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EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

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TABLE OF CONTENTS

PREFACE ■

1. INTRODUCTION ■

1.1. Rationale for Expert Consensus Decision Pathway ■

1.1.1. Newer Nonstatin Therapies ■

2. METHODS ■

2.1. Background ■

2.2. Process ■

3. ASSUMPTIONS AND DEFINITIONS ■

4. PATHWAY SUMMARY GRAPHIC ■

Figure 1. Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider ■

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

5.1. Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention (Figures 2A-2D) ■

5.1.1. Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention (Figure 2A) ■

Figure 2A. Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention ■

5.1.2. Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention (Figure 2B) ■

Figure 2B. Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention ■

5.1.3. Adults With Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Secondary Prevention (Figures 2C and 2D) ■

Figure 2C. Adults With Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes Without Clinical or Genetic Diagnosis of Familial Hypercholesterolemia, on Statin Therapy for Secondary Prevention ■

Figure 2D. Adults With Clinical ASCVD at Very High Risk and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes and With Clinical Diagnosis or Genetic Confirmation of Familial Hypercholesterolemia, on Statin for Secondary Prevention ■

5.2 Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Primary Prevention (Figure 3) ■

Figure 3. Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes on Statin Therapy for Primary Prevention ■

5.2.1. Adults With LDL-C ≥190 mg/dL With or Without Concomitant ASCVD Risk Factors (Figure 3) ■

5.2.2. LDL-C ≥190 mg/dL and Pregnancy ■

5.2.3. Familial Hypercholesterolemia in Children and Adolescents ■

5.3. Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention (Figure 4) ■

Figure 4. Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention ■

5.3.1. Adults Aged 40-75 Years With Diabetes and Without Clinical ASCVD and Baseline LDL-C <190 mg/dL, on Statin Therapy for Primary Prevention (Figure 4) ■

5.3.2. Adults Aged 20-39 Years With CV Risk Factors and/or Diabetes-Specific Risk Enhancers or Adults Aged >75 Years (Figure 4) ■

5.4. Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL) (Figure 5) ■

Figure 5. Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL) ■

5.5. Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥190 mg/dL (Figure 6) ■

Figure 6. Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥190 mg/dL ■

5.6. Adults With Possible Statin-Associated Side Effects (Figure 7) ■

Figure 7. Adults With Possible Statin-Associated Side Effects ■

5.7. Special Populations ■

5.7.1. Patients With Symptomatic Heart Failure ■

5.7.2. Patients on Maintenance Hemodialysis ■

5.7.3. Patients Considering Pregnancy (or Already Pregnant) ■

5.7.4. Race/Ethnicity-based Limitations ■

5.7.5. Patients With Previous Organ Transplantation ■

5.7.6. Other Special Populations ■

6. CONCLUSIONS ■

REFERENCES ■

APPENDIX 1

Author Relationships With Industry and Other Entities (Relevant) . . . . . ■

APPENDIX 2

Peer Reviewer Relationships With Industry and Other Entities (Comprehensive) . . . . . ■

APPENDIX 3

Abbreviations . . . . . ■

PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, health policy statements, appropriate use criteria) to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence is new and evolving or where sufficient data is more limited. Despite this, numerous gaps persist, highlighting the need for more streamlined and efficient processes to implement best practices in patient care.

Central to the ACC's strategic plan is the generation of actionable knowledge—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has shifted from developing isolated documents to creating integrated "solution sets." These are groups of closely related activities, policy, mobile applications, decision-support tools, and other resources necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated tools will be refined over time to match changing evidence and member needs.

Expert Consensus Decision Pathways (ECDPs) represent a key component of solution sets. Standard methodology for developing an ECDP is as follows: for a high-value topic that has been selected by the Science and Quality Committee and prioritized by the Solution Set Oversight Committee, a group of clinical experts is assembled to develop content that addresses key questions facing our members.[1] This content is used to inform the development of various tools that accelerate real-time use of clinical policy at the point of care. ECDPs are not intended to provide single correct answers to clinical questions; rather, they encourage clinicians to consider a range of important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as standalone policy.

Nicole M. Bhave, MD, FACC
Chair, ACC Solution Set Oversight Committee

1. INTRODUCTION

In 2013, the ACC and American Heart Association (AHA) published the Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (denoted as the 2013 ACC/AHA cholesterol guideline in this document)[2] along with a companion Guideline on the Assessment of Cardiovascular Risk in asymptomatic individuals.[3]

To reflect newer information on the use of ezetimibe therapy as an adjunct to statin therapy in higher-risk patients, the ACC published the 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 (denoted as the 2016 ACC nonstatin ECDP in this document).[4] In 2017, cardiovascular outcomes data from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial demonstrated that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with evolocumab on a background of statin therapy was efficacious in patients with stable atherosclerotic cardiovascular disease (ASCVD) and additional high-risk features.[5] The 2017 Focused Update of the 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 (denoted as the 2017 ACC nonstatin ECDP in this document) was published to provide more evidence-based guidance for incorporation of PCSK9 monoclonal antibodies (mAbs) into clinical practice.[6] The ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, demonstrating the benefits of PCSK9 inhibition with alirocumab on a background of statin therapy in patients with acute coronary syndrome (ACS), was not published until 2018. However, due to U.S. Food and Drug Administration (FDA) approval of alirocumab for low-density lipoprotein cholesterol (LDL-C) lowering,

TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease

recommendations were provided for both PCSK9 mAbs in the 2017 ACC nonstatin ECDP.

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (denoted as the 2018 AHA/ACC/multisociety cholesterol guideline in this document) continued to endorse the net clinical benefits of statin therapy in the 4 main patient management groups, the importance of the appropriate intensity of statin therapy, achieving expected percent reductions in LDL-C, and the role of the clinician-patient discussion and shared decision-making. However, there were a number of key modifications or refinements of recommendations from the 2013 ACC/AHA cholesterol guideline:

- Patients with ASCVD were categorized into 1 of 2 groups: not at very high risk or at very high risk. Very high-risk patients have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (see **Table 1**). Based on evidence from IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), FOURIER, and ODYSSEY Outcomes, this very high-risk group of patients has demonstrated cardiovascular benefits from the addition of ezetimibe, evolocumab, and alirocumab.[5-9]
- Consistent with expert guidance provided in the 2017 ACC nonstatin ECDP, [6] the 2018 AHA/ACC/multisociety cholesterol guideline recommends use of an LDL-C threshold of ≥70 mg/dL (1.8 mmol/L) to consider the addition of nonstatin therapy to maximally tolerated statin therapy in patients with ASCVD.[7]
- Ezetimibe is recommended as the initial nonstatin therapy in patients with clinical ASCVD who are receiving maximally tolerated statin therapy and have an LDL-C level ≥70 mg/dL.[7]
- In patients with clinical ASCVD who are judged to be at very high risk and are being considered for PCSK9 mAb therapy, maximally tolerated LDL-C-lowering therapy should include maximally tolerated statin therapy and ezetimibe.[7]
- The 2018 AHA/ACC/multisociety cholesterol guideline includes the following value statement: "At mid-2018 list prices, PCSK9 mAbs have a low cost value (>$150,000 per quality-adjusted life year [QALY]) compared with good cost value (<$50,000 per QALY)."[7]
- In patients with primary severe hypercholesterolemia LDL-C ≥190 mg/dL, recommendations are provided for the addition of ezetimibe, PCSK9 mAbs, or bile acid sequestrants (BAS) (see Section 5.2).[7]
- In primary prevention patients at borderline or intermediate risk of ASCVD by the Pooled Cohort Equation (PCE), the clinician-patient risk discussion should include risk-enhancing factors that may confer a higher risk state and may support a decision to initiate or intensify statin therapy (see **Table 2**). Risk-enhancing factors are useful for further personalizing the initial risk estimate based on patient-specific factors that are not considered in the PCE and may carry greater lifetime risk. Several risk-enhancing factors may also be specific targets of therapy beyond the risk factors in the PCE.[7]
- In adults without diabetes and with LDL-C levels ≥70 to 189 mg/dL at a 10-year ASCVD risk of 7.5% to <20%, if the decision about statin therapy is uncertain, it is recommended to consider measuring coronary artery calcification.[7]
  - If the coronary artery calcium (CAC) score is 0 AU, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (diabetes, family history of premature coronary heart disease, cigarette smoking);
  - If the CAC score is 1 to 99 AU and less than the 75th percentile for the age/sex/race group, it is reasonable to initiate statin therapy for patients ≥55 years of age;
  - If the CAC score is 100 AU or higher or in the 75th percentile or higher for the age/sex/race group, it is reasonable to initiate statin therapy.

TABLE 2 Risk-Enhancing Factors for Clinician-Patient Risk Discussion

Risk-Enhancing Factors
■ **Family history of premature ASCVD** (men aged <55 years; women aged <65 years)
■ **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL [4.1-4.8 mmol/L); non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L]*
■ **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes the diagnosis
■ **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
■ **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
■ **History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia**
■ **High-risk races/ethnicities** (eg, South-Asian ancestry)
■ **Lipids/biomarkers:** Associated with increased ASCVD risk ■ **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL) ■ If measured: 1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) 2. **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a). 3. **Elevated apoB ≥130 mg/dL:** A relative indication for its measurement would be triglycerides ≥200 mg/dL. A level ≥130 mg/dL corresponds to LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor 4. **ABI** <0.9

*Optimally, 3 determinations. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; AIDS = acquired immunodeficiency syndrome; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); RA = rheumatoid arthritis.

The 2018 AHA/ACC/multisociety cholesterol guideline recommendations significantly refine personalization of risk assessment in primary prevention, more accurately characterize the risk of recurrent ASCVD events in secondary prevention, and carefully guide clinicians in matching the intensity of LDL-C-lowering therapies, both statin and nonstatin therapies, to the patient's level of risk.

Since publication of the 2018 AHA/ACC/multisociety cholesterol guideline, 3 additional nonstatin therapies—bempedoic acid, evinacumab, and inclisiran—have received FDA approval for management of hypercholesterolemia. While awaiting ongoing cardiovascular outcomes trials and subsequent revision of evidence-based guidelines, the ACC recognized that clinicians, patients, and payers may seek more specific recommendations on when to use newer nonstatin therapies if the response to statin therapy, ezetimibe, and/or PCSK9 mAbs is deemed inadequate.

1.1. Rationale for Expert Consensus Decision Pathway

In 2021, the ACC convened this 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 and 2018 AHA/ACC/multisociety cholesterol guidelines and attempts to provide further recommendations for clinicians and patients regarding use of newer nonstatin 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 2018 AHA/ACC/multisociety cholesterol guideline until such time as the next round of guidelines can formally review recent scientific evidence and cardiovascular outcomes trials of newer agents for ASCVD risk reduction are completed. Specifically, the ACC convened this writing committee to answer the following questions regarding the use of nonstatin therapies:

1. In what patient populations should newer nonstatin therapies be considered?
2. In what situations should newer nonstatin 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 newer nonstatin therapies are to be added, which therapies should be considered and in what order to maximize patient benefit and preference?

1.1.1. Newer Nonstatin Therapies

Bempedoic acid is a small molecule that inhibits ATP-citrate lyase, an enzyme in the cholesterol synthesis pathway that is upstream of the rate-limiting enzyme HMG CoA reductase.[10] This results in up-regulation of the LDL receptor with improved clearance of LDL and reduction in blood LDL-C levels. Bempedoic acid is administered orally as a prodrug and is activated by very-long-chain acyl-CoA synthetase-1, an enzyme present in liver cells, but not muscle cells. This has been considered a possible advantage in patients with statin-associated muscle symptoms. The CLEAR Tranquility (Evaluation of the Efficacy and Safety of Bempedoic Acid [ETC-1002] as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C) and CLEAR Serenity (Evaluation of the Efficacy and Safety of Bempedoic Acid in Patients With Hyperlipidemia and Statin Intolerant) trials have demonstrated that monotherapy with bempedoic acid 180 mg daily in patients with statin-associated muscle symptoms on no statin therapy reduced LDL-C levels by approximately 24.5% compared with placebo.[11-13] In patients with ASCVD, heterozygous familial hypercholesterolemia (HeFH), or multiple cardiovascular risk factors, bempedoic acid added to statin therapy resulted in an additional

15% to 17.8% reduction in LDL-C.[13-15] Bempedoic acid 180 mg is also available in a combination preparation with ezetimibe 10 mg. When this combination agent was administered to patients with ASCVD, HeFH, or multiple ASCVD risk factors on statin therapy, there was an additional 38% reduction in LDL-C.[16] Bempedoic acid and the fixed-dose combination with ezetimibe were FDA approved in 2020 and are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD who require additional lowering of LDL-C.[17] Slight increases in tendon rupture (0.5% vs. 0%), gout (1.5% vs. 0.4%), benign prostatic hyperplasia (1.3% vs. 0.1%), atrial fibrillation (1.7% vs. 1.1%), and elevation of creatine kinase levels (1.0% vs. 0.6%) have been observed in smaller trials to date, but the clinical significance may be clarified in larger ongoing trials. At the time of this ECDP, the multinational cardiovascular outcomes trial of bempedoic acid, CLEAR Outcomes (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo), is in progress with expected completion in late 2022.[18] In this trial, 14,014 individuals aged 18-85 years with ASCVD or at high risk for ASCVD and with statin intolerance and LDL-C ≥100 mg/dL have been randomized to bempedoic acid or placebo. The primary endpoint is the composite of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization. Bempedoic acid is commercially available as a branded product, and cost and prior authorization may represent challenges in its implementation. However, it is important to recognize that many patients may not pay the full retail price, and a patient assistance program and discount copay card are available for eligible patients. The availability of a combination preparation of ezetimibe and bempedoic acid may be useful for patients who require additional LDL-C lowering and/or patients with adherence issues with multidrug regimens.

Angiopoietin-like protein 3 (ANGPTL3) is a liver-expressed, secreted protein and inhibitor of lipoprotein lipase and endothelial lipase, 2 of the main enzymes involved in lipoprotein metabolism. It plays a key role in lipid metabolism by increasing the levels of triglycerides and other lipids. Loss-of-function variants in ANGPTL3 have been associated with very low levels of both LDL-C and triglycerides from birth and a 41% lower risk of coronary artery disease, despite the presence of low levels of high-density lipoprotein cholesterol (HDL-C).[19] Both ANGPLT3 loss-of-function variants and ANGPTL3 pharmacologic inhibition reduce LDL-C levels independently of the LDL receptor. Evinacumab is a fully human mAb that is an inhibitor of ANGPTL3. In view of the LDL receptor-independent reduction of LDL-C, evinacumab was initially evaluated in patients with homozygous familial hypercholesterolemia (HoFH), who may have absent or defective LDL receptors.[20] The ELIPSE HoFH (Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia) trial was a double-blind, placebo-controlled, phase 3 trial in which 65 patients with HoFH on stable lipid-lowering therapy with LDL-C ≥70 mg/dL were randomly assigned in a 2:1 ratio to receive an intravenous (IV) infusion of evinacumab (at a dose of 15 mg per kg of body weight) every 4 weeks or placebo. The primary outcome was the percent change from baseline in LDL-C at week 24. The mean baseline LDL-C level in the 2 groups was 255 mg/dL, despite maximum doses of background lipid-lowering therapy. There was a 47.1% relative reduction from baseline in LDL-C in patients treated with evinacumab, as compared with an increase of 1.9% in the placebo group. The between-group least-squares mean difference was -49.0 percentage points (95% confidence interval [CI]: -65.0 to -33.1 percentage points; $P < 0.001$); the between-group least-squares mean absolute difference in the LDL-C was -132.1 mg/dL (95% CI: -175.3 to -88.9 mg/dL; $P < 0.001$). LDL-C was lower in the evinacumab group than in the placebo group in patients with 2 null variants (-43.4% vs +16.2%) as well as in those with non-null variants (-49.1% vs -3.8%). Adverse events were similar in the 2 groups. No patients discontinued either evinacumab or placebo due to an adverse event, and there were no deaths. Antidrug antibodies did not develop during the treatment period in any of the patients.[20] In 2021, evinacumab received FDA approval and is indicated as an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with HoFH.[21] It is administered at a dose of 15 mg/kg by IV infusion over approximately 1 hour once monthly (every 4 weeks). Although the safety and effectiveness of LDL-C lowering by evinacumab have been demonstrated in patients with other causes of hypercholesterolemia, including those with HeFH, current FDA approval includes only HoFH.[22] The effects of evinacumab on cardiovascular morbidity and mortality have not been studied. The cost of the drug itself may be covered under 3 options: 1) physician purchase through major medical benefits (site of care buys evinacumab and bills the patient's health plan under medical benefits); 2) specialty pharmacy through major medical benefits (benefits are assigned to a network specialty pharmacy, which bills for the cost of evinacumab); or 3) specialty

pharmacy through prescription drug benefit (evinacumab is covered under the pharmacy benefit and the specialty pharmacy bills for the cost of the drug). There are also costs associated with administration of the infusion that are billed through medical benefits. The need for and cost of monthly IV infusion by a health care provider may be barriers for individuals with HoFH. However, it is important to recognize that infusion support programs or patient assistance options are available for eligible patients. Evinacumab is also being investigated for treatment of patients with high and severe hypertriglyceridemia.[23]

Inclisiran is a long-acting, synthetic small interfering ribonucleic acid that selectively and catalytically silences the translation of PCSK9 messenger ribonucleic acid through binding to the ribonucleic acid-induced silencing complex and inhibits hepatic translation of the PCSK9 protein, thereby up-regulating LDL receptor density on hepatocytes. Thus, inclisiran inhibits production of PCSK9 at an intracellular level, unlike PCSK9 mAbs, which extracellularly bind to the protein once produced. It is important to note that PCSK9 mAbs were previously referred to as PCSK9 inhibitors or PCSK9i. In view of the development of inclisiran, which also inhibits PCSK9, terminology in this document is PCSK9 mAbs for evolocumab and alirocumab. As the first and only small interfering ribonucleic acid targeting PCSK9, inclisiran is currently referred to by drug name.

