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New Cholesterol Guidelines: An Update for Pharmacists

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New Cholesterol Guidelines: An Update for Pharmacists

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Abstract
The American College of Cardiology and American Heart Association published new blood cholesterol guidelines in November 2013. The new guidelines place an emphasis on evidence-based treatment of dyslipidemias and primarily use randomized controlled trials to create recommendations for health care providers. Major changes from the previous guidelines include eliminating low-density lipoprotein goals, the classification of statins by lipid-lowering potential and the creation of four major statin benefit groups. The new guidelines also establish the role of non-statins in dyslipidemias and use the Pooled Cohort Risk Assessment Equations to calculate patients' risk for cardiovascular events and the need for cholesterol-lowering medications. Pharmacists play a vital role on the health care team and should be aware of the changes in the cholesterol guidelines in order to improve patient care.

Introduction
According to the Centers for Disease Control and Prevention (CDC), 33.5 percent of American adults have elevated levels of low-density lipoprotein cholesterol (LDL-C), causing hyperlipidemia. This is problematic because high LDL-C levels are linked with an increased incidence of coronary heart disease (CHD), heart attack and stroke. Cardiac death remains the number one cause of mortality in the United States. Many factors influence cholesterol levels, including diet, weight, physical activity, gender, heredity variables and age. Because so many variables exist, treating hyperlipidemia can be a complex process. Treatment complexity creates a need for guidelines to help health care professionals manage their patients' hyperlipidemia. The purpose of the following review is to inform pharmacists about the major changes between the Adult Treatment Panel (ATP) III hyperlipidemia guidelines and the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines that were published in 2013.

Background—Development of New Cholesterol Guidelines
Before the new guidelines were established, the ATP III guidelines released in 2001, and subsequently revised in 2004, were utilized by many health care professionals. These guidelines had nine steps and set LDL-C goals, which were the primary targets of therapy. They also suggested target levels of total cholesterol and high-density lipoprotein (HDL-C). Through the nine-step process, the evaluation of a patient was completed and therapy was determined; treatment options included HMG-CoA reductase inhibitors, bile acid sequestrants, nicotinic acid and fibric acids. Additional risk (via predisposed factors and a calculated Framingham Score) could be calculated, and specific treatment guidelines were outlined if the patient was presenting with metabolic syn-

drome or excessively high levels of triglycerides (TGs). Overall, these previous guidelines were widely accepted by the health care community.

The new guidelines were written by the ACC and the AHA to achieve the goals of decreasing the incidence of cardiovascular diseases and the management of existing disease states through education, research, guidelines and standard practice. Four guidelines were created for: cardiovascular risk, lifestyle modifications, management of blood cholesterol, and management of obese and overweight adults. The ACC and AHA collaborated with the National Heart, Lung and Blood Institute (NHLBI) to develop these guidelines in the hopes that they would improve upon the previous ATP III guidelines. The process for writing the new guidelines began in 2008 where the NHLBI wished to develop critical questions (CQs) that would define the new guidelines through systematic evidence reviews. In 2011, the decision was made to select only the highest quality evidence to review, in response to the Institute of Medicine’s report of trustworthy clinical guidelines. In June 2013, NHLBI began work with the ACC and AHA to complete the four guidelines mentioned above, making them pertinent to the widest population possible for review. Expert panels did not evaluate evidence beyond 2011 (unless specified) and these guidelines are to be updated in 2014.

Rigorous evidence review was performed in the creation of these new guidelines. The ACC/AHA recruited unspecified expert reviewers to examine the content of each document to be used for the new guidelines and to certify that each one had been peer reviewed by NHLBI Advisory Council representatives, key federal agencies and scientific experts; there were no substantive changes made in content used as most was undisputed. Evidence found through these randomized controlled trials (RCTs), meta-analyses and observational studies provided the ACC/AHA with information to classify recommendations of treatment and procedures through the grading of the strength of those recommendations with grades A through E and grade N, which they established themselves. Grade A indicates a strong recommendation, meaning there is a high certainty that the net benefit is substantial with respect to evidence found. Grade D indicates a recommendation against treatment due to evidence of risk or harm to the patient. Grades B and C fall between these two. Grade E shows that evidence is insufficient but a recommendation was still made, and grade N shows that evidence suggests no recommendation for or against. If evidence was ambiguous or minimal, recommendations were not made using those sources. These grades are used to notify the primary care physicians or other medical professionals of the best course of action to take based on evidence.
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Three CQs embodied the guidelines: 1) What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD)? 2) What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD? and 3) For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

