C in patients with no history of CVD.\textsuperscript{47} A previous meta-analysis of patients with stable CHD or with ACS in 4 secondary prevention trials (including TNT,\textsuperscript{48} IDE-AL,\textsuperscript{49} PROVE IT–TIMI 22,\textsuperscript{50} and A to Z\textsuperscript{51}) found that a 16% relative risk reduction in coronary death or MI (p < 0.00001) was associated with intensive versus more moderate statin therapy.\textsuperscript{57} In addition, data from the PROVE IT–TIMI 22 trial showed that intensive statin therapy improved prevention of cardiovascular events in patients with ACS.\textsuperscript{59,52}

### Table 2. Lipid-Lowering Medications–Mean Percentage Change in Lipids Reported in Prescribing Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg/day</th>
<th>Length of Treatment, weeks</th>
<th>Effect of Monotherapy on Lipid Concentrations, % Change\textsuperscript{a}</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL-C</td>
<td>TG</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin\textsuperscript{16}</td>
<td>10-80 10</td>
<td>6 16</td>
<td>↓39-60</td>
<td>↓19-37</td>
</tr>
<tr>
<td>fluvastatin\textsuperscript{17}</td>
<td>20-80 24</td>
<td></td>
<td>↓22-36</td>
<td>↓12-25</td>
</tr>
<tr>
<td>lovastatin\textsuperscript{18}</td>
<td>10-80 6 10-80 12-48</td>
<td>40-80 12</td>
<td>↓21-32</td>
<td>↑10-19</td>
</tr>
<tr>
<td>pravastatin\textsuperscript{20}</td>
<td>10-80 6-8</td>
<td></td>
<td>↓22-37</td>
<td>↓11-24</td>
</tr>
<tr>
<td>rosuvastatin\textsuperscript{21}</td>
<td>5-40 6</td>
<td></td>
<td>↓45-63</td>
<td>↓10-35</td>
</tr>
<tr>
<td>simvastatin\textsuperscript{22}</td>
<td>5-80 6-24</td>
<td></td>
<td>↓26-47</td>
<td>↓12-33</td>
</tr>
<tr>
<td><strong>Bile acid sequestrant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>colesevelam\textsuperscript{23}</td>
<td>4.5 g 24</td>
<td></td>
<td>↓18</td>
<td>↑9</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ezetimibe\textsuperscript{24}</td>
<td>10 12</td>
<td></td>
<td>↓18</td>
<td>↓8</td>
</tr>
<tr>
<td><strong>Fibrate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fenofibrate\textsuperscript{25}</td>
<td>48-145 12-24</td>
<td></td>
<td>↓21</td>
<td>↓29</td>
</tr>
<tr>
<td><strong>Prescription omega-3 fatty acid ester</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA/DHA\textsuperscript{26,c}</td>
<td>4.0 g 6-16</td>
<td></td>
<td>↑45</td>
<td>↓45</td>
</tr>
<tr>
<td><strong>Nicotinic acid (niacin)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>niacin extended-release\textsuperscript{27}</td>
<td>0.5-2.0 g\textsuperscript{d} 5-12 (or longer)</td>
<td>6-16</td>
<td>↓7-16</td>
<td>↓16-38</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

\textsuperscript{a}Based on US prescribing information.

\textsuperscript{b}Defined as monotherapy achieving 50% or greater reduction in LDL-C.

\textsuperscript{c}Containing mostly EPA and DHA.

\textsuperscript{d}Dosing was started at 0.50 g/day and increased every 4 weeks by 0.5 g/day, to a maximum dose of 2.0 g/day.
Table 3 provides a summary of recent studies of statins or statin combination therapies.32,33,58 One of the primary prevention trials included in the Cholesterol Treatment Tri-
list’s meta-analysis was the JUPITER study, a large placebo-controlled trial of rosvu-
statin 20 mg in men and women without elevated LDL-C (baseline median LDL-C 108
mg/dL) but with high levels of high-sensitivity C-reactive protein (hsCRP) (≥2.0 mg/L).32 The results showed that inten-
tensive rosvuvasatin therapy, which was associated with mean reductions of 50% in LDL-C and 37% in hsCRP, re-
sulted in a large relative risk reduction (vs placebo) for the composite end point of MI, stroke, arterial revascularization,
hospitalization for unstable angina, and cardiovascular death (hazard ratio [HR] 0.56; 95% CI 0.46 to 0.69; p < 0.00001) after 1.9 years’ follow-up.32 Reductions in both LDL-C and hsCRP were associated with decreased risk for cardiovascular events,59 and attainment of very low LDL-C (<50 mg/dL) was associated with the greatest risk reduction (HR 0.35; 95% CI 0.25 to 0.49).60 These findings sug-
gest that statin therapy may provide greater benefit not only for high-risk patients, but also for individuals without hypercholesterolemia but at increased vascular risk, as in-
dicated by hsCRP levels of 2.0 mg/L or greater. However, the value of hsCRP in assessing risk and predicting treatment efficacy in diverse patient populations remains controversial. MESA detected only a weak association be-
tween hsCRP and subclinical atherosclerosis in otherwise healthy community-dwelling adults.61 A large placebo-
controlled study of simvastatin 40 mg in 20,000 high-risk patients in the UK found no significant association be-
tween baseline CRP and the effectiveness of statin therapy in reducing CVD risk.62

