Cholesterol Management in Primary Care

EVIDENCE REVIEW

Healthy Hearts for Oklahoma (H2O)
The Oklahoma Cooperative for AHRQ's EvidenceNOW

ADVANCING HEART HEALTH IN PRIMARY CARE

NaRCAD

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Managing High Cholesterol in Primary Care

Introduction

In 2014, 263 million prescriptions were written for lipid-lowering drugs at an annual cost of approximately $13.7 billion. Nevertheless, less than half of those medically eligible for treatment of high cholesterol currently receive medication, even among high-risk patients, despite widely-accepted guidelines for management and solid evidence to guide therapy.

Primary care physicians are on the front lines of advancing care for patients at risk of atherosclerotic cardiovascular disease (ASCVD), and the management of high cholesterol levels is a key element in that effort. In recent years, clinical studies and professional guidelines have reconsidered the approach to cholesterol-lowering medications and have changed the paradigm for assessment and treatment of patients with high cholesterol.

This clinical brief summarizes current practice guidelines and the evidence base on which those guidelines are based. This brief focuses on statins because the evidence supporting their use to reduce risk of CVD is particularly strong. We will, however, briefly review the evidence on non-statin lipid-lowering drugs and provide guidance for using these agents to lower ASCVD risk.

Epidemiology

While the prevalence of hyperlipidemia has declined slightly in the past 20 years, about half of all adults in the U.S. have at least “borderline high-risk” cholesterol levels and about one-third of all adults have elevated LDL cholesterol. According to the third report of the National Cholesterol Education Program on the detection, evaluation, and treatment of high blood cholesterol in adults (ATP III) published in 2003, optimal levels of cholesterol are considered to be LDL < 100 mg/dL (and < 70 mg/dL in some high-risk individuals) and total cholesterol < 200 mg/dL. The more recent cholesterol guidelines published in 2013 by the American College of Cardiology and the American Heart Association do not identify optimal cholesterol levels, but instead promote the importance of risk stratification, which will be discussed in more detail below. Importantly, a graded and continuous association exists between serum LDL concentration, atherosclerosis progression, and cardiovascular mortality (Figure 1).
Figure 1: Association between cardiovascular disease and LDL cholesterol levels

Oklahoma suffers from particularly high rates of CVD, as illustrated in the following statistics.

- In 2011, Oklahoma men had the second worst heart disease death rate in the nation, and Oklahoma women had the third worst rate.
- In 2012 heart disease was the leading cause of death among all adults in Oklahoma.

According to the Oklahoma State Department of Health, however, nearly half of heart disease deaths among Oklahoma males, and a third of heart disease deaths among Oklahoma females are potentially preventable.

Treatment overview

All guidelines for the treatment of hypercholesterolemia stress the importance of encouraging and supporting healthy eating habits, increased physical activity, and the maintenance of a normal BMI in patients, and interventions to meet these goals have been shown to produce modest, yet potentially significant, results. In overweight patients, there is a dose-response relationship between the amount of weight lost and the improvement in lipid profile. For example, a 3 kg weight loss is associated with a mean reduction in triglycerides of at least 15 mg/DL, and a 5–8 kg weight loss is associated with LDL-C reductions of about 5 mg/dL, and HDL-C increases of 2-3 mg/dL. Adopting a diet high in cholesterol-lowering foods, such as plant sterols, viscous fibers, and soy protein can reduce LDL-C by up to 13%.

For many patients, however, lifestyle changes are insufficient, or difficult to sustain on a long-term basis. When lifestyle changes alone fail to lower LDL to normal levels, abundant evidence supports treating hypercholesterolemia with statins to reduce cardiovascular mortality in patients with and without known coronary artery disease.

