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Managing hyperlipidemia

The updated cholesterol treatment guidelines

Abstract: The ACC/AHA 2013 cholesterol treatment guidelines focus on lowering the risk of heart disease and stroke and not on targeted treatment goals in adult patients. This article offers a synopsis of the new guidelines and how to apply them in clinical practice.

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For years, patients have been urged to focus on their cholesterol numbers—in particular, their low-density lipoprotein (LDL) levels. Practitioners were also taught to focus on these numbers, and in some cases, their quality of care was assessed using specific LDL targets. This is no longer the case. The new American College of Cardiology and American Heart Association (ACC/AHA) 2013 cholesterol treatment guidelines focus on lowering the risk of heart disease and stroke and not on targeted treatment goals in adult patients.[1] The guidelines recognize that more intensive treatment with HMG-CoA reductase inhibitors (statins) is superior to less intensive treatment for many patients, and that when indicated, statin therapy outweighs the risk of developing diabetes and myopathy.[2] The current guideline represents a substantial departure from the Adult Treatment Panel (ATP) III report from 2002 that promoted specific lipid-level goals associated with various risk levels.[3]

Different features of the new guidelines

The new guidelines differ from the previous ACC/AHA guidelines in that the scope is more limited, focussing on three main critical questions that address who to treat with what treatment, and how intensively to treat. The strengths of the recommendations are expressed using both the National Heart, Lung, and Blood Institute (NHLBI) and ACC/AHA formats with various chart colors that represent the strength of the recommendation, which are determined based on substantial data derived from randomized clinical trials, meta-analyses, and observational studies.[1] These trials largely involved fixed doses of statins in populations at risk for the development and consequences of atherosclerotic cardiovascular disease (ASCVD).

Trials that included patients with New York Heart Association (NYHA) Class II-IV heart failure or those receiving hemodialysis were excluded. In addition, the trials reviewed were not designed to evaluate the effect of titrated statin treatment to achieve prespecified LDL or non-high-density

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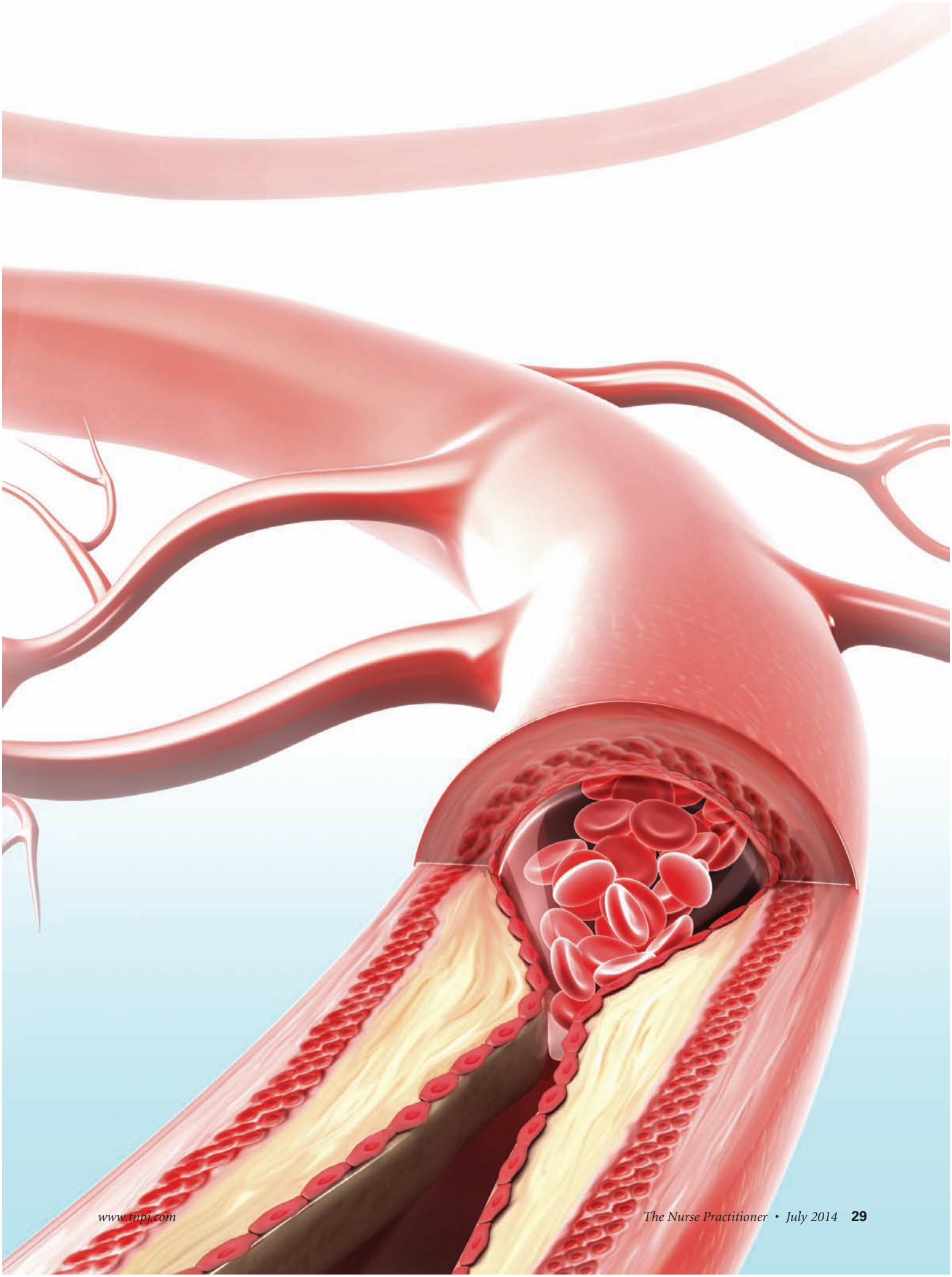