In a pooled patient-level analysis of 3,660 patients in phase 3 trials of inclisiran (ORION-9 [Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease], ORION-10 [Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol], and ORION-11 [Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol]), the drug demonstrated a mean placebo-corrected change in LDL-C at day 510 of −50.7% (95% CI: −52.9% to −48.4%; $P < 0.0001$). The corresponding time-adjusted mean change in LDL-C was −50.5% (95% CI: −52.1% to −48.9%; $P < 0.0001$). Injection site reactions were more frequent with inclisiran than with placebo (5.0% vs 0.7%) but were predominantly mild, and none was severe or persistent. Safety was otherwise similar in both groups.[24,25] Inclisiran was FDA approved in December 2021 and is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD who require additional lowering of LDL-C.[26] The recommended dosage of inclisiran, in combination with maximally tolerated statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months thereafter. The effect of inclisiran on cardiovascular morbidity and mortality has not been determined. However, 2 cardiovascular outcomes trials, ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) and VICTORION-2P (A Randomized, Double-blind, Placebo-controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease), are currently in progress. ORION-4 is being conducted at 180 clinical sites in the United Kingdom and the United States. Approximately 15,000 participants aged 55 years or older with pre-existing ASCVD and LDL-C ≥100 mg/dL on maximally tolerated statin therapy will be randomized to inclisiran sodium 300 mg or placebo (given by subcutaneous injection on the day of randomization, at 3 months, and then every 6 months) in a 1:1 ratio for a planned median duration of about 5 years. The primary endpoint is a composite of coronary heart disease death, nonfatal MI, fatal or nonfatal ischemic stroke, or urgent coronary revascularization procedure.[27] VICTORION-2P is being conducted in approximately 15,000 participants in the United States, Canada, and Europe. Participants aged ≥40 years have established ASCVD, are on high-intensity statin therapy (with or without ezetimibe), and have LDL-C ≥70 mg/dL. The primary endpoint is major adverse cardiac events, including CV death, nonfatal MI, and nonfatal ischemic stroke.

There are no head-to-head comparisons of the PCSK9 mAbs and inclisiran, although when comparing similarly designed trials, the LDL-C-lowering response to inclisiran appears to be approximately 10% less than that seen with the PCSK9 mAbs. The twice-yearly administration by subcutaneous injection after the initial 2 doses at baseline and 3 months is a potentially attractive aspect of this therapy, particularly in patients with adherence concerns. It should be noted that health plan coverage may vary for inclisiran, as it must be administered by a clinician and is billed under medical benefit rather than pharmacy benefit coverage. Current cost of therapy with inclisiran in the initial year of therapy is higher than annual costs of the PCSK9 mAbs, but the cost difference is less in subsequent years. However, it is important to recognize that many patients may not pay full price, and a patient assistance program and copay support are available for eligible patients.

2. METHODS

2.1. 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 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 nonstatin therapies (ezetimibe and PCSK9 mAbs) into treatment strategies for higher-risk patients as a critical gap in clinical care. The 2017 ACC nonstatin ECDP was subsequently published and helped to inform the 2018 AHA/ACC/multisociety cholesterol guideline.[6,7] With the rapid development and commercial availability and changes in pricing and access to newer nonstatin agents (bempedoic acid, evinacumab, and inclisiran), the ACC convened this writing committee for the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk to provide guidance for implementation of these newer nonstatin therapies.

2.2. Process

The ACC and the Solution Set Oversight Committee recognize the importance of avoiding real or perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI policy in determining what constitutes a relevant relationship, with additional vetting by the Solution Set Oversight Committee.

ECDP writing groups must be chaired or cochaired by an individual with no relevant RWI. Although vice chairs and writing group members may have relevant RWI, they must constitute less than 50% of the writing group. Relevant disclosures for the writing group and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2. To ensure complete transparency, a comprehensive list of disclosure information for the writing group, including relationships not pertinent to this document, is available in a Supplemental Appendix. Writing committee members are discouraged from acquiring relevant RWI throughout the writing process.

The writing committee began its deliberations by endorsing the construct of the 4 patient management groups identified by the 2018 AHA/ACC/multisociety cholesterol guideline (see **Figure 1**).[2] The writing committee then considered the potential for net ASCVD risk-reduction benefit of the use or addition of nonstatin therapies in each of the 4 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 and 2018 AHA/ACC/multisociety cholesterol guidelines, for all patient groups, the current consensus emphasizes that lifestyle modifications (ie, adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remain critical components of ASCVD risk reduction, both before and in concert with the use of cholesterol-lowering drug therapies. Dietary adjuncts for lowering atherogenic cholesterol may also be considered for patients with dyslipidemia, including phytosterols and viscous soluble dietary fibers.[28] In addition, referral to a registered dietitian (RD)/registered dietitian nutritionist (RDN) may be considered to improve understanding of heart-healthy dietary principles and individualize nutrition recommendations. Adherence to lifestyle modifications should be regularly assessed at the time of initiation or modification of statin therapy and during monitoring of ongoing therapy. As this ECDP specifically addresses considerations for the incorporation of nonstatin therapies in selected high-risk patient populations, it is critical that the clinician assess and reinforce adherence to intensive lifestyle changes before the initiation of these additional agents. The reader is referred to the 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement from the American Heart Association and the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the ACC/AHA Task Force on Clinical Practice Guidelines for comprehensive recommendations.[29,30]

Monitoring of response to LDL-C–lowering therapies: In agreement with the 2013 ACC/AHA and 2018 AHA/ACC/multisociety guidelines, the writing committee recommends the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and LDL-C), followed by

a second lipid panel 4 to 12 weeks following initiation of statin therapy, to determine a patient's adherence and response 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 maximal ASCVD risk reduction. When any modification is made to LDL-C-lowering therapy, including intensification of lifestyle intervention, increase in statin therapy intensity, or the addition of nonstatin therapies, the writing committee recommends the use of a fasting lipid panel 4 to 12 weeks after treatment modification to determine a patient's adherence and response to therapy. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated.

Approaches to statin-associated side effects: Because the overwhelming body of evidence for ASCVD risk reduction with lipid-lowering therapies is from statin randomized controlled trials (RCTs), evidence-based statin therapy of appropriate intensity is recommended as first-line therapy in all 4 patient management groups. However, following initiation of statin therapy, some individuals may experience unacceptable adverse effects when taking the recommended intensity of statin therapy, the most commonly reported being muscle-related symptoms.[31] The incidence of statin intolerance is relatively low in large RCTs, and evidence from the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes) trials demonstrates that the majority of symptoms may be related to a "nocebo" effect.[32,33] In view of the challenges of managing patients with perceived statin-associated side effects (SASEs), the availability of a number of nonstatin therapies, cost concerns, consideration of frequency and routes of administration, patient preferences, and variations in approved indications for newer therapies, the writing committee felt that expert guidance on the use of nonstatin therapies in such patients is needed. An algorithm for management of patients with SASEs in each of the patient management groups is provided in this update (see Section 5.6).

Nonstatin therapies: Currently available strategies and therapies that are considered in this ECDP for the management of LDL-C-related ASCVD risk are described in **Table 3**.

As outlined in **Table 3**, and reflected in the algorithms shown later, there are important considerations in the choice of nonstatin therapies that may make a treatment modality preferable in specific patient populations (eg, 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, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies, and, importantly, patient preferences. Before initiation of combination therapy, and in assessment of the value of dose adjustment or addition of further drug therapies, 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 (see **Table 4**). Of note, BAS may be considered as an optional alternative agent for those with ezetimibe intolerance and with triglycerides <300 mg/dL or due to patient preferences, but there is no evidence for a net cardiovascular risk reduction benefit of BAS in addition to statin therapy. BAS are, therefore, noted generally as an option in the footnotes of the algorithms.

The writing committee undertook an iterative process to identify higher-risk patient subgroups among each of the patient management 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. In some cases, criteria for higher-risk subgroups were previously identified in the 2018 ACC/AHA/multisociety cholesterol guideline, such as the "at very high risk" subgroup in patients with existing ASCVD, and the "risk-enhancing factors" identified for primary prevention. In other cases (eg, for patients with diabetes, familial hypercholesterolemia [FH] phenotype, or with measured CAC scores) high-risk features were chosen by consensus of the ECDP writing committee, based on the review of available evidence. In addition, the writing committee considered the current evidence base for each nonstatin therapy, with a preference for those therapies that have an evidence base that includes demonstrated reduction in ASCVD events in well-designed and well-conducted RCTs, rather than evidence derived solely from observational studies or studies using intermediate surrogate endpoints, such as LDL-C lowering. The writing committee first considered a base case of a patient without significant comorbidities within each of the 4 patient management benefit groups. The appropriate strategies and the order of consideration were first determined for these patients. Once the writing committee reached consensus on this scenario, members undertook an iterative process of discussion and consideration

TABLE 3 Strategies and Nonstatin Agents Considered for Management of LDL-Related ASCVD Risk

Strategy/Agent	Comments
Referral to another clinician	
Referral to lipid specialist	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, baseline LDL-C ≥190 mg/dL, or intolerance to at least 2 (preferably 3) statin therapies with 1 attempt at the lowest FDA-approved dose and a trial of an alternative statin therapy regimen (eg, every-other-day dosing) ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction ■ **Considerations in referring:** Lipid specialists may be available for virtual visits for patients in some rural or remote locations
Referral to RD/RDN	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, or baseline LDL-C ≥190 mg/dL ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction
Nonstatin agents that may be used to manage LDL-related ASCVD risk	
Ezetimibe[34]	■ **Mechanism of action:** Inhibits NPC1L1 protein; reduces cholesterol absorption in small intestine. ■ **FDA-approved indication(s):** As adjunct to diet to: 1) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with primary hyperlipidemia, either alone or in combination with statin therapy; 2) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) ↓ TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; and 4) ↓ sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia) ■ **Dose:** 10 mg orally daily, with or without food. Take either ≥2 h before or ≥4 h after BAS, if used in combination ■ **Mean % reduction in LDL-C (per PI):** Monotherapy—18%; combination therapy with statin therapy (incremental reduction)—25% ■ **Contraindication:** History of hypersensitivity to this medication. ■ **Warnings/precautions:** 1. Not recommended in patients with moderate/severe hepatic impairment. 2. Persistent elevations in hepatic transaminases may occur with concomitant statin therapy. Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy. 3. Cases of myopathy and rhabdomyolysis have been reported when ezetimibe was used alone or in combination with statin therapy. ■ **Adverse effects:** Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities. In combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use ■ **Drug-drug interactions:** Cyclosporine, fibrates, BAS ■ **CV outcomes trials:** IMPROVE-IT[8] (The addition of ezetimibe to moderate-intensity statin therapy in patients with recent ACS resulted in incremental lowering of LDL-C and reduced the primary composite endpoint of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years); SHARP[35] (Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years) ■ **Other prescribing considerations:** Generally well tolerated. Generic available
PCSK9 mAb (alirocumab,[36] evolocumab[37])	■ **Mechanism of action:** Human mAb to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C ■ **FDA-approved indication(s):** ***Alirocumab and evolocumab:*** 1) ↓ LDL-C in adults with primary hyperlipidemia (including HeFH) as adjunct to diet, either alone or in combination with other lipid-lowering therapies ***Alirocumab:*** 1) ↓ risk of MI, stroke, and unstable angina requiring hospitalization in adults with ASCVD; 2) ↓ LDL-C in adults with HoFH as adjunct to other LDL-C-lowering therapies ***Evolocumab:*** 1) ↓ risk of MI, stroke, and coronary revascularization in adults with ASCVD; 2) ↓ LDL-C in pediatric patients (aged ≥10 years) with HeFH as adjunct to diet and other LDL-C-lowering therapies; 3) ↓ LDL-C in adults and pediatric patients (aged ≥10 years) with HoFH as adjunct to diet and other LDL-C-lowering therapies ■ **Dose and route of administration:** ***Alirocumab:*** Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD or primary hyperlipidemia: initiate 75 mg SC every 2 weeks. If more LDL-C reduction needed, may ↑ dose to 150 mg every 2 weeks. Alternative starting dose is 300 mg SC every 4 weeks. For the 300-mg dose, administer 2 (150-mg) injections consecutively at 2 different injection sites. In adults with HeFH undergoing LDL apheresis or adults with HoFH, administer 150 mg SC every 2 weeks ***Evolocumab:*** Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD, adults with primary hypercholesterolemia, including with established clinical ASCVD or HeFH, or in pediatric patients (aged ≥10 years) with HeFH, administer 140 mg SC every 2 weeks or 420 mg SC once monthly in abdomen, thigh, or upper arm. In adults or pediatric patients (aged ≥10 years) with HoFH, administer 420 mg SC once monthly; if more LDL-C reduction is needed after 12 weeks, may ↑ dose to 420 mg every 2 weeks. In adults or pediatric patients (age ≥10 years) with HoFH on LDL apheresis, may initiate 420 mg SC every 2 weeks to correspond with apheresis schedule; evolocumab should be given after apheresis is complete. To administer 420-mg dose, either use the prefilled single-dose on-body infuser or give 3 (140-mg) injections consecutively within 30 min.