ATTENUATION OF ATHEROSCLEROSIS

Accumulating evidence suggests that intensive statin therapy can slow or reverse the progression of atheroscle-
rosis in patients with coronary artery disease (CAD). Results of the REVERSAL study comparing the effects of atorvastatin 80 mg and pravastatin 40 mg on atherosclerotic disease progression in patients with CAD (mean LDL-C at baseline, 150 mg/dL) showed that only patients receiving intensive therapy (mean LDL-C at end of study, 79 mg/dL) experienced no increase in coronary atheroma burden (percentage change in total atheroma volume).63 SATURN as-
essed the effects of atorvastatin 80 mg and rosuvastatin 40 mg on the progression of atherosclerosis in patients with coronary disease. Percent of atheroma volume, the primary efficacy end point, significantly (p < 0.001) decreased from baseline by 0.99% in the atorvastatin group and 1.22% in the rosuvastatin group; however, there was no significant difference between the treatment groups (p = 0.17).64 In ASTEROID, patients with CAD receiving rosu-
vastatin 40 mg for 2 years achieved a greater than 50%

mean reduction in LDL-C and a 15% increase in HDL-C.65 In addition, rosuvastatin treatment was associated with a significant decrease in atherosclerotic disease burden, as determined by intravascular ultrasound. Similarly, in Japanese patients with stable CAD and dyslipidemia, 1.5 years of therapy with rosuvastatin 20 mg or less was associated with significant reductions from baseline in atherosclerotic plaque volume.66

PLEIOTROPIC EFFECTS OF STATINS

Published studies suggest that statins may have additional benefits beyond cholesterol lowering.67 Statins are thought to improve endothelial function partly by lowering the cholesterol concentrations and by stimulation and up-regulation of endothelial nitric oxide synthase. Statins also may induce angiogenesis by promoting the proliferation, migration, and survival of endothelial progenitor cells. Statins can potentially inhibit platelet deposition and decrease platelet thrombus formation. In addition, statins may have plaque-stabilizing and antiinflammatory properties. However, the contribution of these effects beyond the lipid-modulating effects of this drug class on cardiovascu-
lar outcomes is unknown.

