

Familial Hypercholesterolemia and the 2013 American College of Cardiology/American Heart Association Guidelines: Myths, Oversimplification, and Misinterpretation Versus Facts



Familial hypercholesterolemia (FH) is a genetic condition resulting in severe, lifelong elevations in low-density lipoprotein cholesterol and a marked increased risk of early-onset coronary disease. FH is treatable when identified, yet is vastly under-recognized and undertreated. Although the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of cholesterol presented a paradigm shift, we believe that there have been serious oversimplifications, misinterpretations, and erroneous reporting about the current ACC/AHA cholesterol guidelines that have contributed to suboptimal care for these subjects. In summary, the ACC/AHA guidelines place tremendous emphasis on the identification of patients with FH, the initiation of high-intensity statin therapy, the need to obtain follow-up lipid values to assess the efficacy and compliance to lifestyle and medical therapy, and the role of nonstatin drugs when needed for optimal care of the individual patient. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;116:481–484)

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol to reduce risk of atherosclerotic cardiovascular disease (ASCVD) were presented and published online in November 2013 and in journal form in July 2014.¹ The guidelines presented a paradigm shift for those who merited cholesterol-lowering drug therapy in addition to healthy lifestyle.

Although an informed debate over the scientific and clinical merits of these new guidelines is to be expected, the publication of statements that misinterpret or even mis-state what the guidelines recommended has been common. This may have adverse impacts on both the practice and reimbursement of medical care. The issues of oversimplification, misplaced emphasis, and, unfortunately, error in interpreting the guidelines were noted at the Second Annual Global Familial Hypercholesterolemia Summit (“Bridging the Gaps in Care of Familial Hypercholesterolemia”) in New York² with patients and health care providers. At the meeting, a majority of the health care providers who attended admitting to hearing stories from their patients in which patients were told there was no need to be on combination therapy, there was no need to get repeat lipid profiles, reimbursement was denied for lipid testing, reimbursement for second drugs beyond statins was reduced with higher copays, and in situations where an agent, ezetimibe, was completely denied. Furthermore, data presented at the Summit using newly obtained data from the national FH patient registry CASCADE FH (CAscade SCreening for Awareness and DETection of FH)³ highlighted the difficulty in treating patients with familial

hypercholesterolemia (FH) in the United States. For instance, initial data from >1,200 patients with FH seen at leading lipid clinics around the United States indicated that the average LDL-C level was 143 mg/dl despite 1/3 of patients being on ≥ 3 lipid-lowering therapies.

In this editorial, we focus on 4 critical areas addressed in the ACC/AHA guidelines:

1. Screening and identification of subjects with FH as a specific high-risk patient group.
2. The importance of high-intensity statin therapy regardless of the estimated 10-year ASCVD risk or age.
3. The need for follow-up lipid values to assess response to therapy.
4. The role of nonstatin lipid-lowering medications.

FH is an autosomal co-dominant genetic disease characterized by profound, lifelong elevations of low-density lipoprotein cholesterol (LDL-C)⁴ leading to a 20-fold increased lifetime risk of coronary heart disease compared with the general population.⁵ Natural history studies in the pre-statin era suggested that untreated men have a 50% risk of a fatal or nonfatal coronary event by age 50 and untreated women have a 30% risk by age 60.^{5–9} Recent genetic studies from the National Heart, Lung, and Blood Institute-funded exome sequencing project¹⁰ and several European countries have revealed that FH may affect close to 1 in every 200 subjects (many more than the classic estimates of 1:500).^{11,12} Importantly, these studies also confirmed results from earlier work,¹³ demonstrating that FH accounts for ~2% of all annual myocardial infarctions in Americans <60 years old. Yet only a small fraction of affected patients have been identified in the United States.⁴ Unfortunately, the failure to identify FH can have dire consequences because of delays in implementation of guideline-based therapeutic approaches to lower LDL-C. Specifically,

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See page 483 for disclosure information.

Table 1
Myths versus facts concerning treatment of FH patients in ACC/AHA 2013 guidelines

Myths	Facts
An elevated LDL-C level by itself cannot be used to justify initiation of statin therapy. The newly developed pooled cohort risk equation should exclusively be used to trigger initiation of statins for primary prevention.	Statin therapy is recommended when LDL-C levels ≥ 190 mg/dl as these individuals have a high pre-test probability of FH and are at high risk of ASCVD regardless of other risk factors. In fact the pooled cohort risk equations are not appropriate for FH patients. Moreover, if a risk decision is uncertain in a younger individual, an LDL-C of ≥ 160 mg/dl could be used (often in conjunction with a strong family history of premature ASCVD) as an additional factor to inform the risk discussion.
Only patients with ASCVD or high 10-year risk merit high intensity statin therapy	Individuals with FH merit high intensity statin therapy given the lifelong burden of high LDL-C levels and attendant ASCVD risk. 10-year risk estimation is expressly not indicated.
There is no need to follow lipid panels and check LDL-C after initiation of statin therapy.	LDL-C levels should be evaluated 3-12 weeks after initiating statin therapy and periodically (3-12 months per the clinician) thereafter to be sure the desired LDL-C lowering is achieved. This is especially important in FH patients with an extremely elevated pretreatment LDL-C levels (eg > 300 mg/dl) in whom even the maximally expected 50% reduction in LDL-C with high intensity statin may still leave an unacceptably high residual risk. In fact the guidelines explicitly state that <i>at least</i> a 50% reduction in LDL-C should be achieved but are not prejudiced against greater LDL-C reductions in this patient population (“in addition to a maximally tolerated dose of statin, nonstatin cholesterol-lowering medications are often needed to lower LDL-C to acceptable levels in these individuals”).
There is no role for non-statin lipid lowering medications.	The guidelines didn't endorse non-statins as “initial” lipid lowering therapy. Many FH patients will require two or more medications to achieve optimal LDL-C levels. In addition, a sizeable minority of patients will be intolerant of high intensity statin regimens and will require augmentation with non-statin lipid lowering medications. In the guidelines, preference is given to medications that have shown to reduce ASCVD outcomes in randomized clinical trials. With the release of the results of IMPROVE-IT, ezetimibe can be added to bile acid binding resins as potential second (or third) line therapies.