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TABLE 3 Continued

Strategy/Agent	Comments
	■ **Mean % LDL-C reduction (per PI):** ***Alirocumab:*** when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 mg SC 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 SC every 4 weeks, ↓ LDL-C by an additional 64% and 58%, respectively. ■ **Contraindication:** History of hypersensitivity to the medication. ■ **Warnings/precautions:** Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. ■ **Adverse effects:** ***Alirocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, injection site reactions, influenza; in patients with ASCVD: noncardiac chest pain, nasopharyngitis, myalgia. No evidence of increase in cognitive adverse effects observed in ODYSSEY Outcomes or CANTAB.[9,38] ***Evolocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions; in patients with ASCVD: diabetes, nasopharyngitis, upper respiratory tract infection. No evidence of an increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS.[5,39] ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions identified for alirocumab or evolocumab ■ **CV outcomes trials:** ***Alirocumab:*** ODYSSEY Outcomes[9] in 18,600 post-ACS (4-52 weeks) patients on evidence-based statin therapy; Demonstrated that addition of alirocumab reduced the primary endpoint of CHD death, MI, ischemic stroke, or hospitalization for UA. ***Evolocumab:*** FOURIER[5] in 27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization, or hospitalization for unstable angina. ■ **Other prescribing considerations:** Robust LDL-C reduction, cost, SC administration at home, may require prior authorization. ***Evolocumab:*** Advise latex-sensitive patients that the needle covers on the products contain latex.
Bempedoic acid[40]	■ **Mechanism of action:** ACL inhibitor; inhibits cholesterol synthesis in the liver; increases LDL receptor density. Bempedoic acid and its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 180 mg orally once daily, with or without food. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—17%-18%. ■ **Contraindication:** none ■ **Warnings/precautions:** 1) May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs, as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2) Discontinue immediately if the patient experiences rupture of a tendon. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17] ■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[17] ■ **Drug-drug interactions:** Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials not completed. CLEAR Outcomes trial completion expected later in 2022. ■ **Other prescribing considerations:** cost; pill burden; requires prior authorization
Bempedoic acid and ezetimibe[41]	■ **Refer to section on ezetimibe for information specific to this agent.** ■ **Mechanism of action:** See the mechanisms of action for bempedoic acid and ezetimibe included in this table. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 1 tablet (180 mg bempedoic acid/10 mg ezetimibe) orally, once daily, with or without food. Swallow whole. Take either ≥2 hours before or ≥4 hours after BAS, if used in combination. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—38%. ■ **Contraindication:** History of hypersensitivity to ezetimibe. ■ **Warnings/precautions:** 1. May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2. Discontinue immediately if the patient experiences tendon rupture. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17]

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TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremities, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, influenza. Consider alternative therapy if history of tendon disorder or rupture; discontinue immediately if tendon rupture occurs. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[42] ■ **Drug-drug interactions:** Cyclosporine; fibrates. Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials for bempedoic acid not completed. Completion of CLEAR Outcomes trial expected later in 2022. CV outcomes trial will not be required for fixed-dose combination of ezetimibe and bempedoic acid. ■ **Prescribing considerations:** ↓ LDL-C within the range of moderate-intensity statin therapy; cost; requires prior authorization
Inclisiran[43]	■ **Mechanism of action:** siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician. ■ **Mean % reduction in LDL-C (per PI):** 48%-52% ■ **Contraindications (per PI):** None ■ **Warnings/precautions (per PI):** None ■ **Adverse effects:** Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions (per PI):** None ■ **CV outcomes trials:** CV outcomes trials not yet completed. ORION-4 currently in progress with estimated completion in 2026. VICTORION-2P currently in progress with estimated completion in 2027. ■ **Other prescribing considerations:** robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization.
BAS[44,45]	■ **Mechanism of action:** Nonabsorbed, lipid-lowering polymer that binds bile acids in the intestine and impedes their reabsorption. As the bile acid pool ↓, the hepatic enzyme cholesterol 7-α-hydroxylase is up-regulated, 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 ↑ numbers of hepatic LDL receptors. These compensatory effects result in ↑ clearance of LDL particles from the blood, in turn resulting in ↓ serum LDL-C levels. Serum TG levels may ↑ or remain unchanged. ■ **FDA-approved indication(s):** ***Colesevelam:*** As an adjunct to diet and exercise to 1) ↓ LDL-C in adults with primary hyperlipidemia; 2) ↑ glycemic control in adults with type 2 diabetes; 3) ↓ LDL-C in boys and post-menarchal girls (aged 10-17 years) with HeFH who are unable to reach LDL-C targets after an adequate trial of diet therapy and lifestyle modifications. ***Cholestyramine, colestipol:*** ↓ LDL-C with primary hyperlipidemia, as adjunct to diet ■ **Dose and route of administration:** ***Colesevelam:*** Tablets: 6 tablets orally once daily or 3 tablets orally twice daily; take tablets with a meal and liquid. Suspension: one 3.75-g packet orally daily, or one 1.875-g packet orally twice daily; mix powder with 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; ***Cholestyramine:*** 8-16 g/day orally, divided into 2 doses; **Colestipol:** 2-16 g/day orally, given once or in divided doses ■ **Mean % LDL reduction (per PI):** ***Colesevelam:*** Monotherapy—15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy—additional 10%-16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg). ***Cholestyramine:*** Monotherapy—10.4% vs placebo. ***Colestipol:*** not provided in PI. In dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively[46] ■ **Contraindications (per PI):** ***Colesevelam:*** TG >500 mg/dL; history of hypertriglyceridemia-induced pancreatitis; bowel obstruction. ***Cholestyramine:*** History of serious hypersensitivity to this medication. ***Colestipol:*** Complete biliary obstruction, history of serious hypersensitivity to this medication. ■ **Warnings/precautions:** May ↑ TG and cause acute pancreatitis, monitor TG, discontinue if signs and symptoms of acute pancreatitis occur; may cause GI obstruction, avoid with gastroparesis, other GI motility disorders, and history of major GI tract surgery with risk for bowel obstruction; may cause vitamin K or fat-soluble vitamin deficiencies, oral vitamins should be given ≥4 hours before this medication; may decrease absorption of other medications, other medications should be given ≥4 hours before this medication. Some products contain phenylalanine, which may be harmful to patients with phenylketonuria.

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TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Constipation, dyspepsia, and nausea. ■ **Use during pregnancy/lactation:** Considered safe to use ■ **Drug-drug interactions:** In general, BAS may decrease absorption of other medications; it is a good practice for all other medications to be given ≥4 hours before BAS. Concomitant use of BAS is known to decrease absorption of cyclosporin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan, phenytoin, sulfonylureas, thyroid replacement therapy, warfarin; give these medications ≥4 hours before BAS. For patients on warfarin, monitor INR frequently during BAS initiation and then periodically. Cholestyramine may increase exposure to metformin; monitor glycemic control. ■ **CV outcomes trials:** In LRC-CPPT, 3,806 asymptomatic middle-aged men with primary hypercholesterolemia were randomized to cholestyramine resin vs placebo for an average of 7.4 years. The cholestyramine 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 colesevelam and colestipol on cardiovascular morbidity and mortality have not been determined ■ **Considerations in prescribing:** Pill burden; inconvenience in preparation of oral suspension preparations; drug interactions, GI side effects; exacerbation of hypertriglyceridemia; orally administered, colesevelam lowers HbA_{1c} 0.5% in diabetes; CV outcomes data not available for all products
Agents that may be used to treat HoFH under care of a lipid specialist	
Evinacumab[21]	■ **Mechanism of action:** Human monoclonal antibody that binds to and inhibits ANGPTL3. Promotes VLDL processing and clearance upstream of LDL formation ■ **FDA-approved indication(s):** ↓ LDL-C in adults and pediatric patients (aged ≥12 years) with HoFH as adjunct to other LDL-C–lowering therapies ■ **Dose and route of administration:** 15 mg/kg administered by healthcare professional as IV infusion once monthly (every 4 weeks). See PI for preparation and administration instructions. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with other lipid-lowering therapies (incremental reduction)—49%. ■ **Contraindication:** History of serious hypersensitivity to this medication. ■ **Warnings/precautions:** 1. Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. 2. May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥5 months following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-833-385-3392). ■ **Adverse effects:** nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions have been identified ■ **CV outcomes trials:** The effect of evinacumab on CV morbidity and mortality has not been determined ■ **Other prescribing considerations:** See prescribing information for complete preparation and administration instructions. Robust LDL-C reduction; cost, IV administration, requires prior authorization
Lomitapide[47]	■ **Mechanism of action:** Directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits synthesis of chylomicrons and VLDL and leads to ↓ LDL-C ■ **FDA-approved indications:** ↓ LDL-C, TC, apoB, and non-HDL-C in patients with HoFH, as adjunct to a low-fat diet and other lipid-lowering treatments (including LDL apheresis, where available) ■ **Dose and route of administration:** Initiate 5 mg orally once daily. Titrate dose based 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, up to the 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 ■ **Black box warnings:** 1. May cause elevations in liver transaminases; measure ALT, AST, alkaline phosphatase, total bilirubin before initiating this medication; during treatment, adjust dose if ALT or AST ≥3 times the upper limit of normal; discontinue this medication for clinically significant liver toxicity. 2. 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. Because of the risk of hepatotoxicity, lomitapide is only available through the REMS program ■ **Contraindications:** 1) Pregnancy; 2) concomitant use with strong/moderate CYP3A4 inhibitors; 3) moderate/severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests. ■ **Warnings/precautions:** 1) May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥2 weeks following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-877-902-4099).

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TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** 1. CYP3A4 inhibitors increase exposure to lomitapide. Strong/moderate CYP3A4 inhibitors are contraindicated with lomitapide. Avoid grapefruit juice. 2. Do not exceed 30 mg daily of lomitapide when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives. 3. Increases plasma concentration of warfarin; monitor INR regularly, especially with lomitapide dose adjustment. 4. Increased systemic exposure to simvastatin and lovastatin exposure with lomitapide. Limit statin dose when coadministered due to myopathy risk. 5. Consider dose reduction of P-glycoprotein substrates because of possible increased absorption with lomitapide. 6. Separate lomitapide dosing with BAS by at least 4 hours. ■ **CV outcomes trials:** The effect of lomitapide on CV morbidity and mortality has not been determined ■ **Considerations in prescribing:** Cost, oral administration, requires strict adherence to low-fat diet and gradual dose escalation to reduce GI side effects, requires daily doses of specific vitamins (Vitamin E 400 IU, linoleic acid ≥200 mg, alpha-linolenic acid ≥210 mg, eicosapentaenoic acid ≥110 mg, docosahexaenoic acid ≥80 mg); requires monitoring of transaminase levels, long-term consequences of hepatic steatosis unknown, prescriber training, REMS program
LDL apheresis	■ **Mechanism of action:** Selectively removes apo B-containing lipoproteins, producing an acute reduction in LDL-C. ■ **FDA approved indication:** Patients with FH unresponsive to pharmacologic and dietary management who are either functional homozygotes with an LDL-C >500 mg/dL, functional heterozygotes with no known CV disease but an LDL-C >300 mg/dL, or functional heterozygotes with known cardiovascular disease and LDL-C >200 mg/dL ■ **Dose and route of administration:** Extracorporeal technique performed weekly or biweekly ■ **Mean % LDL-C reduction:** With weekly or biweekly treatment, average LDL-C can ↓ to ~50–60% of the original levels. LDL-C increases after each apheresis session but does not return to the original level ■ **Adverse effects:** Problems with venous access; transient hypotension, fatigue; bleeding; hypocalcemia; iron deficiency due to regular phlebotomy for diagnostic purposes; heparin allergy; and bradykinin syndrome (especially with ACEi) ■ **Drug-drug interactions:** ACEi should not be used with dextran sulfate method owing to risk of bradykinin syndrome ■ **CV outcomes trials:** Limited due to ethical considerations in RCTs of very high-risk patients with HoFH, but it is reasonable to assume reductions in CV disease events are proportional to the degree of LDL-C lowering ■ **Considerations in prescribing:** Cost, extracorporeal technique, inconvenient, locations not readily available in some regions, time-consuming, robust reduction in LDL-C

↑ = increase; ↓ = decrease; ACEi = angiotensin-converting enzyme inhibitor; ACL = adenosine triphosphate-citrate lyase; ACS = acute coronary syndrome; ACSVl1 = acyl-CoA synthetase-1; ALT = alanine transaminase; apoB = apolipoprotein B-100; ASCVD = atherosclerotic cardiovascular disease; ANGPTL3 = Angiopoietin-like 3; AST = aspartate aminotransferase; BAS = bile acid sequestrant; CANTAB = Cambridge Neuropsychological Test Automated Battery; CHD = coronary heart disease; CKD = chronic kidney disease; CLEAR Outcomes = Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant With Bempedoic Acid [ETC-1002] or Placebo; CV = cardiovascular; CYP3A4 = Cytochrome P450 3A4; EBBINGHAUS = Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects; FDA = Food and Drug Administration; FH = familial hypercholesterolemia; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GI = gastrointestinal; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; mAb = monoclonal antibody; MI = myocardial infarction; NPC1L1 = Niemann-Pick C1 like 1; ODYSSEY = Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; ORION-4 = A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; PI = prescribing information; RD/RDN = registered dietician/registered dietician nutritionist; REMS = Risk Evaluation and Mitigation Strategy; SC = subcutaneous; SHARP = Study of Heart and Renal Protection; siRNA = synthetic small interfering ribonucleic acid; TC = total cholesterol; TG = triglycerides; UA = unstable angina; VICTORION-2P = A Randomized, Double-blind, Placebo-controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease; VLDL = very low-density lipoprotein

of special circumstances for subpopulations with comorbidities, and then updated the strategies to create a clinical pathway or algorithm that could be followed by clinicians for each patient scenario. All issues were discussed, and all algorithms were finalized with full consensus of the writing committee members.

Persistent or severe hypertriglyceridemia: The writing committee did not directly consider or recommend adjunctive approaches for persistent or severe hypertriglyceridemia (lifestyle modifications, prescription omega-3 fatty acids, fibric acid derivatives) because these were recently addressed in detail in the 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia (denoted in this document as the 2021 ACC ECDP on management of hypertriglyceridemia).[48] Clinicians are referred to that ECDP, as needed, at the appropriate point in each algorithm.

TABLE 4 Factors to Consider in the Clinician–Patient Discussion

Potential for additional ASCVD risk reduction from addition of nonstatin therapy to evidence-based statin therapy to lower LDL-C	■ Percentage LDL-C reduction achieved with evidence-based statin therapy (if <50% and not on maximally tolerated statin, should increase statin therapy first and reinforce lifestyle modifications) *and* whether patient is above LDL-C threshold for consideration of nonstatin therapies ■ For patients with ASCVD, patient's status as very high risk or not very high risk on evidence-based statin therapy (see Table 1)* ■ For patients without ASCVD or baseline LDL-C ≥190 mg/dL, patient's baseline predicted 10-year ASCVD risk prestatin and presence of risk-enhancing factors (see Table 2)† ■ Available scientific evidence of ASCVD risk reduction (and magnitude of benefit) when nonstatin 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 nonstatin therapy when added to evidence-based statin therapy‖
Potential for clinically significant adverse events or drug–drug interactions from addition of nonstatin therapy to evidence-based statin therapy for lowering LDL-C	■ See Table 3
Cost considerations	■ Potential out-of-pocket cost of therapy to the patient (eg, insurance plan coverage, pharmacy or medical benefit, copayment, availability of assistance programs).
Patient preferences and considerations	■ Patient's perception of benefit from addition of nonstatin therapy ■ Convenience of nonstatin therapy (eg, route, setting [home or medical office], and frequency of administration, pill burden, storage) ■ Potential of nonstatin therapy to jeopardize adherence to other evidence-based therapies ■ Cost of nonstatin 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. See Table 1 for criteria for defining patients at very high risk.
†Use the Pooled Cohort Equations to estimate 10-y ASCVD risk. See Table 1 for criteria for defining patients at very high risk.
‡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. Evidence from FOURIER and ODYSSEY Outcomes demonstrate 2% absolute/15% relative ASCVD risk reduction. Data are lacking for addition of BAS to statins, bempedoic acid, inclisiran, and evinacumab. 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 therapy with LDL-C ≥130 mg/dL may receive more benefit from the addition of a nonstatin 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.

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

3. ASSUMPTIONS AND DEFINITIONS

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

1. The writing committee endorses the evidence-based approaches to ASCVD risk reduction in adults enumerated in the 2018 AHA/ACC/multisociety cholesterol guideline.[7]
2. The algorithms herein begin with the assumption that the patient is in 1 of the 4 evidence-based patient management groups identified in the 2018 AHA/ACC/multisociety cholesterol guideline:
   a. Adults aged ≥20 years with clinical ASCVD on statin therapy for secondary prevention;
   b. Adults aged ≥20 years with LDL-C ≥190 mg/dL (not due to secondary modifiable causes) on statin therapy for primary prevention;
   c. Adults aged 40-75 years without ASCVD, but with diabetes and LDL-C <190 mg/dL, on statin therapy for primary prevention; and
   d. Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70 to 189 mg/dL and an estimated 10-year risk for ASCVD ≥7.5%, on statin therapy for primary prevention.

   Patients not in 1 of these 4 patient management groups who may be at elevated risk for ASCVD events (patients with heart failure, patients on maintenance hemodialysis, women considering pregnancy or already pregnant, and patients with previous organ transplantation) are considered in a separate section and should receive individualized care in the context of shared decision-making between the clinician and patient (see Section 5.7).
3. These algorithms assume that the patient is currently taking the maximally tolerated dose of statin therapy or has attempted to take statin therapy as a result of shared decision-making and that the clinician and patient are trying to determine whether additional therapy is needed to further reduce ASCVD risk. If a patient has a less-than-anticipated LDL-C response to the statin dose, additional clinical approaches are

warranted in all scenarios. 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 writing 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. Patients who are unable to tolerate even moderate-intensity statin therapy should be evaluated for statin intolerance and considered for referral to a lipid specialist. The clinician and patient should attempt to intensify lifestyle modifications and may consider the incorporation of soluble dietary fiber and phytosterols as part of this approach. Other major ASCVD risk factors, including tobacco use, diabetes, elevated blood pressure, and obesity, should be addressed as needed and controlled as well. These steps are referred to as "*routine clinical assessment and interventions*" in later discussion.

