2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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This document was approved by the American College of Cardiology Board of Trustees and Executive Committee in March 2016.


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The American College of Cardiology (ACC) develops a number of clinical policy documents to provide members with guidance on clinical topics. Although clinical practice guidelines remain the primary mechanism for offering evidence-based recommendations, such guidelines may contain gaps in their guidance regarding clinical decision making, particularly when equipoise is present in a topic. Expert consensus documents are intended to provide guidance for clinicians in areas where evidence may be limited, are new and evolving, or lack sufficient data to fully inform clinical decision making.

In an effort to increase the impact of ACC clinical policy on patient care, an ACC Presidential Task Force was formed in 2014 to examine the processes and format of ACC’s clinical documents. The main recommendation of the task force was a new focus on concise decision pathways and/or key points of care, instead of the traditional longer documents. The task force also established criteria for identifying high-value clinical topics to be addressed, as well as an innovative approach to collecting stakeholder input through roundtable or think tank meetings. To complement the new focus on brief decision pathways and key points, expert consensus documents were rebranded Expert Consensus Decision Pathways (ECDPs).

Although decision pathways have a new format, they maintain the same goal of expert consensus documents: to develop clinical policy based on expert opinion in areas which important clinical decisions are not adequately addressed by the available existing trials. ECDPs are designed to complement the guidelines and bridge the gaps in clinical guidance that remain. In some cases, topics covered by ECDPs will be addressed subsequently by ACC/AHA guidelines as the evidence base evolves. The writing groups are charged with developing algorithms that are more actionable and can be implemented in the form of tools or apps to accelerate the use of these documents at point of care. Expert consensus decision pathways are intended, not to provide a single correct
answer, but to encourage clinicians to ask certain questions and consider important factors as they reach a decision on a treatment plan together with patients. There may be multiple pathways that can be taken for treatment decisions and the goal is to help clinicians and patients make a more informed decision together.

James L. Januzzi, MD, FACC, Chair
ACC Task Force on Clinical Expert Consensus Documents

1. INTRODUCTION

In 2013, the American College of Cardiology and American Heart Association (ACC/AHA) published the new Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (1) along with a companion Guideline on the Assessment of Cardiovascular Risk in asymptomatic individuals (2). Using a rigorous process of independent evidence review and synthesis based largely on results from randomized clinical trials (RCTs), the 2013 ACC/AHA guideline panel found that the vast majority of evidence indicating efficacy and safety of low-density lipoprotein cholesterol (LDL-C) lowering for risk reduction came from trials of statin drugs. On the basis of this large and consistent body of evidence, 4 major statin benefit groups were identified for whom the atherosclerotic cardiovascular disease (ASCVD) risk reduction clearly outweighs the risk of adverse events (Table 1) (1). These 4 groups comprised adult patients ≥21 years of age with clinical ASCVD; adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes); adults aged 40 to 75 years without ASCVD, but with diabetes and with LDL-C 70 to 189 mg/dL; and adults ages 40 to 75 years without ASCVD or diabetes, with LDL-C 70 to 189 mg/dL, and an estimated 10-year risk for ASCVD of ≥7.5% as determined by the Pooled Cohort Equations (2). Subsequent independent guideline groups, including the 2014 Joint British Societies Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3) (3), the 2014 Veterans’ Administration/Department of Defense Guidelines on Management of Dyslipidemia (4), and the recent U.S. Preventive Services Task Force draft recommendations (5), have used similar, rigorous approaches to reviewing and synthesizing evidence, resulting in similar treatment recommendations.

Central to the 2013 ACC/AHA guideline panel approach was the concept of “net ASCVD risk-reduction benefit”; in other words, is the likelihood of preventing a major ASCVD event or death greater than the likelihood of a serious adverse event with a given drug therapy? Statins clearly have demonstrated net benefit for the 4 statin benefit groups, whereas other drug therapies available in 2013 had either marginal net ASCVD risk-reduction benefit or had been shown not to provide additional benefit beyond statins. The evidence base from large RCTs of statins consisted of comparisons of fixed-dose statin therapy versus placebo, or higher-intensity versus lower-intensity statin therapy (Table 2) (1). Patients treated with statin versus placebo, or with higher- versus lower-intensity statin therapy, experienced significantly greater ASCVD risk reduction with minimal serious adverse event rates, typically similar to the adverse event rates in placebo comparator groups (6). Of note, the 2013 ACC/AHA guideline panel emphasized the role of shared decision making between clinicians and patients, with consideration of net benefit as well as patient preferences, especially in the setting of primary prevention, in which the marginal benefits may be small for patients at lower risk for ASCVD events in the near term (1).

The amount of ASCVD risk reduction observed with statins was directly related to the amount of LDL-C lowering achieved as a percentage of baseline. For example, in trials showing efficacy of high-intensity statin therapy, patients on average had ≥50% reduction in LDL-C from baseline. In trials showing efficacy of moderate-intensity statin therapy, patients typically had on average 30% to <50% reduction in LDL-C from baseline. These levels of therapeutic response were therefore taken to indicate adequate response and adherence to therapy.

Because no large RCTs have evaluated the outcome of drug titration to specific LDL-C targets, the 2013 ACC/AHA cholesterol guideline panel did not make specific recommendations regarding lipoprotein goals of therapy. Instead, the panel recommended initiating either high- or moderate-intensity statin therapy on the basis of patient ASCVD risk characteristics and the potential for net benefit; however, the panel did note that groups of patients with the greatest benefit from statin therapy tended to fall into ranges of LDL-C indicating efficacy of statin therapy. For example, the guideline panel indicated that “in those already on a statin, in whom baseline LDL-C is unknown, an LDL-C level <100 mg/dL was observed in most individuals receiving high-intensity statin therapy” (1). This statement was based on the findings from trials such as Treating to New Targets, in which patients with clinical coronary heart disease (CHD) were randomized to fixed-dose atorvastatin 80 mg versus 10 mg daily as an active comparator (7). The patients receiving 80 mg of atorvastatin achieved a mean LDL-C of 77 mg/dL, with the majority achieving <100 mg/dL, whereas the patients receiving 10 mg of atorvastatin achieved a mean LDL-C of 101 mg/dL. This difference was associated with a significant 22% reduction in major cardiovascular events in the trial.

In summary, the 2013 ACC/AHA cholesterol guideline panel recommended using either high- or moderate-intensity statin therapy for patients in the 4 statin benefit groups at risk for ASCVD in primary and secondary prevention scenarios, with dose adjustments as
necessitated by factors such as adverse effects, advanced age, drug–drug interactions, and comorbidities. The panel determined that a high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol [TC], triglycerides, high-density lipoprotein cholesterol [HDL-C], and calculated LDL-C) followed by a second fasting lipid panel 4 to 12 weeks after initiation of statin therapy, to determine a patient’s adherence and confirm anticipated response to therapy. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated to assess adherence and responsiveness to therapy (1).

At the time of guideline publication, the panel could find no data supporting the routine use of U.S. Food and Drug Administration (FDA)-approved non-statin drugs combined with statin therapy for LDL-C reduction with the goal of further reducing ASCVD events. In addition, no published RCTs that assessed ASCVD outcomes in statin-intolerant patients were found. Therefore, the panel recommended that:

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 non-statin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with LDL-C ≥190 mg/dL, and those with diabetes 40 to 75 years of age. 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 (1).

The guidance for use of non-statin therapy was intentionally broad to allow for the discretion of clinicians treating patients with individual circumstances that cannot be anticipated by guidelines or have not been evaluated in clinical trials. In addition, the 2013 ACC/AHA guideline panel recognized that there were several ongoing trials examining the addition of non-statin therapy to statins, such as the HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trials (8,9), as well as other novel non-statin agents in development (e.g., proprotein convertase subtilisin/kexin 9 [PCSK9] inhibitors). The recommendations for use of non-statin therapy were constructed to allow for consideration of individual patient circumstances and future trial data in the clinical setting. In fact, the results of HPS2-THRIVE (published in 2014) (9) subsequently showed no benefit and significant harms from a long-acting niacin/laropiprant preparation in addition to moderate-intensity statin (simvastatin) compared with moderate-intensity statin alone in patients with clinical ASCVD, despite further lowering of LDL-C with niacin. The IMPROVE-IT trial (published in 2015) (8) in patients with recent acute coronary syndromes (ACSs) demonstrated further reductions in LDL-C with the addition of ezetimibe to a moderate-intensity statin (simvastatin) compared with moderate-intensity statin monotherapy. Combination therapy demonstrated a statistically significant, but clinically modest, reduction in events over 7 years of follow-up, and no safety concerns were observed with the addition of ezetimibe (8).

More recently, the FDA approved 2 monoclonal antibodies to PCSK9, alirocumab and evolocumab, which inhibit binding of PCSK9 to the LDL receptor, thus increasing LDL receptor density. Both agents were approved as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional lowering of LDL-C. In addition, evolocumab was approved for use in combination with other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C (10,11). These agents dramatically reduce LDL-C levels over and above statin therapy, with favorable short-term outcomes data up to 18 months (11,12). Long-term cardiovascular outcomes trials are ongoing for both alirocumab and evolocumab, as well as for bococizumab, a PCSK9 inhibitor that is not yet FDA approved.

Rationale for Expert Consensus Decision Pathway

The ACC recognized that clinicians and patients may seek firmer and more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate. Therefore, the ACC convened this expert consensus decision pathway writing committee to address current gaps in care for LDL-C lowering to reduce ASCVD risk. This effort relies extensively on the evidence base established by the 2013 ACC/AHA cholesterol guideline and attempts to provide further recommendations for clinicians and patients regarding use of non-statin therapies. It should be noted that this process did not involve formal systematic reviews, grading of evidence, or synthesis of evidence. The goal was to provide practical guidance for clinicians and patients in situations not covered by the 2013 ACC/AHA guideline until such time as the next round of guidelines has the opportunity to formally review recent scientific evidence and cardiovascular outcomes trials are completed with new agents for ASCVD risk reduction. Specifically, this panel was convened by the ACC to answer the following questions regarding use of non-statin therapies:

1. In what patient populations should non-statin therapies be considered?
2. In what situations should non-statin therapies be considered, that is, when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?

3. If non-statin therapies are to be added, which agents or therapies should be considered and in what order?

## 2. METHODS

### Background

In 2013, the ACC launched “LDL: Address the Risk” as a multistakeholder quality initiative designed to improve patient outcomes by driving awareness of gaps in lipid management and the importance of managing LDL-related risk. On September 16, 2015, the second LDL: Address the Risk Think Tank meeting was convened to bring together expert clinicians along with a broad set of stakeholders from patient advocacy groups, health plans, pharmacy benefit managers, drug manufacturers, electronic health record vendors, and health systems to discuss the newest developments in management of dyslipidemia and to consider implications for the care of high-risk patients with dyslipidemia. Participants in this LDL: Address the Risk Think Tank identified the need for expert consensus guidance regarding the incorporation of non-statin therapies into treatment strategies for higher-risk patients as a critical gap in clinical care.