SAFETY OF STATINS

Statin therapy is generally safe and well tolerated.28,47 However, statins may increase the risk of myopathy and commonly are associated with increased levels of hepatic transaminases.28 The risk of myopathy may increase with statin dose, patient age, the presence of specific comorbidities (eg, hypothyroidism, renal impairment), and the use of specific concomitant medications.16,21 Although statins have been associated with cases of rhabdomyolysis, an analysis of 35 randomized controlled trials (N = 135,243) showed that the odds of developing rhabdomyolysis were numerically, but not statistically significantly, greater in the statin group than in the control group (odds ratio [OR] 1.04; 95% CI 0.82 to 1.30; p = 0.073).28 The recent Choles-
terol Treatment Trialists’ meta-analysis found no signifi-
cant difference in overall adverse effects between more-
and less-intensive statin therapy.47 However, results of SEARCH revealed a more than 20-fold difference in the rate of myopathy between patients who received simva-
statin 20 mg (0.03%) and those who received simvastatin 80 mg (0.6%).51 In addition, 7 (0.01%) of the 6031 patients in the 80-mg group developed rhabdomyolysis, and more than 60% of the myopathy cases were attributed to a vari-
ant in the gene that encodes for the organic anion-trans-
porting polypeptide OATP1B1, which regulates the hepatic uptake of statins.66 Food and Drug Administration–mandated changes to the prescribing information of simva-
statin, implemented in June 2011, restrict the use of simva-
Table 3. Recent Major Outcome Studies of Treatment with Statins or Statin Combination Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up</th>
<th>Population</th>
<th>Treatments</th>
<th>Lipid Levels, mg/dL</th>
<th>Primary End Point</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin 80 mg</td>
<td>LDL-C</td>
<td>BL</td>
<td>EOS</td>
</tr>
<tr>
<td>SEARCH (2010)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.7 years</td>
<td>N = 12,064 MI survivors (UK)</td>
<td>Simvastatin 20 mg</td>
<td>TG</td>
<td>205</td>
<td>NR</td>
</tr>
<tr>
<td>SHARP (2011)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.9 years</td>
<td>N = 9270 CKD (international)</td>
<td>Simvastatin 20 mg plus ezetimibe 10 mg Placebo</td>
<td>HDL-C</td>
<td>40.2</td>
<td>0.8&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACCORD lipid (2010)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.7 years</td>
<td>N = 5518 Type 2 diabetes with/without CHD (US, Canada)</td>
<td>Simvastatin 20 mg or 40 mg&lt;sup&gt;b&lt;/sup&gt; plus fenofibrate 54 mg or 160 mg</td>
<td>Event</td>
<td>0.96 (0.83 to 1.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>JUPITER (2008)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9 years</td>
<td>N = 17,802 No CHD LDL-C &lt; 130 mg/dL hsCRP ≥ 2 mg/L (international)</td>
<td>Rosuvastatin 20 mg Placebo</td>
<td>LDL-C</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>SEAS (2008)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>52 months</td>
<td>N = 1873 Mild to moderate asymptomatic aortic stenosis (Europe)</td>
<td>Simvastatin 40 mg plus ezetimibe</td>
<td>TG</td>
<td>126</td>
<td>NR</td>
</tr>
<tr>
<td>JELIS (2007)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.6 years</td>
<td>N = 18,645 Hypercholesterolemia (Japan)</td>
<td>Statins plus EPA 1800 mg</td>
<td>LDL-C</td>
<td>181</td>
<td>181</td>
</tr>
<tr>
<td>AIM-HIGH (2011)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 years</td>
<td>N = 3414 Cardiovascular disease and dyslipidemia</td>
<td>Simvastatin plus placebo</td>
<td>LDL-C</td>
<td>74</td>
<td>67</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; BL = baseline; CFB = change from baseline; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; EOS = end of study; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NR = not reported; RR = risk ratio; TG = triglycerides.

<sup>a</sup>Indicated lipid values are means or medians, depending on study and parameter.

<sup>b</sup>After run-in with simvastatin 20 mg.

<sup>c</sup>Difference versus control group.

<sup>d</sup>At 4-year follow-up.

<sup>e</sup>The dose of simvastatin was modified over course of the study because of changing guidelines.
stain 80 mg to patients who have been taking that dosage for 12 months or more without evidence of muscle toxicity.22 Any patient receiving statin therapy who develops signs of myopathy or rhabdomyolysis should be examined carefully to assess the need for dose reduction, treatment suspension, or change in therapy.

Statin therapy significantly increases the risk of elevated aspartate aminotransferase and alanine aminotransferase.28 Therefore, hepatic enzymes should be measured before statin therapy is initiated and monitored if clinically indicated thereafter.69 Physicians should be aware of the signs and symptoms of hepatotoxicity (eg, malaise, fatigue, lethargy, jaundice, hepatomegaly, increased indirect bilirubin level, and elevated prothrombin time).60 Statin therapy should be discontinued in patients with serious liver injury with symptoms, hyperbilirubinemia or jaundice, or both.69 Statin therapy should not be restarted unless an alternative etiology for hepatotoxicity is found.69

Postmarketing surveillance has reported rare cognitive impairment adverse events (eg, memory loss, forgetfulness, amnesia, memory impairment, confusion) with statin use.69 These adverse events were reported most often in patients older than 50 years; symptoms generally were not serious and were reversible upon statin discontinuation. These reports were not associated with dementia, patient age, statin dose, or concomitant medication use. The data did not suggest that these cognitive adverse events lead to clinically significant cognitive decline.