4. These algorithms were crafted based on the principle of potential net ASCVD risk reduction benefit, meaning that the potential benefits of additional nonstatin 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, frequency and route of administration, potential to jeopardize adherence to evidence-based therapies, and importantly, patient preferences. Before initiation of combination therapy or with further adjustment or consideration of additional drug 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 (see **Table 4**).
5. Critical to the decision-making process for use of additional nonstatin therapies in select high-risk patients is the definition of "thresholds" for consideration of net ASCVD risk reduction benefit. The writing committee endorsed the evidence-based findings from the 2013 ACC/AHA and 2018 AHA/ACC/multisociety cholesterol guidelines regarding the use of appropriate intensity statin therapy and the indicators of efficacy (eg, ≥50% LDL-C reduction for high-intensity statin therapy doses and 30% to 49% reduction for moderate-intensity doses). In addition, the writing 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 writing committee therefore judged that it was appropriate to continue 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. Throughout this guidance, absolute LDL-C levels are considered as "thresholds" for considering the addition of nonstatin therapies, and not LDC-C goals. The writing committee emphasizes that these are not firm triggers for adding medication but are factors that may be considered within the broader context of an individual patient's clinical situation.
6. The writing committee recognizes that there are different means for measuring LDL-C, including direct measurement, calculation using the Friedewald equation, and newer methods.[49] The writing committee endorses use of the Friedewald equation, given that the majority of RCTs used this method and that it is the most widely available means in clinical practice. However, the writing 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.[50,51] Newer methods should be considered by health systems and laboratories whenever possible. The use of the Martin-Hopkins method provides a more accurate assessment of LDL-C in individuals with very low levels of LDL-C or with hypertriglyceridemia.[51-53] A new method for calculating LDL-C proposed by investigators at the National Heart, Lung, and Blood Institute may also be more precise, but additional validation is needed.[52] The algorithms include use of non–HDL-C thresholds as an additional alternative for decision-making. If a statin therapy dose is adjusted or nonstatin therapy is added or adjusted, the writing committee emphasizes the importance of monitoring the LDL-C response within 4 to 12 weeks to avoid therapeutic inertia and maximize LDL-C lowering as quickly as possible.
7. Non–HDL-C represents the combination of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) and represents all potentially atherogenic particles. The main protein embedded in LDL and VLDL is apolipoprotein B (apoB) and, like non–HDL-C, apoB is a stronger indicator of atherogenicity than LDL-C alone.[7] Several investigators have identified a strong

association between apoB and ASCVD and a high correlation between apoB and non-HDL-C. Non-HDL-C is simply calculated from the routine lipid panel as total cholesterol minus HDL-C and provides an inexpensive assessment of all atherogenic lipoproteins. Therefore, recommendations for non-HDL-C thresholds are included with LDL-C thresholds in this expert consensus guidance.

8. The 2018 AHA/ACC/multisociety cholesterol guideline indicates that calcium scoring may be considered in select patients at borderline or intermediate risk (≥5.0% to <20%) for whom the risk decision regarding statin therapy is uncertain.[7] Despite a strong body of evidence demonstrating the clear association between coronary calcium and risk of ASCVD events, there is currently limited evidence for cardiovascular outcomes benefits of a strategy for implementation of statin and nonstatin therapies based on calcium scoring. Therefore, the writing committee has provided guidance for management strategies in patients with evidence of subclinical atherosclerosis on imaging studies.

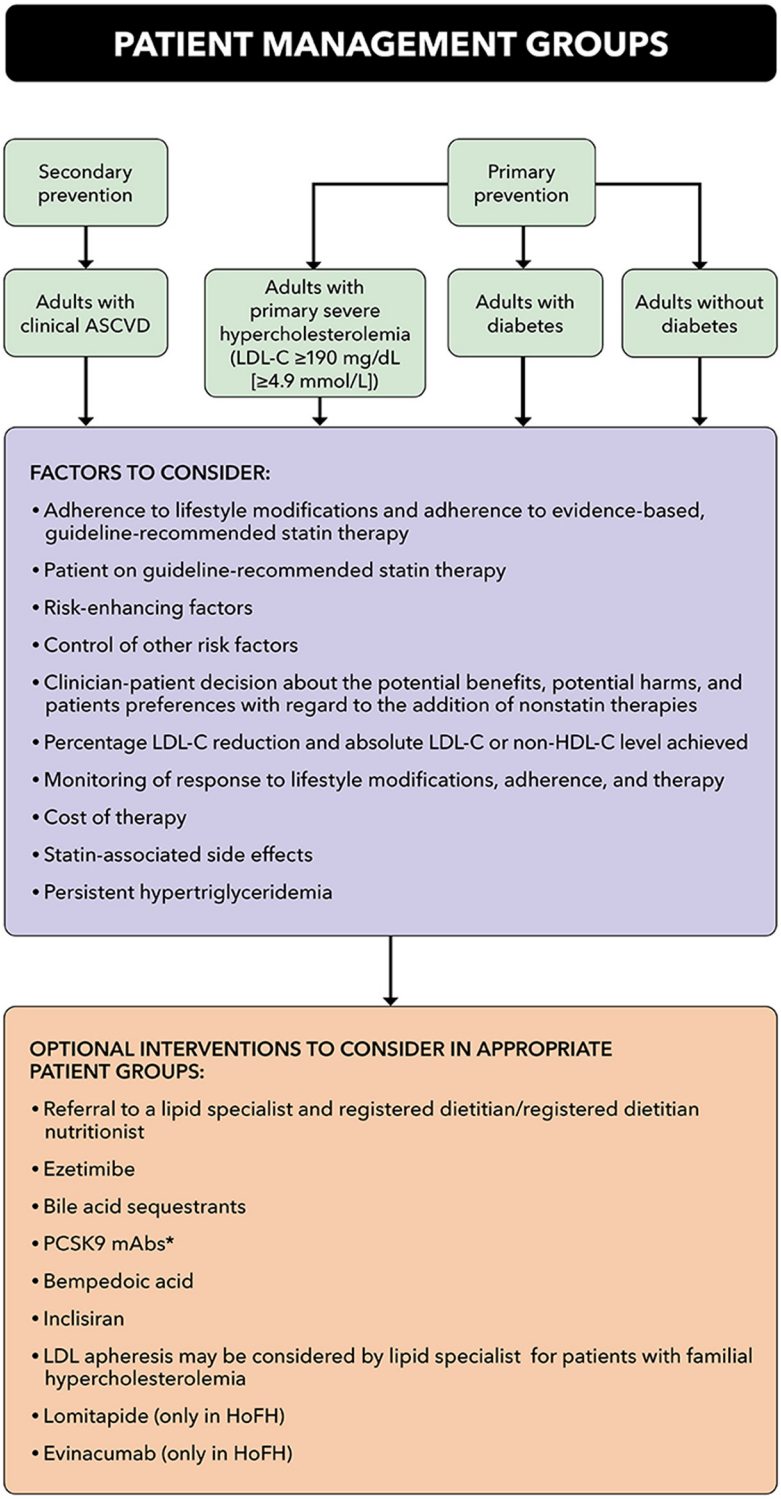
Subclinical atherosclerosis is defined in this document as significant atherosclerotic plaque observed in an asymptomatic patient on any of the following diagnostic studies: coronary artery calcification noted on computed tomography (CT) studies, including calcium scoring, cardiac CT coronary angiography, chest CT for ruling out pulmonary embolism, chest CT for lung cancer screening, or diagnostic chest CT; carotid plaque noted on carotid ultrasound or angiography; or abnormal ankle-brachial index or plaque noted on peripheral arterial angiography.

9. At the time of publication of the 2018 AHA/ACC/multisociety cholesterol guideline, the annual retail cost of each of the PCSK9 mAbs was approximately $14,000. The guideline authors therefore included a value statement that, "PCSK9 inhibitors have a low cost value (>$150,000 per quality-adjusted life year [QALY]) compared to good cost value (<$50,000 per QALY)."[7] Since that time, the cost of the PCSK9 mAbs has been substantially reduced, although concerns regarding the cost-effectiveness of these agents remain, and prescription volumes have remained relatively stable.[54] The guidance in this ECDP does not provide a specific cost value statement for nonstatin therapies, but relies upon the clinician-patient discussion and shared decision-making to consider the additional LDL-C lowering desired, costs, patient preferences, frequency and route of administration, and convenience.
10. Each algorithm discussed later 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.
11. Several of the algorithms provide an iterative and hierarchical approach to the consideration or selection of nonstatin therapies. These are denoted by recycling arrows in the figures (to indicate iterative assessment), numbering of the order in which options should be considered, and stepwise visual presentation. Nonstatin therapies were placed at different levels in the order of consideration based on the writing committee's consensus views on the availability and strength of high-quality trial evidence for event reduction, the degree of LDL-C lowering that is desired, the potential cost of therapy, and the ease of administration.
12. At the present time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and benefits for cardiovascular outcomes in the FOURIER and ODYSSEY Outcomes trials.[5,9] The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently underway, and their completion is anticipated in 2026 and 2027, respectively.[55,56] In view of the twice-yearly dosing regimen, inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject may also be considered for therapy with inclisiran. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe; therefore, if inclisiran is to be used, it should be used in place of a PCSK9 mAb.

4. PATHWAY SUMMARY GRAPHIC

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 arrows represent recommended steps, whereas the dashed arrows indicate optional interventions that may be considered. Readers should refer to the individual algorithms for the detailed clinical workflow for each patient scenario.

FIGURE 1 **Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider**



*PCSK9 mAb includes alirocumab and evolocumab. ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies.

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

The writing committee created algorithms for each of the patient groups, which are described below. For ease of clinical use, these are also summarized visually in Figures 2 to 5.

5.1. Adults With Clinical ASCVD on Statin Therapy for Secondary Prevention (Figures 2A to 2D)

Patients with clinical ASCVD are defined from the RCT inclusion criteria as those with ACS or history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, or transient ischemic attack or peripheral artery disease (PAD) presumed to be of atherosclerotic origin. The writing committee identified several subgroups of patients with clinical ASCVD, including those at very high risk, those not at very high risk, and those with baseline LDL-C ≥190 mg/dL. Each of these subgroups is addressed in a separate algorithm, as discussed later.

As noted previously, according to the 2018 AHA/ACC/multisociety cholesterol guideline, patients with ASCVD are categorized into 1 of 2 groups: those not at very high risk or those at very high risk. Very high-risk patients have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (see Table 1). Based on evidence from IMPROVE-IT, FOURIER, and ODYSSEY Outcomes, this very high-risk group of patients has demonstrated cardiovascular outcomes benefits from the addition of ezetimibe, alirocumab, or evolocumab.

High-intensity statin therapy should be initiated in adults aged ≤75 years 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 drug or dose selection or safety (eg, potential for statin-drug interactions, hepatic or renal dysfunction, frailty, or ethnicity-specific statin-associated risks [eg, potential need for lower dosing in persons of East-Asian heritage], among other factors). In individuals with clinical ASCVD who would otherwise receive high-intensity statin therapy, 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 statin therapy is used, the objective is to achieve a 30% to 49% reduction in LDL-C and, for high-intensity statin therapy, ≥50% LDL-C reduction.

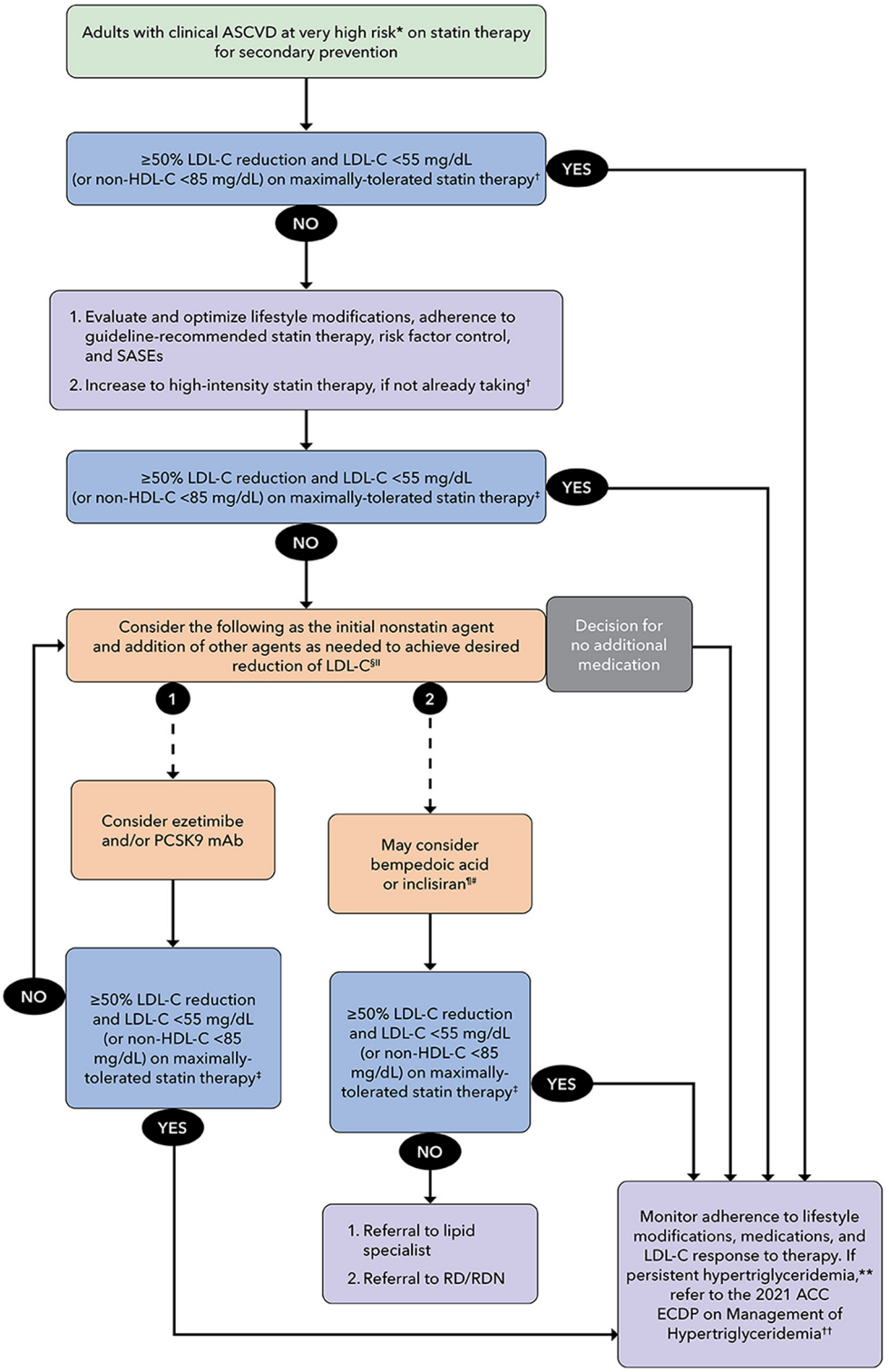
As per the 2013 ACC/AHA and 2018 AHA/ACC/multisociety cholesterol guidelines, few people aged >75 years were enrolled in the statin therapy RCTs, but available evidence supports the continuation of statin therapy beyond the age of 75 years in persons who are already taking and tolerating these agents. A larger amount of data supports the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD aged >75 years. Whereas data are limited, it is reasonable to consider initiation of high-intensity statin therapy for secondary prevention in individuals aged >75 years, but such a decision should be based on expected benefit and competing comorbidities.[7]

5.1.1. Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention (Figure 2A)

Patients in this group have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (see Table 1). Adults with clinical ASCVD at very high risk should be treated first at the maximally tolerated statin intensity. If patients have achieved ≥50% reduction in LDL-C from baseline and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL), it is reasonable to continue statin therapy and monitor adherence to medications, lifestyle modifications, and ongoing LDL-C response to therapy.

In view of the favorable net clinical benefit of the addition of nonstatin therapies in patients with clinical ASCVD at very high risk on high-intensity statin therapy and lifestyle management and the very low levels of LDL-C achieved in RCTs of nonstatin therapies, a lower LDL-C threshold of LDL-C ≥55 mg/dL (or non-HDL-C ≥85 mg/dL) is recommended by the writing committee. There is evidence from clinical trials that individuals who achieve LDL-C <55 mg/dL experience lower event rates than those with higher LDL-C. Preference should be given to therapies with demonstrated cardiovascular outcomes benefits. Prospective and observational trials demonstrate a direct and significant relationship between LDL-C level and atherosclerosis progression and ASCVD event risk, and absolute LDL-C reduction is directly associated with ASCVD risk reduction.[5,8,9,60,61] There appears to be no LDL-C level below which benefit ceases. Current evidence indicates that lifelong very low LDL-C levels in the range of 15-30 mg/dL in patients with hypobetalipoproteinemia or PCSK9 loss-of-function mutations and in shorter-term lipid-lowering clinical trials are associated with a lower incidence of ASCVD without adverse effects.[62] Primary prevention patients in the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial on statin monotherapy at increased

FIGURE 2A Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention



Continued on the next page

cardiovascular risk achieved a median LDL-C of 55 mg/dL with a reduction in cardiovascular events compared with placebo.[63]

If a patient has a less-than-anticipated response (<50% reduction in LDL-C or LDL-C ≥55 mg/dL or non-HDL-C ≥85 mg/dL) with maximally tolerated statin therapy, routine clinical assessment and interventions are warranted (see Section 3.3). If the patient still has <50% reduction in LDL-C or LDL-C ≥55 mg/dL (or non-HDL-C ≥85 mg/dL), the patient and clinician should have a discussion focused on shared decision-making regarding the addition of a nonstatin therapy to maximally tolerated statin therapy. The clinician-patient discussion is described in **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 modifications and ongoing LDL-C response to therapy.