### Process

The guidance that follows in this document was informed by the scientific evidence presented and expert opinions considered during the Think Tank, and by subsequent review and deliberation on available evidence by the expert consensus writing committee. Although the Think Tank provided valuable insight into the practical issues and gaps in care, this document is a separate and independent activity aimed specifically at addressing the questions raised during the meeting.

The work of the writing committee was supported exclusively by the ACC without commercial support. Writing committee members volunteered their time to this effort. Conference calls of the writing committee were confidential and attended only by committee members and society staff. All members of the writing committee, as well as those selected to serve as peer reviewers of this document, were required to disclose relationships with industry and other entities (RWE). Writing committee and peer reviewer RWE relevant to this document are included in Appendixes 1 and 2, respectively. A formal peer review process was completed consistent with ACC policy and included expert reviewers nominated by the ACC (see Appendix 2). A public comment period was also held to obtain further feedback. Following reconciliation of all comments, this document was approved for publication by the governing bodies of the ACC and endorsed by the National Lipid Association.

The expert consensus writing committee began its deliberations by endorsing the construct of the 4 statin benefit groups identified by the 2013 ACC/AHA cholesterol guideline (Table 1) (1). The committee then considered the potential for net ASCVD risk-reduction benefit of the use or addition of non-statin therapies in each of the 4 statin benefit groups. Within each of these groups, higher-risk subgroups were considered separately given the potential for differences in the approach to combination therapy in each of these unique groups.

**Lifestyle intervention:** In agreement with the 2013 ACC/AHA cholesterol guideline, for all patient groups, the current consensus emphasizes that lifestyle modification (i.e., adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of ASCVD risk reduction, both before and in concert with the use of cholesterol-lowering drug therapies. In addition, referral to a registered dietitian nutritionist (RDN) may be considered to improve understanding of heart-healthy dietary principles and individualize nutrition recommendations. Adherence to lifestyle modification should be regularly assessed at the time of initiation or modification of statin therapy and during monitoring of ongoing therapy. As this document specifically addresses considerations for the incorporation of non-statin therapies in selected high-risk patient populations, it is critical that the clinician assess and reinforce adherence to intensive lifestyle changes prior to initiation of these additional agents. The reader is referred to the 2013 ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk (12) and the National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2 (13) for lifestyle recommendations for healthy adults and management of dyslipidemias.

**Monitoring of response to LDL-C lowering therapies:** In agreement with the ACC/AHA guideline, the writing committee recommends the use of an initial fasting lipid panel (TC, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy, to determine a patient’s adherence to statin therapy. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated. Adherence to both medication and lifestyle regimens is required for ASCVD risk reduction. When any modification is made to LDL-C lowering therapy, including intensification of lifestyle intervention, increase in statin intensity, or the addition of non-statin therapies, the writing committee recommends the use of
a fasting lipid panel 4 to 12 weeks after treatment modification to determine a patient’s response and adherence. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated.

**Approaches to statin intolerance:** Because the overwhelming body of evidence for ASCVD risk reduction with lipid-lowering therapies is from statin RCTs, evidence-based statin therapy of appropriate intensity is recommended in all 4 statin benefit groups; however, following initiation of therapy, some individuals may experience unacceptable adverse effects when taking the recommended intensity of statin, the most commonly reported being muscle-related symptoms (14). Although muscle-related side effects may occur while on statin therapy, true statin intolerance is uncommon (15,16). A systematic approach to evaluation of possible statin-related adverse effects is critically important to encourage adherence to evidence-based statin treatment. A careful history can help to determine whether symptoms are consistent with statin-related effects, which tend to be myalgias or weakness in large proximal muscle groups. Other causes of muscle symptoms must be ruled out (e.g., hypothyroidism, vitamin D deficiency, recent exercise) and drug-drug interactions that can increase systemic statin exposure must be considered. Some patients, such as women, individuals of Asian descent, and the elderly, may be at increased risk for statin-related muscle symptoms; however, these patients may be able to tolerate a lower statin intensity, an alternative statin, or alternative dosing strategies without problems. The approach to statin intolerance should include discontinuation of statin therapy and subsequent rechallenge to verify recurrence of muscle-related symptoms. Whereas there is not a universally accepted definition of statin intolerance, most experts recommend that patients are documented to have unacceptable muscle-related symptoms that resolve with discontinuation of therapy and occur with rechallenge on at least 2 to 3 statins, preferably ones that use different metabolic pathways and have different lipophilicity, and 1 of which is prescribed at the lowest approved dose. Although not studied in RCTs, if the lowest dose of multiple statins cannot be tolerated on a daily basis, consideration should be given to alternative dosing strategies such as use of statins with long half-life administered 3 times per week or once per week (17). Non-statin therapies are not considered to be an alternative to evidence-based statin therapy unless statin intolerance has been systematically and rigorously evaluated and documented. The ACC Statin Intolerance App (http://www.acc.org/StatinIntoleranceApp) incorporates the guidance of both the ACC/AHA guideline and the National Lipid Association’s 2014 Statin Intolerance Panel for the comprehensive evaluation and management of potential statin-related side effects (1,15). The app facilitates and adds structure to the clinician-patient discussion and includes questions to evaluate muscle-related symptoms, step-by-step guidance in the management of statin-related muscle symptoms, and a drug comparison tool for consideration of statin characteristics and potential drug-drug interactions.

**Non-statin therapies:** Currently available strategies and agents that are considered in this document for the management of LDL-related ASCVD risk are described in Table 3. Dietary adjuncts for lowering atherogenic cholesterol may also be considered for patients with dyslipidemia, including phytosterols and soluble dietary fibers (13). As outlined in Table 3, there are important considerations in the choice of non-statin pharmacological agents that may make a treatment modality preferable in specific patient populations (e.g., pregnant women, elderly patients, patients with diabetes). These considerations include the extent of available scientific evidence for net ASCVD risk-reduction benefit, safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience and medication storage, pill burden, route of administration, potential to jeopardize adherence to evidence-based therapies, and importantly, patient preferences. Before initiation of combination therapy, it is imperative for clinicians and patients to engage in a discussion that addresses the potential for net benefit, including absolute ASCVD risk-reduction benefits and potential harms, prescribing considerations, and patient preferences for treatment (Table 4) (1).

The expert consensus writing committee undertook an iterative process to determine the higher-risk patient groups that should be considered for additional LDL-C lowering therapies, the appropriate strategies that should be considered for each group, and the order in which those strategies should be considered. The committee first considered a base case of a patient without significant comorbidities within each of the four statin benefit groups. The appropriate strategies and the order of consideration were first determined for these patients. Once the committee reached consensus on this scenario, members undertook an iterative process of discussion and consideration of special circumstances for subpopulations with comorbidities, and then updated the strategies in order to create a clinical pathway, or algorithm, that could be followed by clinicians for each patient scenario. All issues were discussed and all pathways were finalized with full consensus of the committee members. Of note, the writing committee did not consider therapies for severe hypertriglyceridemia (prescription omega-3 fatty acids, fibrin acid derivatives), which have been addressed elsewhere recently (17,18). On the basis of currently available evidence of non-efficacy and potential harms, the committee judged that there are no clear indications for the routine use of niacin preparations as additional non-statin therapies, and niacin is therefore
not recommended for use in any of the clinical situations addressed below.

Special populations not included in 1 of the 4 statin benefit groups (patients with heart failure, patients on maintenance hemodialysis, and women considering pregnancy or already pregnant) are considered in a separate section below.

3. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation, specific assumptions and definitions were considered by the writing committee in the development of this document.

1. The expert consensus writing committee endorses the evidence-based approaches to ASCVD risk reduction in adults enumerated in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (1).

2. These algorithms begin with the assumption that the patient is in 1 of the 4 evidence-based statin benefit groups identified in the 2013 ACC/AHA cholesterol guideline:
   a. Patients with clinical ASCVD;
   b. Patients with LDL-C ≥190 mg/dL, not due to secondary causes;
   c. Patients aged 40 to 75 years with diabetes mellitus and LDL-C 70 to 189 mg/dL; and
   d. Patients aged 40 to 75 years with no diabetes, but with LDL-C 70 to 189 mg/dL and predicted 10-year ASCVD risk ≥7.5%.

   Patients not in 1 of these 4 groups who may be at elevated risk for ASCVD events should receive individualized care in the context of shared decision making between the clinician and patient (see Special Populations).

3. These algorithms assume that the patient is currently taking or has attempted to take a statin, as a result of shared decision making, and that the clinician and patient are trying to determine whether additional therapy is needed to reduce ASCVD risk further.

4. These algorithms were crafted based on the principle of potential net ASCVD risk-reduction benefit, meaning that the potential benefits of additional non-statin therapy should outweigh any potential for harm. Other considerations include the extent of available scientific evidence for safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering, cost, convenience and medication storage, pill burden, route of administration, potential to jeopardize adherence to evidence-based therapies, and importantly, patient preferences. Before initiation of combination therapy, it is imperative for clinicians and patients to engage in a discussion that addresses the potential for net benefit, including absolute ASCVD risk-reduction benefits and potential harms, prescribing considerations, and patient preferences for treatment (Table 4).

5. Critical to the decision-making process for use of additional non-statin therapies in select high-risk patients was the definition of the concept of thresholds for consideration of net ASCVD risk-reduction benefit. The expert consensus writing committee endorsed the evidence-based findings from the 2013 ACC/AHA cholesterol guideline regarding the use of appropriate intensity statin therapy and the indicators of efficacy (e.g., ≥50% LDL-C reduction for high-intensity statin doses and 30% to <50% reduction for moderate-intensity doses). In addition, the committee acknowledged that patients in the RCTs demonstrating efficacy and safety of LDL-C lowering therapy tended to achieve absolute LDL-C levels within a given range. Therefore, assuming adherence to therapy, patients with LDL-C levels above that range may not achieve maximal benefit and might be considered for additional therapy. The committee, therefore, judged that it was appropriate to provide levels of LDL-C, or “thresholds,” in terms of both percentage LDL-C reduction from baseline and absolute on-treatment LDL-C measurement, which, if not achieved by adherent patients, would serve as factors to consider in decision making regarding further therapy. The writing committee emphasizes that these are not firm triggers for adding medication but factors that may be considered within the broader context of an individual patient’s clinical situation.