Key Differences

No LDL Treatment Goals

The ATP III guidelines recommended LDL-C treatment goals for patients depending on their risk of coronary heart disease. Those with CHD, a CHD risk equivalent (carotid artery disease, peripheral artery disease, abdominal aortic aneurysm or diabetes), or a 10-year Framingham risk over 20 percent had an LDL-C goal of less than 100 mg/dL. Patients with moderate risk of cardiovascular events had an LDL-C goal of less than 130 mg/dL, and those with a lower risk had an LDL-C goal of less than 160 mg/dL. Risk factors included age (men 45 years or older and women 55 years or older), family history of premature CHD, cigarette smoking, low HDL-C (less than 40 mg/dL) and hypertension (above 140/90 mmHg or on medications for blood pressure). The 2004 update to ATP III added an optional LDL-C goal of less than 70 mg/dL in high-risk patients; this included patients who have CHD with diabetes, metabolic syndrome, acute coronary syndrome or severe uncontrolled risk factors. Therapeutic lifestyle changes as well as cholesterol-lowering medications could be used to reach an LDL-C goal.

The Expert Panel that established the new ACC/AHA guidelines eliminated LDL-C and non-HDL treatment goals for patients. Instead, the panel created four major statin benefit groups with a specific statin intensity level that provides optimal treatment of patients within each group. Treatment goals were not included because the Panel did not find evidence in RCTs to support utilizing specific LDL-C and non-HDL goals. All RCTs reviewed by the Panel compared statins to a placebo or compared lower dose statins to higher dose statins; no RCTs that involved titrating statin doses to reach specific LDL-C or non-HDL goals were found, and there was thus no evidence to recommend specific treatment goals for patients like those included in ATP III. The RCT evidence instead showed that it is necessary to use the appropriate statin intensity in the major statin benefit groups in order to reduce the risk of ASCVD.

Additionally, the Expert Panel found that treating LDL-C to a certain goal allowed undertreatment or overtreatment of many patients at risk for ASCVD. For instance, a patient who has not reached the LDL-C goal assigned by his doctor may have been prescribed a non-statin to help further lower cholesterol; this new medication puts the patient at risk for more side effects and drug interactions. This would now be considered overtreatment if the patient is already taking the recommended intensity of statin for his ASCVD risk factors; non-statins will be discussed later in this article, but overall the new guidelines do not support the use of non-statins in cholesterol-lowering alone or in combination with statins.

Undertreatment can occur when a patient reaches their LDL-C goal while taking a suboptimal statin dose for his risk of ASCVD, and therefore his or her dose is never increased to an appropriate level as defined by the new guidelines.

To monitor a patient’s adherence to statin therapy, a baseline lipid panel should be taken as well as a second lipid panel four to 12 weeks after statin therapy is started; after this initial assessment, lipid panels should be completed every three to 12 months as necessary. Baseline liver function tests should be obtained, but it is not necessary to continue measuring liver function unless the patient has symptoms of hepatotoxicity. In patients with an increased risk of muscle pain (such as those with a personal or family history of muscle pain, statin intolerance or the presence of a concomitant medication that increases the risk of myopathy), it is reasonable to get a baseline creatine kinase and then remeasure creatine kinase if muscle symptoms develop.

Statin Classification Groups

The Panel defines the intensity of statin therapy based on the expected percent LDL-C response to a certain statin and its dose. The definitions “high-intensity,” “moderate-intensity” and “low-intensity” statin therapy were developed from the Panel’s systematic reviews of RCTs and meta-analyses. High-intensity statin therapy lowers LDL-C by ≥50 percent, moderate-intensity statin therapy lowers LDL-C by 30 percent to <50 percent, and low-intensity statin therapy lowers LDL-C by <30 percent. Evidence showed the relative decrease in ASCVD risk from statin medications is related to the degree by which LDL-C is lowered, rather than having a specific treatment goal.

Four Major Statin Benefit Groups

Whereas ATP III classified patients into risk groups in order to develop LDL-C treatment goals, the new guidelines created four major statin benefit groups in which the benefits of reducing the risk of ASCVD outweigh potential adverse effects of statins. These groups were established from RCT data that showed primary and secondary prevention of ASCVD with moderate-intensity and high-intensity statins; evidence of ASCVD outcomes was used to determine “who should get which therapy at what intensity.”

