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The 2013 ACC/AHA Cholesterol Treatment Guidelines: Applicability to Patients with Diabetes

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Abstract Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide and the management of blood cholesterol is a cornerstone of medical therapy for the primary and secondary prevention of cardiovascular disease. Patients with diabetes represent an important high-risk group in whom clinicians should advocate the use of statins and lifestyle modification for the reduction of ASCVD. The recent 2013 ACC/AHA guidelines on managing blood cholesterol provide an important framework for the effective implementation of this important risk reduction strategy. The guidelines identify four groups of individuals who have been shown to benefit from statin therapy and update the dosing and monitoring recommendations based on evidence from published, large-scale randomized controlled trials (RCTs) with clinical hard endpoints. Primary care physicians and specialists play key roles in identifying populations at elevated ASCVD risk and providing effective care for patients, especially those with diabetes. This article will summarize the 2013 ACC/AHA guidelines on managing blood cholesterol and provide a

practical management overview in order to facilitate implementation of these guidelines for patients with diabetes.

Keywords Primary prevention · Diabetes · Cholesterol · Statins · Guidelines

Abbreviations

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
DASH	Dietary Approaches to Stop Hypertension
LDL-C	Low-density lipoprotein-cholesterol
RCT	Randomized controlled trial

Introduction

In 2011, coronary heart disease (CHD) alone was responsible for 1 in 7 deaths and 635,000 myocardial infarctions in the USA [1•]. Additionally, 795,000 Americans suffered an acute stroke and 8.5 million lived with peripheral arterial disease. The estimated combined direct and indirect cost of cardiovascular disease and stroke was \$320.1 billion in 2011 [1•]. Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality in the USA in general, and particularly in patients with diabetes [1•]. Despite this, recent studies find evidence for significant undertreatment of high-risk patient populations. Only an estimated 58.2 % of individuals with CHD and 52.0 % of patients with diabetes who are older than 40 years of age were taking statins in 2010 [2]. Therefore, a significant proportion of high-risk patients with diabetes are not receiving evidenced based statin therapies.

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The 2013, the American College of Cardiology/American Heart Association cholesterol guidelines specifically address this undertreatment.

Understanding the Framework of the Current Guidelines

In late 2013, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines published recommendations on managing blood cholesterol. These guidelines were authored by an expert panel originally appointed by the National Heart Lung and Blood Institute (NHLBI) to update the previous Adult Treatment Panel III (ATP III) guidelines [3•]. As with prior cholesterol guidelines, these new recommendations were written with the goal of reducing the risk of atherosclerotic disease (notably myocardial infarctions and cerebrovascular accidents) in adults [4]. Again, as stated in prior recommendations, the foundation of cardiovascular prevention consists of cost-effective and safe lifestyle modification [5•]. Thus these new guidelines also advise clinicians to prioritize lifestyle modification through diet, exercise, weight maintenance, and smoking cessation. In addition, the committee reviewed available high-quality data (RCTs, systematic reviews, and meta-analyses) to specifically define which strategies were most effective at reducing the specific cardiovascular outcomes of myocardial infarction, stroke, and cardiovascular death. The guideline writing panel concluded that the most powerful strategy, with the greatest evidence base, is statin therapy. The new guidelines are a departure from the past; most notably prior guidelines offered *several* options for pharmacotherapies to reduce cholesterol, but the new guidelines state that at the time of writing statins were, by far, the best evidence-based ASCVD risk-reducing therapies. Further clarifying and simplifying the recommendations, the guidelines stress the 3Rs: right patient, right statin, and right dosage.