6. The expert consensus writing committee recognizes that there are different means for measuring LDL-C—through direct measurement or calculation using the Friedewald equation. The committee endorses use of the Friedewald equation in most cases, given that the majority of RCTs used this method, that it is the most widely available means in clinical practice, and that it tends to cost less. Nonetheless, the committee acknowledges that there can be significant discrepancies in levels of directly measured versus calculated LDL-C within the same sample, especially at lower LDL-C levels (19,20). The uncertainty in LDL-C measurement provides further support for the committee’s position that the thresholds for consideration of net ASCVD risk-reduction benefit should merely be factors to be considered and not firm triggers for intensification of therapy.

7. Each algorithm below provides a suggested clinical workflow for consideration of additional therapies. The associated text in this document and the footnotes in the figures provide important context and additional considerations and should be read carefully by users. At the end of this document, several special populations are considered for whom individualized care is recommended.
4. CENTRAL ILLUSTRATION

Figure 1 displays the patient populations addressed by the writing committee, factors to consider at each clinical stage, and potential interventions to consider. The solid arrow represents recommended steps, whereas the dashed arrow indicates optional interventions that may be considered. Readers should refer to the individual algorithms for the detailed clinical workflow for each patient scenario.

5. DESCRIPTION AND RATIONALE: APPROACH TO PATIENT GROUPS WHO MAY BE CONSIDERED FOR ADDITIONAL THERAPY

The expert consensus writing committee created decision pathway algorithms for each of the patient groups, which are described below. For ease of clinical use, these are also summarized in Figures 2, 3, 4, and 5.

Adults ≥21 Years of Age With Clinical ASCVD, on Statin for Secondary Prevention - Figures 2A-2C

Patients with clinical ASCVD are defined from the RCT inclusion criteria as those with ACS or history of myocardial infarction (MI), stable or unstable angina, coronary revascularization, stroke, transient ischemic attack presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization. The committee identified several subgroups of patients with clinical ASCVD, including those without other comorbidities, those with comorbidities, and those with baseline LDL-C ≥190 mg/dL. Each of these subgroups is addressed in a separate algorithm below. Comorbidities were defined as diabetes mellitus, recent (<3 months) ASCVD event, ASCVD event while already taking statin therapy, baseline LDL-C ≥190 mg/dL not due to secondary causes, poorly controlled other major ASCVD risk factors, elevated lipoprotein(a), or chronic
LDL-C kidney disease (CKD). Patients with ASCVD and baseline LDL-C $\geq 190$ mg/dL are addressed in a separate algorithm. Patients with symptomatic heart failure, those on maintenance hemodialysis, and those with planned or current pregnancy require individualized care (see Special Populations later in the text).

High-intensity statin therapy should be initiated for adults $\leq 75$ years of age with clinical ASCVD who are not receiving statin therapy or the intensity should be increased in those receiving a low- or moderate-intensity statin, unless they have a history of intolerance to high-intensity statin therapy or have other characteristics that may influence safety. In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when either high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin therapy should be used as the second option, if tolerated. As noted, if moderate-intensity statins are employed, the objective is to achieve a 30% to $<50\%$ reduction of LDL-C, and for high-intensity statins, $\geq 50\%$ LDL-C reduction.

As per the ACC/AHA guideline, fewer people $>75$ years of age were enrolled in the statin RCTs, but available evidence does support the continuation of statins beyond 75 years of age in persons who are already taking and tolerating these drugs. A larger amount of data support the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD who are $>75$ years of age; however, the limited information available does not clearly support initiation of high-intensity statin therapy for secondary prevention in individuals $>75$ years of age.

**Stable clinical ASCVD without comorbidities, on statin for secondary prevention (Figure 2A).** Patients in this group have stable chronic ASCVD without the presence of diabetes, a recent ($<3$ months) ASCVD event, an ASCVD event while already taking a statin, poorly controlled other major ASCVD risk factors, elevated lipoprotein(a), CKD, symptomatic heart failure, maintenance hemodialysis, or baseline LDL-C $\geq 190$ mg/dL not due to secondary causes. These patients should be treated first with maximally tolerated statin intensity. If patients have a $\geq 50\%$ reduction in LDL-C from baseline (and may consider LDL-C $<100$ mg/dL), it is reasonable to continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If a patient has a less-than-anticipated response ($<50\%$ reduction in LDL-C and may consider LDL-C $\geq 100$ mg/dL), additional clinical approaches are warranted. First, the clinician and patient should address statin adherence by assessing the number of missed statin doses per month and evaluating any barriers to adherence. The committee emphasizes that if an adherent patient has not been tried on a high-intensity statin, the dose should be increased to a high-intensity dose at this time. Patients who are unable to tolerate even a moderate-intensity statin should be evaluated for statin intolerance and considered for referral to a lipid specialist. The clinician and patient should attempt to intensify lifestyle modification and may consider the incorporation of soluble dietary fiber and phytosterols as part of this approach. Other major ASCVD risk factors, including tobacco use and elevated blood pressure, should be addressed and controlled as well. If the patient has now achieved the anticipated response to therapy, with $\geq 50\%$ reduction in LDL-C (and may consider LDL-C $<100$ mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has $<50\%$ reduction in LDL-C (and may consider LDL-C $\geq 100$ mg/dL), the patient and clinician should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen. The clinician-patient discussion is described in Table 4 and should address: the potential for additional ASCVD risk reduction that could be expected from the addition of a non-statin therapy to lower LDL-C further; the potential for adverse events or drug-drug interactions from addition of non-statin therapy (Table 3); and patient preferences, including considerations of the patient’s perception of net benefit, convenience/burden of additional therapy, cost, quality of life, and the potential to jeopardize adherence to other evidence-based therapies. If a decision is made to pursue no additional medication at this point, it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

Although there is a gap in RCT evidence demonstrating outcomes benefits of using combination therapy in stable clinical ASCVD patients, the expert consensus writing committee supports consideration of adding ezetimibe 10 mg daily as the first non-statin agent, given the benefits on ASCVD outcomes and demonstrated safety of ezetimibe in patients with ACS treated with ezetimibe-simvastatin versus simvastatin monotherapy (Table 3) (8). A bile acid sequestrant (BAS) may be considered as a second-line agent for those with ezetimibe intolerance and with triglycerides $<300$ mg/dL, but there is no evidence for benefit of BAS in addition to statins in this population (21). If the goals of therapy defined in the clinician-patient discussion have been achieved with addition of ezetimibe, it is reasonable to continue the statin-ezetimibe therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If ASCVD patients without comorbidities, who are on maximally tolerated statin-ezetimibe or non-statin...
combination therapy in the setting of documented statin intolerance, achieve a less-than-anticipated response with <50% reduction in LDL-C (and may consider LDL-C $\leq 100$ mg/dL), it is reasonable to engage in a clinician-patient discussion with consideration of the net benefit of alirocumab or evolocumab (in addition to or in place of ezetimibe) as a second step to achieve further LDL-C reduction. If a PCSK9 inhibitor is prescribed,
clinicians should continue maximally tolerated statin and monitoring for adherence to medications and lifestyle, side effects, and ongoing LDL-C response to therapy.

Clinical ASCVD with comorbidities, on statin for secondary prevention (Figure 2B). Patients in this group have ASCVD with comorbidities including diabetes, recent (<3 months) ASCVD event, ASCVD event while
already taking a statin, poorly controlled other major ASCVD risk factors, elevated lipoprotein(a), or CKD not on hemodialysis. These patients should be treated first with maximally tolerated statin intensity. Patients presenting with ACS should have a lipid panel obtained within 24 hours of the acute event for accurate assessment of baseline LDL-C. If patients have a ≥50% reduction in LDL-C from baseline (and may consider LDL-C <70 mg/dL or non−HDL-C <100 mg/dL for patients with diabetes), it is reasonable to continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy. Due to the frequency of elevated non−HDL-C despite near-normal levels of LDL-C in patients with diabetes, non−HDL-C thresholds are included for this high-risk patient population. The algorithm for patients with ASCVD and with comorbidities (Figure 2B) addressed in this section closely mirrors the algorithm for patients with ASCVD without comorbidities (Figure 2A), with the exception of the consideration of the lower LDL-C threshold (<70 mg/dL) and non−HDL-C threshold (<100 mg/dL for patients with diabetes). The committee judged this to be appropriate given the higher-risk nature of this patient population with comorbidities.

Clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes, on statin for secondary prevention (Figure 2C). Patients with ASCVD and primary, severe elevations of LDL-C ≥190 mg/dL have very high risk for future ASCVD events because of their lifetime exposure to markedly elevated LDL-C levels. This risk is accelerated in the presence of other ASCVD risk factors (22,23). Patients with LDL-C ≥190 mg/dL are more likely to have heterozygous (HeFH) or homozygous (HoFH) familial hypercholesterolemia, genetic disorders associated with severe hypercholesterolemia, and a family history of severe hypercholesterolemia and premature ASCVD. Early treatment is highly beneficial. Long-term drug therapy of patients with severe hypercholesterolemia can substantially reduce the risk of ASCVD and requires lifelong treatment and regular follow-up. Referral to a lipid specialist should be strongly considered for patients with LDL-C ≥190 mg/dL and is definitely recommended for children, adolescents, women during pregnancy, and patients with HoFH or severe HeFH (22,23). Because hypercholesterolemia in these high-risk individuals is often genetically determined, family screening is especially important in this group to identify additional family members who would benefit from assessment and early treatment. Cascade screening, a process of systematic assessment of close biologic relatives, should be performed for all patients with HeFH or HoFH to identify others with the disease who would benefit from treatment (24).