The first benefit group consists of individuals with clinical ASCVD, which is defined as a history of myocardial infarction, acute coronary syndromes, coronary or arterial revascularization, stable or unstable angina, peripheral arterial disease of an atherosclerotic origin, or stroke or transient ischemic attack. Because these patients have a high risk of ASCVD events and subsequent death, high-intensity statins are recommended if they are 75 years old or younger. Moderate-intensity statins should be used in patients over 75 years of age because there is no data to show additional ASCVD risk reduction with high-intensity statins in this population, but there is an increased risk of adverse events.

Patients with an LDL-C of 190 mg/dL or higher constitute the second major statin benefit group. Elevations of LDL-C of
Table 1. High-Intensity, Moderate-Intensity and Low-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
</tr>
</tbody>
</table>

- **Atorvastatin 40†-80 mg**
- **Rosuvastatin 20 (40) mg**
- **Simvastatin 10 mg**
- **Pravastatin 10-20 mg**
- **Lovastatin 20 mg**
- **Fluvastatin 20-40 mg**
- **Pitavastatin 2-4 mg**

Specific statins and doses in bold were evaluated in RCTs or meta-analysis and demonstrated a reduction in major cardiovascular events. Statins and doses that are italicized are approved by the FDA but were not tested in the RCTs.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.

†Evidence from 1 RCT only

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

190 mg/dL or higher lead to a higher lifetime risk of ASCVD and are often associated with a genetic predisposition for hypercholesterolemia. High-intensity statins are recommended for these patients to reduce ASCVD risk; non-statins can also be used in these patients to further lower LDL-C if it has not reached the expected level of lowering or the level is still undesirable for the patient’s risk of ASCVD.

Individuals with diabetes between the ages of 40 and 75 years make up the third statin benefit group. Diabetes causes an increased lifetime ASCVD risk and leads to greater morbidity and mortality once ASCVD develops. Diabetics with an estimated 10-year ASCVD risk calculated with the Pooled Cohort Risk Assessment Equations (which will be described later in this article) of 7.5 percent or greater should receive high-intensity statin therapy; moderate-intensity statins are recommended for diabetics with a lower estimated 10-year ASCVD risk. Clinical judgment should be exercised when evaluating diabetics who are less than 40 years old or over 75 years old.

Finally, the last major statin benefit group is comprised of patients between 40 and 75 years old with an LDL-C between 70 and 189 mg/dL who do not have clinical ASCVD or diabetes. The risk of ASCVD in these patients who have a 7.5 percent or higher estimated 10-year ASCVD risk is reduced with either moderate-intensity or high-intensity statin therapy. Clinical judgment and patient preference should be included in the decision as to what intensity is appropriate for the patient and for patients with a lower estimated 10-year ASCVD risk.

For all benefit groups, patients who cannot tolerate the recommended statin intensity should be prescribed the highest intensity statin that they are able to tolerate.

Role of Non-Statins

Another significant change related to cholesterol therapy recommendations involves non-statin medications; however, first-line recommendations are similar to previous guidelines. Like the ATP III guidelines, the new guidelines recommend statins as the drugs of first choice for treating hyperlipidemia. Research has consistently shown that statins are the most effective drugs for lowering LDL-C. Additionally, statins are generally safe and well-tolerated medications. The Panel concluded that statin therapy is far superior to any other medication on the market. The clinical trials reviewed on non-statin medications lacked clinical efficacy or were unreliable. With numerous trials supporting statin use and limited evidence favoring non-statin medications, the Panel restricts its recommendations on non-statin medications to a few circumstances.

Non-statin therapies discussed in the old guidelines included bile acid sequestrants, nicotinic acid, fibric acid derivatives (fibrates), hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs). Though statins were still recommended as first-line treatment, these non-statin therapies were recommended liberally. For instance, bile acid sequestrants could be used in patients with moderate elevations in LDL-C, in younger patients with high LDL-C levels, in women with high LDL-C considering pregnancy, in patients only needing modest decreases in LDL-C and for
combination therapy in patients with highly elevated LDL-C.\textsuperscript{5} Under the new guidelines, non-statin therapy is only recommended if the following criteria are met: the patient has a high ASCVD risk and is currently on the maximum tolerated intensity of statin therapy and continues to have a response less than expected and if the ASCVD risk-reduction benefits outweigh the potential for adverse effects or if a patient is a candidate for statin treatment but is completely statin intolerant. Statin intolerant patients are those who experience serious side effects such as myalgia, rhabdomyolysis and elevated hepatic aminotransferases during statin use. High-risk individuals include those with clinical ASCVD <75 years of age, individuals with baseline LDL \geq 190 mg/dL, and individuals 40 to 75 years of age with diabetes.\textsuperscript{6} See Figure 1 for a summary of the recommendations.

