

# Overview of Prevention and Treatment of Atherosclerosis With Lipid-altering Therapy for Pharmacy Directors

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## Abstract

Cardiovascular (CV) disease is the leading cause of mortality and one of the leading causes of disability worldwide. Its economic burden is enormous, and the estimated direct and indirect costs of the disease in 2006 exceeded \$400 billion.

Low-density lipoprotein cholesterol is recognized as a major cause of coronary heart disease and other clinical forms of atherosclerotic disease, and an elevated low-density lipoprotein cholesterol level remains the primary target of lipid-lowering therapy.

Recent retrospective evidence points to deficiencies in the management of patients with atherosclerosis in the clinical practice setting. Enhancing awareness of the need to monitor and treat dyslipidemia in atherosclerosis, and of the benefits of such treatment reported in recent studies, may help to narrow this treatment gap. This review will examine the development of atherosclerosis and the role atherosclerosis plays in the underlying pathophysiology of CV disease. Imaging methods for assessing progression of atherosclerosis and new recommendations for risk-reduction therapy in patients with established atherosclerotic vascular disease are discussed. Emphasis is on newer data regarding the effect of statins in retarding progression of atherosclerosis or even inducing regression of atherosclerosis.

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Cardiovascular (CV) disease is the leading cause of mortality and one of the leading causes of disability worldwide.<sup>1</sup> In the United States, more than 70 million adults have 1 or more types of CV disease, the most prevalent of which are hypertension, coronary heart disease (CHD), stroke, heart failure, and congenital heart defects.<sup>1</sup> The economic burden of CV disease is enormous. Estimated direct and indirect costs of CV disease in 2006 exceeded \$400 billion.<sup>1</sup> Acute coronary syndromes (ACS), characterized by ST-segment elevation myocardial infarction (MI) or unstable angina/non-ST-segment elevation MI, account for about half of deaths related to CV disease, with annual direct costs estimated to be \$75 billion.<sup>2</sup>

For ischemic stroke alone, the Stroke Program at the University of Michigan Medical School projected total US direct and indirect costs will exceed \$2 trillion over the period 2005-2050 (in 2005 dollars).<sup>3</sup> Furthermore, patients at risk for CV events will significantly contribute to the future economic burden associated with CV disease, even in the short term.<sup>4</sup>

Low-density lipoprotein cholesterol (LDL-C) is recognized as the primary factor in the development and progression of atherosclerotic disease, and elevated LDL-C level remains the primary target of lipid-lowering therapy.<sup>5,6</sup> Publication of the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III in 2001,<sup>5</sup> and the full report in 2002,<sup>7</sup> enhanced awareness of the importance of lipid-lowering therapy for both primary prevention of CHD and secondary prevention of CV events in patients with established CHD. In the years following publication of NCEP ATP III, results of several additional clinical trials of lipid-lowering therapy were published that addressed issues not examined in earlier studies.<sup>6,8</sup> These new data have led to new recommendations. Newer studies have also demonstrated benefits of statins in slowing progression or even inducing regression of atherosclerosis.

However, despite the widespread availability of these recommendations and recent studies, and knowledge of the clear association of atherosclerosis and CV disease, evidence from a recent retrospective

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analysis of more than 10 000 patients with newly diagnosed atherosclerosis points to deficiencies in management in a real-world clinical practice setting.<sup>9</sup> In particular, baseline LDL-C levels were not even obtained in most patients, and only one third with a baseline LDL-C level had a second lipid profile in 1-year postdiagnosis. Most patients were not prescribed lipid-lowering therapy at the time of diagnosis, or after diagnosis, regardless of baseline LDL-C level. This undertreatment was seen despite the fact that more than half of patients had an LDL-C level  $\geq 100$  mg/dL at diagnosis of atherosclerosis.