Primary prevention

Three landmark trials demonstrated that statins lower cholesterol levels and reduce the risk of CVD events, including CVD mortality, in patients without pre-existing CVD.
The 1995 West of Scotland Coronary Prevention Study (WOSCOPS) of 6595 middle-aged men randomized to either pravastatin 40 mg, or placebo and followed for about 5 years showed a 33% relative reduction of coronary mortality (1.9% versus 1.3%; P=0.04) in the pravastatin group compared to placebo. Major coronary events (nonfatal MI or death from CHD) were 31% lower in the pravastatin participants compared to the placebo group.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPs) of approximately 6600 men and women with no history of CAD randomized participants to lovastatin (20–40 mg) or placebo with both arms receiving low saturated fat and low cholesterol diet intervention. After an average follow-up of 5.2 years, lovastatin reduced LDL levels by about 25% and reduced the incidence of first major coronary events (fatal or nonfatal MI, unstable angina, or sudden cardiac death) by 37% (RR 0.63; 95% CI: 0.50-0.79). There were too few events to perform a survival analysis on coronary mortality.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) of 10,300 patients was stopped after 3 years due to a 36% relative reduction of nonfatal MI or CHD mortality and a 21% relative reduction in total cardiovascular events in the atorvastatin treated participants, whose baseline LDL level was reduced from 131 mg/dL to 88 mg/dL.

More recently, a 2011 Cochrane meta-analysis of 14 studies of statin use for primary prevention published between 2001 and 2007 found that statins reduced all-cause mortality by 14% (OR 0.86, 95% CI 0.79 to 0.94) and reduced combined cardiovascular endpoints by 30% (RR 0.70; 95% CI: 0.61-0.79). A 2012 individual patient-level analysis pooled data for 174,149 participants from 27 trials and stratified patients by 5-year risk of major CV event. On average, patients treated with statins who experienced a 39 mg/dL reduction in LDL had a 21% reduction in major CVD events (RR 0.79; 95% CI: 0.77-0.81), an association that held true even for the 2 lowest risk groups.

Taken together, these trials suggest that statins for primary prevention are effective over a wide range of LDL-C levels and provide a similar relative risk reduction as has been observed in secondary prevention trials (see Figure 2 below).

**Secondary prevention**

Meta-analyses of the effect of treatment in patients with known coronary artery disease have found a reduction in the absolute risk of death of about 15%. A review of primary and secondary prevention trials found that every 10% decrease in serum cholesterol was associated with a 15% decrease in coronary heart disease mortality and an 11% decrease in total mortality risk, with no change in non-cardiac mortality. Finally, a meta-analysis of data from >90,000 patients with known CVD risk found that statin therapy can reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 20% per 39 mg/dL reduction in LDL levels. The absolute benefit relates mainly to the patient’s absolute risk level and to the absolute reduction in LDL cholesterol achieved.
ASCVD risk assessment

The 2003 Adult Treatment Panel III guidelines recommended treating patients with statins who had certain high-risk clinical comorbidities (such as coronary artery disease or diabetes) or who were at high risk of developing ASCVD over 10-years, as assessed by the Framingham Risk Score. The Framingham risk score uses variables such as age, gender, cholesterol levels, smoking status, and hypertension to predict the risk of fatal or non-fatal MI and is well validated in European and American populations.22
Subsequent risk scores have been developed that use additional risk factors as well as alternate end-points. The Reynolds risk score, developed in 2007, includes family history of CHD and high-sensitivity-CRP levels.23,24 The Framingham risk score has been modified to predict global CVD events, including coronary events, stroke, claudication, and incident heart failure.25 Most of these risk scores were derived in predominately white populations and later validated in cohorts with white and black patients. Using these tools, cardiovascular risk tends to be overestimated in certain ethnic groups, including Hispanic and Japanese-American men, Native-American women, and Chinese men and women.26

The 2013 Pooled Cohort ASCVD Risk Equations (ASCVD calculator), released as part of the 2013 ACC/AHA cholesterol guidelines, was developed to approximate CVD risk in a racially diverse patient population using data pooled from the Framingham cohort as well as the ARIC and CARDIA studies. The calculator predicts 10-year risk of “hard” cardiovascular end-points, including coronary heart disease death, non-fatal MI, and fatal and non-fatal stroke among white and non-Hispanic blacks. Similar to prior risk scores, the ASCVD calculator overestimates cardiovascular risk in Hispanic and Asian-Americans.5 Even among white and black populations, several studies have suggested that the ASCVD calculator more generally overestimates cardiovascular risk compared to the Framingham-based calculators.27 Of note, these calculators have never been tested against each other in an RCT.