The Panel suggests that health care providers review patients’ adherence to both lifestyle changes and medications and rule out secondary causes of hyperlipidemia before considering non-statins. Research showed non-statins do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects. In the few studies on non-statin medications that have been conducted, non-statins did not show significant additional ASCVD event reductions as compared to statins.\textsuperscript{6,8}

As an example, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial, researchers looked at whether or not increasing HDL-C with extended-release niacin along with decreasing LDL-C with simvastatin would decrease the number of cardiovascular disease events. All patients were given 40 mg of simvastatin and then randomized to receive either niacin or placebo. Patients taking simvastatin with niacin saw increased reductions in LDL-C and TGs with increases in HDL-C. However, there was no difference in the number of CVD events as compared to placebo. The trial was discontinued early due to a lack in incremental benefit in CVD events and an unexplained increase in ischemic stroke in the niacin treatment group.\textsuperscript{6,10}

Similarly, in the Action to Control Cardiovascular risks in Diabetes (ACCORD) trial, researchers sought to determine whether or not fenofibrate treatment reduces the risk of CVD events. Patients were randomized into two groups: simvastatin with fenofibrate or simvastatin plus placebo. Again, the addition of a non-statin did not significantly reduce the risk of CVD events. Unlike niacin combination therapy, fenofibrate combination therapy did not additionally lower LDL-C levels and only had a minimal to moderate impact on HDL-C and TGs respectively. In a small patient group on fenofibrate and simvastatin, patients might have had a decrease in CVD events. Participants affected included those with TGs \geq 204 mg/dL and HDL-C <40 mg/dL. Side effects in both treatment groups were similar except in regard to increased creatinine levels and elevated alanine aminotransferase levels. Patients on fenofibrate and simvastatin had an increased incidence of an alanine aminotransferase (ALT) greater than five times the upper limit of normal. The number of CVD events in women with controlled diabetes was higher in the fenofibrate and simvastatin group as compared to placebo. The lack of a significant decrease in CVD events and the seemingly increased risk of certain adverse events with fenofibrate use with simvastatin led the Panel to forgo recommending fenofibrate as first-line therapy for hyperlipidemia.\textsuperscript{6,11}

The Panel also questioned the validity and generalizability of the other non-statin studies reviewed.\textsuperscript{8} These new non-statin recommendations may decrease the sales of non-statins and simplify patients’ treatment regimens, since they highly encourage physicians to prescribe statins.

**Pooled Cohort Risk Assessment Equations**

The Pooled Cohort Risk Assessment Equations were developed by the Risk Assessment Work Group in order to estimate the 10-year ASCVD risk, which is utilized to identify individuals who are candidates for statin therapy. These equations can be used to predict stroke in patients and to also predict CVD related events in patients who are non-Hispanic Caucasians and African-Americans. Patients who can be evaluated with these equations may be between ages 40 and 79, may be with or without diabetes, and have LDL-C levels of 70 to 189 mg/dL. The risk assessment does not require the counting of risk factors for determining statin therapy initiation. Rather, it focuses on evidence from a global ASCVD risk assessment. This assessment is derived from trials in which statin effectiveness in various patient subgroups was determined (where statins reduce ASCVD events despite existing risk factors). Statin efficacy for improvement of ASCVD events versus statin adverse effects was used for identifying groups of patients who could benefit from the use of statins. Currently, there is an underestimation of high-risk patients who would benefit from statin therapy given the evidence found through reviewing RCT data, but the new guidelines also overestimate the portion of the population who are considered low-risk patients who may benefit from statin therapy. These 10-year ASCVD risk assessments create a large gray area in the medical field in regard to where the use of statins may now be warranted, because some patients who would not have qualified to receive a statin according to the previous ATP III guidelines, would now qualify based on the new guidelines.\textsuperscript{6,12}

**Limitations to the New Guidelines**

There are several limitations to these new cholesterol guidelines. First, the guidelines focus on patient populations that are represented well in RCTs; there are some patients with a high risk of ASCVD who were not represented well in RCTs and were thus excluded from the guidelines. Clinical judgment is important in patient care, particularly where RCT data is lacking as well as in patient populations excluded from the guidelines; the guidelines should not replace clinical judgment, but should be used to inform health care providers. Another limitation is that an independent contractor graded the quality of the evidence used to develop the guidelines. The Expert Panel only considered RCTs, systematic reviews, and meta-analyses graded as fair to good quality by the independent contractor and therefore could have missed
Figure 1. Statin Therapy Monitoring Therapeutic Response and Adherence.