These data suggest a gap between evidence-based guidelines and their application in clinical practice. Enhancing awareness of the need to monitor and treat dyslipidemia in atherosclerosis, and of the benefits of such treatment reported in recent studies, may help to narrow this gap. This review will examine the events leading up to development of atherosclerosis and the role that atherosclerosis plays in the underlying pathophysiology of CV disease. Imaging methods for assessing progression of atherosclerosis and new recommendations for risk-reduction therapy in patients with established atherosclerotic vascular disease are discussed. Emphasis is placed on newer data regarding the effect of statins in retarding progression of atherosclerosis.

### Role of Atherogenesis as the Underlying Cause of CV Disease

Atherosclerosis is the main cause of CV disease, including ischemic stroke, CHD, and ACS.<sup>10-18</sup> The clinical course related to atherosclerotic changes may not be a gradual and progressive one; rather, patients may remain asymptomatic for years, with sudden death marking the first clinical manifestation.<sup>11</sup> Equally unpredictable is the onset of CV events, which have not correlated well with the commonly used Framingham risk status model. The majority of events are seen in patients categorized as low or intermediate risk of CHD based on the Framingham risk equation.<sup>11</sup> These data highlight the need for early diagnosis and treatment of subclinical disease.

Advances in recent research have provided greater understanding of the underlying pathophysiology of atherosclerosis. Evidence now supports that atherosclerosis is a progressive, dynamic, inflamma-

tory process, which can indeed be modified by preventive and therapeutic measures.<sup>15,16,19</sup> LDL-C is the major cause of atherosclerosis and CV disease, and LDL particles in hypercholesterolemic patients provide the initial inflammatory response leading to thrombus formation. The higher the LDL-C level, the greater the risk of atherosclerotic heart disease; conversely, the higher the level of high-density lipoprotein cholesterol (HDL-C), the lower the risk.

There is unequivocal evidence to show that lowering LDL-C can prevent atherosclerotic CV disease and that therapy with the 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) can reduce the occurrence of CV events via LDL-C-lowering—especially in higher doses—and raising HDL-C; anti-inflammatory actions may also be contributory.<sup>8,20-22</sup> Although lowering LDL-C is the primary goal of therapy, good evidence points to low HDL-C levels as an independent predictor of CV disease.<sup>5,20</sup> Studies using statins and other agents that promote rises in HDL-C levels have suggested benefits of this strategy in preventing new or recurrent CV events,<sup>5,8,20,23,24</sup> although data from such trials have been insufficient to recommend a specific goal value for raising HDL-C. However, results of these studies suggest that simultaneous reduction of LDL-C while increasing HDL-C may be required for optimal clinical benefit.

### Pathophysiology of Atherosclerosis

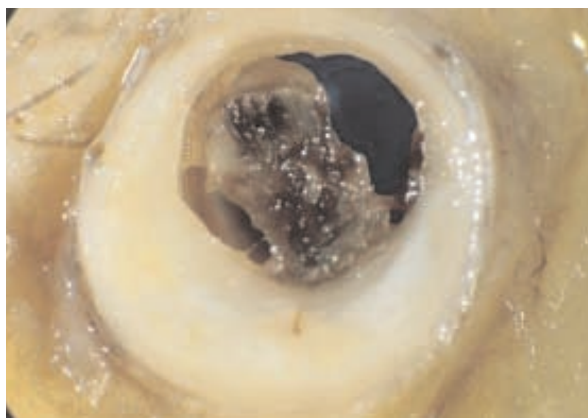
**The Atherosclerotic Plaque (Lesion).** Atherosclerotic plaques consist of lipids, inflammatory cells, connective-tissue elements, smooth-muscle cells, thrombi, and calcium deposits.<sup>14,16,19,25</sup> At the center are foam cells and extracellular lipid droplets, forming a core that is surrounded by smooth-muscle cells and a collagen matrix; lesions are infiltrated by T-cells, mast cells, and macrophages, which show signs of activation and result in cytokine production.<sup>16,19</sup> All aspects of plaque formation and the progressive atherosclerotic process are related to inflammatory responses.