If a decision is made to proceed with the addition of nonstatin therapy to maximally tolerated statin therapy, based on the results of IMPROVE-IT, FOURIER, and ODYSSEY Outcomes demonstrating improved cardiovascular outcomes and excellent safety profiles, the addition of ***either*** ezetimibe ***or*** a PCSK9 mAb as the initial nonstatin therapy should be considered for this very high-risk patient group (see **Figure 2A**).[5,8,9] Considerations that may favor the initial choice of ezetimibe include patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations, ease of use, and patient preferences. A post hoc analysis of IMPROVE-IT identified 9 clinical variables (heart failure, hypertension, age >75 years, diabetes, stroke, coronary artery bypass graft, PAD, eGFR <60 mL/min/1.73^2, and smoking) that may help predict patients with the greatest likelihood of benefit from the addition of ezetimibe to statin therapy following ACS.[64] The writing committee also noted that there may be interindividual variability in response to ezetimibe, with some patients experiencing >20% reduction in LDL-C.[65]

A PCSK9 mAb may be preferred as the initial nonstatin agent in patients with clinical ASCVD at very high risk who require >25% additional lowering of LDL-C or based on clinician-patient decision-making. Potential considerations with the use of alirocumab or evolocumab compared with ezetimibe include greater LDL-C lowering, administration by subcutaneous injection, the every 14-day or monthly dosing schedule, potential storage requirements (eg, refrigeration), and costs. The price of PCSK9 mAbs has decreased substantially since FDA approval in 2015, and the annual cost of therapy is approaching the predicted cost-effectiveness threshold of approximately $4,500 per year.[66] The decreased costs, evidence for cardiovascular disease risk reduction, and tolerability of PCSK9 mAbs has improved the willingness-to-pay threshold of insurers, thus increasing access to these agents and making them feasible as an initial nonstatin agent in patients with clinical ASCVD who are at very high risk.[67,68]

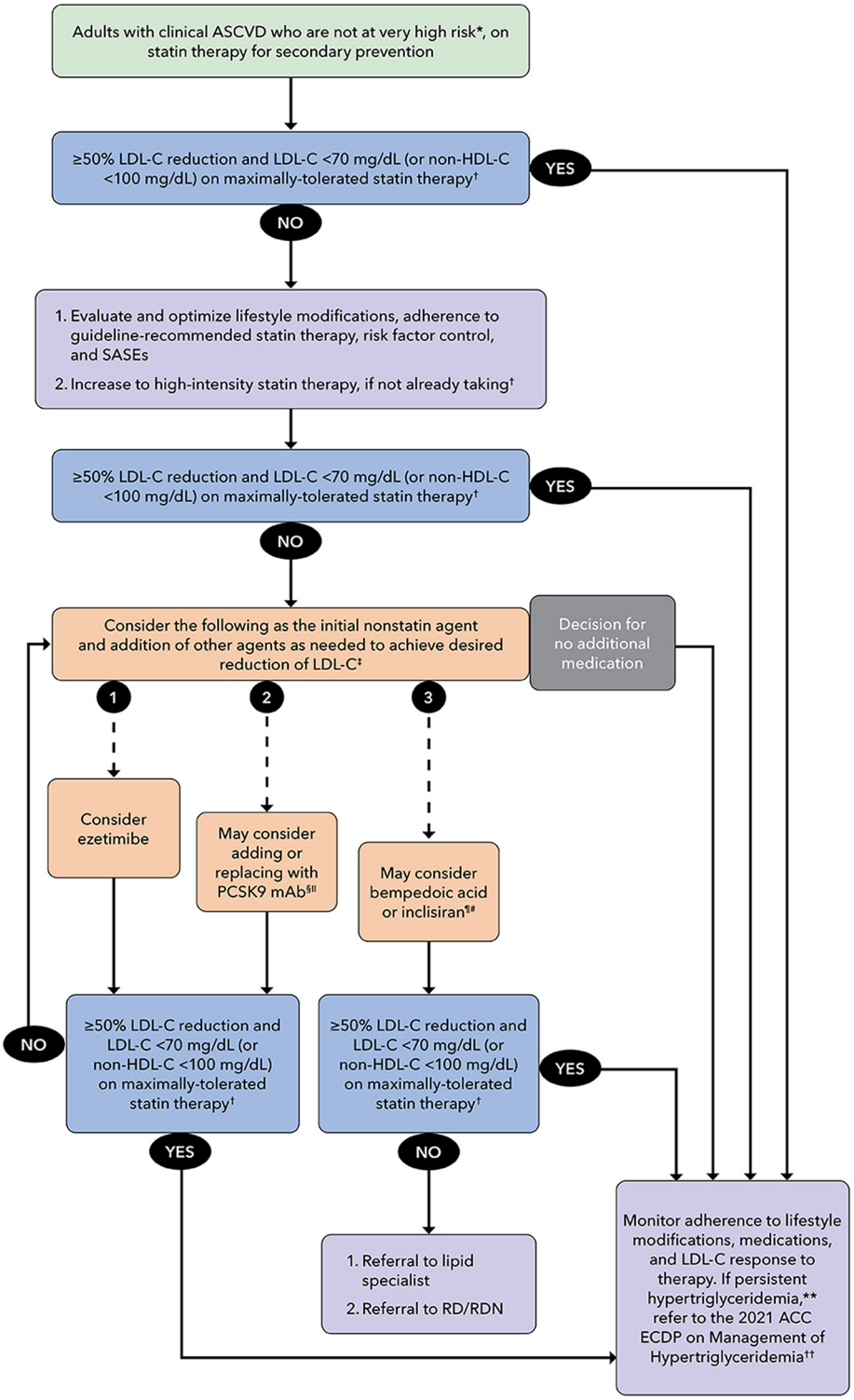
The writing committee also notes that in some patients with clinical ASCVD at very high risk who require greater

FIGURE 2A Continued

*See **Table 1** for criteria for defining patients at very high risk. †In very high-risk patients who require greater lowering of LDL-C at the time of an ASCVD event, initiation of combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe or maximally tolerated statin therapy with/without ezetimibe and PCSK9 mAbs may be considered.[9,57-59] ‡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. §If adults with clinical ASCVD at very high risk on a statin therapy for secondary prevention require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial nonstatin therapy. It is reasonable to engage in a clinician–patient discussion with consideration of net risk reduction benefits of a PCSK9 inhibitor, cost, administration by subcutaneous injection, an every 14-day or monthly dosing schedule, and storage requirements (refrigeration). Consider only if on maximally tolerated statin therapy with persistent <50% LDL-C reduction or LDL-C ≥55 mg/dL (or non-HDL-C ≥85 mg/dL). Strongly consider if the patient is unable to tolerate even low-intensity statin therapy or alternative statin therapy dosing regimens (every other day, twice weekly, or weekly) and persistent <50% LDL-C reduction (or LDL-C ≥55 mg/dL or non-HDL-C ≥85 mg/dL). ‖Clinicians should preferentially prescribe drugs that have been shown in randomized controlled trials to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions and to consider patient preferences. ¶No outcome studies exist for bempedoic acid or inclisiran. #PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be used in place of a PCSK9 mAb. **Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. ††Refer to the 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; ECDP = Expert Consensus Decision Pathway; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody; RD/RDN = registered dietitian/registered dietitian nutritionist; SASEs = statin-associated side effects.

FIGURE 2B Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention



Continued on the next page

LDL-C reduction than any additional therapy alone can expect to achieve, it may be reasonable to consider the simultaneous addition of 2 agents to reduce the risk of recurrent events more rapidly. Options may include either combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe or maximally tolerated statin therapy with or without ezetimibe and a PCSK9 mAb.[9,57-59]

If patients with clinical ASCVD at very high risk require additional LDL-C lowering (patient has achieved <50% reduction in LDL-C and LDL-C ≥55 mg/dL or non-HDL-C ≥85 mg/dL) after the addition of a single nonstatin agent (ezetimibe or PCSK9 mAb) to maximally tolerated statin therapy, the addition of a second evidence-based nonstatin agent (eg, ezetimibe plus PCSK9 mAb) should be considered.

If additional LDL-C lowering is warranted (patient has achieved <50% reduction in LDL-C or LDL-C ≥55 mg/dL or non-HDL-C ≥85 mg/dL) despite maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, the addition of bempedoic acid may be considered. Clinicians may also consider the use of inclisiran *in place of* a PCSK9 mAb. Although there are currently no outcome studies for bempedoic acid, this agent may be beneficial for further LDL-C reduction or if evidence-based agents are contraindicated or not tolerated. Considerations that may favor the addition of bempedoic acid include the need for further LDL-C reduction (with a mean expected reduction of approximately 17%), documented statin intolerance, and ease of use for patients who prefer to avoid injectable medications. Bempedoic acid should be used with caution in patients who have a history of gout or tendon rupture.[14]

At the current time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes.[5,9] The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently in progress and are anticipated to be completed in 2026 and 2027, respectively. However, in view of the twice-yearly dosing regimen, inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject may also be considered for therapy with inclisiran. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be used in place of a PCSK9 mAb. If a patient with clinical ASCVD at very high risk has a continued <50% reduction in LDL-C or LDL-C ≥55 mg/dL (or non-HDL-C ≥85 mg/dL) on maximally tolerated statin therapy with or without ezetimibe or other adjunctive nonstatin therapies, referral should be made to a lipid specialist and a RD/RDN.

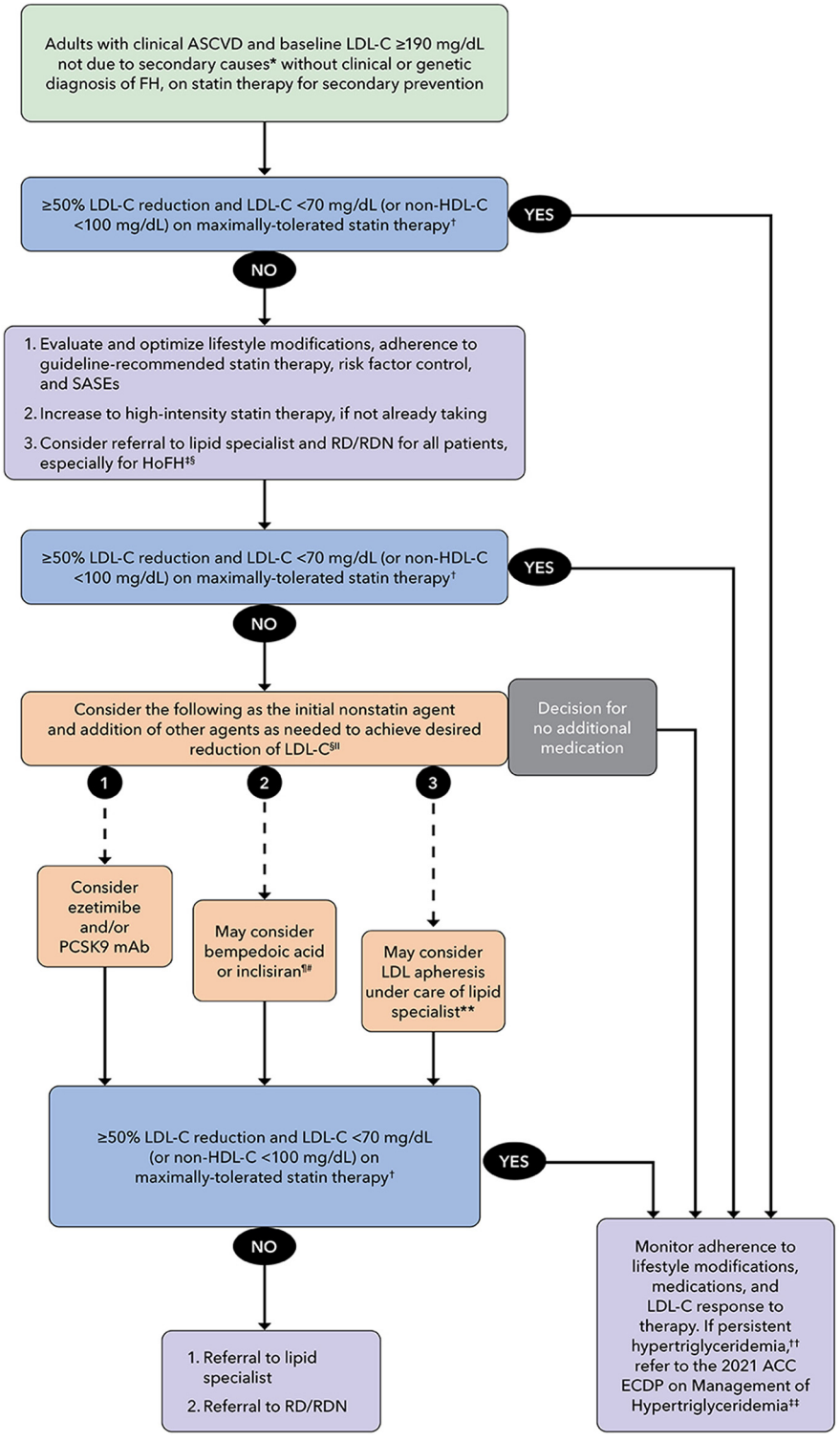
Percent LDL-C and absolute LDL-C and non-HDL-C reductions should be the primary treatment considerations for patients with clinical ASCVD at very high risk. However, patients with persistent hypertriglyceridemia

FIGURE 2B Continued

* See Table 1 for criteria for defining patients at very high risk. †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. ‡Clinicians should preferentially prescribe drugs that have been shown in randomized controlled trials to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions and consider patient preferences. §Consider only if on maximally tolerated statin therapy and either ezetimibe or bile acid sequestrants, with persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). Strongly consider if patient is unable to tolerate even low-intensity statin therapy or alternative statin therapy dosing regimens (every other day, twice weekly, or weekly) and attempts to lower LDL-C with ezetimibe or a bile acid sequestrant result in persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). It is reasonable to engage in a clinician-patient discussion with consideration of net risk reduction benefits of a PCSK9 inhibitor, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration). ‖Strongly consider a PCSK9 inhibitor if the patient is unable to tolerate even low-intensity statin therapy or alternative statin therapy dosing regimens (every other day, twice weekly, or weekly) and attempts to lower LDL-C with ezetimibe or a bile acid sequestrant result in persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). ¶No outcome studies exist for bempedoic acid or inclisiran. #A PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of their demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. **Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. ††Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; ECDP = Expert Consensus Decision Pathway; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody; RD/RDN = registered dietitian/registered dietitian nutritionist; SASE = statin-associated side effect

FIGURE 2C Adults With Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes Without Clinical or Genetic Diagnosis of Familial Hypercholesterolemia, on Statin Therapy for Secondary Prevention



Continued on the next page

despite adherence to lifestyle modifications and medications should be treated according to the 2021 ACC ECDP on management of hypertriglyceridemia. Hypertriglyceridemia is associated with increased cardiovascular risk and pancreatitis (especially in patients with triglyceride levels ≥500 mg/dL). Therefore, treatment of persistent hypertriglyceridemia beyond statin and nonstatin LDL-lowering therapies may be warranted in patients with clinical ASCVD at very high risk.[48]

5.1.2. Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention (Figure 2B)

Patients in this group have clinical ASCVD and do not meet the criteria for very high risk of a future ASCVD event (see Table 1). For this group of patients, the writing committee considered a desirable response to therapy as having achieved ≥50% reduction in LDL-C from baseline and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL). This definition was based on strong evidence showing that patients with clinical ASCVD have improved outcomes with higher-intensity statin therapy and significant reductions in LDC-C.[8,69,70] Percent reduction of LDL-C (≥50%) has been shown to add predictive value to statin therapy benefit better than achieved LDL-C levels (<70 mg/dL).[71] Meta-analysis in this patient population has shown a 22% proportional risk reduction for major vascular events for each 38-mg/dL (1-mmol/L) reduction in LDL-C, and this is true even if baseline LDL is <77 mg/dL (2 mmol/L).[60] Therefore, after achieving a ≥50% reduction in LDL-C from baseline, further reductions in LDL-C should be discussed with the patient if LDL-C remains ≥70 mg/dL. If patients with ASCVD who are not at very high risk have a ≥50% reduction in LDL-C from baseline and achieve LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL), it is reasonable to continue statin therapy and continue to monitor adherence to medications and lifestyle modifications and ongoing LDL-C response to therapy.