These patients should be treated first with maximally tolerated statin therapy. If patients have ≥50% reduction in LDL-C from baseline (and may consider LDL-C <70 mg/dL), it is reasonable to continue statin therapy, monitor adherence to medication and lifestyle, and ongoing LDL-C response to therapy. In patients who have a less-than-anticipated response on maximally tolerated statin therapy with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL), the clinician and patient should address statin adherence by assessing the number of missed statin doses per month and evaluating any barriers to adherence. The committee emphasizes that if an adherent patient has not been tried on high-intensity statin, the dose should be increased to a high-intensity dose at this time. Patients who are unable to tolerate even a moderate-intensity statin should be evaluated for statin intolerance and considered for referral to a lipid specialist. Other major ASCVD risk factors, including tobacco use, elevated blood pressure, and diabetes, should be controlled as well. The committee also emphasizes that all such patients should be considered for referral to a lipid specialist and RDN, especially if they have documented HoFH. If the patient has now achieved the anticipated response to therapy (≥50% reduction in LDL-C and may consider LDL-C <70 mg/dL or non−HDL-C <100 mg/dL in patients with diabetes), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL), the patient and clinician should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen (Table 4). Although there is a gap in the evidence demonstrating outcomes benefit when combined with high-intensity statin therapy, the addition of ezetimibe may be considered based upon the improved ASCVD outcomes and demonstrated safety of the combination of ezetimibe with moderate-intensity simvastatin versus simvastatin monotherapy (8). A BAS may be considered as a second-line alternative to ezetimibe if triglycerides <300 mg/dL. In the opinion of the expert consensus writing committee, in a patient with ASCVD and baseline LDL-C ≥190 mg/dL with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL) it is reasonable to consider a PCSK9 inhibitor as a first step rather than ezetimibe or BAS given PCSK9 inhibitors’ greater LDL-C lowering efficacy. Regardless of the therapy chosen as the initial non-statin therapy that is added, the response to therapy should be monitored as described above. If the reduction in LDL-C is inadequate (<50% reduction in LDL-C and may consider LDL-C ≥70 mg/dL) with addition
**FIGURE 2C** Patients ≥21 Years of Age with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

Patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes, on statin for secondary prevention

- Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin
  - NO
  - YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients, especially for homozygous FH

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 3)

- NO
- YES

Optional non-statin medications to consider

- Consider ezetimibe (or BAS second line)
- Consider PCSK9 inhibitor

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin/other medications

- NO
- YES

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin/other medications

- NO
- YES

Referral to lipid specialist and RDN recommended

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BAS = bile acid sequestrant, FH = familial hypercholesterolemia, LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin 9, RDN = registered dietitian nutritionist.

*e.g., hypothyroidism, nephrology, extreme dietary patterns

†The Expert Panel emphasizes that these are not firm triggers for adding medication, but they are factors that may be considered within the broader context of an individual patient’s clinical situation.

‡See section on strategy for assessment and management of statin intolerance.

§May consider mipomersen or lomitapide or LDL apheresis in appropriate patients.

||Consider BAS if ezetimibe intolerant and triglycerides <300 mg/dL.
of the initial non-statin therapy, consideration of the net benefit of adding a second non-statin agent to achieve further LDL-C reduction is reasonable for patients on maximally tolerated statin–ezetimibe, statin–PCSK9 inhibitor, or non-statin combination therapy in the setting of documented statin intolerance. If combination statin and non-statin therapy with ezetimibe (or a BAS) and a PCSK9 inhibitor have been attempted and the patient still has <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL), the committee recommends referral to a lipid specialist and RDN.

Specialized therapies, such as mipomersen, lomitapide, or LDL apheresis, may be needed to control LDL-C in patients with ASCVD and baseline LDL-C ≥190 mg/dL who have an inadequate response to statins with or without ezetimibe and PCSK9 inhibitors (25). In the opinion of the expert consensus writing committee, these therapies are best administered under the care of a lipid specialist. LDL apheresis may be considered in patients with ASCVD and phenotypic HeFH and LDL-C ≥190 mg/dL despite maximally tolerated statin with or without ezetimibe and PCSK9 inhibitors (26). The writing committee has recommended using 190 mg/dL on maximal treatment as the level at which LDL apheresis should be considered in such patients, in order to remain consistent with the cutoffs employed in the ACC/AHA guideline. In those with phenotypic HoFH, evolocumab should be considered before LDL apheresis except in those who have been documented to be LDL receptor negative (27).

**Adults ≥21 Years of Age With LDL-Cholesterol ≥190 mg/dL (Not Due to Secondary Modifiable Causes) on Statin for Primary Prevention - Figure 3**

Patients with baseline elevation of LDL-C ≥190 mg/dL not due to secondary modifiable causes are at very high risk of first and recurrent ASCVD events because of their lifetime exposure to markedly elevated LDL-C levels. This risk is accelerated in the presence of other ASCVD risk factors (18,19). Patients with LDL ≥190 mg/dL are more likely to have HeFH or HoFH, genetic disorders associated with severe hypercholesterolemia, and a family history of severe hypercholesterolemia and premature ASCVD. This disorder has an autosomal codominant pattern of inheritance and is caused most commonly by mutations in the gene coding for the LDL receptor, with >1,600 different identified mutations (22). Early treatment is highly beneficial. Long-term drug therapy of patients with severe hypercholesterolemia can substantially reduce the risk of ASCVD and requires lifelong treatment and regular follow-up. Referral to a lipid specialist should be considered for patients with LDL-C ≥190 mg/dL and is definitely recommended for children, adolescents, women during pregnancy, and patients with HoFH or severe HeFH (18,19).

Because hypercholesterolemia in these high-risk individuals is often genetically determined, family screening is especially important in this group to identify additional family members who would benefit from assessment and early treatment. Cascade screening, a process of systematic assessment of close biologic relatives, should be performed in all people with HeFH or HoFH to identify others with the disease who would benefit from treatment (24).

Depending on the gene mutation, expression, and pattern of inheritance (i.e., homozygous or heterozygous), patients with LDL-C ≥190 mg/dL may have variable responses to pharmacological therapies. Therefore, response to lifestyle modification and maximally tolerated statin therapy should be monitored, reversible ASCVD risk factors must be treated, and more intensive combination therapy may be indicated. A low-saturated fat, low-cholesterol diet should be encouraged in all patients with severe hypercholesterolemia and patients should be referred to a RDN; however, even with strict adherence, diet has limited impact on the severity of hypercholesterolemia in this high-risk patient population (28).

**LDL-C ≥190 mg/dL with clinical ASCVD.** This clinical situation is addressed in the preceding text and in Figure 2C.

**LDL-C ≥190 mg/dL with or without concomitant ASCVD risk factors (Figure 3).** Although all patients with baseline LDL-C ≥190 mg/dL are at high risk for first and recurrent ASCVD events because of their lifetime exposure, the presence of concomitant risk factors or risk markers for ASCVD (including a family history of premature ASCVD events, tobacco use, diabetes, hypertension, CKD, evidence of subclinical atherosclerosis, elevated lipoprotein(a), or elevated high-sensitivity C-reactive protein) further increases ASCVD risk significantly. Management of these patients should address and attempt to control all other causal ASCVD risk factors to the extent possible.

These patients should be treated first with maximally tolerated statin therapy. If patients have a ≥50% reduction in LDL-C from baseline (and may consider LDL-C <100 mg/dL), it is reasonable to continue statin therapy, monitor adherence to medication and lifestyle, and ongoing LDL-C response to therapy. In patients who have a less-than-anticipated response on maximally tolerated statin therapy with <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL), the clinician and patient should address statin adherence by assessing the number of missed statin doses per month and evaluating any barriers to adherence. The committee emphasizes that if an adherent patient has not been tried on high-intensity statin, the dose should be increased to a high-intensity dose at this time. If the patient is unable to
FIGURE 3 Patients ≥21 Years of Age without Clinical ASCVD and with Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Primary Prevention

Patients without clinical ASCVD and with baseline LDL-C ≥190 mg/dL not due to secondary causes, on statin for primary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin†

NO

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡
   Referral to lipid specialist recommended if statin intolerant.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients, especially if LDL-C ≥250 mg/dL or homozygous FH.§

YES

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

NO

Optional non-statin medications to consider

Consider ezetimibe
(or BAS second line).¶

Consider PCSK9 inhibitor.

YES

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin/other medications†

NO

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin/other medications†

NO

Referral to lipid specialist recommended

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BAS = bile acid sequestrant, FH = familial hypercholesterolemia, LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin 9, RDN = registered dietitian nutritionist.

†e.g., hypothyroidism, nephrosis, extreme dietary patterns

‡The Expert Panel emphasizes that these are not firm triggers for adding medication, but they are factors that may be considered within the broader context of an individual patient’s clinical situation.

§See section on strategy for assessment and management of statin intolerance.

¶May consider mipomersen, lomitapide, or LDL apheresis for appropriate patients.

¶¶Consider BAS if ezetimibe intolerant and triglycerides <300 mg/dL.
tolerate even a moderate-intensity statin, they should be evaluated for statin intolerance and considered for referral to a lipid specialist. Other major ASCVD risk factors, including tobacco use, elevated blood pressure, and diabetes, should be controlled as well. The committee also emphasizes that all such patients should be considered for referral to a lipid specialist and RDN, especially if the patient has documented HoFH. If the patient has now achieved the anticipated response to therapy (>50% reduction in LDL-C and may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL in patients with diabetes), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL in patients with diabetes), the patient and clinician should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen (Table 4). Depending upon the additional desired percentage reduction in LDL-C, consideration may be given to either ezetimibe or a PCSK9 inhibitor in combination with maximally tolerated statin therapy in these very high-risk patients. Although there is a gap in the evidence demonstrating outcomes benefit when combined with high-intensity statin therapy, the addition of ezetimibe may be considered given the improved ASCVD outcomes and demonstrated safety of the combination of ezetimibe with moderate-intensity simvastatin versus simvastatin monotherapy (8). A BAS may be considered as a second-line alternative to ezetimibe if triglycerides ≥300 mg/dL. If a patient with primary baseline LDL-C ≥190 mg/dL is unable to tolerate ezetimibe when added to maximally tolerated statin therapy, it is reasonable to consider a PCSK9 inhibitor before a BAS given PCSK9 inhibitors’ greater LDL-C lowering efficacy. The committee also notes that for patients with baseline LDL-C ≥190 mg/dL and without other high-risk features or comorbidities, achievement of ≥50% reduction in LDL-C and LDL-C <130 mg/dL is a reasonable therapeutic outcome that may not require further intensification of therapy.

Table 4

| LDL-C | HDL-C | ASCVD | Age
|-------|-------|-------|------
| <100  | <45   | No    | 40-
| 100-129| >45   | Yes   | 69
| 130-189| <45   | No    | 40-
| 190+  | <45   | Yes   | 69

Specialized therapies may be needed to control LDL-C in patients with or without concomitant ASCVD risk factors and LDL-C ≥190 mg/dL. mipomersen and lomitapide are only approved for the treatment of HoFH and may be prescribed at the discretion of lipid specialists. The mechanisms of action of these novel agents do not involve upregulation of the LDL receptor and may be of particular benefit in LDL receptor-negative HoFH patients. LDL apheresis may be considered by lipid specialists in patients with phenotypic HeFH and LDL-C ≥190 mg/dL despite maximally tolerated medical therapy, and for all patients with phenotypic HoFH with LDL-C ≥300 mg/dL on maximally tolerated therapy, including evolocumab.