Statin use also has been associated with increases in glycosylated hemoglobin and fasting serum glucose concentrations and the incidence of diabetes.69 The JUPITER study (N = 17,802) was the first large-scale clinical trial to detect a small but statistically significant increase in the incidence of diabetes with statin therapy, compared with placebo (270 vs 216 reports of diabetes; p = 0.01).32 A subsequent meta-analysis of 13 trials including more than 90,000 participants revealed that statin therapy increased the risk of diabetes by 9% (95% CI 2 to 17).70 Similar results were obtained by a network meta-analysis of 170,255 patients from 76 randomized trials (OR 1.09; 95% CI 1.02 to 1.16).28 A recent meta-analysis of 5 large secondary prevention studies of high- and low-dose atorvastatin, pravastatin, or simvastatin (PROVE IT–TIMI 22, TNT, IDEAL, A to Z, SEARCH) found that more intensive therapy significantly reduced the risk of cardiovascular events (OR 0.84; 95% CI 0.7 to 0.94), but also significantly increased the risk of diabetes (OR 1.12; 95% CI 1.04 to 1.22).71 However, the absolute risk of new-onset diabetes associated with 1 year of intensive therapy was substantially lower (number needed to treat [NNT] to see 1 new case, 498; 95% CI 1.04 to 1.22) than the odds of cardiovascular benefit (NNT to prevent 1 case of a cardiovascular event, 155; 95% CI 0.75 to 0.94). Interestingly, high-dose compared with low-dose simvastatin significantly increased the risk of diabetes without a concomitant significant benefit in secondary prevention. The molecular basis for the increased risk of diabetes with statin therapy remains to be elucidated, but possible mechanisms have been proposed. Statins may directly affect muscle or liver insulin action. Findings from an in vivo model of statin-induced myopathy suggest that statins may be associated with the development of muscle insulin resistance.71,72 Patients taking statins should be counseled to continue to maintain an optimal weight and exercise regularly.

**Optimal Therapy in Special Patient Populations**

**TYPE 2 DIABETES**

All patients with type 2 diabetes are at high risk of cardiovascular events.23 Statins have been shown to provide effective CVD risk reduction in diabetic patients.39,40 A meta-analysis of data from 18,686 participants in 14 randomized trials demonstrated a significant (21%) proportional reduction in major vascular events for every 38.6 mg/dL reduction in LDL-C in participants with diabetes (RR 0.79; 95% CI 0.72 to 0.86; p < 0.0001).40 The same proportional risk reduction was observed in participants without diabetes (RR 0.79; 95% CI 0.76 to 0.82; p < 0.0001). Although these results suggest that the efficacy of statins is not affected by a person’s diabetic status, some diabetic patients receiving statins may have residual cardiovascular risk attributable to non–LDL-C (surrogate for an increase in apoB or lipoprotein particle number) lipid abnormalities such as low HDL-C and high TG. Several studies evaluated the potential clinical benefit of combination therapy with statins and fibrates, which are known to raise HDL-C and lower TG (Table 3). The original 5-year results of the FIELD study failed to show significant risk reduction in coronary events for fenofibrate versus placebo in patients with type 2 diabetes (N = 9795).73 However, a subgroup analysis of the FIELD study found a significant 27% relative RR (RR 0.73; 95% CI 0.58 to 0.91; p = 0.005) for fenofibrate versus placebo in patients with marked dyslipidemia (defined as TG ≥204 mg/dL and HDL-C <42 mg/dL).74 Similar to the findings of FIELD, recent results of the ACCORD lipid study showed that fenofibrate provided no significant additional risk reduction benefit in diabetic patients achieving mean LDL-C concentrations of 80 mg/dL with statin therapy (Table 3).88 Notably, the addition of fenofibrate to statin therapy lowered TG concentrations but did not affect LDL-C or HDL-C concentrations, compared with placebo (Table 3). Also similar to the results of FIELD, a prespecified subgroup analysis of patients with high TG (≥204 mg/dL) and low HDL-C (≤34 mg/dL) concentrations in the ACCORD lipid study revealed a trend toward greater risk reduction with combination therapy. In addition, results from the ACCORD
lipid study suggested a sex-specific treatment effect, with a benefit for men and possible harm for women. Overall, the results of FIELD and ACCORD suggest that, for most patients, a fibrate is unlikely to provide a benefit in risk reduction. However, for some patients, particularly those with high TG concentrations and low HDL-C receiving suboptimal statin therapy, fenofibrate may be beneficial. Fibrate therapy overall has been associated with significant reduction in the risk for nonfatal MI in 2 recent meta-analyses.\textsuperscript{75,76} One meta-analysis included patients with type 2 diabetes mellitus,\textsuperscript{75} and most of the patients in the other meta-analysis had low HDL-C concentrations (ranging from 35 to 40 mg/dL) and high TG concentrations (ranging from 150 to 180 mg/dL).\textsuperscript{76}