lipoprotein (non-HDL) goals as previously recommended by ATP III. What is similar, however, is that lifestyle modification (for example, a heart healthy diet, regular physical exercise, avoidance of tobacco products, maintaining a healthy weight) continues to be a critical component of ASCVD risk reduction in concert with drug therapies. Recommendations for hypertriglyceridemia are addressed in the AHA statement, and thus, pharmacologic treatment is not addressed in new ACC/AHA lipid guidelines.[4]

The basic four

On the basis of the evidence reviewed, four major groups of patients (for whom the benefit of statins outweighs the risk) were identified. These include individuals with the following[1]:

- Evidence of ASCVD as defined by acute coronary syndromes, or a history of a myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease considered to be of atherosclerotic origin
- Primary LDL cholesterol levels of 190 mg/dL or greater
- Type 1 or type 2 diabetes ages 40 to 75 years with an LDL cholesterol of 70 to 189 mg/dL and without clinical ASCVD
- A 10-year risk of ASCVD 7.5% or greater and an LDL cholesterol of 70 to 189 mg/dL without clinical ASCVD or diabetes according to the new Pooled Cohort Equations.

Patients' risk for the development of ASCVD is determined according to the new Pooled Cohort Equations, which can be downloaded from: my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp. (Applications for smartphones can be found online.) The cardiovascular risk calculator is a companion tool to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[5] The risk calculator is a spreadsheet that enables providers to estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke based on previous clinical studies.[5] The calculator requires information about age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, and diabetes/smoking status.

There are some concerns, however, with this new risk calculator. The risk calculator has not been prospectively tested for accuracy in predicting cardiovascular risk, and when compared with observed event rates in three large-scale primary prevention cohorts, the new ACC/AHA risk-prediction algorithm overestimated observed risks.[2] This may also be problematic because there are some instances where the risk-assessment algorithm may not be consistent with best medical practice. As more data become available, this risk calculator will likely be updated.

In the previously noted *Basic Four* patients, high-intensity statin therapy that is designed to reduce LDL cholesterol by more than 50% is recommended (see *High-, moderate-, and low-intensity statin therapy*). For patients who are unable to tolerate high-intensity statin, moderate-intensity statin therapy

High-, moderate-, and low-intensity statin therapy[1]

Therapy used in randomized controlled trials (RCTs) reviewed by the expert panel.*

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin (40†) *80* mg Rosuvastatin 20 *(40)* mg	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg twice daily** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20 mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

Specific statins and doses in **bold** were evaluated in RCTs and meta-analysis. Statins and doses that are FDA-approved but were not tested in the RCTs reviewed are in *italics*.

* Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

† Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL, the Incremental Decrease through Aggressive Lipid Lowering Study.

‡ 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.