**LDL-C ≥190 mg/dL and pregnancy.** Special consideration for lipid management is needed in all premenopausal women and during pregnancy with or without FH (see Special Populations, later in the text). Statins should only be used in premenopausal women who are using effective contraception and are not nursing.

**Familial hypercholesterolemia in children and adolescents.** Management of FH in children and adolescents is beyond the scope of this manuscript and has been reviewed in detail elsewhere. The reader is referred to references cited for excellent guidance on this important topic (22,23).

**Adults Aged 40 to 75 Years Without ASCVD, but With Diabetes and LDL-C 70 to 189 mg/dL, on Statin for Primary Prevention - Figure 4**

Patients with diabetes are at higher risk for ASCVD events due to diabetes itself and also to the concomitant burden of other cardiometabolic risk factors that tend to cluster in patients with type 1 or type 2 diabetes. Furthermore, the effects of acute ASCVD events appear to be more severe among patients with diabetes, making intensive prevention efforts even more necessary.

**Diabetes and LDL-C 70 to 189 mg/dL with 10-year ASCVD risk <7.5% and without high-risk features (retinopathy, CKD, albuminuria, elevated Lp(a), subclinical atherosclerosis).** For the small proportion of patients aged 40 to 75 years with diabetes, with 10-year ASCVD <7.5%, and without high-risk features, a high level of evidence supports the use of moderate-intensity statin therapy. In addition to adherence to appropriate lifestyle interventions, use of soluble dietary fiber and phytosterols may also be considered. Younger patients without ASCVD but with ASCVD risk factors typically have low 10-year predicted risks for ASCVD but high lifetime predicted risks. In such patients, it is reasonable to consider lifetime risks for ASCVD, as recommended by the 2013 risk assessment guidelines (2). However, making decisions for drug therapy based on lifetime ASCVD risk is problematic because of the limited data on treatment of younger adults and on long-term safety and efficacy of lipid-lowering therapy. Nonetheless, consideration of lifetime risk estimates in counseling patients may be useful to motivate lifestyle changes or adherence to therapy.

In patients with diabetes who achieve inadequate lowering of LDL-C or non-HDL-C despite adherence to lifestyle recommendations and moderate-intensity statin therapy, the recommended threshold for consideration of the net benefit of increasing to high-intensity statin
therapy is failure to achieve 30 to <50% reduction in LDL-C (and may consider on-treatment LDL-C <100 mg/dL or non-HDL-C ≥130 mg/dL). Due to the frequency of elevated non-HDL-C despite near-normal levels of LDL-C in diabetics, non-HDL-C thresholds are included in this high-risk patient population.

If a patient with diabetes and 10-year ASCVD risk <7.5% without high-risk features has a less-than-anticipated response to therapy, consideration of optional non-statin medications (e.g., ezetimibe) may be appropriate.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BAS = bile acid sequestrant, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, RDN = registered dietitian nutritionist.

*The Expert Panel emphasizes that these are not firm triggers for adding medication, but they are factors that may be considered within the broader context of an individual patient’s clinical situation. Due to increase in triglycerides often present in diabetes, may also consider combination therapy if non-HDL-C ≥130 mg/dL.
†See section on strategy for assessment and management of statin intolerance.
‡Consider BAS if ezetimibe intolerant and triglycerides <300 mg/dL. Colesevelam may have modest salutary effects on HbA1c and may worsen hypertriglyceridemia.
response, with <30% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL), additional clinical approaches may be warranted. Intensification of lifestyle modification should be addressed and statin adherence should be evaluated, including the number of missed statin doses per month and consideration of barriers to adherence. Other major ASCVD risk factors, including tobacco use and elevated blood pressure, should be addressed and controlled as well. If the patient has now achieved the anticipated response to therapy, with 30% to <50% reduction in LDL-C (and may consider LDL-C <100 mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has <30% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL), the patient and clinician may consider increasing the statin dose to a high-intensity statin. If the patient has now achieved the anticipated response to therapy, it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If escalation to high-intensity statin results in <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL), the clinician and patient should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen (Table 4). If a decision is made to pursue no additional medication at this point, it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

In patients with diabetes and <7.5% predicted 10-year ASCVD risk on maximally tolerated statin therapy, the potential for net ASCVD risk-reduction benefit of combination therapy may be considered in patients with <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL). Baseline LDL-C ≥190 mg/dL or non-HDL-C ≥190 mg/dL not due to secondary causes, complex mixed dyslipidemias, or severe hypertriglyceridemia. Ezetimibe is the preferred initial non-statin therapy due to tolerability, convenience, and single-tablet daily dose. Bas may have a modest hypoglycemic effect that may be beneficial in some diabetic patients if fasting triglycerides are <300 mg/dL. Bas may also be considered if patients have an inadequate response to ezetimibe or if patients are ezetimibe intolerant.

In the absence of ASCVD or baseline LDL-C ≥190 mg/dL not due to secondary causes, the PCSK9 inhibitors do not have an established role for primary prevention of ASCVD in patients with diabetes. Referral to a lipid specialist is recommended for patients with diabetes and statin intolerance, baseline LDL-C ≥190 mg/dL not due to secondary causes, complex mixed dyslipidemias, or severe hypertriglyceridemia.

Diabetes and LDL-C 70 to 189 mg/dL with 10-year ASCVD risk ≥7.5% (Figure 4). The committee identified higher-risk subgroups of patients with diabetes for special consideration, including those with concomitant ASCVD risk factors, predicted 10-year ASCVD risk ≥7.5% by the Pooled Cohort Equations, CKD, albuminuria, retinopathy, evidence of subclinical atherosclerosis, elevated lipoprotein(a), or elevated high-sensitivity C-reactive protein. Management of these patients should include strategies to control all other causal ASCVD risk factors to the greatest extent possible. Higher-risk subgroups of patients with diabetes are potential candidates for high-intensity statin therapy. Thus, all diabetic patients aged 40 to 75 years should undergo assessment of 10-year ASCVD risk and comprehensive risk factor evaluation. Younger patients without ASCVD, but with ASCVD risk factors, typically have low 10-year predicted risks for ASCVD, but high lifetime predicted risks. In such patients, it is reasonable to consider lifetime risks for ASCVD, as recommended by the 2013 risk assessment guidelines (2). However, making decisions for drug therapy on the basis of lifetime ASCVD risk is problematic because of the limited data on treatment of younger adults and on long-term safety and efficacy of lipid-lowering therapy. Nonetheless, consideration of lifetime risk estimates in counseling patients may be useful to motivate lifestyle changes or adherence to therapy.

The only trial of high-intensity statin therapy in primary prevention was performed in a population without diabetes (29); however, the high level of evidence considered by the ACC/AHA expert panel for event reduction with statin therapy in individuals with ≥7.5% estimated 10-year ASCVD risk who did not have diabetes was sufficiently compelling to recommend high-intensity statin therapy preferentially for diabetic patients aged 40 to 75 years with a ≥7.5% estimated 10-year ASCVD. This recommendation recognized that these individuals are at substantially increased lifetime risk for ASCVD events, death, and significantly greater morbidity and worse survival following the onset of clinical ASCVD. In addition to intensive lifestyle modifications, the addition of soluble dietary fiber and phytosterols may also be incorporated in primary prevention patients with diabetes prior to consideration of combination therapy with a non-statin agent.

In higher-risk patients with diabetes who achieve inadequate lowering of LDL-C or non-HDL-C with high-intensity statin therapy, the potential net ASCVD risk-reduction benefit of combination therapy may be considered for patients with <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL). Ezetimibe is preferred as the initial non-statin therapy due to its tolerability, convenience, and...
single-tablet daily dose. Colesevelam has a modest hypoglycemic effect that may be of benefit in some diabetic patients with fasting triglycerides <300 mg/dL or in patients who are ezetimibe intolerant. Of note, the writing committee did not consider therapies (prescription omega-3 fatty acids, fibric acid derivatives) for severe hypertriglyceridemia, which is common in patients with diabetes, since this topic has been addressed elsewhere recently (15,17).

In the absence of ASCVD or baseline LDL-C ≥190 mg/dL, the committee judges that at present, PCSK9 inhibitors do not have an established role for primary prevention of ASCVD in patients with diabetes. Referral to a lipid specialist is recommended for diabetic patients with statin intolerance, baseline LDL-C ≥190 mg/dL, complex mixed dyslipidemias, and severe hypertriglyceridemia.

**Adults Aged 40 to 75 Years Without Clinical ASCVD or Diabetes, With LDL-C 70 to 189 mg/dL and an Estimated 10-Year Risk for ASCVD of ≥7.5%, on Statin for Primary Prevention - Figure 5**

Patients without clinical ASCVD or diabetes, who have LDL-C 70 to 189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, were found to be in a group with net benefit from statin therapy by the 2013 ACC/AHA cholesterol guideline panel (1). Based on a high level of evidence, the guideline recommended that these patients be considered for treatment with moderate- to high-intensity statin. Younger patients without ASCVD but with ASCVD risk factors typically have low 10-year predicted risks for ASCVD but high lifetime predicted risks. In such patients, it is reasonable to consider lifetime risks for ASCVD, as recommended by the 2013 risk assessment guidelines (2). However, making decisions for drug therapy based on lifetime ASCVD risk is problematic because of the limited data on treatment of younger adults and on long-term safety and efficacy of lipid-lowering therapy. Nonetheless, consideration of lifetime risk estimates in counseling patients may be useful to motivate lifestyle changes or adherence to therapy.

In primary prevention patients, the clinician-patient discussion prior to the initiation of a statin is particularly important in order to consider factors that might increase or decrease the individual patient’s predicted risk, potential absolute benefits and harms from statin therapy, possible drug-drug interactions, and patient preferences for prevention approaches. In the opinion of the expert consensus writing committee, non-statin agents should play a limited role in primary prevention given the lack of RCT data when added to statin and should be reserved only for patients who have not achieved sufficient lowering of LDL-C after intensification of moderate- to high-intensity statin dosing or who have been rigorously evaluated and systematically documented to be statin-intolerant. Because the net ASCVD risk-reduction benefit is likely to be lower in primary prevention without diabetes, few patients should be considered for additional therapies at this time beyond a maximally tolerated intensity of statin. The 2013 guidelines also recommended consideration of statin therapy for patients with 5% to <7.5% 10-year ASCVD risk, in the context of a clinician-patient discussion and consideration of other factors. Given the marginal additional benefit that would be anticipated for this lower-risk group, the expert consensus writing committee does not recommend routine use of non-statin therapy for these patients.