**The Atherosclerotic Process.** Atherosclerosis occurs preferentially at certain sites within the arterial tree, and local conditions such as shear stress and turbulent blood flow result in endothelial dysfunction.<sup>14,19</sup> All medium-sized and large arteries are affected, including the coronary, carotid, cere-

■ **Figure. Stable Versus Unstable Plaque**



**A**



**B**

**Panel A** shows the established stable plaque. In this cross-section of a human coronary artery, there is an established fibrolipid plaque with a core of lipid. The lipid core is separated from the lumen by the plaque cap. The plaque only occupies part of the circumference of the artery, leaving a segment of normal arterial wall. **Panel B** demonstrates thrombosis caused by erosion. The human coronary artery is largely occluded by a mass of thrombus, which is adherent to the surface of a plaque. The plaque itself is intact.

Adapted with permission from Reference 25.

bral, and major extremity arteries, and the aorta and its branches. The affected endothelium expresses surface molecules that attract circulating inflammatory cells and facilitate their migration into the subendothelial space.<sup>19</sup> In particular, LDL-C particles infiltrate the arterial wall in hypercholesterolemic patients and are retained in the intima, with most accumulation at sites of hemodynamic strain; this initiates the inflammatory process in the arterial wall.<sup>16,26</sup> LDL-C is modified via oxidation or

enzymatic reaction, which results in release of inflammatory lipids that in turn result in expression of leukocyte adhesion molecules from endothelial cells.<sup>16</sup>

After migrating into the subendothelial space, monocytes are transformed into macrophages, which take up oxidized LDL particles to form foam cells.<sup>19,26</sup> The earliest structural change in atherosclerosis is a subendothelial accumulation of the lipid-laden foam cells, forming a fatty streak.<sup>19</sup> As the lesion progresses, vascular smooth-muscle cells migrate from the arterial media to the site of injury, where they proliferate and produce matrix proteins, such as collagen and elastin. Smooth-muscle cells proliferate further, and there is an increase in production of extracellular matrix, resulting in the fully formed fibrous plaque with a fibrous cap that faces the arterial lumen<sup>16,19,25</sup> (**Figure, Panel A**).<sup>25</sup> The cap separates the thrombogenic lipid core from circulating platelets and coagulation proteins, preventing thrombus formation.<sup>19</sup>

Although a coronary artery plaque large enough to cause significant stenosis can lead to myocardial ischemia, stenosis does not always occur; in fact, lumen diameter may actually increase during early atherosclerotic stages.<sup>19,25,27</sup> Current thinking is that plaque activation rather than stenosis leads to thrombus formation and myocardial ischemia or infarction.<sup>16</sup> The expanding plaque (even one that does not narrow the lumen) may eventually become exposed due to endothelial erosion or plaque rupture, each leading to thrombosis.<sup>19,25</sup> Both plaque rupture and endothelial erosion are related to increased inflammatory activity within the plaque, and the main stimulus for this inflammation is the reaction of oxidized intimal LDL and macrophages.<sup>25</sup> Erosion with thrombus around exposed subendothelial connective tissue is shown in the **Figure (Panel B)**.

Minor episodes of endothelial erosion or plaque rupture may occur asymptotically; however, repeated cycles of erosion or rupture, thrombosis, and repair gradually increase the size of the plaque.<sup>19,25</sup> Major episodes, with thrombi large enough to impede blood flow, result in symptoms.<sup>25</sup>

#### Detection and Monitoring of Atherosclerosis

Several invasive and noninvasive imaging techniques have been used to detect/diagnose athero-

sclerotic lesions, facilitate risk stratification, and measure atherosclerosis progression and lesion regression in response to lipid-lowering regimens. Some of these are coronary angiography, intravascular ultrasound (IVUS), IVUS-based palpography, angioscopy, intravascular thermography, optical coherence tomography, elastography, magnetic resonance imaging (MRI), computed tomography (CT), B-mode ultrasonography, electron-beam CT, immunoscintigraphy, and molecular imaging.