The 2013 ACC/AHA cholesterol guidelines recommend using the ASCVD calculator, and further recommend using a 7.5% or greater 10-year risk of ASCVD as a threshold for initiating statins for primary prevention. This is a lower threshold than that suggested in prior guidelines but represents a more meaningful balance of statin risk versus benefit. Some authors have suggested a higher 10-year ASCVD risk threshold, such as 10% or 12.5%, for statin initiation.28

The risk of developing diabetes from statin treatment is estimated to be 1 in 1000 per year for low-intensity statin and 3 in 1000 per year for high-intensity statin.6 In this setting, 100 patients with a 10-year risk of ASCVD of 10% would need to take a moderate-dose statin daily for 10 years to prevent two heart attacks; among these patients, one would develop diabetes as a result of statin therapy.4

The new cholesterol guidelines make two important recommendations:

1. Clinicians should use shared decision making with the patient when discussing statin initiation for primary prevention. The discussion should include potential for ASCVD risk reduction, adverse effects such as muscle aches and diabetes, and patient preferences.

2. A 10-year ASCVD risk of 7.5% should be used as a guideline for initiating the discussion about statin initiation and should not be used as an absolute threshold.

Among patients with borderline ASCVD risk (10-year risk 5-10%) or among patients with an uncertain risk-benefit profile, the presence of one or more of the following risk factors may lower the threshold for statin initiation:6

- LDL ≥ 160 mg/dL
- Family history of premature ASCVD (< 55 years in 1st degree male relative or < 65 years in 1st degree female relative)
- High-sensitivity C-reactive protein ≥ 2 mg/L
- Coronary artery calcium score ≥ 300 Agatston units
Ankle brachial index < 0.9
Elevated lifetime risk of ASCVD

A 2015 longitudinal community-based cohort study of 2435 statin-naive participants found that the ACC/AHA guidelines for determining statin eligibility, compared with the ATP III, were associated with greater accuracy and efficiency in identifying increased risk of incident CVD and subclinical coronary artery disease, particularly in intermediate-risk participants.29

The use of a clinical decision aid may be helpful in discussing the risks and benefits of statin therapy. The Mayo Clinic Decision aid (http://statindecisionaid.mayoclinic.org) facilitates the use of the ASCVD, ATP-III, and Reynolds risk calculators.

**Table 3: Common cardiovascular risk calculators**

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Outcome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD Risk Calculator</td>
<td>CHD death, non-fatal MI, and fatal and non-fatal stroke</td>
<td>Derived in racially diverse cohort. Outcomes are “hard” CV endpoints that patients care about</td>
</tr>
<tr>
<td>Framingham Risk Score (ATP-III calculator)</td>
<td>Fatal and non-fatal MI</td>
<td>Statin initiation threshold previously recommended at 20%. Using a lower threshold is reasonable.</td>
</tr>
<tr>
<td>Framingham Risk Score (Global CVD)</td>
<td>Coronary events, cerebrovascular events, PAD, heart failure</td>
<td>May be helpful to provide global CV risk to patients</td>
</tr>
<tr>
<td>Reynolds Risk Score</td>
<td>MI, ischemic stroke, coronary revascularization, or CV death</td>
<td>Includes family history, diabetes status, and hs-CRP levels in risk calculation</td>
</tr>
</tbody>
</table>

MI: myocardial infarction. PAD: peripheral arterial disease. CV: cardiovascular
Coronary events: MI, coronary death, acute coronary syndrome, angina; Cerebrovascular events: ischemic or hemorrhagic stroke, transient ischemic attack; PAD: intermittent claudication.


Testing lipid levels

The two main guidelines for lipid screening make similar recommendations, with small points of difference. The 2013 ACC/AHA guidelines are based on cholesterol screening beginning at age 40 and continuing every 5 years until age 79 for individuals without clinical ASCVD. The U.S. Preventive Services Task Force (USPSTF) recommends initiating screening in men at age 35 years, and in women at age 45 years, except for patients with increased risk for cardiovascular, for whom the starting age is 20. A repeat screening interval of 5 years is suggested for low-risk individuals, with a shorter interval in those with borderline results.