**Statin Therapy: Monitoring therapeutic response and adherence**
*(See 2013 ACC/AHA Blood Cholesterol Guideline)*

- **Assess medication and lifestyle adherence**
  - Fasting lipid panel

- **Indicators of anticipated therapeutic response and adherence to selected statin therapy:**
  - High-intensity statin therapy reduces LDL-C approx. ≥50% from the untreated baseline.
  - Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.

- **Anticipated therapeutic response?**
  - Yes
    - Reinforce continued adherence
      - Follow-up 3-12 mo
      - Yes: Anticipated therapeutic response?
      - No: Reinforce medication adherence
  - No
    - Less-than-anticipated therapeutic response
      - Intolerance to recommended dose of statin therapy?
      - Yes: Management of statin intolerance
      - No: Reinforce medication adherence

- **Reinforce improved adherence**
  - Increase statin intensity
  - OR
  - Consider addition of nonstatin drug therapy
  - Follow-up 4-12 wk & thereafter as indicated

potentially relevant data in observational studies not included in the analysis.6

Further research is necessary in order to update the guidelines in the future, particularly in areas where evidence is currently lacking. The RCTs in the future could study the effects of titrating a statin dose to achieve a specific LDL-C goal compared to a single fixed dose. Other subgroups that could benefit from statin therapy may also be found through RCTs and observational studies as well as additional information on the current benefit groups. Studies can also be conducted to learn more about adding non-statin therapies to achieve cholesterol-lowering and potential LDL-C treatment goals.6,13

These new ACC/AHA cholesterol guidelines have been very controversial among health care professionals. First, many providers disagree with the lack of LDL-C or other treatment goals for patients; the lack of goals makes long-term follow-up and monitoring seem unnecessary if there is no way to monitor the patient’s progress. Additionally, patient’s LDL-C values helped to monitor the residual risk of ASCVD events while on statin therapy, and the new guidelines do not account for the pathophysiology of cardiovascular disease. Next, the new guidelines state that non-statin therapy do not add to cholesterol lowering and reduction of ASCVD risk when combined with statins. This may deter pharmaceutical companies from pursuing the production of non-statin medications and prevent new cholesterol-lowering medications from being developed. Because multidrug therapy is frowned upon in these guidelines, patients who could benefit from multiple cholesterol-lowering medications can be prevented from receiving this treatment; this includes patients with cardiovascular disease who are on the maximum dose of a high-intensity statin and still have high cholesterol.13-15

The new guidelines only cover patients who are between the ages of 40 and 75, which leaves providers with no guidance for patients who are younger or older than this; by the time a patient without ASCVD who has an LDL-C of 180 mg/dL and other risk factors for ASCVD is 40 years old, it is often too late for effective prevention of ASCVD itself, but statins must be used to reduce the risk of recurrent ASCVD events. Finally, the guidelines did not include LDL-C treatment goals because the Expert Panel believed that treatment goals lead to undertreatment or overtreatment of many patients in order to reach the LDL-C goal. However, the new guidelines can still lead to undertreatment and overtreatment. In the example above, the patient with ASCVD risk factors is not receiving statin therapy to prevent the development ASCVD because the risk calculator is not designed to be used until age 40, and even then the patient might not have a 7.5 percent or higher estimated 10-year ASCVD risk; this would be considered undertreatment since he or she is not receiving appropriate care to prevent ASCVD.13-15

Role of Pharmacists
Pharmacists play an important role in cholesterol management and need to be aware of the changes made with the ACC/AHA guidelines. Pharmacists are able to educate patients on the proper use and adverse effects of the medications they are prescribed; in addition, they can answer questions that patients have about their cholesterol and the new guidelines. As the drug experts on the health care team, pharmacists can inform other providers on appropriate statins to use in specific patient populations and about non-statin options in patients who need additional cholesterol lowering or cannot tolerate statins as well as ensure that statins are a necessary and safe addition to a patient’s therapy.16,17

Conclusion
The new ACC/AHA cholesterol guidelines are a major shift in the treatment approach to dyslipidemias. Statins are considered the mainstay of cholesterol-lowering therapy and should be the drug of choice in any patient requiring treatment for dyslipidemia or to prevent ASCVD. Non-statin play a minor role in lipid-lowering therapy and are therefore not recommended by the guidelines unless a patient is statin intolerant. The guidelines created four major statin benefit groups, and each group has a statin intensity appropriate to treat patients falling within that category. Pharmacists are well positioned to apply the new guidelines in cholesterol management as well as educate patients about the new guidelines and the role of statins in lowering cholesterol.

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