A detailed discussion of these techniques, many of which are mainly research-oriented, is beyond the scope of this review. The emphasis here is primarily on imaging techniques routinely used in the clinical setting to assess atherosclerosis progression and changes in response to statins. In this context, one strategy for monitoring changes in a patient's risk of clinical events (eg, MI or death) is to use an intermediate (surrogate) end point; that is, one that can be identified before a clinical event occurs and has prognostic value.<sup>28</sup> Trials using intermediate end points require fewer patients than clinical-outcome trials and all patients contribute to study findings.<sup>28</sup> Typically, trials utilizing intermediate end points are also shorter in duration, which reduces the period of time that beneficial treatment is withheld from control groups, and can speed up the development of compounds, allowing an early and rapid insight into a drug's ability to influence CV disease.<sup>28</sup>

Atherosclerosis progression/regression is widely used as an intermediate end point in clinical and observational trials of lipid-altering therapy. The 3 imaging methods used most frequently in the clinical setting for assessing atherosclerotic changes are carotid intima-media thickness (IMT) measurements using B-mode ultrasonography, IVUS, and MRI.<sup>11,28-31</sup>

**Carotid IMT.** B-mode ultrasound is widely used to measure carotid IMT, an early change that precedes the development of the macroscopic plaque.<sup>31</sup> An increase in IMT is an accurate measure of sub-clinical atherosclerosis, and several studies have demonstrated that changes in carotid IMT are a strong predictor of future CV events.<sup>28,29,32</sup>

In the Atherosclerosis Risk in Communities (ARIC) study, the risk of a recurrent CV event was twice as high in individuals with a mean carotid IMT of  $\geq 0.98$  mm compared with those with a

measurement of  $< 0.7$  mm.<sup>33</sup> Moreover, in a meta-analysis of 8 observational studies with general population-based samples, involving 37 195 subjects with mean follow-up of 5.5 years, carotid IMT was a strong predictor of both stroke and MI.<sup>29</sup>

Carotid IMT is increasingly being used for CV risk stratification and as an intermediate end point in clinical trials.<sup>29</sup> It has limited ability to determine extent of plaque burden and nature of plaque composition.<sup>30</sup> However, its noninvasive nature, involving no radiation exposure, is well suited for use in longitudinal studies.<sup>28,29</sup>

**IVUS.** Performed during coronary angiography, IVUS can quantify the extent of atherosclerotic plaque, and has been considered the gold standard for this by some investigators.<sup>30</sup> An ultrasound transducer at the catheter tip is used to obtain tomographic images of the arterial wall. The catheter is withdrawn, either manually or using a motorized pullback device.<sup>30,31</sup> Motorized catheter pullback allows withdrawal at a constant rate, permitting accurate determination of plaque volume within the entire arterial segment.<sup>28,31</sup>

Although standard IVUS does not provide good characterization of plaque composition, analysis of radio frequency backscatter from the ultrasound transducer has been reported to characterize plaque components.<sup>30,31</sup> The major disadvantage of IVUS is invasiveness, limiting use to subjects with clinical indications for coronary angiography. However, the precision and reproducibility it offers may allow for shorter-duration studies with smaller sample sizes.<sup>28</sup>

In vivo, IVUS has confirmed the observation previously made by autopsy—that the extent of atheroma is greater than that detected by angiography.<sup>28,30</sup> It has not yet been definitively demonstrated that IVUS results correlate with clinical outcomes.<sup>30</sup>

**MRI.** MRI can quantify atheroma extent and distinguish its components<sup>30</sup>; it is highly sensitive to small changes in plaque size and possibly composition.<sup>28</sup> High-resolution MRI has been shown to distinguish intact, thick fibrous caps from thin or disrupted fibrous caps, and intraplaque thrombus from extra plaque thrombus.<sup>34</sup>

Currently, use of MRI is generally limited to imaging the walls of medium to large vessels (eg,

■ **Table 1. Major Risk Factors Other Than LDL-C\***

Cigarette smoking
Hypertension (blood pressure of 140/80 mm Hg or greater, or on antihypertensive medication)
Low HDL-C (<40 mg/dL) <sup>†</sup>
Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
Age (men 45 years or older; women 55 years or older)
<p>*Diabetes mellitus is regarded as a CHD risk equivalent.  <sup>†</sup>HDL-C levels of 60 mg/dL or higher count as a “negative” risk factor; its presence removes 1 risk factor from the total count.                  LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease.                  Adapted with permission from Reference 5.</p>

carotid, aorta); improvements are needed to obtain a clearer image and accurately assess the smaller coronary vessels.<sup>28</sup> Advantages of MRI are its non-invasive nature and lack of ionizing radiation.