Fasting or non-fasting lipid screening?

Current guidelines recommend a fasting lipid profile in order to calculate the LDL cholesterol level (LDL cholesterol = total cholesterol − HDL cholesterol − [triglycerides ÷ 5]). In non-fasting states LDL and triglyceride levels can vary by as much as 20%. However, some patients do not undergo lipid testing due to the inconvenience of fasting or early morning blood draws. Given the possible benefits of increased patient adherence to screening and the ease of testing, it is reasonable to offer non-fasting lipid testing for lower-risk individuals on a routine clinic visit and to use fasting lipid profile testing for higher-risk patients.

Lifestyle modification

For motivated patients with a 10-year risk of ASCVD > 7.5%, 3-6 months of therapeutic lifestyle changes can be attempted before statin initiation for primary prevention. The 2013 ACC/AHA guidelines recommend the following dietary practices for patients who would benefit from a lower LDL-C:

- Diet high in vegetables, fruits, and whole grains
- Low-fat dairy products
- Protein primarily from fish, legumes, and poultry
- Healthy fats (vegetable oils and nuts)
- Limit sugar-sweetened beverages and red meats
- Only 5-6% of calories should come from saturated fat
- Reduce percentage of calories from trans fat

For more detailed guidance, see the following recommended diets to lower LDL-C:

<table>
<thead>
<tr>
<th>Diet</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH diet</td>
<td><a href="https://www.nhlbi.nih.gov/health/health-topics/topics/dash">https://www.nhlbi.nih.gov/health/health-topics/topics/dash</a></td>
</tr>
<tr>
<td>AHA diet</td>
<td><a href="http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Nutrition-Center_UCM_001188_SubHomePage.jsp">http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Nutrition-Center_UCM_001188_SubHomePage.jsp</a></td>
</tr>
</tbody>
</table>
The recommended exercise regimen for patients wanting to lower LDL-C:

- Moderate to vigorous intensity aerobic exercise 3-4 times per week lasting on average 40 minutes per session

Moderate intensity exercise is defined as: 3-6 metabolic equivalent of tasks (METS): e.g., walking briskly (3-5 miles per hour), bicycling slower than 10 miles per hour, yoga, gardening. Vigorous intensity is defined as ≥ 6 METS: e.g., race walking (> 5 miles per hour), jogging, swimming laps, bicycling faster than 10 miles per hour.

**BOTTOM LINE:** for patients with a 10-year risk of ASCVD > 7.5%, attempt therapeutic lifestyle changes for 3-6 months before considering statin therapy. This approach should be used for patients who are highly motivated and have an ASCVD risk that could be reasonably reduced to < 7.5% with optimal risk factor control.

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**Target treatment groups for statins**

The ACC/AHA guidelines identify 4 patient groups with the greatest potential benefit from statin therapy:

**Patients with clinical ASCVD**

Clinical ASCVD includes a history of prior myocardial infarction, acute coronary syndrome, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease.

**Patients with LDL levels: ≥ 190 mg/dL**

Patients with primary severe elevations of LDL (≥ 190 mg/dL) have a high lifetime risk of ASCVD and are likely to have genetic hyperlipidemia. Patients in whom a secondary cause of hyperlipidemia is suspected should be first assessed and treated before pursuing genetic testing. These causes include obesity, medications, hypothyroidism, and nephrotic syndrome.

**Diabetic patients age 40-75 years**

Statins for primary prevention in diabetics should be recommended for those with LDL levels 70-189 md/dL. Patients with levels ≥ 190 mg/dL should receive statin therapy based on level alone, whereas using statins for primary prevention with low LDL levels (< 70 md/dL) has not been studied.

**Patients 40-75 years old at high-risk of ASCVD, defined as a 10-year risk > 7.5%**
Patients without clinical ASCVD with LDL levels < 190 mg/dL who are 40-75 years old with an elevated 10-year risk of ASCVD also benefit greatly from statins. Assessing risk in this primary prevention population will be discussed in detail below. Individuals younger than 40 years or older than 75 years may also benefit from statin therapy if ASCVD risk is high, although this population has not been traditionally included in randomized trials. In these patients, the consideration of additional risk factors and risks of therapy is warranted (see Figure 4).