**CHRONIC KIDNEY DISEASE**

Although statins have been shown to reduce cardiovascular risk in diabetic patients, the benefits of statin monotherapy in diabetic patients undergoing hemodialysis are unclear. In a study of atorvastatin 20 mg in this population, treatment was not associated with significant cardiovascular benefits.\textsuperscript{77} Mixed results were obtained in AURORA, which examined the effects of rosuvastatin 10 mg in hemodialysis patients (27.9% and 24.8% of patients in the rosuvastatin and placebo groups, respectively, had diabetes).\textsuperscript{78} Although AURORA failed to demonstrate cardiovascular benefits of rosuvastatin versus placebo for the total study population,\textsuperscript{79} a subgroup analysis revealed a 32% risk reduction (HR 0.68; 95% CI 0.51 to 0.90) for cardiac events in diabetic patients undergoing hemodialysis receiving rosuvastatin.\textsuperscript{79} Results of SHARP in patients with chronic kidney disease (CKD), 23% of whom had type 2 diabetes, demonstrated that combination therapy with low-dose simvastatin and ezetimibe was associated with a significant reduction in major atherosclerotic events, compared with placebo (HR vs placebo 0.83; 95% CI 0.74 to 0.94; \textit{p} = 0.0021) (Table 3).\textsuperscript{80} However, it remains unclear whether the observed benefit was due to simvastatin, ezetimibe, or both. Notably, a recent subgroup analysis of the TNT study found that after a median follow-up of 4.8 years, intensive therapy with atorvastatin 80 mg, compared with atorvastatin 10 mg, was associated with a 35% RR reduction in 546 patients with CAD, diabetes, and CKD (HR 0.65; 95% CI 0.43 to 0.98; \textit{p} = 0.04).\textsuperscript{80}

Current evidence suggests that intensive statin monotherapy may be effective in diabetic patients with CKD, whereas statin/ezetimibe combination therapy is effective in patients with CKD, regardless of diabetic status.

**HYPERTRIGLYCERIDEMIA AND MIXED DYSLIPIDEMIA**

Recent findings from a large retrospective study of more than 27,000 patients with mixed dyslipidemia (ie, elevated LDL-C and TG and low HDL-C) suggest that attaining optimal values for lipids other than LDL-C may further reduce cardiovascular risk.\textsuperscript{81} In addition to being the most effective LDL-C-lowering therapy, statins have variable and generally modest effects on HDL-C and TG concentrations (Table 2). Combinations of statins and fibrates often are considered for patients with high LDL-C and TG concentrations because fibrates lower TG concentrations more effectively than statins and combination therapy may provide greater improvement of non–HDL-C and HDL-C than statin monotherapy.\textsuperscript{82} Results of a randomized, double-blind study in 474 patients with hypercholesterolemia and elevated TG showed that rosuvastatin 5-20 mg combined with fenofibrate 135 mg provided significantly better improvement of lipid profiles, including concentrations of LDL-C, HDL-C, TG, and apoB, compared with simvastatin 40 mg.\textsuperscript{83} However, a study conducted in Greece that evaluated 90 patients with hyperlipidemia (LDL-C >160 mg/dL, TG >200 mg/dL) found rosuvastatin 40 mg to be superior to rosuvastatin 10 mg plus fenofibrate 200 mg at lowering LDL-C and non–HDL-C.\textsuperscript{84}

As discussed, data from the ACCORD lipid and FIELD studies provided limited evidence that diabetic patients with high TG and low HDL-C may receive a cardiovascular risk reduction benefit from fenofibrate, with or without statin therapy.\textsuperscript{55,74} However, the increased risk of myopathy resulting from a drug i8nteraction may limit the statin doses that can be used in combination with fibrates. Multiple mechanisms of drug interactions between statins and fibrates have been proposed, including inhibition by fibrates of statin glucuronidation and metabolism via CYP3A4.\textsuperscript{85} Fenofibrate is less likely than gemfibrozil to affect statin glucuronidation,\textsuperscript{85,86} and rosuvastatin,\textsuperscript{87} pravastatin,\textsuperscript{88} flu- vastatin,\textsuperscript{89} and pitavastatin\textsuperscript{90} appear not to be metabolized primarily by CYP3A4. Thus, the risk of myopathy may be lower with these statins plus fenofibrate than with other statin/fibrate combinations. In a recent double-blind clinical study, none of the 355 dyslipidemic patients who received rosuvastatin (5-20 mg) plus fenofibrate 135 mg for 8 weeks experienced drug-related myopathy.\textsuperscript{83}