Obstacles to coronary imaging include cardiac and respiratory motion, small caliber and tortuosity of the coronary vessels, and artifacts caused by stents and sternal wires in patients who have had prior procedures. These obstacles will likely be resolved; experience in coronary imaging is still limited.<sup>34</sup>

**Treatment of Atherosclerosis**

Atherosclerosis is a CHD/CHD risk-equivalent condition, and patients with atherosclerosis are at high risk for subsequent CV events (>20% per 10 years).<sup>5,7,8</sup> CHD risk equivalents (**Table 1**) other than clinical atherosclerotic disease are diabetes and the presence of multiple (2+) risk factors with a 10-year risk of >20%.<sup>5</sup>

LDL-C is the major cause of atherosclerosis and CV disease; it is identified as the primary target of lipid-lowering therapy in the NCEP reports of ATP II and ATP III. All patients with CHD or CHD risk equivalents are considered high risk, and the ATP III recommendation for such patients is an LDL-C goal of <100 mg/dL, in addition to adherence to guidelines for therapeutic lifestyle changes and modification of other existing risk factors, which include smoking, hypertension, and low HDL-C levels.<sup>5,7</sup>

Since the complete NCEP ATP III report was published in 2002, several major clinical trials comparing intensive versus less-intensive therapy have

demonstrated that further lipid lowering below the recommended goal confers additional benefit for secondary prevention.<sup>8,35,36</sup> Based on available evidence, an LDL-C goal of <70 mg/dL is now considered a reasonable therapeutic option in high-risk individuals.<sup>6,8</sup> However, the optimal LDL-C target or “how low to go” has not been clearly established.<sup>31</sup>

An overview of new American Heart Association/American College of Cardiology secondary prevention guidelines for patients with atherosclerotic disease is highlighted in **Table 2**.<sup>6</sup>

Available lipid-lowering therapies for patients with or without established CHD include fibrates (eg, gemfibrozil), bile acid sequestrants (eg, colestevlam), niacin, a cholesterol absorption inhibitor (ezetimibe), and statins.<sup>22,37</sup> Statins have been shown to be the most effective agents for lowering LDL-C,<sup>22,35</sup> and also lower triglycerides.<sup>37</sup> They are considered the lipid-lowering agents of choice for secondary prevention in high-risk patients.<sup>9,11,37</sup>

**Efficacy of Statins in Atherosclerosis**

Secondary prevention with statins is well-documented to reduce the risk of CHD, CV events, and mortality.<sup>22,37</sup> The intensity of therapy in high-risk patients is warranted to achieve LDL-C targets recommended by current guidelines.<sup>5,8</sup> Trials have documented the ability for all statins to lower LDL-C.<sup>38-51</sup> In a multicenter trial comparing the LDL-C lowering with rosuvastatin, atorvastatin, simvastatin, and pravastatin (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses [STELLAR]), an across the dose range analysis found rosuvastatin (10, 20, 40, or 80 mg) to reduce LDL-C by a mean of 8.2% more than atorvastatin (10, 20, 40, or 80 mg), 12% to 18%, and 26% greater than simvastatin (10-80 mg) or pravastatin (10-40 mg), respectively.<sup>38</sup>

**Slowing Progression/Inducing Regression of Atherosclerosis.** The 3 previously described imaging techniques—carotid IMT, IVUS, and MRI—have provided an opportunity to assess the impact of statin therapy on the extent and composition of atherosclerotic plaques in the clinical setting,<sup>31</sup> serving as surrogate end points.<sup>28</sup> Some clinical

studies using these techniques to assess benefits of statin therapy on slowing or reversing the atherosclerotic process are discussed here.