**Statin therapy**

Statins are the only class of medications shown to improve mortality in primary and secondary prevention of coronary artery disease (CAD), and their benefits also apply to elderly patients without life-threatening co-morbid conditions.¹²,³³

**Statin Intensity**

The 2013 Cholesterol Guidelines classified statins according to the degree by which they reduce LDL levels (Table 4). On average, high intensity statins will reduce LDL levels by ≥ 50% whereas moderate intensity statins will reduce LDL levels by 30% to 50%.

**Table 4. Classification of statins by degree to which they reduce LDL**

<table>
<thead>
<tr>
<th>High-intensity statins</th>
<th>Moderate-intensity statins</th>
<th>Low-intensity statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL by ≥ 50%</td>
<td>Lowers LDL by 30-50%</td>
<td>Lowers LDL by &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg*</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg**</td>
<td>Rosuvastatin 5-10 mg**</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin XL 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Atorvastatin 80 mg daily is preferred but 40mg daily can be used if higher dose not tolerated
** All statins available as generic except Rosuvastatin (Crestor)

Patients with clinical ASCVD should receive a high-intensity statin. In certain circumstances, such as age > 75 years or concern about side effects, a moderate-intensity statin can be used.

**BOTTOM LINE:** Because equipotent doses of statins appear equally effective and equally safe, which statin to prescribe should be based primarily on the amount of LDL lowering required to achieve the desired goal, and on affordability for the patient.
Statin treatment algorithms

The figures below from the 2013 ACC/AHA guidelines may help guide the use of statins and the choice of statin intensity. Figure 3 provides a treatment strategy for patients with clinical ASCVD, very high LDL levels, or diabetes. Figure 4 is an algorithm for treating patients with statins for primary prevention of ASCVD.

Figure 3. Statin treatment algorithm for patients with clinical ASCVD, very high LDL levels, or diabetes mellitus

Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Age ≥21 y and a candidate for statin therapy

Yes

Clinical ASCVD

No

LDL-C ≥190 mg/dL

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y

Yes

Moderate-intensity statin

Yes

Estimated 10-y ASCVD risk ≥7.5%†

High-intensity statin

Age >75 y OR if not candidate for high-intensity statin

Moderate-intensity statin

Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Treatment goals

Most studies evaluating the treatment impact of statin therapy have used fixed doses of statin therapy to lower levels of LDL cholesterol. Few studies titrated statin dose to reach a target level; in these cases, total cholesterol levels were usually targeted. Based on treatment strategies studied in RCTs, the 2013 Cholesterol Guidelines do not recommend titrating statin dose to a specific LDL level. Instead, the guidelines suggest measuring a baseline LDL level and then monitoring LDL for the percentage LDL reduction from that baseline expected with the statin used as a way to assess patient adherence to the statin.⁶
Statin initiation and follow-up

Recommended baseline and follow-up labs are presented in Table 5 below.

### Table 5: Recommended baseline and follow-up labs

<table>
<thead>
<tr>
<th>Recommended lab testing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to statin initiation</td>
<td>Fasting lipid panel and ALT level</td>
</tr>
<tr>
<td>4-12 weeks after statin initiation</td>
<td>Fasting lipid panel</td>
</tr>
<tr>
<td>Up to every 12 months thereafter</td>
<td>Fasting lipid panel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>As needed lab testing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine Kinase (CK)</td>
<td>Check at baseline in patients at high risk of myopathy (personal or family history of muscle disease, statin intolerance, or medications that increase risk). Check during follow-up if muscle symptoms or generalized fatigue</td>
</tr>
<tr>
<td>ALT</td>
<td>Check during follow-up if evidence of hepatotoxicity</td>
</tr>
</tbody>
</table>

On follow-up lipid panel testing, evaluate for anticipated therapeutic response: LDL decrease by > 50% for high intensity statin or 30-50% for moderate intensity statin. If a patient has a smaller response and therapy is tolerated, assess adherence to lifestyle changes and medication regimen. In some cases, screening for secondary causes of hyperlipidemia will be necessary. If improvement in adherence does not improve LDL response, some patients may benefit from non-statin therapy to lower cholesterol (see section on non-statin therapies below).