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C = low-density lipoprotein cholesterol.

aggressive LDL-C lowering in patients with FH has been shown to lower an affected adult's risk of cardiovascular disease to that of the general population¹⁴ and seems to alter the natural progression of disease in children.¹⁵

Multiple national and international guidelines including the recent ACC/AHA cholesterol treatment guidelines place special emphasis on this population and underscore aggressive cholesterol-lowering strategies.^{1,4,5,16–18} Perhaps even more important, if FH is not recognized, family-based cascade screening efforts are not possible. The Center for Disease Control and these same guidelines recommend cascade screening efforts because they are highly efficacious, cost effective, and life saving.^{16,19–23}

The new AHA/ACC guidelines are perhaps the most aggressive guidelines in regard to both screening and identification of subjects with FH. In contrast to other criteria, such as Simon Broome or the Dutch Lipid Clinic Network criteria, which are used for the diagnosis of FH, that require a specific point score based on clinical findings, such as tendinous xanthomas, genetic testing, and more extreme elevations of LDL-C, the ACC/AHA guidelines recognized that subjects with a primary elevation of LDL-C ≥ 190 mg/dl had an increased probability of having hypercholesterolemia on a genetic basis.²⁴ This group includes those with FH.

All the investigators have encountered instances in either the lay press or at scientific meetings where the guidelines were misquoted in this area. For example, in 1 meeting, a commentator incorrectly stated that the guidelines do not treat a patient in his 30s with an LDL-C of 180 mg/dl and a family history of premature ASCVD. Actually, this patient had 2 of the factors that you could use to inform a risk decision when

the risk decision was uncertain, namely family history of premature ASCVD and primary LDL-C ≥ 160 mg/dl. Thus, according to the guidelines, this patient who likely had genetic hypercholesterolemia did merit consideration of statin therapy and would be treated by most clinicians.

The guidelines clearly stated that 10-year ASCVD risk calculations were inappropriate in those with primary elevations of LDL-C ≥ 190 mg/dl. Here the substantial lifetime risk was crucial. Thus, despite the headlines, clinicians are in error when they apply the pooled cohort equations to those in this group.

Also, the guidelines specifically did not endorse a “set it and forget it” regimen. They indicated that lipids should be checked 4 to 12 weeks after the initial dosing and then 3 to 12 months thereafter based on clinician's judgment.²⁴ The further lipid testing was specifically designed to determine if the percent lowering recommended using the appropriate intensity of a statin was achieved. Repeat testing was recommended to not only review statin safety but also to keep LDL-C as low as it was initially maximally tolerated statin therapy and optimal lifestyle.

Although the guidelines did not endorse nonstatins as first-line drugs, they did discuss situations where they could be considered. That's why there is an entire safety section on nonstatins in the guidelines. The guidelines specifically indicated that nonstatins could be used in “high-risk” groups such as LDL-C ≥ 190 mg/dl, secondary prevention, or those with diabetes aged 40 to 75 years and LDL-C ≥ 70 mg/dl if the response to statin therapy was not adequate or if the appropriate statin intensity was not tolerated or safe. They indicated a preference for those

statins shown to provide net benefit in RCTs. The 2013 guidelines specifically stated:

Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a nonstatin cholesterol-lowering therapy. High-risk subjects include those with ASCVD, those with LDL-C \geq 190 mg/dl, and those with diabetes at 40 to 75 years. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences.

We thought it would be useful to highlight some of the myths about the guidelines in reference to subjects with FH (Table 1).

FH remains a treatable cause of heart disease in the United States with many remaining gaps in the identification and treatment of these patients.²⁵ We hope that misconceptions based on oversimplifications, misinterpretations, and erroneous reporting about the current ACC/AHA cholesterol guidelines will no longer contribute to suboptimal care for these subjects. As clearly reviewed earlier, the ACC/AHA guidelines place tremendous emphasis on the identification of patients with FH and the need for cascade screening, the initiation of high-intensity statin therapy, the need to obtain follow-up lipid values to assess the efficacy and compliance to lifestyle and medical therapy, and the role of nonstatin drugs when needed for optimal care of the individual patient.

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