Primary prevention patients with 10-year ASCVD risk ≥7.5% without diabetes but with high risk markers may be considered for the addition of non-statin therapy. The committee identified several high-risk markers that may be informative, including: 10-year ASCVD risk ≥20%; primary LDL-C ≥160 mg/dL at baseline; other major ASCVD risk factor(s) that are poorly controlled; family history of premature ASCVD with or without elevated lipoprotein(a); evidence of accelerated subclinical atherosclerosis (e.g., coronary artery calcification); elevated hs-CRP; and other risk-modifying conditions, such as CKD, HIV, and chronic inflammatory disorders. If a patient without high-risk markers has a 30% to <50% reduction on a moderate-intensity statin (and may consider LDL-C <100 mg/dL), it is reasonable to continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If a patient has a less-than-anticipated response, with <30% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL), or has ≥1 high-risk markers, additional clinical approaches are warranted. First, the clinician and patient should address statin adherence by assessing the number of missed statin doses per month and evaluating any barriers to adherence. Patients unable to tolerate even a moderate-intensity statin should be evaluated for statin intolerance and considered for referral to a lipid specialist. The clinician and patient should attempt to intensify lifestyle modification and soluble dietary fibers; phytosterols may be considered as part of this approach. Other major ASCVD risk factors, including tobacco use and elevated blood pressure, should be addressed and controlled as well. If the patient has now achieved the anticipated response to therapy, with a 30% to <50% reduction in LDL-C (and may consider LDL-C <100 mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has <30% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL),
the patient and clinician should increase the statin dose to a high-intensity statin (if this has not already been done), especially if high-risk markers are present. If the patient has now achieved the anticipated response to therapy, with ≥50% reduction in LDL-C (and may consider LDL-C <100 mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.
If escalation to high-intensity statin (or initial high-intensity statin therapy) does not result in >50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL) and if high-risk markers are present, the clinician and patient should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to their regimen (Table 4). If a decision is made to pursue no additional medication at this point, it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

For primary prevention patients with high-risk markers who have achieved less-than-anticipated response to maximally tolerated statin therapy with <50% LDL-C reduction (and may consider LDL-C ≥100 mg/dL), ezetimibe (or a BAS as a second-line agent) may be considered as a potential additional agent. A BAS should only be considered if the patient is ezetimibe intolerant and has multiple other ASCVD risk factors. PCSK9 inhibitors should not be considered in this patient population at this time given the lack of safety and efficacy data. If ezetimibe or a BAS is prescribed, clinicians should continue maximally tolerated statin and continue to monitor for adherence to medications and lifestyle, side effects, and ongoing LDL-C response to therapy.

**Special Populations**

Patients with symptomatic heart failure, those on maintenance hemodialysis for end-stage renal disease, and those with planned or current pregnancy require individualized care.

**Patients with symptomatic heart failure.** Existing data regarding the use of statins in patients with symptomatic heart failure are equivocal because such patients have been largely excluded from RCTs. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Heart Failure) trials directly addressed the use of statins in patients with symptomatic heart failure and reduced left ventricular ejection fraction (30,31). The CORONA trial randomized 5,011 patients aged 60 years or older with ischemic etiology of heart failure and an ejection fraction ≤40% and New York Heart Association (NYHA) functional class II to IV symptoms to 10 mg of rosuvastatin versus placebo (31). The GISSI-HF trial randomized 4,574 patients aged ≥18 years with heart failure of ischemic and non-ischemic etiology with ejection fraction ≤40% (or >40% if hospitalized within the past year) also to 10 mg of rosuvastatin versus placebo (30). Neither the CORONA nor the GISSI-HF trial demonstrated significant reductions in primary endpoints or major secondary endpoints. Both trials were notable for the very high all-cause mortality rates experienced by study participants regardless of randomization status, suggesting very high competing risks; however, a recent individual-level pooled data meta-analysis of these trials, which also accounted for the competing risks of mortality, demonstrated a significant 19% reduction in MI rates among patients with ischemic etiology of heart failure (32). Thus, the writing committee judges that it is reasonable to consider use of statins in patients with symptomatic heart failure due to ischemic etiology who, in the clinician’s judgment, have reasonable expectation of surviving long enough to achieve benefit from the statin therapy (i.e., 3 to 5 years or more). No data exist examining the use of non-statin therapies in heart failure patients, and heart failure is an exclusion criterion in recent PCSK9 inhibitor trials.

In light of the aforementioned considerations, the approach to patients with ASCVD and NYHA functional class II to III heart failure due to ischemic heart disease should generally follow the algorithm for patients with ASCVD and comorbidities, with the exception that use of a PCSK9 inhibitor is not recommended at this time (Figure 2B). Decisions about the use of other non-statin agents in these patients is a matter of clinical judgment after consideration of the potential net clinical benefit in the context of the patient’s projected longevity and other comorbidities.

**Patients on maintenance hemodialysis.** The issues surrounding the use of statins and non-statin therapies in patients on maintenance dialysis parallel those for patients with symptomatic heart failure. The SHARP (Study of Heart and Renal Protection) trial (33) randomized patients with chronic kidney disease (3,023 on dialysis) to simvastatin 20 mg plus ezetimibe 10 mg versus matching placebo. Whereas simvastatin-ezetimibe therapy was associated with a significant 17% reduction in the trial primary endpoint of major atherosclerotic events overall, the reduction was smaller and non-significant in dialysis patients, and particularly hemodialysis patients (although power was limited to detect benefit in this smaller subgroup). The all-cause mortality rate was again notably high in this patient population (33). The effect of simvastatin-ezetimibe remained significant in the subgroup with CKD not on dialysis. The AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial of patients aged 50-80 years with end-stage renal disease receiving maintenance hemodialysis compared rosuvastatin 10 mg versus placebo and found no significant benefit in any vascular outcomes in the setting of extremely high all-cause mortality rates in these patients (34).
The committee, therefore, includes patients with CKD not on dialysis as a higher-risk subset in patients with ASCVD who may merit consideration for more intensive LDL-C lowering with use of a non-statin medication (Figure 2B). Similarly, patients with CKD not on dialysis but without ASCVD, on statins for primary prevention, are considered to be at higher risk than the general population (Figures 4 and 5).

In light of the aforementioned considerations, the approach to patients with ASCVD on maintenance dialysis, and particularly hemodialysis, should be individualized. Decisions about the use of statins and other non-statin agents in these patients is a matter of clinical judgment after consideration of the potential net clinical benefit in the context of the patient’s projected longevity and other comorbidities. For patients in whom statin therapy and possibly addition of non-statin therapies is judged to be of potential net benefit, the algorithms in Figure 2B may apply, with the exception of the use of a PCSK9 inhibitor, which is not recommended at this time.

Patients considering pregnancy (or already pregnant). Statins should only be used in premenopausal women who are using effective contraception and are not nursing. Premenopausal women with ASCVD or baseline LDL-C ≥190 mg/dL often have underlying genetic lipid disorders, particularly familial hypercholesterolemia, and/or multiple poorly controlled risk factors. Women who are currently on lipid-lowering drugs should be advised to discontinue pharmacologic therapy, with the exception of BAS, generally at least 1 month and preferably 3 months before attempted conception, or immediately if the patient is already pregnant (13). Patients who have been prescribed lipid-lowering therapy for clinical ASCVD or baseline LDL-C ≥190 mg/dL who become pregnant should be counseled on intensive lifestyle modifications; referral to a lipid specialist and RDN is strongly recommended. Patients on lipid-lowering therapy in the setting of diabetes or elevated 10-year ASCVD risk who desire to become pregnant or are already pregnant should have lipid therapy discontinued, be monitored for significant elevations in LDL-C during pregnancy (recognizing that a progressive rise in both LDL-C and triglycerides is physiologic during pregnancy), and be counseled on lifestyle modifications (13). Such patients may be managed with BAS. Of note, pregnant patients who are managed with BAS should be monitored for vitamin K deficiency. Statin and ezetimibe therapy may be resumed after completion of breastfeeding (13).

There are concerns for fetal harm associated with statins, although recent large observational studies have not demonstrated evidence of harm with statin use (35). Lomitapide is not recommended in patients with HoFH during pregnancy due to concerns for fetal harm. There are no available safety and efficacy data for the use of PCSK9 inhibitors or mipomersen in pregnancy. The writing committee suggests consideration of LDL apheresis in pregnant patients with HoFH and patients with severe HeFH and LDL-C ≥300 mg/dL despite lifestyle therapy. In FH patients with ASCVD and pregnancy, LDL apheresis may be considered when LDL-C ≥190 mg/dL.

Other special populations. Detailed recommendations for other special populations of patients with specific comorbidities or conditions are beyond the scope of this document, and few if any data exist to guide such recommendations. In such situations, the committee therefore urges the particular need for thoughtful clinician-patient discussion of the potential benefits and harms of statin and non-statin therapies, and of patient preferences, in the context of the individual patient’s clinical situation.

6. CONCLUSION

Since the publication of the 2013 ACC/AHA cholesterol guidelines, RCTs evaluating the safety and efficacy of non-statin therapies (including large trials of ezetimibe and extended-release niacin with laropiprant added to moderate-dose statins in higher-risk patients) have provided important information regarding the potential benefits and harms of these agents in ASCVD risk reduction when used in combination with evidence-based statin therapy. In addition, the approval of 2 PCSK9 inhibitors for LDL-C lowering in specific high-risk patients has resulted in gaps in expert guidance regarding the role of available non-statin therapies. This expert consensus decision pathway addresses current gaps in care for LDL-C lowering to reduce ASCVD risk, and recommendations build on the evidence base established by the 2013 ACC/AHA cholesterol guideline. The algorithms endorse the 4 evidence-based statin benefit groups identified in the 2013 ACC/AHA cholesterol guidelines and assume that the patient is currently taking or has attempted to take a statin, given that this is the most effective initial therapy. Recommendations attempt to provide practical guidance for clinicians and patients regarding the use of non-statin therapies to further reduce ASCVD risk in situations not covered by the guideline until such time as the scientific evidence base expands and cardiovascular outcomes trials are completed with new agents for ASCVD risk reduction.
TABLE 1  Four Statin Benefit Groups and Major Recommendations From the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (1)

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Major Recommendations</th>
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| 1. Adults aged ≥ 21 years with clinical ASCVD (including history of or current acute coronary syndrome, myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin) | 1. For patients age ≤ 75 years, high-intensity statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns)  
2. For patients age > 75 years, moderate-intensity statin |
| 2. Adults aged ≥ 21 years with LDL-C ≥ 190 mg/dL (not due to modifiable secondary causes) | 1. High-intensity statin therapy to achieve ≥ 50% reduction in LDL-C statin (or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns)  
2. May consider combining statin and non-statin therapy to further reduce LDL-C  
3. Cascade screening of close biologic relatives should be performed to identify others with the disease who would benefit from treatment. |
| 3. Adults aged 40-75 years without ASCVD but with diabetes and with LDL-C 70-189 mg/dL | 1. Moderate-intensity statin  
2. If 10-year ASCVD risk ≥ 7.5%, consider high-intensity statin. |
| 4. Adults aged 40-75 years without ASCVD or diabetes, and with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥ 7.5% | 1. Estimate 10-year ASCVD risk using Pooled Cohort Equations (2):  
a. If ≥ 7.5%, moderate- or high-intensity statin;  
b. If ≤ 5 to < 7.5%, consider moderate-intensity statin.  
2. In selected individuals with 10-year ASCVD risk < 5%, or age < 40 or > 75 years, individualize decisions based on presence of other high-risk features.*  
3. Before initiation of statin therapy for primary prevention, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug-drug interactions, as well as patient preferences for treatment. |

*The 2013 ACC/AHA guideline recommends consideration of other ASCVD risk factors (LDL-C ≥ 160 mg/dL, family history of premature ASCVD, hs-CRP ≥ 2.0 mg/L, CAC score ≥ 300 Agatston units, ABI < 0.9, and high lifetime ASCVD risk).