Niacin is the most effective agent for raising HDL-C concentrations and also lowers TG. Therefore, it is often used to improve lipid profiles in patients with mixed dyslipidemia receiving statins, despite its frequent association with flushing of the face, neck, and trunk.\textsuperscript{88} Recent randomized controlled studies of niacin and other lipid-lowering therapies are summarized in Table 4.\textsuperscript{89,92} In the ARBITER 2 trial, a single-center, placebo-controlled study at Walter Reed Army Medical Center, addition of niacin extended-release to statin therapy significantly increased HDL-C (\textit{p} < 0.001) and slowed the progression of atherosclerosis during the 12-month treatment period in 161 patients, mostly men, receiving statin therapy, with LDL-C less than 130 mg/dL and HDL-C less than 45 mg/dL.\textsuperscript{92} The results of the
The subsequent ARBITER-6 HALTS study, which compared the effects of up to 14 months of add-on therapy with niacin with those of ezetimibe on atherosclerosis in dyslipidemic patients with CHD or with CHD receiving statin therapy, suggested a significant benefit of niacin and no benefit of ezetimibe in this patient group (Table 4). However, the benefit of raising HDL-C with niacin in patients with mixed dyslipidemia is in question after the recent termination of the AIM-HIGH study in 3414 CVD patients from the US and Canada with mixed dyslipidemia. Data from a 32-month follow-up period showed that adding high-dose niacin to simvastatin increased HDL-C and lowered TG but did not significantly reduce the primary composite end point of cardiovascular events. A definitive answer as to the potential benefits of niacin therapy in patients with past MI may have to await the results of the ongoing HPS2-THRIVE trial (clinicaltrials.gov identifier NCT00461630).

The risk reduction benefits of omega-3 acid esters also remain unclear. Results of JELIS demonstrated significant cardiovascular benefits of eicosapentaenoic acid (EPA) 1800 mg daily in secondary prevention for Japanese patients with hypercholesterolemia on statin therapy. In contrast, findings of a large systematic review of data from more than 35,000 participants of 29 randomized controlled studies reporting an outcome of total mortality or coronary artery restenosis following angioplasty suggest that omega-3 fatty acids are safe and well tolerated but overall may have only modest benefit (RR 0.93). Moreover, low-dose supplementation with EPA-DHA (docosahexaenoic acid) or ALA (alpha-linolenic acid) did not significantly reduce the rate of major cardiovascular events among elderly Dutch patients (78% men; mean age, 69 years) who had an MI and were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. Similarly, in a randomized placebo-controlled study of highly purified omega-3 fatty acids, patients with acute MI receiving guideline-adjusted lipid-lowering therapy received currently no further benefit from omega-3 fatty acids. There are currently no studies evaluating the effect of omega-3 fatty acids on cardiovascular outcome in patients with TG concentrations between 200 and 499 mg/dL or greater than 500 mg/dL. However, several studies are being planned.

**FAMILIAL HYPERCHOLESTEROLEMIA**

FH is a common hereditary disorder caused by genetic defects that may affect the function of the LDL receptor, apoB, or PCSK9. Untreated patients with FH are at high risk for CAD because of severely elevated LDL-C. Effective, life-long control of LDL-C from an early age is essential to minimize atherosclerotic disease progression and

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**Table 4. Recent Randomized Controlled Trials of Statin Combination Therapy Assessing CIMT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Population</th>
<th>Treatment</th>
<th>LDL-C, mg/dL</th>
<th>TG, mg/dL</th>
<th>HDL-C, mg/dL</th>
<th>Change in CIMT, mean (SD), mm</th>
<th>p Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENHANCE (2008)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24 months</td>
<td>N = 720</td>
<td>Simvastatin 80 mg plus ezetimibe</td>
<td>319</td>
<td>47</td>
<td>0.0111 (0.0038)</td>
<td>0.29</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>FH (multinational)</td>
<td>Simvastatin 80 mg plus placebo</td>
<td>318</td>
<td>47</td>
<td>0.0058 (0.0037)</td>
<td></td>
<td></td>
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<tr>
<td>ARBITER 6-</td>
<td>≥14 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N = 315</td>
<td>Ezetimibe</td>
<td>85</td>
<td>43</td>
<td>0.0016 (0.0024)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>HALTS CHD,</td>
<td></td>
<td>CHD, stable</td>
<td>Niacin (extended release)</td>
<td>83</td>
<td>42</td>
<td>–0.0102 (0.0026)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>statin therapy</td>
<td></td>
<td></td>
<td>50</td>
<td>(p &lt; 0.001)</td>
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<td>(US)</td>
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<tr>
<td>Avellone (2010)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30 months</td>
<td>N = 86</td>
<td>Simvastatin 20-80 mg plus ezetimibe 10 mg Pts. with history of acute MI</td>
<td>301</td>
<td>46</td>
<td>–0.459</td>
<td>0.0385</td>
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<tr>
<td></td>
<td></td>
<td>Heterozygous</td>
<td>Pts. with atherosclerotic plaques but no history of CV events</td>
<td>301</td>
<td>47</td>
<td>–0.394</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FH (Italy)</td>
<td></td>
<td></td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBITER 2</td>
<td>12 months</td>
<td>N = 167</td>
<td>Niacin (extended release)</td>
<td>87</td>
<td>39</td>
<td>0.014 (0.104)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>(2004)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Coronary</td>
<td>Placebo</td>
<td>91</td>
<td>40</td>
<td>0.044 (0.100)</td>
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<tr>
<td></td>
<td></td>
<td>vascular disease</td>
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<tr>
<td></td>
<td></td>
<td>and low HDL-C</td>
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</table>