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Examples of application of 2013 ACC/AHA guidelines[1]

High-intensity statin treatment (Rx)	Moderate-intensity statin Rx	Statin Rx not recommended
• White male, age 45 • Total cholesterol (TC) 270 mg/dL • HDL 43 mg/dL • BP 140/90 mm Hg • Nondiabetic, not on antihypertensive medications • Smoker • Calculated 10-year risk ASCVD: 12.4%	• Black male, age 74 • TC 160 mg/dL • HDL 40 mg/dL • BP 115/70 mm Hg • Nonsmoker, nondiabetic, not on any antihypertensive medications • Calculated 10-year risk ASCVD: 11.2%	• White female, age 64 • TC 220 mg/dL • HDL 48 mg/dL • BP 120/65 mm Hg • Nonsmoker, nondiabetic, on antihypertensives • Calculated 10-year risk ASCVD: 6.8%
• Black female, age 65 • TC 225 mg/dL • HDL 33 mg/dL • BP 130/80 mm Hg • Type 1 diabetes Nonsmoker, taking antihypertensive medications • Calculated 10-year risk ASCVD: 25.9%	• White female, age 40 • TC 240 mg/dL • HDL 29 mg/dL • BP 128/70 mm Hg • Type 2 diabetes • No antihypertensive medications • Nonsmoker • Calculated 10-year risk ASCVD: 5.6%	• Black female, age 46 • TC 240 mg/dL • HDL 55 mg/dL • BP 140/80 mm Hg • Nondiabetic, nonsmoker, taking antihypertensive medications • Calculated 10-year risk ASCVD: 4.5%

that aims for a reduction of 30% to 50% is recommended.[1] Moderate-intensity statin therapy is also recommended for patients with diabetes and a 10-year risk of ASCVD of less than 7.5%.[1] (See *Examples of application of 2013 ACC/AHA guidelines.*) Thus far, there is not sufficient evidence to support the addition of a nonstatin (such as niacin, fenofibrate, ezetimibe) to further lower the risk of ASCVD.

What about the patient who is not in one of the four statin-therapy groups where there is uncertainty in starting a statin? In this situation, additional factors may be considered to inform treatment decision making, which include[1]:

- Primary LDL-C 160 mg/dL or greater or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset younger than 55 years of age in a first-degree male relative or younger than 65 years of age in a first-degree female relative
- High-sensitivity C-reactive protein 2 mg/L or greater
- Coronary artery calcium score 300 Agatston units or greater, or 75 percentile or greater for age, sex, and ethnicity
- Ankle-brachial index less than 0.9
- Elevated lifetime risk of ASCVD.

Initiating and monitoring statin therapy

When starting a patient on a statin, as always, a thorough history and physical exam is first and foremost. Needed lifestyle modifications should be discussed, and goals should be set. As with any drug therapy, a discussion of potential benefits along with possible adverse reactions is needed. Recommended lab studies, in addition to a lipid profile, include baseline liver function studies. Further testing depends upon other risk factors and/or comorbidities along with other medications that might be prescribed. For instance, if a fenofibrate were to be prescribed for a patient with a triglyceride level over 500 mg/dL, then a renal panel to include a serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (GFR) would be needed. Creatine kinase (CK) may be useful in patients who are at an increased risk for adverse muscle events, such as those patients with a personal or family history of statin intolerance, muscle disease, or concomitant drug therapy that can increase the likelihood of myopathy.[1] CK may also be needed for patients on statins who complain of muscle symptoms. After statins are started, liver panel, including transaminases, alkaline phosphatase, and bilirubin, along with a fasting lipid profile, should be measured 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter as clinically indicated. During statin therapy, if symptoms suggest hepatotoxicity such as unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera, then a liver panel should be measured. The guideline suggests that if the LDL cholesterol, on two subsequent readings, is less than 40 mg/dL, the statin dose can be decreased.[1]

Statin intolerance

In general, myalgia exists when a patient experiences muscle aches or weakness without associated CK elevation; myopathy occurs when the muscle pain or soreness is accompanied with a CK greater than 10× the upper limit of normal (ULN); myositis is defined as muscle symptoms and CK elevation; and rhabdomyolysis as muscle symptoms, significant CK elevations usually greater than 10× ULN with

urinary myoglobin with possible evidence of organ damage, such as renal compromise.[6,7] If any symptoms suggesting statin intolerance develop during therapy, discontinue the statin, obtain a CK, and evaluate the patient for other conditions that might increase the risk of muscle symptoms. Conditions that predispose patients to statin intolerance include, but are not limited to, hypothyroidism, vitamin D insufficiency, kidney or hepatic dysfunction, rheumatologic disorders such as polymyalgia rheumatica, corticosteroid myopathy, or primary muscle disease.[1] These disorders need to be ruled out and treated prior to restarting the statin. When symptoms resolve, the patient should be started on a lower-dose statin. Although not noted in the guidelines, patients can often be started on a lower daily dose of a statin, given two to three times per week and gradually increased to the optimal dose.[8]

Circumstantial treatment

The new ACC/AHA guidelines are an attempt to define practices for the majority of patients. It is important to be mindful that guidelines are never a replacement for clinical judgment. The new ACC/AHA guidelines focus on treatments that have been shown to reduce ASCVD events. The guidelines are not, and were never intended to be, a comprehensive approach to lipid management.

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