What is New in the Guidelines?—Right Patient, Right Statin, and Right Dosage

As stated above, the framework of the 2013 ACC/AHA guideline differs from prior guidelines in several ways. The most impactful changes were the decision to only include the highest quality data (e.g., RCTs) to inform recommendations and to focus on hard cardiovascular outcomes, rather than the surrogate markers of cholesterol level or subclinical atherosclerosis alone, as the previous guidelines had done [6]. Using high-quality data that focused on clinical endpoints formed the basis for another key difference in the current guidelines: defining *specific populations* in whom the recommended

therapy was likely to benefit. In the guidelines these are known as the four “statin-benefit groups” (Fig. 1):

1. Adults with clinical established ASCVD
2. Adults with primary LDL-C ≥ 190 mg/dL
3. Adults (40–75 years of age) with either type 1 or type 2 diabetes with LDL of 70 to 189 mg/dl
4. Adults (40–75 years of age) with ≥ 7.5 % 10 years ASCVD risk with LDL of 70 to 189 mg/dl

The identification of the last group requires application of a new risk assessment calculator. A 10-year risk calculator based on pooled cohort studies was developed to help select high-risk populations in the absence of established ASCVD [7]. Since the pioneering and continuous Framingham Heart Study that began in 1948, researchers have elucidated the predisposing factors for ASCVD [8]. Within this calculator, the risk factors that predict the 10-year risk of cardiovascular death, myocardial infarction, and stroke include age, sex, African American ethnicity, total and HDL cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current tobacco use. The new risk calculator contains ethnicity and diabetes as additional risk factors that are not included in the Framingham 10-year risk calculator. Predicted risks are calculated from ethnic and gender specific pooled groups. The calculator also estimates the risk of myocardial infarction and stroke, rather than just myocardial infarction alone, as was the case with the previously recommended calculator. Individuals between the ages of 40 and 75 with a 10-year risk of at least 7.5 % for an ASCVD event are considered likely to benefit from statin therapy. For patients between 5.0 and 7.5 %, statin therapy may be beneficial. Several additional factors not included in the risk calculator can be considered in revising a patient's risk upward: family history of early ASCVD in a first degree relative, hs-CRP, CT coronary artery calcium scoring, and ankle-brachial index. These factors are

Fig. 1 The four statin-benefit groups. ASCVD atherosclerotic cardiovascular disease, CV cardiovascular, LDL low-density lipoprotein, LDL-C low-density lipoprotein-cholesterol

helpful in making an individual decision at the patient-clinician level.

Perhaps, one of the biggest paradigm shifts in the new guidelines is the move away from focusing on low-density lipoprotein-cholesterol (LDL-C) goals. The new guidelines state that there is insufficient evidence to support continued use of LDL-C goals and instead, the appropriate intensity of statin therapy is recommended (Table 1). The overarching reason for not recommending LDL-C goals is that no primary or secondary prevention RCTs actually used an LDL-C goal as means of prescribing or titrating cholesterol lowering therapies. The lack of evidence for LDL-C goals has been discussed extensively prior to the 2013 ACC/AHA guideline [9].

Another important change in the new cholesterol guideline is direction on the recommended intensity of statin therapy as mentioned above. High-intensity statins that reduce LDL-C levels by more than 50 % on average are recommended for individuals with clinical ASCVD, LDL-C $\geq$ 190, high-risk patients with diabetes, and those with a 10-year risk of ASCVD events $\geq$ 7.5 %. Moderate-intensity statins that lower LDL-C by 30–50 % are recommended for lower-risk diabetic patients. Moderate-intensity statins may be used in those who cannot tolerate higher dose statins for primary prevention or patients over the age of 75.

Evidence Supporting the Guidelines for Patients with Diabetes

In the 2013 AHA/ACC new guidelines, patients with diabetes, both type 1 and type 2 are identified as a statin-benefit group in the new guidelines. Patients with diabetes are at a high risk of cardiovascular disease. Investigators from the Emerging Risk Factors Collaboration performed a meta-analysis of 97 studies and including 820,900 persons and they found that diabetes causes at least 233,000 deaths annually in the USA [10]. They also found that the hazard ratio (HR) for death from

a number of causes was increased in patients with diabetes. This collaboration found:

- HR 1.8 death from any cause
- HR 1.25 death from cancer
- HR 2.32 death from vascular disease
- HR 1.73 death from any other cause

The risk of death from vascular disease was highest in patients with diabetes when compared to patients without diabetes. This first emphasizes the importance of cholesterol risk modification as a preventive strategy for diabetics. Data from the Cholesterol Treatment Trialists meta-analysis have shown that statins are effective in reducing risk in patients with and without diabetes [11].