<sup>a</sup>p Value for difference between groups.
<sup>b</sup>Study terminated early after planned interim analysis demonstrated clear superiority of extended-release niacin compared with ezetimibe.

BL = baseline; CIMT = carotid intima-media thickness; CHD = coronary heart disease; CV = cardiovascular; EOS = end of study; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglycerides.
lifetime cardiovascular risk.\textsuperscript{97} In addition to strict lifestyle modification, intensive LDL-C–lowering therapy with potent statins such as atorvastatin and rosvastatin generally is required to achieve the 50\% or more reduction in LDL-C recommended by current National Lipid Association treatment guidelines.\textsuperscript{97, 98} Results of the ASAP study demonstrated the benefit of intensive statin therapy (atorvastatin 80 mg) versus conventional therapy (simvastatin 40 mg) in slowing the progression of atherosclerosis in patients with heterozygous FH.\textsuperscript{99} After 2 years of treatment, atorvastatin-mediated attainment of a mean LDL-C concentration of 160 mg/dL was associated with significant regression in CIMT, compared with simvastatin therapy (p = 0.0001).\textsuperscript{99} Statin therapy also reduces LDL-C effectively in children with heterozygous FH, but the long-term effects of statins in children have not been evaluated.\textsuperscript{100} Therefore, statin therapy generally is not recommended for children younger than 8 years.\textsuperscript{101}

Similar to statins, ezetimibe is primarily an LDL-C–lowering agent but is less potent than most statins. The ENHANCE study evaluated the effects on atherosclerosis of adding ezetimibe to high-dose simvastatin in patients with heterozygous FH previously treated with statins. The addition of ezetimibe improved LDL-C and TG profiles (Table 4).\textsuperscript{89} Neither the combination therapy nor simvastatin monotherapy induced CIMT regression; however, baseline mean CIMT values were low in both the combination therapy and simvastatin monotherapy groups (0.70 and 0.69 mm, respectively). The small CIMT values at baseline suggest that hypercholesterolemia was aggressively managed before the study. Ezetimibe and other LDL-C–lowering agents, such as bile-acid sequestrants, should remain treatment options for hypercholesterolemic patients who do not tolerate high-dose statins or have very high concentrations of LDL-C, such as individuals with heterozygous FH.\textsuperscript{97} Recent clinical data suggest that in patients with hypercholesterolemia at moderately high or high risk of coronary heart disease, low-dose rosvastatin (5-10 mg) in combination with ezetimibe 10 mg may lower LDL-C more effectively than rosvastatin monotherapy titrated to higher doses.\textsuperscript{102}

**Summary**

Intensive statin therapy provides significant CVD risk reduction in diverse populations of patients with dyslipidemia and should be considered as the primary treatment option for patients who do not reach recommended lipid goals with lifestyle intervention. For patients who do not tolerate intensive statin therapy or do not achieve adequate LDL-C concentrations with statin monotherapy, other LDL-C–lowering agents, including ezetimibe and bile-acid sequestrants, in combination with appropriate doses of statins, should be con-