**Efficacy Based on Carotid IMT.** Early studies demonstrated that the rate of progression of carotid IMT could be slowed by use of lovastatin or pravastatin in patients with or without CHD.<sup>31</sup> Some of these studies included “low-risk” patients with subclinical atherosclerosis, suggesting the potential for statins to delay or prevent the onset of CHD.<sup>11</sup> These data were extended by subsequent investigations of the impact of intensive versus moderate lipid lowering with statins. In one trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol [ARBITER]), regression of the common carotid IMT was seen in patients treated with atorvastatin 80 mg/day, whereas progression of carotid IMT was stable in the moderately intensive treatment group (pravastatin 40 mg/day).<sup>31,52</sup> Patients in this study (N = 161) were a mix of clinical and subclinical atherosclerosis. They met ATP II criteria for lipid-lowering therapy, were mostly men (71%), and 46% had known CV disease. The mean baseline LDL-C was 152 mg/dL and mean age was 60 years. Stratification of patients by risk was not provided. Mean baseline carotid IMT was similar in each group (0.62 mm); over 12 months, the mean change in carotid IMT was -0.034 mm in the atorvastatin group and 0.025 mm in the pravastatin group.

Results from the Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin (METEOR) study demonstrated a reduction in the progression of the atherosclerosis disease process. This was a 2-year, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effects of rosuvastatin 40 mg/day on B-mode ultrasound measurement of carotid IMT in low-risk individuals with subclinical atherosclerosis (N = 984).<sup>53</sup> These individuals were middle-aged (mean, 57 years) with either age or Framingham risk scores of <10% as the only risk factor for CHD. In addition, they had moderate carotid IMT increases and elevated LDL-C levels (mean, 154 mg/dL). The primary end point was the annualized rate of change in maximum carotid IMT for 12 carotid sites, based on all scans during the study period. LDL-C was reduced

**Table 2. Secondary Prevention Goals for Coronary and Other Atherosclerotic Disease: AHA/ACC Guidelines\***

<p><b>Smoking</b></p> <ul style="list-style-type: none"> <li>• Complete cessation</li> <li>• No exposure to environmental tobacco smoke</li> </ul>
<p><b>Blood Pressure</b></p> <ul style="list-style-type: none"> <li>• &lt;140/90 mm Hg</li> <li>• &lt;130/80 mm Hg if coexistent diabetes or chronic kidney disease</li> </ul>
<p><b>Lipids</b></p> <ul style="list-style-type: none"> <li>• Assess fasting lipid profile in all patients</li> <li>• LDL-C: &lt;100 mg/dL (further reduction to &lt;70 mg/dL is reasonable)</li> <li>• If triglycerides are &gt;200 mg/dL, non-HDL-C should be &lt;130 mg/dL</li> </ul>
<p><b>Physical Activity</b></p> <ul style="list-style-type: none"> <li>• 30 minutes, 7 days per week (minimum of 5 days per week)</li> </ul>
<p><b>Body Weight</b></p> <ul style="list-style-type: none"> <li>• Maintain BMI of 18.5-24.9 kg/m<sup>2</sup></li> <li>• Waist circumference of &lt;40 inches in men, &lt;35 inches in women</li> </ul>
<p><b>Diabetes Management</b></p> <ul style="list-style-type: none"> <li>• A1C &lt;7%</li> </ul>
<p><b>Antithrombotic Agents</b></p> <ul style="list-style-type: none"> <li>• Aspirin 75-162 mg/day in all patients</li> <li>• In patients post-ACS or percutaneous coronary intervention with stent placement, initiate and continue clopidogrel 75 mg/day in combination with aspirin for up to 12 months (consult specific guidelines)</li> <li>• Warfarin to INR of 2-3 for paroxysmal or chronic atrial fibrillation or flutter, and post-MI when indicated (close monitoring for bleeding indicated when warfarin given with aspirin and/or clopidogrel)</li> </ul>
<p><b>RAAS Blockers</b></p> <ul style="list-style-type: none"> <li>• Consider ACE inhibitor for all patients</li> <li>• Consider ARB in patients intolerant of ACE inhibitors</li> <li>• Consider combination ARB and ACE inhibitor therapy in systolic dysfunction heart failure</li> </ul>
<p><b>Beta-blockers</b></p> <ul style="list-style-type: none"> <li>• Use in all patients who have had MI, ACS, or left ventricular dysfunction with or without heart failure</li> </ul>
<p><b>Influenza Vaccination</b></p> <ul style="list-style-type: none"> <li>• Administer to all patients with CV disease</li> </ul>
<p>*These are abbreviated goals and not complete; consult original publication for detailed information. AHA indicates American Heart Association; ACC, American College of Cardiology; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; A1C, glycosylated hemoglobin; ACS, acute coronary syndromes; INR, international normalized ratio; MI, myocardial infarction; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular. Adapted with permission from Reference 6.</p>