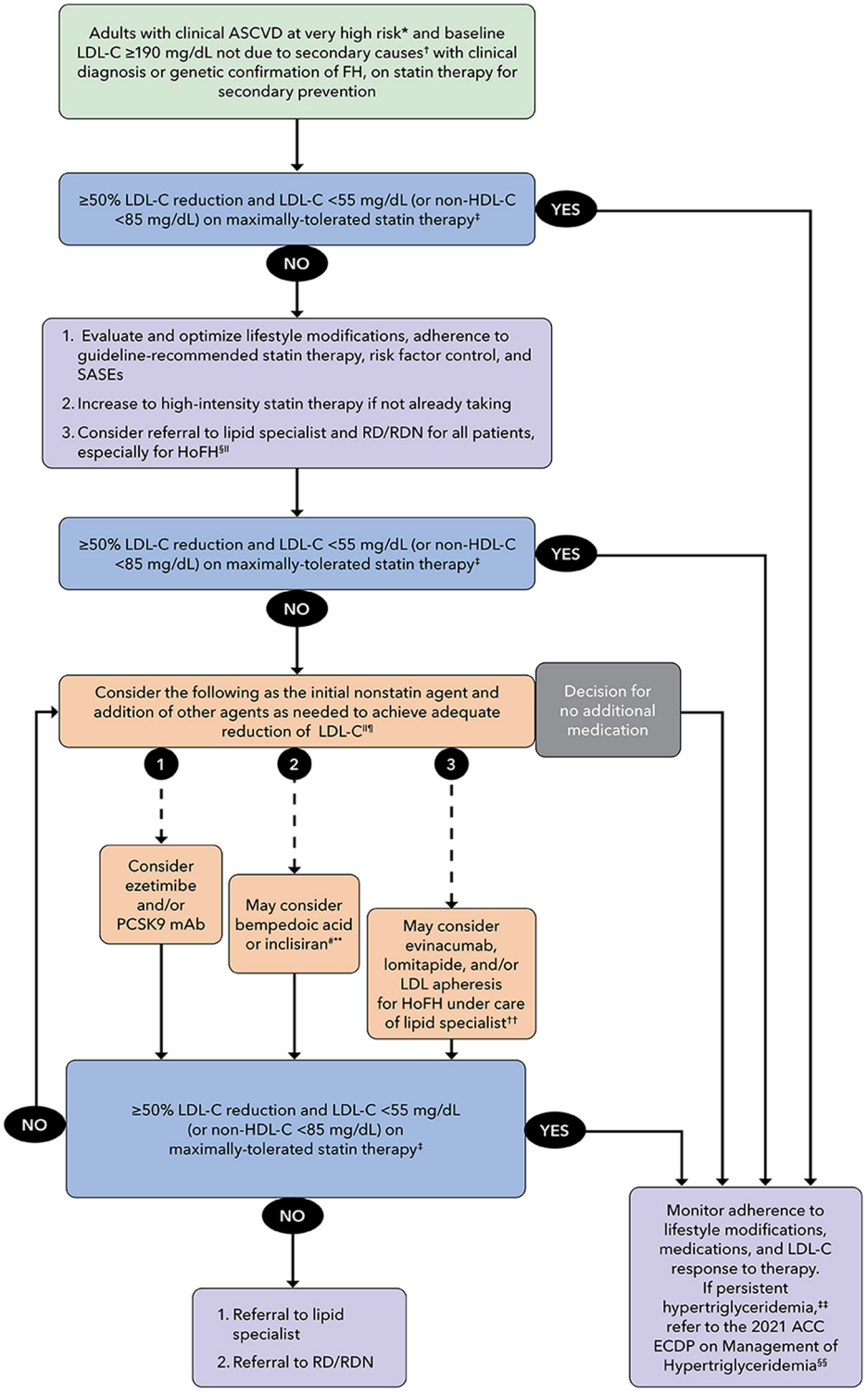
If a patient has a less-than-anticipated response (<50% reduction in LDL-C or LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL), routine clinical assessment and interventions are warranted (see **Section 3.3**). If the patient still has inadequate lowering of LDL-C, the patient and clinician should enter a discussion focused on shared decision-making regarding the addition of a nonstatin medication to the current regimen (see 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 modifications and ongoing LDL-C response to therapy.

Although there is a gap in RCT evidence demonstrating outcomes benefits of using ezetimibe plus statin therapy in clinical ASCVD patients who are not at very high risk, the writing committee supports consideration of adding ezetimibe 10 mg daily as the initial nonstatin agent, given the benefits on ASCVD outcomes and demonstrated safety of ezetimibe in patients with ACS treated with ezetimibe plus simvastatin versus simvastatin monotherapy (see Table 3).[28] Considerations that may favor the addition of

FIGURE 2C Continued

*For example, hypothyroidism, nephrosis, extreme dietary patterns (eg, anorexia nervosa). †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. ‡May consider lomitapide or LDL apheresis in appropriate patients. §If patients with clinical ASCVD and LDL-C ≥190 mg/dL require >25% additional lowering of LDL-C, a PCSK9 mAb may be preferred as the initial nonstatin agent. It is reasonable to engage in a clinician–patient discussion with consideration of net risk reduction benefits of a PCSK9 inhibitor, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (eg, refrigeration). Consider only if on maximally tolerated statin therapy with persistent <50% LDL-C reduction and LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). Strongly consider PCSK9 mAb if the patient is unable to tolerate even low-intensity statin therapy or alternative statin therapy dosing regimens (every other day, twice weekly, or weekly) and attempts to lower LDL-C with ezetimibe or a bile acid sequestrant result in persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). ‖Clinicians should preferentially prescribe drugs that have been shown in randomized controlled trials to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions and consider patient preferences. ¶No outcome studies exist for bempedoic acid or inclisiran. #A PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of their demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. **Limited data are available for apheresis. Patients with clinical ASCVD and persistent elevation of LDL-C >200 mg/dL without a clinical or genetic diagnosis of familial hypercholesterolemia, may be candidates for LDL apheresis under the care of a lipid specialist. ††Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. ‡‡Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol. 2021;78(9):960-993.*
ASCVD = atherosclerotic cardiovascular disease; ECDP = Expert Consensus Decision Pathway; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin 9 monoclonal antibody; RD/RDN = registered dietitian/registered dietitian nutritionist; SASE = statin-associated side effect

FIGURE 2D Adults With Clinical ASCVD at Very High Risk and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes and With Clinical Diagnosis or Genetic Confirmation of Familial Hypercholesterolemia, on Statin for Secondary Prevention



Continued on the next page

ezetimibe include patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations with availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, and patient preferences. A recent post hoc analysis of IMPROVE-IT identified 9 clinical variables (congestive heart failure, hypertension, age >75 years, diabetes, stroke, coronary artery bypass graft, PAD, eGFR <60 ml/min/1.73 m^2, and smoking) that may help predict patients with the greatest likelihood of benefit from the addition of ezetimibe to statin therapy following ACS.[64] The writing committee also noted that there may be interindividual variability in the response to ezetimibe, with some patients experiencing >25% reduction in LDL-C.[65] If the goals of therapy defined in the clinician-patient discussion have been achieved with the addition of ezetimibe, it is reasonable to continue the statin-ezetimibe combination therapy and continue to monitor adherence to medications and lifestyle modifications and ongoing LDL-C response to therapy.

If patients who are on maximally tolerated statin-ezetimibe or nonstatin combination therapy in the setting of documented statin intolerance achieve a less-than-anticipated response with <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL), it is reasonable to engage in a clinician-patient discussion with consideration of the net benefit of adding a PCSK9 mAb (in addition to or in place of ezetimibe) as a second step to achieve further LDL-C reduction. However, patients who have already been treated with high-dose statins or combination lipid-lowering therapy may have slightly less capacity to further up-regulate LDL-receptor activity with PCSK9 inhibition or may require higher doses of the PCSK9 mAb.[72] If a PCSK9 mAb is prescribed, clinicians should continue maximally tolerated statin therapy and monitor for adherence to medications and lifestyle modifications, side effects, and ongoing LDL-C response to therapy.

The writing committee also notes that in some patients with clinical ASCVD, not at very high risk, who require greater LDL-C reduction than any additional agent alone can be expected to achieve, it may be reasonable to consider the simultaneous addition of 2 agents to more rapidly reduce the risk of recurrent events. Options may include either combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe or maximally tolerated statin therapy with or without ezetimibe and PCSK9 mAb.

If additional LDL-C lowering is desired after the addition of ezetimibe and/or a PCSK9 mAb (<50% reduction in LDL-C or LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL), it is reasonable to engage in a clinician-patient discussion with consideration of the net benefit of bempedoic acid. This medication may be especially useful in patients with statin-associated myalgias. At the time of writing this EDCP, the CLEAR Outcomes trial with bempedoic acid was not yet completed, so preference should be given to ezetimibe and PCSK9 mAbs as first- and second-line nonstatin agents. Considerations that may favor the addition of bempedoic acid include further desired LDL-C

FIGURE 2D Continued

*See **Table 1** for criteria for defining patients at very high risk. †For example, hypothyroidism, nephrosis, extreme dietary patterns (eg, anorexia nervosa). ‡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. §May consider lomitapide or LDL apheresis in appropriate patients. ||If patients with clinical ASCVD and LDL-C ≥190 mg/dL require >25% additional lowering of LDL-C, a PCSK9 mAb may be preferred as the initial nonstatin agent. It is reasonable to engage in a clinician-patient discussion with consideration of net risk reduction benefits of a PCSK9 inhibitor, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (eg, refrigeration). Consider only if on maximally tolerated statin therapy with persistent <50% LDL-C reduction and LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). Strongly consider PCSK9 mAb if patient is unable to tolerate even low-intensity statin therapy or alternative statin therapy dosing regimens (every other day, twice weekly, or weekly) and attempts to lower LDL-C with ezetimibe or bile acid sequestrant result in persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). ¶Clinicians should preferentially prescribe drugs that have been shown in randomized controlled trials to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions and consider patient preferences. #No outcome studies exist for bempedoic acid or inclisiran. **A PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of their demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. ††No outcomes studies exist for evinacumab and lomitapide, and limited data are available for apheresis. ‡‡Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. §§Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; ECDP = Expert Consensus Decision Pathway; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin 9 monoclonal antibody; RD/RDN = registered dietitian/registered dietitian nutritionist; SASE = statin-associated side effect

reduction (with a mean expected reduction of approximately 17%), documented statin intolerance, intolerance of other nonstatin medications, and ease of use for patients who prefer to avoid injectable medications. Bempedoic acid should be used with caution for patients who have a history of gout or tendon rupture.

At the current time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes.[5,9] The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently in progress and are anticipated to be completed in 2026 and 2027, respectively. However, in view of the twice-yearly dosing regimen, inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject may also be considered for therapy with inclisiran. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. If a patient has a continued <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) on maximally tolerated statin therapy with or without ezetimibe and/or bempedoic acid, and prescription of inclisiran is being considered, referral should be made to a lipid specialist. When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy.

Percent LDL-C and absolute LDL-C and non-HDL-C reductions should be the primary treatment outcomes for patients with clinical ASCVD who are not at very high risk. However, patients with persistent hypertriglyceridemia despite adherence to lifestyle modifications and medications should be treated according to the 2021 ACC ECDP on management of hypertriglyceridemia. Hypertriglyceridemia is associated with increased cardiovascular risk and pancreatitis (especially in patients with triglyceride levels ≥500 mg/dL). Therefore, treatment of persistent hypertriglyceridemia beyond statin and nonstatin LDL-C-lowering therapies may be warranted in patients with clinical ASCVD who are not at very high risk.

5.1.3. Adults With Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy for Secondary Prevention (Figures 2C and 2D)

The approach to management of patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL is similar to the algorithms for patients with clinical ASCVD. For patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL likely due to polygenic hypercholesterolemia and without a clinical diagnosis or genetic confirmation of FH (see **Table 5**), clinicians should follow the algorithm outlined in **Figure 2C**. If patients have ≥50% reduction in LDL-C from baseline and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL), it is reasonable to continue statin therapy and monitor adherence to medication and lifestyle modifications 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 or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL), routine clinical assessment and interventions are warranted (see **Section 3.3**). The writing committee also emphasizes that all such patients should be considered for referral to a lipid specialist and RD/RDN, especially if they have documented HeFH or HoFH. If the patient has now achieved the anticipated response to therapy (≥50% reduction in LDL-C and LDL-C <70 mg/dL or non-HDL-C <100 mg/dL), it is reasonable to continue current therapy and to continue monitoring adherence to medications and lifestyle modifications and the ongoing LDL-C response to therapy.

If after these interventions, the patient still has <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL), the addition of a nonstatin medication to the current regimen should be considered (see **Table 3**). If a decision is made to proceed with the addition of nonstatin therapy to maximally tolerated statin therapy, based on the results of IMPROVE-IT, FOURIER, and ODYSSEY Outcomes demonstrating improved cardiovascular outcomes and excellent safety profiles, the addition of ***either*** ezetimibe ***or*** a PCSK9 mAb as the initial nonstatin agent should be considered (see **Table 3**).[9]

Although there is a gap in RCT evidence demonstrating outcomes benefits of using ezetimibe plus statin therapy in clinical ASCVD patients with baseline LDL-C ≥190 mg/dL, the writing committee supports that ezetimibe 10 mg daily may be considered as the initial nonstatin agent for these patients when additional LDL-C lowering is desired. Considerations that may favor the initial choice of ezetimibe include patients who require <25% additional lowering of LDL-C, cost considerations with recent availability of generic ezetimibe, ease of use as oral agent with low pill burden, and patient preferences. The writing committee also noted that there is interindividual variability in the response to ezetimibe, with some patients experiencing >25% reduction in LDL-C.[64]

If patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL require >25% additional lowering of LDL-C or have additional very high-risk factors, as defined previously (Section 5.1.1 and Figure 2A), a PCSK9 mAb

TABLE 5 FH Diagnostic Categories

ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C <160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes Presence of both abnormal LDL-C–raising gene defects (LDL receptor, apoB, or PCSK9) and LDL-C–lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed FH, positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) or autosomal-recessive FH If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 years of age, homozygous FH highly likely	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-raising gene defects (LDL receptor, apoB, or PCSK9); includes the rare autosomal-recessive type Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

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apoB = apolipoprotein B; CAD = coronary artery disease; FH = familial hypercholesterolemia; ICD-10 = International Classification of Disease-10th Revision; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

may be preferred as the initial nonstatin agent. It is reasonable to engage in a clinician-patient discussion with consideration of net risk reduction benefits of a PCSK9 mAb, as well as cost, administration by subcutaneous injection, the every 14-day or monthly dosing schedule, and, potentially, storage requirements (eg, refrigeration).