### Adverse Effects

Adverse effects associated with statin use tend to be dose-related. Although monitoring for hepatotoxicity was previously recommended for patients taking statin, the actual incidence of new liver disease was so low that this approach was not beneficial. Patients should be screened for normal liver function before starting a statin.

### Muscle related symptoms

Statins are safe and generally well-tolerated. Randomized controlled trials found little to no excess muscle adverse event rates, such as rhabdomyolysis or myalgias. A rare but serious side effect of statins is statin-associated myopathy, affecting 1 per 1000 to 1 per 10,000 people on standard dose statins. In contrast to RCTs, patient registries have demonstrated that up to 29% of patients experience statin-associated muscle symptoms with higher rates of statin...
discontinuation or non-adherence. Among patients with statin-associated muscle symptoms who discontinue therapy, over 90% are ultimately able to tolerate the same statin or a different statin with careful reintroduction and monitoring.

If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria.

If mild to moderate muscle symptoms develop during statin therapy:

- Discontinue the statin until the symptoms can be evaluated.
- Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).
- If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
- If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
- Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
- If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms.
- If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.

Patients who are intolerant to this strategy may ultimately tolerate alternate day or twice-weekly dosing strategies. Alternatively, patients may need to be treated with non-statin therapies, depending on the clinical indication.

The 2013 AHA/ACC guidelines do not recommend routine creatine kinase (CK) testing for patients receiving statins, however such measurement is reasonable for those thought to be at risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy. Measuring CK levels is also reasonable in patients with muscle pain, tenderness, stiffness, cramping, weakness, or general fatigue.

**Diabetes**

Statin treatment appears to increase the incidence of diabetes by a very small amount. This increased risk is generally out-weighed by the benefit derived from statin use.

In a subgroup analysis of the Cholesterol Treatment Trialists (CTT) meta-analysis of 14 statin trials including 71,370 non-diabetic participants, there was one extra case of diabetes over 4 years for every 255 people treated with statin. In the same studies statin treatment resulted in a
reduction of 5.4 major coronary events (coronary mortality and non-fatal myocardial infarction) per 255 patients treated for the same period of time.\textsuperscript{38}

In an analysis of the JUPITER trial a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed.\textsuperscript{39} When compared to 6095 participants without risk factors for diabetes, there was a 52% reduction in primary endpoints (HR 0.48; 95% CI: 0.33–0.68) but no new cases of diabetes. It was calculated that the use of statins accelerated the average time to diagnosis of diabetes by 5.4 weeks.\textsuperscript{39}

Although the absolute risk of causing new-onset diabetes with statins is low, the risk of incident diabetes needs to be considered whenever statins are prescribed. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines.\textsuperscript{6} Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.\textsuperscript{6}

**Cognitive impairment**

Concerns have been raised about the association between statin use and memory loss or cognitive impairment. Meta-analyses of RCTs have not confirmed that statins negatively impact memory; however such changes could have been underreported.\textsuperscript{40} Although the literature is inconclusive, the FDA has acknowledged that statins may be associated with cognitive impairment in rare cases, though causality is not certain.\textsuperscript{41} The expert panel of the 2013 ACC/AHA cholesterol guidelines did not find evidence that statins had an adverse effect on cognitive changes or risk of dementia.\textsuperscript{6}

**Guidelines for minimizing adverse effects**

The 2013 AHA/ACC guidelines suggest that the following characteristics may predispose patients to statin adverse effects:\textsuperscript{6}

- Multiple or serious comorbidities, including impaired renal or hepatic function.
- History of previous statin intolerance or muscle disorders.
- Unexplained hepatic transaminase (ALT) elevations ≥3 times upper limit of normal.
- Patient characteristics or concomitant use of drugs affecting statin metabolism.
- Age >75 years.
- History of hemorrhagic stroke.
- Asian ancestry.