significantly by rosuvastatin compared with placebo (49% vs 0.3%;  $P < .001$ ); increases in HDL-C were also significant in favor of rosuvastatin (8% vs 2.8%;  $P < .001$ ). A statistically significant slowing in the rate of progression of maximum carotid IMT was observed in the rosuvastatin group relative to the placebo group for the 12 carotid sites, as well as for each individual segment.

The METEOR study suggests that rosuvastatin can slow progression even in asymptomatic individuals with subclinical atherosclerosis. The lack of significant regression of atherosclerosis in METEOR in the rosuvastatin group might have been predicted, considering the low-risk status of the population and presence of only subclinical disease. In contrast, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden (ASTEROID) (discussed below), which demonstrated regression via IVUS of coronary atherosclerosis with the same dose of rosuvastatin, comprised patients with more advanced disease, which likely enabled detection of regression that was not seen in the lower-risk individuals in METEOR.<sup>53</sup>

However, a subsequent subanalysis of the METEOR study found that, in the placebo group, higher rates of progression were evident in those with 2 or more risk factors, with little effect on carotid IMT baseline thickness. In the rosuvastatin group, a greater trend toward regression was seen in patients with more risk factors and greater baseline thickness.<sup>54</sup>

**Efficacy Based on IVUS.** The ASTEROID trial used IVUS imaging to assess whether intensive statin therapy could cause regression in coronary atherosclerosis.<sup>23</sup> In this multicenter, open-label, blinded, end-point study, 507 patients with CHD/advanced atherosclerosis received rosuvastatin 40 mg/day for 2 years. The mean LDL-C level was significantly reduced from 130 mg/dL at baseline to 61 mg/dL (−53%;  $P < .001$ ) on treatment; HDL-C levels increased by 15% ( $P < .001$ ). This was accompanied by significant atherosclerosis regression on IVUS. The mean change in percent atheroma volume (entire coronary vessel) was −0.98%; the mean change in volume of the most diseased 10-mm segment was −6 mm<sup>3</sup>. There was a 6.8% median reduction in total atheroma volume after 2 years of

treatment. ASTEROID is the first major study to clearly show regression of coronary atherosclerosis.<sup>23</sup>

In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial (N = 654), patients with angiographically demonstrated coronary artery disease were randomized to a moderate (pravastatin 40 mg/day) or an intensive (atorvastatin 80 mg/day) lipid-lowering regimen for 18 months.<sup>55</sup> The primary efficacy outcome was percent change in atheroma volume, as measured by IVUS. Mean LDL-C was reduced from 150 mg/dL at baseline (both arms) to 110 mg/dL with pravastatin and to 79 mg/dL with atorvastatin. The atherosclerosis progression rate (change in atheroma volume) was significantly lower in the atorvastatin group. Overall, patients in the pravastatin group had progression, whereas those in the atorvastatin group showed no significant change from baseline. Atherosclerosis regression was not observed with either agent.