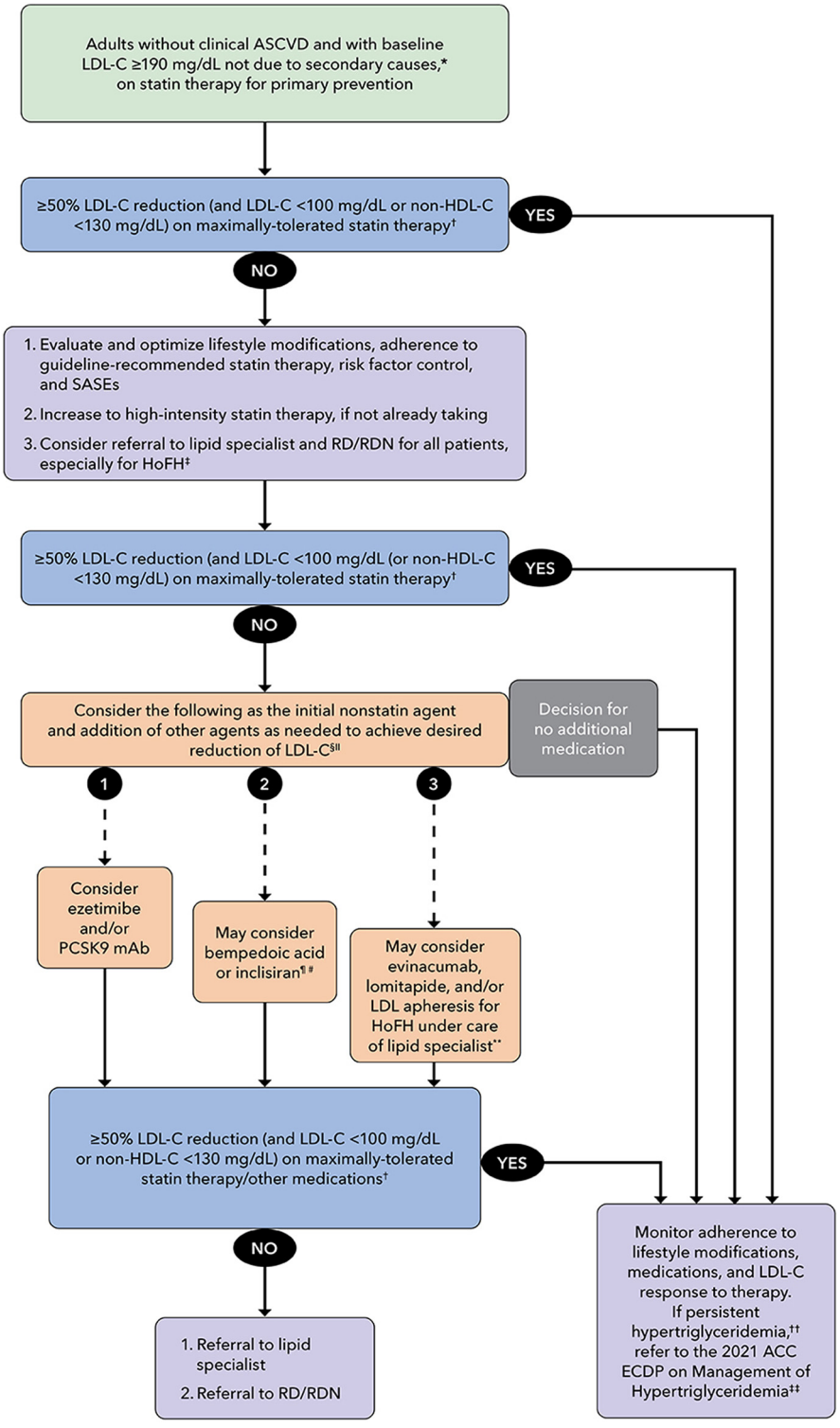
The writing committee also notes that in some patients with clinical ASCVD and LDL-C ≥190 mg/dL who require greater LDL-C reduction than any additional agent alone can expect to achieve, it may be reasonable to consider the simultaneous addition of 2 agents to more rapidly reduce the risk of recurrent events. Options may include either combination therapy with high-intensity or maximally tolerated statin and ezetimibe or maximally tolerated statin with or without ezetimibe and a PCSK9 mAb.

If additional LDL-C lowering is desired (<50% reduction in LDL-C or LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL) after the addition of ezetimibe and/or a PCSK9 mAb, it is reasonable to engage in a clinician-patient discussion with consideration of the net benefit of bempedoic acid. This medication may be especially useful in patients with statin-associated myalgias. At the time of writing this ECDP, the CLEAR Outcomes trial with bempedoic acid was not completed, so preference should be given to ezetimibe and PCSK9 mAbs as first- and second-line nonstatin agents. Considerations that may favor the addition of bempedoic acid include further desired LDL-C reduction (with a mean expected reduction of approximately 17%), documented statin intolerance, intolerance of other nonstatin medications, and ease of use for patients who prefer to avoid injectable medications. Bempedoic acid should be used in caution with patients who have a history of gout or tendon rupture.

At the current time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes.[5,9] The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently in progress and are anticipated to be completed in 2026 and 2027, respectively.[55] However, in view of the twice-yearly dosing regimen, inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject may also be considered for therapy with inclisiran. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. If a patient has a continued <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) on maximally tolerated statin with or without ezetimibe and/or bempedoic acid, and the patient is considered for prescription of inclisiran, referral should be made to a lipid specialist. When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy.

If combination statin and nonstatin therapy with ezetimibe, PCSK9 mAb, bempedoic acid, or inclisiran has been attempted and the patient still has <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL), the writing committee recommends referral to a lipid specialist and RD/RDN. Patients with

FIGURE 3 **Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes on Statin Therapy for Primary Prevention**



Continued on the next page

clinical ASCVD and persistent elevation of LDL-C ≥200 mg/dL without a clinical or genetic diagnosis of FH may be candidates for LDL apheresis under the care of a lipid specialist.

Patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL and a clinical diagnosis or genetic confirmation of FH (see Table 5) may be at very high risk, and intensification of therapy and the addition of nonstatin therapies should be considered if there is <50% reduction in LDL-C or LDL-C ≥55 mg/dL on maximally tolerated statin therapy, as outlined in Figure 2D. Specialized therapies, such as evinacumab or lomitapide, may be needed to control LDL-C in patients with HoFH who have an inadequate response to statins with or without ezetimibe and PCSK9 inhibitors (see Table 3).[20] LDL apheresis may be indicated in patients with clinical ASCVD and HeFH or HoFH who have an inadequate response to statins with or without ezetimibe and PCSK9 inhibitors. In the opinion of the writing committee, these therapies are best administered under the care of a lipid specialist.

Percent LDL-C and absolute LDL-C and non-HDL-C reductions should be the primary treatment targets for patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL. However, patients with persistent hypertriglyceridemia despite adherence to lifestyle modifications and medications should be treated according to the 2021 ACC ECDP on Management of Hypertriglyceridemia. Hypertriglyceridemia is associated with increased cardiovascular risk and pancreatitis (especially in patients with triglyceride levels ≥500 mg/dL). Therefore, treatment of persistent hypertriglyceridemia beyond statin therapy and nonstatin LDL-C-lowering therapies may be warranted in patients with clinical ASCVD and LDL-C ≥190 mg/dL.

5.2. Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin Therapy 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; therefore, 10-year ASCVD risk assessment is not necessary in this population. Rather, the suggested algorithm in Figure 3 should be followed. ASCVD risk is accelerated in the presence of other ASCVD risk factors.[73,74] Most patients with LDL ≥190 mg/dL have polygenic hypercholesterolemia. However, these individuals are more likely to have HeFH or HoFH, genetic disorders associated with severe hypercholesterolemia, and a family history of severe hypercholesterolemia and premature ASCVD (see Table 5).

Pooled data from 6 large U.S. epidemiological studies of individuals at index ages 20 to 79 years demonstrated an increased risk of ASCVD events for those with LDL-C ≥190 mg/dL compared with those with LDL-C <130 mg/dL (hazard ratios [HRs]: 5.0 for coronary heart disease and 4.1 for ASCVD).[75] A U.S. and European gene-sequencing study of 26,025 individuals with LDL-C ≥190 mg/dL showed an almost 4-fold increase in the odds for coronary artery disease events in those with defined deleterious mutations of LDLR, apolipoprotein B, or PCSK9 compared with those with LDL-C ≥190 mg/dL in the absence of those mutations.[76] Early treatment is highly beneficial. Long-term drug therapy in patients with

FIGURE 3 Continued

*For example, hypothyroidism, nephrosis, extreme dietary patterns (eg, anorexia nervosa). †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. ‡May consider evinacumab, lomitapide, or LDL apheresis in appropriate patients. §If patients without clinical ASCVD and with LDL-C ≥190 mg/dL require >25% additional lowering of LDL-C, a PCSK9 mAb may be preferred as the initial nonstatin agent. It is reasonable to engage in a clinician-patient discussion with consideration of net risk reduction benefits of a PCSK9 inhibitor, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration). Consider only if on maximally tolerated statin therapy with persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). Strongly consider if fully statin-intolerant and attempts to lower LDL-C with ezetimibe or BAS result in persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL). ‖Clinicians should 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. ¶No outcome studies exist for bempedoic acid or inclisiran. #PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of their demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. **No outcome studies exist for evinacumab and lomitapide, and limited data are available for LDL apheresis ††Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. ‡‡Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.
ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; ECDP = Expert Consensus Decision Pathway; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAB = proprotein convertase subtilisin/kexin 9 monoclonal antibody; RCT = randomized controlled trial; RD/RDN = registered dietitian/registered dietitian nutritionist; SASE = statin-associated side effect.

severe hypercholesterolemia can substantially reduce the risk of ASCVD and requires lifelong treatment with 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.[73,74] 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 biological relatives, should be performed in all people with HeFH or HoFH to identify others with the disease who would benefit from treatment.[77]

Depending on the gene mutation, expression, and pattern of inheritance (ie, homozygous or heterozygous), patients with LDL-C ≥190 mg/dL may have variable responses to pharmacologic therapies. Therefore, the response to lifestyle modifications 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 an RDN; however, even with strict adherence, diet has limited impact on the severity of hypercholesterolemia in this high-risk patient population.[78]

5.2.1. Adults With 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 for ASCVD (including a family history of premature ASCVD events, tobacco use, diabetes, hypertension, chronic kidney disease [CKD], evidence of subclinical atherosclerosis, elevated lipoprotein [a] [Lp(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.

Individualization of therapy may be appropriate for some patients with baseline LDL-C ≥190 mg/dL on statin therapy for primary prevention based on clinical judgment. The writing committee 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 may be a reasonable therapeutic outcome that does not require further intensification of therapy. However, for patients with baseline LDL-C ≥190 mg/dL and multiple high-risk features or evidence of significant subclinical atherosclerosis (see Section 5.5), failure to achieve ≥50% reduction in LDL-C and LDL-C <70 mg/dl may prompt consideration of intensification of therapy following patient-clinician discussion.

Patients with baseline LDL-C ≥190 mg/dL and additional high-risk features should be treated first with maximally tolerated statin therapy. If patients have a ≥50% reduction in LDL-C from baseline and LDL-C <100 mg/dL (or non-HDL-C <130 mg/dL), it is reasonable to continue statin therapy and monitor adherence to medication and lifestyle modifications 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 or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), routine clinical assessment and interventions are warranted (see **Section 3.3**). The writing committee also emphasizes that all such patients should be considered for referral to a lipid specialist and RD/RDN, especially if the patient has documented HoFH.

If after these interventions, the patient still has <50% reduction in LDL-C or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), the patient and clinician should enter a discussion focused on shared decision-making regarding the addition of a nonstatin medication to the current regimen (see **Table 3**). Consideration may be given to ***either*** ezetimibe ***or*** a PCSK9 mAb in combination with maximally tolerated statin therapy in these very high-risk patients, as both have outcomes data from clinical trials when added to statin therapy, although there is a gap in the evidence demonstrating outcomes benefit when combined with high-intensity statin therapy in primary prevention. Considerations that may favor ezetimibe as the initial nonstatin agent include <25% additional lowering of LDL-C desired, cost considerations with availability of a generic preparation, ease of use as oral agent with low pill burden, and patient preferences. The writing committee also noted that there is interindividual variability in response to ezetimibe, with some patients experiencing >25% reduction in LDL-C. Considerations that may favor a PCSK9 mAb as the initial nonstatin agent include >25% additional LDL-C lowering desired, the presence of additional ASCVD risk factors or conditions (see previous discussion), and patient preferences.

If high-risk patients with baseline LDL-C ≥190 mg/dL require additional LDL-C lowering (<50% reduction in LDL-C or LDL-C ≥100 mg/dL [or non-HDL-C ≥130 mg/dL]) after the addition of a single nonstatin agent (ie, ezetimibe) to maximally tolerated statin therapy, it is reasonable to consider the addition of a second nonstatin agent (ie, ezetimibe plus a PCSK9 mAb).

The writing committee also notes that in some patients with LDL-C ≥190 mg/dL and additional risk factors who require greater LDL-C reduction than any additional agent

alone can be expected to achieve, it may be reasonable to consider the simultaneous addition of 2 agents simultaneously to more rapidly reduce the risk of events. Options may include either combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe or maximally tolerated statin therapy with or without ezetimibe and a PCSK9 mAb.

If additional LDL-C lowering is desired (<50% reduction in LDL-C or LDL-C ≥100 mg/dL [or non-HDL-C ≥130 mg/dL]) after the addition of ezetimibe and/or a PCSK9 mAb, it is reasonable to engage in a clinician-patient discussion with consideration of the net benefit of bempedoic acid. Bempedoic acid has been approved for the treatment of FH by the FDA based upon its demonstrated efficacy in lowering LDL-C but does not yet have outcomes data. This medication may be especially useful in patients with statin-associated myalgias. At the time of writing this ECDP, the CLEAR Outcomes trial with bempedoic acid was not yet completed, so preference should be given to ezetimibe and PCSK9 mAbs as first- and second-line nonstatin agents. Considerations that may favor the addition of bempedoic acid include further desired LDL-C reduction (with a mean expected reduction of approximately 17%), documented statin intolerance, intolerance of other nonstatin medications, and ease of use for patients who prefer to avoid injectable medications. Bempedoic acid should be used with caution in patients who have a history of gout or tendon rupture.

At the current time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes.[5,9] The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently in progress and are anticipated to be completed in 2026 and 2027, respectively.[55] However, in view of the twice-yearly dosing regimen, inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject may also be considered for therapy with inclisiran. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. Inclisiran has been approved for the treatment of FH by the FDA based upon its demonstrated efficacy in lowering LDL-C but does not yet have outcomes data. It may also be considered as an option in the process of shared decision-making regarding nonstatin therapies. If a patient has a continued <50% reduction in LDL-C and LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL) on maximally tolerated statin therapy with or without ezetimibe and/or bempedoic acid, and the patient is considered for prescription of inclisiran, referral should be made to a lipid specialist. When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle, medication, and LDL-C response to therapy.

If combination statin and nonstatin therapy with ezetimibe, PCSK9 mAb, bempedoic acid, or inclisiran has been attempted and the patient still has <50% reduction in LDL-C or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), the writing committee recommends referral to a lipid specialist and RD/RDN.

Specialized therapies, such as evinacumab, lomitapide, or LDL apheresis, may be needed to control LDL-C in patients with ASCVD and baseline LDL-C ≥190 mg/dL and/or phenotypic HoFH who have an inadequate response to statins with or without ezetimibe and PCSK9 inhibitors (see **Table 3**).[20] In the opinion of the writing committee, these therapies are best administered under the care of a lipid specialist.

When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy.

Percent LDL-C and absolute LDL-C and non-HDL-C reductions should be the primary treatment for patients with baseline LDL-C ≥190 mg/dL. However, patients with persistent hypertriglyceridemia despite adherence to lifestyle modifications and medications should be treated according to the 2021 ACC ECDP on management of hypertriglyceridemia. Hypertriglyceridemia is associated with increased cardiovascular risk and pancreatitis (especially in patients with triglyceride levels ≥500 mg/dL). Therefore, treatment of persistent hypertriglyceridemia beyond statin and nonstatin LDL-lowering therapies may be warranted in patients with severe hypercholesterolemia.