The following recommendations can increase the safety of statin use:\textsuperscript{6}

- Perform baseline ALT measure before initiating a statin.
- Measure hepatic function if symptoms suggest hepatotoxicity (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, yellowing of skin or sclera).
- Consider decreasing statin dose when 2 consecutive values of LDL-C levels are <40 mg/dL.
- Avoid initiating simvastatin at 80 mg daily or increasing simvastatin dose to 80 mg daily.
Use caution prescribing statins in patients 75 years or older
Use caution prescribing statins in patients taking concomitant medications that alter drug metabolism or who are taking multiple/complex medications.
Evaluate patients presenting with a confusional state or memory impairment while on statin therapy for non-statin causes such as exposure to other drugs and systemic neuropsychiatric causes, in addition to considering the possibility of adverse effects associated with statin therapy
Have patients avoid grapefruit juice since this may increase risk of side effects

**BOTTOM LINE:** Although statins are associated with a small increased risk of new-onset diabetes, the benefit of treatment will be greater for many patients. Serious muscle events associated with statins are rare but muscle complaints are common. Patients should be monitored closely and asked about these effects, and steps should be taken quickly to assess the full dimensions of symptoms. If an association is found with statins, options include temporarily stopping drug and restarting at a reduced or switching to another statin.

### Non-statin therapies

Table 6 summarizes data for both statins and the available non-statin drugs, which can be considered in patients who are either intolerant of statins or who lack the anticipated response to statins despite adequate adherence.

**Table 6. Efficacy and clinical characteristics of lipid-lowering drugs**

<table>
<thead>
<tr>
<th></th>
<th>LDL Reduction</th>
<th>HDL Increase</th>
<th>Cardiovascular risk reduction</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td>15-30%</td>
<td>Minimal</td>
<td>No significant reduction</td>
<td>Nausea, bloating, cramping; impairs absorption of other drugs</td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td>5-20%</td>
<td>5-20%</td>
<td>13% relative reduction in coronary events; no significant reduction in mortality</td>
<td>Increased creatinine, myopathy. Should not be co-administered with statin.</td>
</tr>
<tr>
<td><strong>Nicotinic acid</strong></td>
<td>10-25%</td>
<td>15-35%</td>
<td>No significant reduction</td>
<td>Flushing, pruritus, nausea, myopathy, hepatotoxicity. Should not be co-administered with statin.</td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td>10-20%</td>
<td>Minimal</td>
<td>6% relative reduction in combined CV events after acute coronary syndrome</td>
<td>Myopathy, elevated transaminases when used with statin.</td>
</tr>
<tr>
<td><strong>PCSK9 Inhibitors</strong></td>
<td>60%</td>
<td>6%</td>
<td>More than 50% relative reduction in all-cause mortality and MI in early studies</td>
<td>Myalgia, neurocognitive effects, injection site reactions (uncommon)</td>
</tr>
</tbody>
</table>
The authors of the 2013 AHA/ACC guidelines found no data supporting the routine use of non-statin drugs combined with statin therapy to further reduce ASCVD events, although those guidelines were written prior to the publication of results from the IMPROVE-IT trial and many of the PCSK9 inhibitor trials.

**Ezetimibe**

The IMPROVE-IT trial studied the incremental benefit of adding ezetimibe to simvastatin therapy in patients recently hospitalized for an acute coronary syndrome. The addition of ezetimibe to simvastatin lowered LDL-C by an additional 24% at one year, compared to simvastatin alone among patients with available lab data. The study also examined the impact of combination therapy on a combined endpoint of cardiovascular death, major coronary event, or non-fatal stroke. The rates of the primary end-point were 32.7% in the ezetimibe plus simvastatin group compared to 34.7% in the simvastatin group at 7 years, a 6% relative reduction in events (HR 0.94, 95% CI 0.89, 0.99, p=0.016).

**Figure 5. Ezetimibe plus simvastatin versus simvastatin alone in reducing combined cardiac events**

![Graph showing the effect of ezetimibe on cardiac events](image-url)
**PCSK9 Inhibitors**

Proprotein convertase subtilisin kexin 9 (PCSK9) is a protease produced predominately in the liver that facilitates the breakdown of hepatocyte LDL receptors and causes decreased clearance of LDL cholesterol. PCSK9 inhibitors are monoclonal antibodies that are injected subcutaneously that inhibit PCSK9 and significantly lower serum LDL levels.