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### Appendix I. Clinical Trial Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A to Z</td>
<td>Aggrastat to Zocor</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes</td>
</tr>
<tr>
<td>AIM-HIGH</td>
<td>Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health</td>
</tr>
<tr>
<td>ARBITER</td>
<td>Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol</td>
</tr>
<tr>
<td>ARBITER–6 HALTS</td>
<td>Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies in Atherosclerosis</td>
</tr>
<tr>
<td>ASAP</td>
<td>Atorvastatin versus Simvastatin on Atherosclerosis Progression</td>
</tr>
<tr>
<td>ASTEROID</td>
<td>A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden</td>
</tr>
<tr>
<td>AURORA</td>
<td>A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events</td>
</tr>
<tr>
<td>ENHANCE</td>
<td>Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression</td>
</tr>
<tr>
<td>FIELD</td>
<td>Fenofibrate Intervention and Event Lowering in Diabetes</td>
</tr>
<tr>
<td>GWTG</td>
<td>Get with the Guidelines</td>
</tr>
<tr>
<td>HPS2-THRIVE</td>
<td>Heart Protection Study 2–Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Incremental Decrease in End Points Through Aggressive Lipid-Lowering</td>
</tr>
<tr>
<td>JELIS</td>
<td>Japan EPA Lipid Intervention Study</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin</td>
</tr>
<tr>
<td>L-TAP 2</td>
<td>Lipid Treatment Assessment Project 2</td>
</tr>
<tr>
<td>MESA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
</tr>
<tr>
<td>PROVE IT–TIMI 22</td>
<td>Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22</td>
</tr>
<tr>
<td>REVERSAL</td>
<td>Results of the Reversal of Atherosclerosis with Aggressive Lipid Lowering</td>
</tr>
<tr>
<td>SATURN</td>
<td>Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin</td>
</tr>
<tr>
<td>SEARCH</td>
<td>Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine</td>
</tr>
<tr>
<td>SHARP</td>
<td>Study of Heart and Renal Protection</td>
</tr>
<tr>
<td>TNT</td>
<td>Treating to New Targets</td>
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</tbody>
</table>
sidered. In particular, a combination of ezetimibe and low-dose statin therapy is recommended for dyslipidemic patients with CKD.\textsuperscript{54} Conclusive evidence for a risk reduction benefit of adding fibrates or niacin to statin therapy remains elusive, at least in terms of the specific populations that have been studied.\textsuperscript{85,103} The potential benefits of using these agents need to be weighed against the risks.

Matthew K Ito PharmD FCCP CLS FNLA, Professor of Pharmacy Practice, College of Pharmacy, Oregon State University/Oregon Health & Science University, Portland, OR

Correspondence: Dr. Ito, iton@ohsu.edu

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Conflict of interest: Dr. Ito has received honoraria for speaking from GlaxoSmithKline, Kowa/Lilly, and Abbott and for serving on advisory boards for Kowa/Lilly and Daiichi Sankyo.

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RÉSUMÉ

Dyslipidémies: Le Suivi des Patients par un Traitemnt Hypolipémiant Optimal

MK Ito


OBJECTIF: Évaluer les traitements actuels et les données récentes issues de la recherche concernant le suivi des dyslipidémies.


SÉLECTION DES ÉTUDES ET DE L’INFORMATION: Les articles publiés en langue anglaise, incluant les essais cliniques multicentriques incluant une grande population, ont été retenus.

SYNTÈSE DES DONNÉES: Les lignes directrices du National Cholesterol Education Program, Adult Treatment Panel III américain sur le traitement des adultes pour la diminution du risque cardiovasculaire recommandent des valeurs cibles de cholestérol-LDL et de cholestérol- non HDL précises, basées sur le risque individuel à 10 ans de maladie coronarienne ou sur le risque global. Chez les patients incapables d’atteindre les valeurs-cibles avec des changements d’habitudes de vie, les singes représentent la première ligne de traitement dans la plupart des cas. Les résultats d’essais cliniques à large échelle et bien contrôlés ont montré que les statines sont efficaces en prévention primaire et secondaire des maladies cardio-vasculaires dans plusieurs populations.
différentes, incluant les patients diabétiques et les personnes âgées, et que le traitement optimal par les statines est plus efficace afin d’atteindre les valeurs-cibles et procure une plus grande réduction significative du risque chez les patients souffrant de maladies coronariennes. Les statines sont généralement bien tolérées mais peuvent augmenter le risque de myopathies. Leur emploi a été associé à une élévation des transaminases, un risque augmenté de diabète, même si le risque absolu de diabète est faible comparativement aux bénéfices liés à la diminution du risque. Le traitement en association, incluant une statine, peut être approprié pour certaines populations, mais les bénéfices de l’association sur la réduction du risque demeurent imprécis. L’ézetimibe représente une importante option de traitement chez les patients hypercholestérolémiques qui ne tolèrent pas un traitement optimal par les statines. Même si les fibrates ou la niacine améliore le profil lipidique global chez les patients présentant une hypertriglycéridémie ou un échec au traitement par les statines, leur efficacité pour réduire le risque cardiovasculaire est controversé et leur utilisation pose des problèmes d’innocuité et de tolérance.

CONCLUSIONS: L’intensification de la modification des habitudes de vie et l’augmentation de la posologie de la statine doivent être tentées en premier chez les patients pour lesquels les valeurs cible de cholestérol-LDL et de cholestérol non-HDL ne sont pas atteintes.

Traduit par Denyse Demers