Data from this meta-analysis also reveal that greater benefits are seen in patients with type 1 compared to those seen in patients with type 2 diabetes; in fact, targeting patients with type 1 diabetes to statin therapy may have even greater benefits, because even though patients with type 1 diabetes tend to be younger and leaner than patients with type 2 diabetes, they have greater burden of vascular disease [11].

The new guidelines devote considerable attention to patients with diabetes because of their high risk. In prior guidelines, diabetes was considered a “cardiovascular risk equivalent” thus the recommendations for patients with diabetes were the same as the recommendations for patients with clinical ASCVD [6]. While the new guidelines acknowledge the high-risk status of diabetic patients without ASCVD or LDL greater than 190 mg/dl, the committee also recognizes that not all diabetic patients have equivalent risk; thus, the new guidelines recommend at least moderate-intensity statin therapy for all patients with diabetes between the ages of 40 and 75. If a patient with diabetes between the ages of 40 and 75 has an estimated 10-year ASCVD risk of greater than 7.5 %, the guidelines recommend high-intensity statin therapy.

The recommendations for patients with diabetes in the new guidelines specifically state that they are for patients between the ages of 40 and 75. For patients younger than age 40 or

Table 1 Intensity class of commonly used statins by dose

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C on average by approximately $\geq$ 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	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40–80 mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

older than age 75, statins are likely to be of benefit, but additional factors should be considered, particularly given the lack of clinical trial evidence. There is virtually no clinical trial data on the use of statins in patients with diabetes less than 40 years. However, available data suggests that statin treatment in patients with diabetes less than 40 years of age are likely to provide benefit [12]. Additional factors that can be considered in patients less than 40 years of age to help in determining if statin therapy is correct for that patient include:

- LDL ≥ 160
- Family history of premature ASCVD
- hs-CRP ≥ 2
- Coronary calcium score ≥ 300
- Ankle-brachial index < 0.9 [11]

ASCVD risk calculator validated and applicable for those aged 40–75. For patients with diabetes under 40 years old, the calculator may overestimate the risk and should not be used. Regarding patients over the age of 75, there is very little clinical trial data on the use of statins in elderly patients with diabetes. We know that elderly patients over the age of 75 may be at greater risk of adverse events from statins and because elderly patients typically take more medications the potential risk of drug-drug interactions is greater in this population. Therefore, patients and providers should discuss anticipated ASCVD risk reduction benefits, potential for adverse effects from statin therapy, drug-drug interactions, and patient preferences.

Recent Studies and the Future Guideline Direction

Given the greater complexity and challenges in controlling lipids in diabetic patients, combination therapy with non-statin cholesterol lowering drugs may be a reasonable strategy. At the time of the guideline publication, the committee found insufficient RCT evidence supporting non-statin cholesterol lowering medications to reduce ASCVD events. However, these medications may be utilized at the provider's discretion in patients with less than a desired therapeutic response to statin treatment.

More recently, the results of Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the combination of simvastatin and ezetimibe compared to simvastatin alone had a modest 2 % absolute risk reduction in the primary composite cardiovascular outcome in patients with post-acute coronary syndrome [13]. In addition, further analysis showed there were more benefits in the subgroup of patients with diabetes. The trial does suggest that further LDL lowering reduces risk without regard to the pharmacologic mechanism, especially in patients with

diabetes. The results also showed the excellent safety of this combination therapy in the post-acute coronary syndrome populations. Further analysis will be needed to understand the benefits of the non-statin cholesterol lowering drug ezetimibe and the specific mechanisms.