Two PCSK9 inhibitors, evolocumab and alirocumab, have been tested in several phase 2 and phase 3 clinical trials. The majority of trials have tested the combination of PCSK9 inhibitor with statin compared to statin alone. Some trials have focused on the comparison with ezetimibe or the combination of ezetimibe plus statin. The GAUSS trials specifically have focused on statin intolerant patients.47

On average, the PCSK9 inhibitors reduce baseline LDL levels by nearly 60% compared to no PCSK9 inhibitor.46 This degree of LDL reduction holds true even for patients on baseline moderate or high-intensity statins. When compared to ezetimibe, PCSK9 inhibitors reduce LDL by 36%.46

Early evidence suggests that PCSK9 inhibitors significantly reduce the risk of CV events, even for patients on statin therapy, however the duration of follow-up has been limited. The ODYSSEY LONG TERM trial followed 2341 patients at high risk for CV events treated with maximally tolerated dose of statin for 78 weeks. In addition to background statin therapy, patients were randomized to receive alirocumab (150mg every 2 weeks) or placebo injection. Alirocumab reduced LDL by 62% compared to placebo and had higher rates of injection-site reactions, myalgia, neurocognitive events, and ophthalmologic events. In a post-hoc analysis, the combined endpoint rate of CV events (death from coronary heart disease, non-fatal MI, fatal or non-fatal stroke, or unstable angina) in the alirocumab group compared to placebo was 1.7% versus 3.3% (HR 0.52, 95% CI 0.31 - 0.90, p=0.02).48

Similar results were found in the unblinded OSLER trial, which compared evolocumab plus standard therapy compared to standard therapy alone. Standard therapy was based on local guidelines for LDL treatment; 70% of patients were on concomitant statin therapy. After a median follow-up time of 11 months, the combined rate of CV events (death, MI, unstable angina, coronary revascularization, stroke, TIA, or heart failure) in the evolocumab group was 0.95% compared to 2.18% in the standard therapy alone group (HR 0.47, 95% CI 0.28-0.78, p=0.003). Neither of these trials were powered to detect a significant difference in mortality. However, a recent meta-analysis of 24 PCSK9 phase 2 and phase 3 trials demonstrated a 55% relative decrease in the odds of all-cause mortality (OR 0.45, 95% CI 0.23-0.86, p=0.015).46

The FDA approved both alirocumab and evolocumab in July 2015 for patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical ASCVD who require additional lowering of LDL cholesterol. A year’s supply of medication is estimated to cost over $14,000 in the United States. Given the high cost and the need by biweekly or monthly injections, it is likely that use of PCSK9 inhibitors will initially be limited to patients at highest ASCVD risk, their long-term role in treatment is likely to emerge in the coming years.
Clinical scenarios

Should I change the statin dose for patients with clinical ASCVD on a low- or moderate-intensity statin?

- Continue current dose if baseline LDL-C has been reduced by ≥ 50% or if the LDL-C < 70 mg/dL
- Increase statin intensity if baseline LDL-C has been reduced by < 50% or the LDL-C ≥ 70 mg/dL

Should I change the statin dose for patients without clinical ASCVD and on a low- or moderate-intensity statin?

- Continue current dose if baseline LDL-C has been reduced by at least 30-50% or if the LDL-C < 100 mg/dL
- Increase statin intensity if baseline LDL-C has been reduced by < 30% or the LDL-C ≥ 100 mg/dL

Should I start/stop statin therapy in patients older than 75 years?

- Continue statin therapy in patients already on a statin if currently tolerating it
- Start moderate-intensity statin in patients with clinical ASCVD
- Consider starting moderate-intensity statin for primary prevention after consideration of comorbidities, drug-drug interactions, and patient preferences
- Have low threshold to stop statin if there are any safety concerns

Conclusions

Hyperlipidemia is one of the risk factors for coronary artery disease and a contributor to CV mortality and morbidity. The use of statins has been proven to reduce CV outcomes in both primary and secondary prevention studies. Statin use remains the best-tested therapy to have a clinically relevant outcome. Although there is evidence that statin use can be associated with myalgia and may raise the risk of developing type 2 diabetes, this risk is generally out-weighed by the benefit derived from statin use.
References