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcification; hs-CRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

TABLE 2  Examples of High-, Moderate-, and Low-Intensity Statin Therapy (Adapted From 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults)

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<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 &lt; 30%.</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg twice daily</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Simvastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 5-10 mg</td>
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Bold face type indicates statins and doses that were evaluated in RCTs included in the 2013 ACC/AHA guideline.

ACC indicates American College of Cardiology; AHA, American Heart Association; LDL-C, low-density lipoprotein cholesterol; and RCT, randomized controlled trial.
<table>
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<th>Strategy/Agent</th>
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<td>Referral to lipid specialist</td>
<td>Consider referring patients with very high risk for ASCVD, complex lipid disorders, statin intolerance or multiple lipid medication intolerances, or familial hypercholesterolemia for consultation with a lipid specialist for advanced management. Considerations in referring: Lipid specialists may not be easily available in some rural or remote locations.</td>
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<tr>
<td>Ezetimibe (36)</td>
<td><strong>Mechanism of action:</strong> Inhibits Niemann-Pick C1 like 1 (NPC1L1) protein; reduces cholesterol absorption in small intestine. <strong>FDA-approved indication(s):</strong> As adjunct to diet to: 1) TC, LDL-C, Apo B, non-HDL-C in patients with primary hyperlipidemia, alone or in combination with a statin; 2) TC, LDL-C, Apo B, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; 4) sitosterol and campesterol in patients with homozgyous sitosterolemia (phytosterolemia). <strong>Dose:</strong> 10 mg PO daily, with or without food. Take either ≥2 hours before or ≤4 hours after BAS if used in combination. <strong>Mean % reduction in LDL-C (per PI):</strong> Monotherapy—18%; combination therapy with statin (incremental reduction)—25% <strong>Adverse effects:</strong> Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinustainis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea. <strong>Drug-drug interactions:</strong> cyclosorin, fribates, BAS <strong>CV Outcomes Trials:</strong> IMPROVE-IT (8) (The addition of ezetimibe to moderate-intensity statin in patients with recent ACS resulted in incremental lowering of LDL-C and reduced primary composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.); SHARP (33) (Simvastatin plus ezetimibe reduced LDL-C and reduced primary endpoint of first major ASCVD event (nonfatal MI or CHD death, non-hemorrhagic stroke, or any arterial revascularization procedure) compared to placebo over a median f/u of 4.9 years). <strong>Prescribing considerations:</strong> Generally well tolerated. Brand only; patent expires 12/2016.</td>
</tr>
<tr>
<td>PCSK9 inhibitors (37,38)</td>
<td><strong>Mechanism of action:</strong> Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL. <strong>FDA-approved indication(s):</strong> Alirocumab and evolocumab: Adjunct to diet and maximally tolerated statin therapy to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction. Evolocumab: Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction. <strong>Dose and route of administration:</strong> Alirocumab—initiate 75 mg SQ every 2 weeks. If more LDL reduction needed, may ↑ dose to 150 mg every 2 weeks. Evolocumab—in primary hyperlipidemia with established clinical ASCVD or HoFH, give 140 mg SQ every 2 weeks or 420 mg SQ once monthly in abdomen, thigh, or upper arm. In HoFH, give 420 mg SQ once monthly. To administer 420 mg, give 3 (140 mg) injections consecutively within 30 minutes. <strong>Mean % LDL-C reduction (per PI):</strong> Alirocumab—when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 SQ every 2 weeks ↓ LDL-C by an additional 45% and 58%, respectively. When added to maximally tolerated statin therapy evolocumab 140 mg every 2 weeks and 420 mg SQ every 4 weeks, ↓ LDL-C by an additional 64% and 58%, respectively. <strong>Adverse effects:</strong> Alirocumab—nasopharyngitis, injection site reactions, influenza. Evolocumab—nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. There have been increases in self-reported cognitive adverse effects in RCTs with both agents (evolocumab vs placebo, 0.9% vs 0.3% and alirocumab vs placebo, 1.2% vs 0.5%). <strong>Drug-drug interactions:</strong> None clinically significant drug-drug interactions identified for alirocumab or evolocumab. <strong>CV outcomes trials:</strong> Currently in progress. Alirocumab—ODYSSEY Outcomes (39) (18,600 post-ACS patients on evidence-based statin therapy; Primary endpoint is CHD death, MI, ischemic stroke, or hospitalization for UA. Estimated study completion is 2/2018). Evolocumab—FOURIER (40) (27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Primary endpoint is CV death, MI, stroke, revascularization or hospitalization for UA. Estimated study completion is 2/2018.). Bococizumab—SPIRE I (41) (Estimated enrollment 17,000 patients at high risk of CV event with LDL-C 70-99 mg/dL on lipid-lowering therapy; Primary endpoint is CV death, MI, stroke, or urgent revascularization. Estimated study completion is 6/2018). Bococizumab—SPIRE II (42) (Estimated enrollment 9,000 patients at high risk of CV event with LDL-C ≥100 mg/dL on lipid-lowering therapy; Primary endpoint is CV death, MI, stroke, or urgent revascularization. Estimated study completion is 3/2018.). <strong>Considerations in prescribing:</strong> Cost, SQ administration, robust LDL-C reduction, CV outcomes trials not completed, burdensome prior authorization process</td>
</tr>
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</table>
| Bile acid sequestrants (43-46) | **Mechanism of action:** Non-absorbed, lipid-lowering polymer that binds bile acids in intestine and impedes their reabsorption. As the bile acid pool ↓, the hepatic enzyme, cholesterol 7α-hydroxylase, is upregulated, which ↑ conversion of cholesterol to bile acids. This causes ↑ demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and ↑ the number of hepatic LDL receptors. These compensatory effects result in ↓ clearance of LDL-C from the blood, in turn resulting in ↓ serum LDL-C levels. Serum TG levels may ↑ or remain unchanged. **FDA-approved indication(s):** Colesevelam: 1) Adults, as adjunct to diet and exercise, to ↓ LDL-C with primary hyperlipidemia; monotherapy or in combination with statin; 2) Adults, as adjunct to diet and exercise, to improve glycemic control with type 2 diabetes mellitus; 3) Boys and post-menarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy (e.g., LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and there is a positive family history of premature CVD or ≥2 other CVD risk factors are present in the pediatric patient) to ↓ LDL-C levels: As monotherapy or in combination with statin. Cholestyramine, colestid: As adjunct to diet to ↓ LDL-C with primary hyperlipidemia. **Dose and route of administration:** 1) Colesevelam: Tablets: 6 tablets PO once daily or 3 tablets PO twice daily; take tablets with a meal and liquid. Suspension: one 3.75-gm packet PO daily, or one 1.875-gm packet PO twice daily; mixed powder with 4-8 ounces of water, fruit juice, or soft drink; take with meal. 3.75 g is equivalent to 6 tablets. 1.875 g is equivalent to 3 tablets; 2) Cholestyramine: 8-16 g/day orally divided into 2 doses; 3) Colesitol: 2 to 16 g/day orally given once or in divided doses. **Mean % LDL reduction (per PI):** Colesevelam: Monotherapy—15% (6 tablets daily); combination with low- to moderate intensity statin—additional 10-16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg). Cholestyramine: Monotherapy—10.4% vs placebo; Colesitol: not provided in PI. In dose-ranging CT with monotherapy, doses of 5 g, 10 g, and 15 g resulted in 16.3%, 22.8%, and 27.2% reduction in LDL-C, respectively. (Superko HR, Greenland P, Manchester RA, et al. Am J Cardiol. 1992;70:135-40.) **Adverse effects:** Constipation, dyspepsia, and nausea. Post-marketing reports with colesevelam include ↓ seizure activity or ↓ phenytoin levels in patients receiving warfarin, ↓ INR in patients receiving thyroid hormone replacement therapy, bowel obstruction, dysphagia, esophagael obstruction, fecal impaction, hypertriglycerideremia, pancreatitis, and increased transaminases.
### TABLE 3 Continued