REVERSAL demonstrated that more intensive lipid-lowering therapy has a greater effect on the intermediate end point of plaque progression, and that the beneficial effect on plaque correlated with the degree of LDL-C reduction achieved.<sup>55</sup> Although REVERSAL was an intermediate or surrogate end-point trial, results from clinical end-point (CV event) trials suggest that halting atherosclerosis progression with intensive lipid-lowering therapy translates into significantly reduced CV morbidity and mortality.<sup>56</sup> In addition, because the REVERSAL and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trials used the same lipid-lowering regimens, the 2 trials taken together support the validity of IVUS changes as an intermediate end point in clinical trials of lipid-lowering therapy.<sup>56</sup>

One ongoing trial is the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS). This is a multicenter, open-label, titrate-to-target study designed to evaluate the effects of rosuvastatin 2.5 to 20 mg/day over 76 weeks on IVUS measurement of atheroma volume in patients with CHD. The investigators seek to enroll 200 patients.<sup>23</sup>

**Efficacy Based on MRI.** The Outcome of Rosuvastatin Treatment on Carotid Artery Athero-

ma: A Magnetic Resonance Imaging Observation (ORION) trial was a randomized, intermediate end-point study designed to measure effects of rosuvastatin 5 or 40 mg on atherosclerosis progression as measured by high-resolution MRI in 43 asymptomatic patients with moderate plaque. Although the initial protocol in this study included titration of subjects in the high-dose group to 80 mg/day (this dose was only used in the clinical development program and never licensed), these subjects were subsequently back-titrated to 40 mg via protocol amendment. After 2 years, LDL-C was significantly reduced from baseline by 39% in the low-dose group and by 58% in the high-dose group (both  $P < .001$ ). MRI changes in carotid artery wall volume did not differ significantly between groups, but significant lipid-rich necrotic core regression was observed in the high-dose group ( $P < .01$ ).<sup>57</sup>

In a further study, 51 hypercholesterolemic patients with asymptomatic aortic or carotid plaques were randomly assigned to simvastatin 20 or 80 mg/day for 18 months. MRI measurements of vessel wall area showed significant reductions from baseline in both groups. There was no significant between-group difference in vessel wall changes, or in on-treatment LDL-C levels; however, the high-dose group had higher baseline LDL-C levels than the low-dose group.<sup>58</sup>

### Formulary Considerations

For reasons provided earlier, statins are the primary agents indicated for secondary prevention in patients with CHD and other atherosclerotic vascular disease. They can reduce the frequency of CV events and mortality in this setting. When selecting a statin or statins for the formulary, several factors must be considered, including comparative efficacy and effectiveness in lowering LDL-C (primary goal of therapy), adverse effects, pharmacokinetics/dose, drug interactions, and cost.

Statins are generally well-tolerated, and their adverse-effect profiles are similar, including more serious events.<sup>37,59</sup> Drug–drug interactions occur most often with lovastatin and simvastatin; the lowest risk of interactions is seen with pravastatin and rosuvastatin.<sup>37</sup> All statins can be given once daily.

In summary and considering all factors, rosuvastatin should be considered for inclusion for manag-

ing patients with an elevated risk of future CHD events due to underlying atherosclerosis.

### Conclusion

Atherosclerosis is the main underlying pathology of CV disease, which is the leading cause of mortality worldwide. A recent retrospective analysis indicates there are many improvement opportunities in the management of atherosclerosis in the clinical setting, suggesting the need for enhanced awareness of newly available guidelines in regard to monitoring and managing lipids in affected patients.<sup>9</sup> In particular, available data indicate that more aggressive lipid-lowering therapy with statins can further improve clinical outcomes relative to less intense therapy. These data are reflected in newer guidelines, which recommend reduction of LDL-C levels to  $<100$  mg/dL in high-risk atherosclerotic patients, including those older than 65 years; a recommended option of lowering to  $<70$  mg/dL should be considered in those at very high risk. Baseline and routine monitoring of lipid levels is essential to ensure achievement and maintenance of LDL-C goals with use of statins. Recent studies have also shown benefit of intensive statin therapy on slowing and even reversing progression of atherosclerosis, as assessed by surrogate imaging measures, such as IVUS and carotid IMT. Results of the METEOR trial have suggested that slowing of disease progression can be achieved by statins even in individuals with subclinical carotid atherosclerosis who are considered at low risk. Closer attention to instituting recent guidelines and clinical-study findings by clinicians in the community can optimize therapy in the atherosclerosis patient and greatly improve long-term outcomes.

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