Another class of promising non-statin cholesterol lowering drug is monoclonal antibody of proprotein convertase subtilisin/kexin type 9 (PCSK9). Of them, the most successful drugs are AMG145 and REGN727 [12, 14]. The Phase III outcome clinical trial of REGN727 (alirocumab), ODYSSEY Outcomes (www.clinicaltrials.gov NCT01663402), targets the high-risk ASCVD population, including patients concomitant with diabetes. This is an international, multicenter, randomized, double-blind, placebo-controlled study in approximately 18,000 patients with a recent acute coronary syndrome, conducted at over 1000 sites worldwide. Recruitment of patients began in 2012 with a projected completion in 2016 [15].

Based on the results of IMPROVE-IT and other forthcoming studies such as ODYSSEY Outcomes, evidence regarding the potential benefits of non-statin based therapies will inform future guidelines. These trials will provide new therapeutic evidence for high-risk ASCVD populations, including patients with diabetes.

In 2015, the AHA/ADA provided a joint update on preventing cardiovascular disease among patients with type 2 diabetes mellitus. The committee consolidated recommendations between prior AHA and ADA recommendations [16•]. The update provides a summary of the evidence for multiple therapies for the reduction of cardiovascular risk. Most importantly, the ADA 2015 guidelines are now in agreement with the 2013 ACC/AHA blood cholesterol guideline with regard to the management of hyperlipidemia [16•, 17].

Limitations/Strengths/Critiques

Using the strongest evidence base, the new guidelines clarify the most effective strategy for reducing ASCVD risk and the four statin-benefit groups. These new guidelines also simplify the choice and intensity of therapies by recommending moderate or high-intensity statin therapy in all populations at risk. This approach not only follows the evidence but also simplifies the implementation. However, this approach also has limitations. One of the changes that was met with most resistance was abandonment of LDL-C goals. Without an LDL-C goal and a focus on intensity of statin therapy, many clinicians are concerned about how best to titrate therapy and when to potentially initiate additional therapy in the absence of an adequate reduction in LDL-C. Achieving a “target” (as is the case for A1C levels) can help clinicians and patients in their discussions about the success of specific

therapies, so the absence of such a target in the current guidelines will have to be reinforced with patients to avoid confusion about the goals of therapy. In addition, this new framework makes it more difficult to identify an appropriate metric for treatment utilization and risk reduction. Finally, as with all guidelines, we must use the available evidence from specifically defined populations to make broad based recommendations. It is not always clear that using the clinical trial populations will directly translate to the best recommendations for an individual patient.

Conclusions

The recent ACC/AHA blood cholesterol guideline provides a robust synthesis of the evidence for primary and secondary prevention of ASCVD and is now endorsed by the ADA. These newer guidelines emphasize reducing hard outcomes such as death, myocardial infarction, and stroke for patient with diabetes. Previous iterations of the cholesterol guidelines integrated studies showing reductions in surrogate markers, which may not correlate directly with patient outcomes. The new guideline provides a simplified approach to identify patients with elevated cardiovascular risk, such as patients with diabetes mellitus, and a high likelihood of benefit from statin therapy. A fixed-dose statin approach is now advocated over the prior “treat to target” method that lacked sufficient RCT evidence. Assessing cardiovascular risk is part of an ongoing conversation between patient and clinician. The ultimate decision to prescribe therapy should result from an informed, shared decision making framework. Because ASCVD is the leading cause of morbidity and mortality in developed countries, primary prevention of ASCVD is of great importance and patients with diabetes are one of the most important primary prevention populations. In addition to lifestyle, statin therapy is the most promising medical invention to reduce ASCVD risk in patients with diabetes. This updated cholesterol guideline promotes a patient-centered and efficient strategy to achieve this goal among all patients at high risk for cardiovascular events.

Compliance with Ethical Standards

Conflict of Interest Boback Ziaieian, John Dinkler, and Yuanlin Guo declare that they have no conflict of interest.

Karol Watson is consultant for Amgen, Astra Zeneca, and Merck & Co.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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