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| **Drug-drug interactions:** cyclosporine, glimepiride, glipizide, levothyroxine, olmesartan coadministered with medoxomil, oral contraceptives containing ethinyl estradiol and norethindrone, phenytoin, warfarin. Drugs with potential interaction should be taken at least 4 hours after BAS to avoid impeding their absorption.  
**CV outcomes trials:** LRC-CPTP (3,806 asymptomatic middle-aged men with primary hypercholesterolemia randomize to cholestyramine resin and versus placebo for an average of 7.4 years. Cholesterol group experienced a 19% reduction in risk (p < 0.05) of the primary endpoint—definite CHD death and/or definite nonfatal MI. The effects of colestipol and colesterol on cardiovascular morbidity and mortality have not been determined.  
**Considerations in prescribing:** Pill burden; inconvenience in preparation of oral suspension preparations; GI side effects; exacerbation of hypertriglyceridemia; orally administered, colestevam lowers HbA1c 0.5% in diabetes; CV outcomes data not available.  
**Phytosterols**  
**Mechanism of action:** Not fully elucidated, but in part related to displacement of cholesterol from the micellar phase. Phytosterols, cholesterol content of micelles and hence, its transport towards the intestinal brush border membrane. May also interfere with transporter-mediated processes of cholesterol uptake via NPC1L1 protein and ABCG5 and ABCG8 transporters.  
**FDA-approved claims:** "For plant sterol esters: (i) Foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. For plant stanol esters: (ii) Foods containing at least 1.7 g per serving of plant stanol esters, eaten twice a day with meals for a total daily intake of at least 3.4 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease."  
**Dose and route of administration:** 1–3 g PO per day consumed with meals either once daily or in divided doses.  
**Mean % LDL-C reduction:** Consumption of 2 g/day of phytosterols + LDL-C by 5%–15%. LDL-C plateau at doses above ~3 g/day.  
**Adverse effects:** Phytosterol esters have "generally recognized as safe" (GRAS) status in the US. Potential safety concern regarding phytosterol consumption in patients with phytosterolemia. Side effects may include mild bloating, diarrhea, or constipation.  
**Drug-drug interactions:** BAS administration should be separated from phytosterol use by 2–4 hours to avoid binding of the latter in the gut.  
**CV outcomes trials:** The effect of phytosterols on cardiovascular morbidity and mortality as not determined.  
**Considerations in prescribing:** Generally well tolerated; modest in LDL-C, CV outcomes data not available.  
**Soluble/viscous fiber**  
**Mechanism of action:** Trapping of cholesterol and bile acids in the small intestine, resulting in absorption/reabsorption.  
**FDA-approved claims:** "Soluble fiber as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease."  
**Dose and route of administration:** Food source must be low in saturated fat and cholesterol, and include one or more of the following whole oat or barley foods: 1) oat bran, 2) rolled oats, 3) whole oat flour, 4) whole grain barley or dry milled barley.  
**Mean % LDL-D reduction:** With intake of 3.0–12.4 g/day, mean TC and LDL-C levels were relative to control by 9.7 and 11.6 mg/dL, respectively.  
**Adverse effects:** Few safety concerns. If viscous fiber supplements such as fiber laxatives are used, it is critical to consume adequate fluid as directed on the product label to avoid intestinal blockage (a rare occurrence).  
**Drug-drug interactions:** Reduced carotenoid absorption. Regular consumption of fruits and vegetables should help to counteract this potential effect.  
**CV Outcomes Trials:** Despite evidence of LDL-C lowering, the effect of soluble/viscous fiber on cardiovascular morbidity and mortality has not been demonstrated in RCTs.  
**Considerations in prescribing:** GI tolerability  
**Mipomersen**  
**Mechanism of action:** An antisense oligonucleotide targeted to human mRNA for apo B-100, the principal apolipoprotein of LDL and its metabolic precursor, VLDL. Mipomersen is complementary to the coding region of the mRNA for apo B-100, and binds by Watson and Crick base pairing. The hybridization of mipomersen to the cognate mRNA results in RNase H-mediated degradation of the cognate mRNA, thus inhibiting translation of the apo B-100 protein.  
**FDA-approved indication(s):** As an adjunct to lipid-lowering medications and diet, in LDL-C, apo B, TC, and non-HDL-C in patients with HoFH. The safety and effectiveness of mipomersen have not been established in patients with hypercholesterolemia who do not have HoFH. The use of mipomersen as an adjunct to LDL apheresis is not recommended.  
**Dose and route of administration:** 200 mg SQ once weekly  
**Mean % LDL-C reduction (per PI):** Response to addition of mipomersen to maximally tolerated lipid-lowering medication in patients with HoFH—25%.  
**Adverse effects:** Injection site reactions, flu-like symptoms, nausea, headache and elevations in serum transaminases, specifically ALT. Increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. May be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Because of the risk of hepatotoxicity, mipomersen is available only through REMS program.  
**Drug-drug interactions:** No clinically relevant pharmacokinetic interactions were reported between mipomersen and warfarin, simvastatin, or ezetimibe.  
**CV Outcomes Trials:** The effect of mipomersen on cardiovascular morbidity and mortality has not been determined.  
**Considerations in prescribing:** Cost, SQ administration, requires monitoring of transaminase levels, long-term consequences of hepatic steatosis unknown, prescriber training, REMS program  
**Lomitapide**  
**Mechanism of action:** Directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL and leads to LDL-C.  
**FDA-approved indications:** As an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to LDL-C, TC, apo B, and non-HDL-C in patients with HoFH.  
**Dose and route of administration:** Initiate 5 mg PO once daily. Titrate up on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to maximum recommended dose of 60 mg daily.  
**Mean % LDL reduction (per PI):** Mean and median percent changes in LDL-C from baseline when added to baseline lipid-lowering therapy were ~40% and ~50%, respectively.  
**Adverse effects:** Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. Increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Hepatic steatosis associated with lomitapide may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.  

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**TABLE 3** Continued

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<th>Strategy/Agent</th>
<th>Comments</th>
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<td><strong>LDL Apheresis</strong></td>
<td>■ Drug–drug interactions: CYP3A4 inhibitors increase exposure to lomitapide. Strong and moderate CYP3A4 inhibitors are contraindicated with lomitapide. Avoid grapefruit juice. Do not exceed 30 mg daily of lomitapide when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives. Increases plasma concentrations of warfarin; monitor INR regularly, especially with lomitapide dose adjustment. Increased systemic exposure to simvastatin and lovastatin exposure with lomitapide. Limit statin dose when co-administered due to myopathy risk. Consider dose reduction of P-gp substrate because of possible increased absorption with lomitapide. Separate lomitapide dosing with BAS by at least 4 hours. Because of the risk of hepatotoxicity, lomitapide available only through REMS program.</td>
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<td><strong>CV outcomes trials</strong>: The effect of lomitapide on cardiovascular morbidity and mortality has not been determined.</td>
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<td><strong>Considerations in prescribing</strong>: Cost, oral administration, requires strict adherence to low-fat diet and gradual dose escalation to reduce GI side effects, requires monitoring of transaminase levels, long-term consequences of hepatic steatosis unknown, prescriber training, REMS program</td>
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ASCVD indicates atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; CHD, coronary heart disease; CV, cardiovascular; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAV, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kevin S; PI, prescribing information; PO, by mouth; REMS, Risk Evaluation and Mitigation Strategy; SQ, subcutaneous; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone; UA, unstable angina; and VLDL, very low density lipoprotein.

**TABLE 4** Factors to Consider in the Clinician-Patient Discussion

1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to evidence-based statin therapy to lower LDL-cholesterol ■ Percentage LDL-C reduction achieved with evidence-based statin therapy (if <50% and not on maximally tolerated statin, should increase statin first and reinforce lifestyle modifications).
   ■ For patients with ASCVD, patient’s baseline ASCVD risk on evidence-based statin therapy (with or without comorbidities).
   ■ For patients without ASCVD or baseline LDL-C >190 mg/dL, patient’s baseline predicted 10-year ASCVD risk pre-statin and presence of high-risk markers.
   ■ Available scientific evidence of ASCVD risk reduction (and magnitude of benefit) when non-statin therapy is added to evidence-based statin therapy.
   ■ Additional desired % LDL-C lowering beyond that achieved on evidence-based statin therapy.
   ■ Mean percentage LDL-C lowering expected with proposed non-statin therapy when added to evidence-based statin therapy.

2. Potential for significant adverse events or drug–drug interactions from addition of non-statin therapy to evidence-based statin therapy for lowering LDL-cholesterol ■ See Table 3.

3. Patient preferences and considerations ■ Patient’s perception of benefit from addition of non-statin therapy.
   ■ Convenience (e.g., route and frequency of administration, pill burden, storage) of non-statin therapy.
   ■ Potential of non-statin therapy to jeopardize adherence to evidence-based therapies.
   ■ Cost of non-statin therapy.
   ■ Anticipated life expectancy, comorbidities, and impact of therapy on quality of life.

*For example, in the Treating to New Targets trial, patients with CHD who received 10 mg of atorvastatin daily had a 5-year event rate of 10.9%, and those who received 80 mg of atorvastatin daily had a 5-year event rate of 8.7%. These numbers (and similar rates from other trials) may inform the number-needed-to-treat. Additional consideration of comorbidities and other poorly controlled or well-controlled risk factors will increase or decrease risk accordingly. Comorbidities are defined as diabetes, recent (≤3 months) ASCVD event, ASCVD event while already taking a statin, baseline LDL-C >190 mg/dL not due to secondary causes, poorly controlled other major ASCVD risk factors, elevated lipoprotein(a), or chronic kidney disease.

†Use the Pooled Cohort Equations to estimate 10-year ASCVD risk. High-risk markers include 10-year ASCVD risk ≥20%, primary LDL-C >160 mg/dL at baseline; poorly controlled other major ASCVD risk factor(s); family history of premature ASCVD with or without elevated LDL(a); evidence of accelerated subclinical atherosclerosis (e.g., coronary artery calcification); elevated hs-CRP, and other risk factors for ASCVD, HIV, and chronic inflammatory disorders.

‡Such evidence exists for ezetimibe from the IMPROVE-IT study, with a 6% relative/2% absolute risk reduction in a composite ASCVD endpoint over 7 years when added to a moderate-intensity statin. Short-term data (<18 months) from PCSK9 inhibitors alirocumab and evolocumab suggest more substantial ASCVD risk reduction. Data are lacking for addition of BAS to statins. Niacin preparations have been associated with no benefit and potential for significant harms when added to statin therapy.

§For example, patients on maximally tolerated statin with LDL-C of 130 mg/dL may receive more benefit from addition of a non-statin therapy than those with on-statin LDL-C of 80 mg/dL.

∥For example, when added to statins, ezetimibe may lower LDL-C an additional 20–25% on average; PCSK9 inhibitors may lower LDL-C an additional 60% on average. For each 40 mg/dL reduction in LDL-C using safe and evidence-based therapies, there appears to be an approximate 20% relative risk reduction in ASCVD. This number, combined with the baseline absolute risk, may inform the number-needed-to-treat.


KEY WORDS ACC Expert Consensus Decision Pathway, ASCVD, bile acid sequestrants, cholesterol, dyslipidemia, ezetimibe, LDL-C, lipids, PCSK9 inhibitors, statins
APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2016 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NON-STATIN THERAPIES FOR LDL-CHOLESTEROL LOWERING IN THE MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

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## APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT) — 2016 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NON-STATIN THERAPIES FOR LDL-CHOLESTEROL LOWERING IN THE MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

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†No financial benefit.

ABC indicates Association of Black Cardiologists; ACC, American College of Cardiology; ACP, American College of Physicians; ACCP, American College of Clinical Pharmacy; AHA, American Heart Association; CT, computed tomography; DSMB, Data Safety Monitoring Board; MR, magnetic resonance; NLA, National Lipid Association; and PCNA, Preventive Cardiovascular Nurses Association.
APPENDIX 3. ABBREVIATIONS

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<td>chronic kidney disease</td>
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