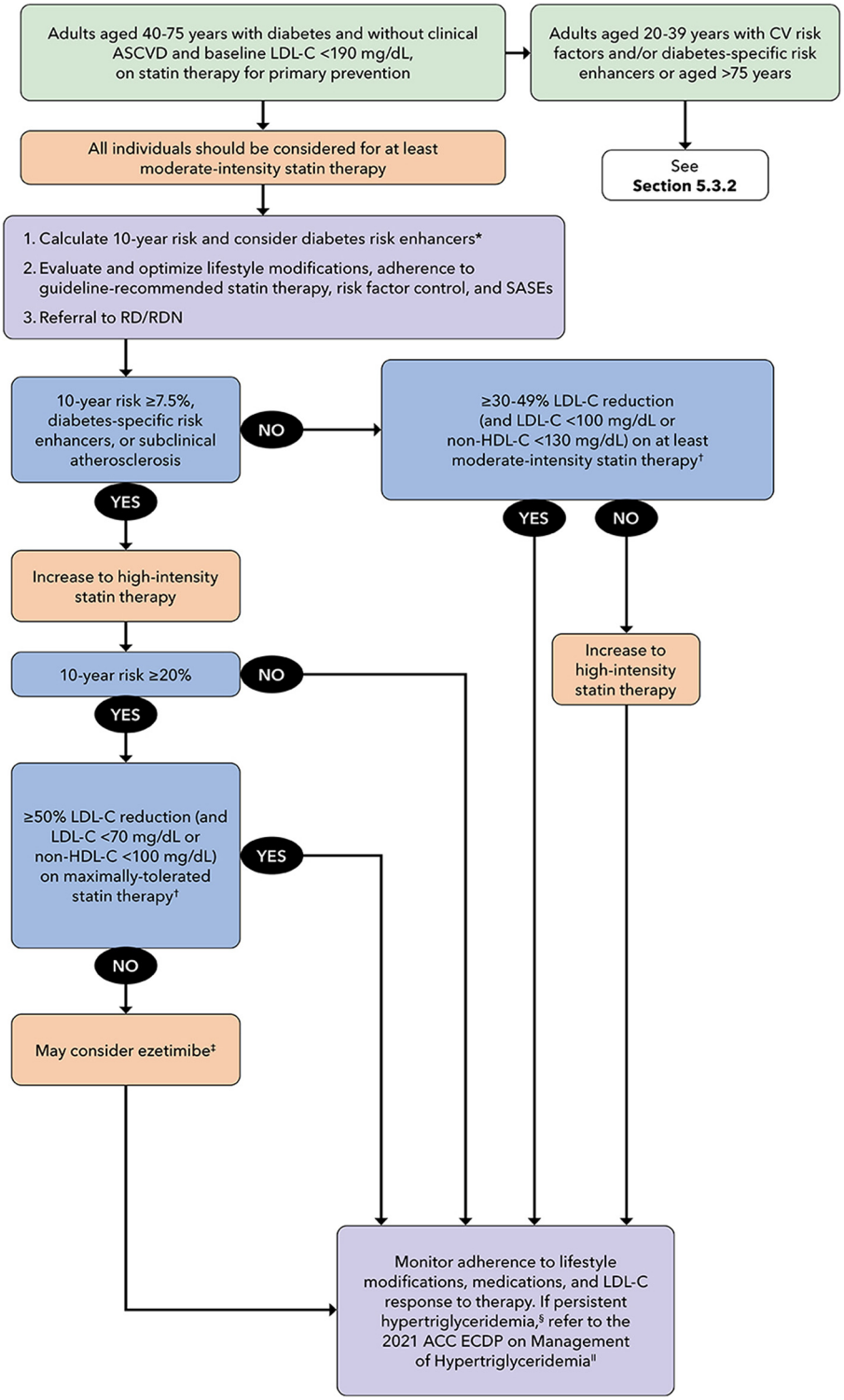
5.2.2. LDL-C ≥190 mg/dL and Pregnancy

Special consideration for lipid management is needed in all premenopausal women with baseline pregestational LDL-C ≥190 mg/dL during pregnancy with or without documented FH (see Section 5.7). Although statins are recommended for use in women who are using effective contraception and are not nursing, or who are postmenopausal, as discussed in Section 5.7.3, the FDA has suggested changes in package labeling to remove the wording that completely contraindicates their use in high-risk individuals who are pregnant.

5.2.3. Familial Hypercholesterolemia in Children and Adolescents

Management of FH in children and adolescents is beyond the scope of this paper and has been reviewed in detail

FIGURE 4 **Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention**



Continued on the next page

elsewhere. Evolocumab has recently been approved by the FDA for children aged 10 years and older. The reader is referred to Wiegman et al[77] and Goldberg et al[74] for excellent guidance on this important topic.

5.3. Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention (Figure 4)

Because primary prevention trials in large cohorts of individuals with diabetes demonstrate that moderate-intensity statin therapy provides significant cardiovascular outcomes benefit, the 2018 AHA/ACC/multisociety cholesterol guideline recommends that all adults aged 40-75 years with diabetes benefit from at least a moderate-intensity statin. Higher-risk subgroups of patients with diabetes (older patients, patients with additional ASCVD risk factors, albuminuria, retinopathy, long duration of diabetes, reduced eGFR <60 ml/min/1.73 m^2, neuropathy, ankle brachial index <0.9) are potential candidates for high-intensity statin therapy. Thus, all patients aged 40-75 years with diabetes should undergo assessment of 10-year ASCVD risk and comprehensive risk factor evaluation. Patients with diabetes have increased morbidity and mortality associated with a first cardiovascular event, making intensive prevention efforts even more critical.

5.3.1. Adults Aged 40-75 Years With Diabetes and Without Clinical ASCVD and Baseline LDL-C <190 mg/dL, on Statin Therapy for Primary Prevention (Figure 4)

For the small proportion of patients aged 40-75 years with diabetes who have 10-year predicted ASCVD risk <7.5% and no additional high-risk features, a high level of evidence supports the use of moderate-intensity statin therapy (anticipated LDL-C reduction 30%-49%).[79] In addition to adherence to appropriate lifestyle interventions, the use of soluble dietary fiber and phytosterols may also be considered.

If patients with diabetes and 10-year ASCVD risk <7.5% achieve inadequate lowering of LDL-C or non-HDL-C despite adherence to lifestyle recommendations and moderate-intensity statin therapy and have <30% to 49% reduction in LDL-C or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), consideration of intensification of therapy is indicated. Due to the frequency of elevated non-HDL-C despite lower levels of LDL-C in patients with diabetes, non-HDL-C thresholds are important to consider in this high-risk patient population.

As a first step, routine clinical assessment and interventions are warranted (see **Section 3.3**). If the patient has now achieved the anticipated response to therapy, with a 30% to 49% reduction in LDL-C and LDL-C <100 mg/dL (or non-HDL-C <130 mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle modifications and ongoing LDL-C response to therapy.

If, after these interventions, the patient still has <30% to 49% reduction in LDL-C or 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 modifications and ongoing LDL-C response to therapy.

If escalation to high-intensity statin therapy results in inadequate percent LDL-C reduction or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), the clinician and patient should enter a discussion focused on shared decision-making regarding the addition of a nonstatin medication to the current regimen (see Table 5). 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 modifications and ongoing LDL-C response to therapy.

If escalation to high-intensity statin therapy results in inadequate percent LDL-C reduction or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), ezetimibe 10 mg daily may be considered as the initial nonstatin agent for most patients when additional LDL-C lowering is desired. Although there is a gap in RCT evidence demonstrating outcomes benefits of using ezetimibe plus statin in primary prevention with diabetes, the writing committee supports ezetimibe as the preferred initial

FIGURE 4 Continued

*Diabetes-specific high-risk features include long duration (≥10 years for type 2 diabetes or ≥20 years for type 1 diabetes, albuminuria ≥30 mcg of albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, ankle-brachial index <0.9. †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. ‡May consider a bile acid sequestrant as optional alternative agent if ezetimibe-intolerant and triglycerides <300 mg/dL. §Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. ‖Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; ECDP = Expert Consensus Decision Pathway; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RD/RDN = registered dietician/registered dietician nutritionist; SASE = statin-associated side effect

nonstatin therapy due to its demonstrated safety, tolerability, convenience, and single-tablet daily dose. BAS may have a modest hypoglycemic effect that may be of benefit in some patients with diabetes 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.

For the greater proportion of patients aged 40-75 years with diabetes who have elevated 10-year ASCVD risk and high-risk features or diabetes-specific risk enhancers, a high level of evidence supports the use of high-intensity statin therapy (anticipated LDL-C reduction ≥50%). If a patient achieves inadequate lowering of LDL-C or non-HDL-C despite adherence to lifestyle recommendations and high-intensity statin therapy, as a first step, routine clinical assessment and interventions are warranted (see **Section 3.3**). If the patient has now achieved the anticipated response to therapy, with ≥50% reduction in LDL-C and LDL-C <100 mg/dL (or non-HDL-C <130 mg/dL), it is reasonable to continue current therapy and continue to monitor adherence to medications and lifestyle modifications and ongoing LDL-C response to therapy.

If high-intensity statin therapy results in inadequate lowering of LDL-C, with <50% reduction in LDL-C or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), the clinician and patient should enter a discussion focused on shared decision-making regarding the addition of a nonstatin medication to the current regimen (see **Table 5**). 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 modifications and ongoing LDL-C response to therapy.

In the absence of ASCVD or baseline LDL-C ≥190 mg/dL not due to secondary causes, the PCSK9 mAbs, bempedoic acid, or inclisiran do not currently have an established, evidence-based role for primary prevention of ASCVD in patients with diabetes. Considerations may be given to use of these medications in patients with diabetes if they are demonstrated to have significant subclinical atherosclerosis (see Section 5.5 and **Figure 6**). When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy.

Percent LDL-C and absolute LDL-C and non-HDL-C reductions should be the primary treatment for patients with diabetes. However, patients with persistent hypertriglyceridemia, despite adherence to lifestyle modifications and medications, should be treated according to the 2021 ACC ECDP on management of hypertriglyceridemia. Hypertriglyceridemia is associated with increased cardiovascular risk and pancreatitis (especially in patients with triglyceride levels ≥500 mg/dL). Therefore, treatment of persistent hypertriglyceridemia beyond statin and nonstatin LDL-lowering therapies may be warranted in patients with diabetes.

5.3.2. Adults Aged 20-39 Years With CV Risk Factors and/or Diabetes-Specific Risk Enhancers or Adults Aged >75 Years (Figure 4)

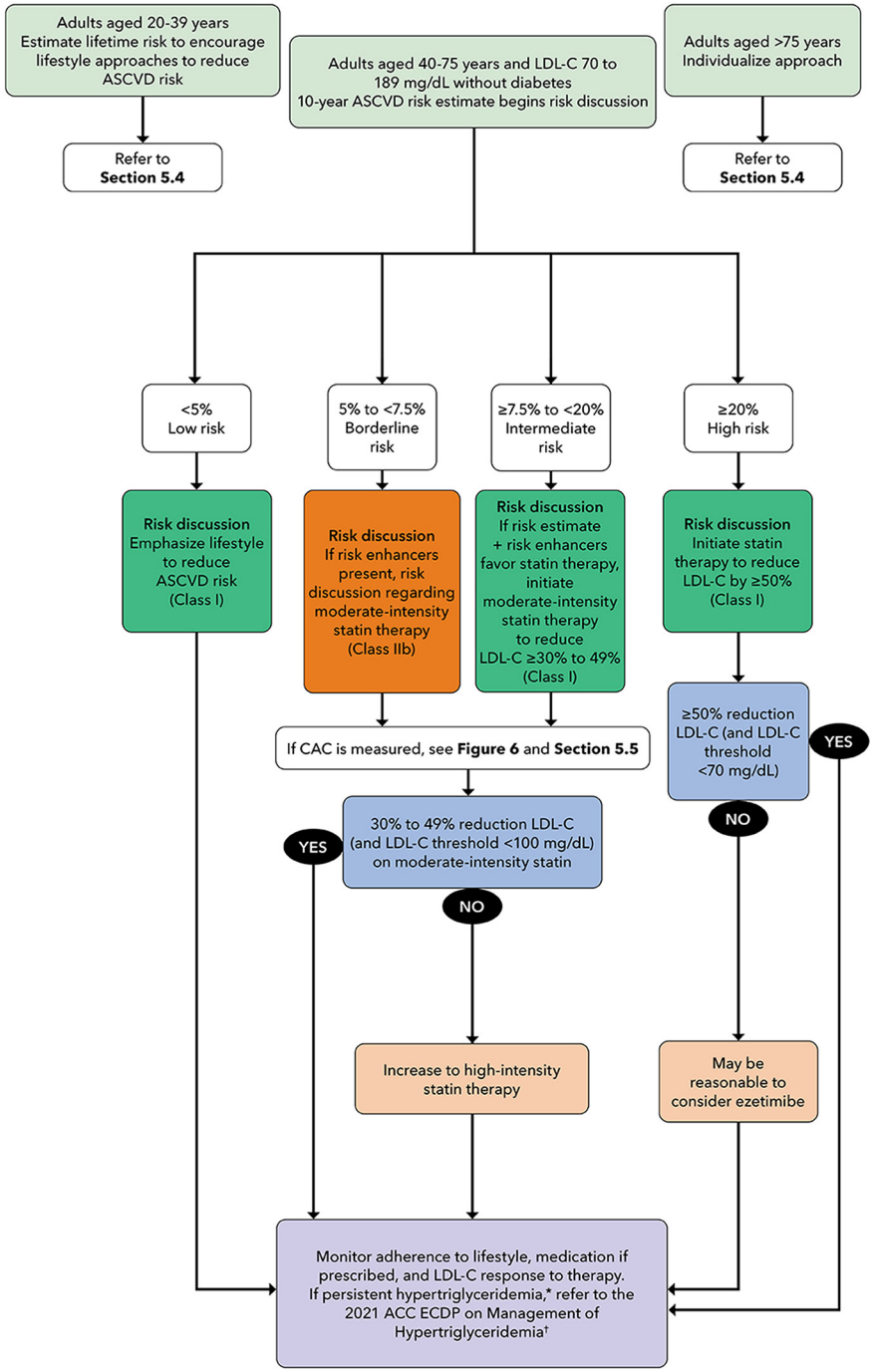
Younger patients with diabetes without ASCVD but with ASCVD risk factors typically have low 10-year predicted risks for ASCVD but high lifetime predicted risks. Risk increases with time and may reach intermediate-risk levels by 30-39 years of age, especially in individuals with longstanding type 2 diabetes and in those with type 1 diabetes of >20 years duration. Consideration of lifetime risk estimates may be useful in counseling patients to motivate lifestyle changes or adherence to therapy. The 2018 AHA/ACC/multisociety guideline recommends that for adults aged 20-39 years with long duration of diabetes, albuminuria, eGFR <60 ml/min/1.73 m^2, retinopathy, neuropathy, or ankle brachial index <0.9, it may be reasonable to initiate statin therapy.

ASCVD risk increases with age in patients with diabetes, with a 10-year fatal CVD risk of 70% in men and 40% in women aged >75 years.[7] Although there is limited RCT evidence of benefits of statin therapy in adults aged >75 years with diabetes, a meta-analysis of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation) trials demonstrated similar benefits in ASCVD reduction among those aged >70 years vs <70 years.[80] Approximately 21% of included patients were aged >75 years and had diabetes. The 2018 AHA/ACC/multisociety cholesterol guideline recommends that it is reasonable to continue moderate- or high-intensity statin therapy in patients with diabetes after the age of 75 years if therapy is well-tolerated. The benefit of initiation of statin therapy in individuals aged >75 years with recent or newly diagnosed diabetes is not well known. It may, therefore, be reasonable to have a clinician-patient discussion in which the potential benefits and risks of initiating statin therapy in this age group are reviewed. The decision to initiate nonstatin therapy in individuals aged >75 years should be individualized based on considerations of expected longevity, frailty, polypharmacy, susceptibility to adverse effects of treatment, and goals of care.[7]

5.4. Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL) (Figure 5)

Patients aged <40 years without ASCVD but with ASCVD risk factors should not be considered for 10-year risk assessment using current tools due to lack of validation in this age range. These patients typically have low short-term risks for ASCVD (because of their young age) but

FIGURE 5 **Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)**



Adapted from Grundy et al.[7] *Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia †Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; ECDP = Expert Consensus Decision Pathway; LDL-C = low-density lipoprotein cholesterol

high lifetime predicted risks. In such patients, estimation of lifetime risks for ASCVD and communication of these risks to encourage a heart-healthy lifestyle may help reduce long-term ASCVD risk. Adults aged <40 years with LDL-C values ≥160 mg/dL and/or a family history of premature cardiovascular disease may benefit from statin consideration. In patients with a family history of premature ASCVD, measurement of Lp(a) may help identify patients who may benefit from early statin initiation due to the high heritability of Lp(a) and its well-known association with higher ASCVD risk.[81] For patients aged >32 years, CAC scoring has been shown to help identify those with a traditional risk factor burden or a family history of premature cardiovascular disease. These patients may be at higher long-term absolute risk for cardiovascular disease and therefore may be more likely to experience potential benefit from statin initiation in early adult life (see Section 5.5.).[82]

In the 2018 AHA/ACC/multisociety cholesterol guideline, patients aged 40-75 years without clinical ASCVD or diabetes, who have LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 5% to <7.5% were judged to be at borderline risk and may have net benefit from moderate-intensity statin therapy.[7] In this group, in the context of shared decision-making and consideration of risk-enhancing factors (see **Table 2**), initiation of moderate-intensity statin therapy may be considered.

Patients with an estimated 10-year ASCVD risk of 7.5% to <20% were considered to be at intermediate risk and found to have net benefit from statin therapy.[7] Based on a high level of evidence, the guideline recommends that such patients be considered for treatment with a moderate-intensity statin.

Patients at borderline or intermediate risk (5% to <20% estimated 10-year ASCVD risk) who are started on a moderate-intensity statin are recommended to achieve a 30% to 49% reduction in LDL-C from baseline and LDL-C <100 mg/dL. These levels of LDL-C reduction have been well-tolerated and demonstrated efficacy in multiple primary prevention trials.[83]

If a patient on a moderate-intensity statin has inadequate lowering of LDL-C, with <30% reduction in LDL-C or LDL-C≥100 mg/dL (or non-HDL-C ≥130 mg/dL), routine clinical assessment and interventions are warranted (see **Section 3.3**). 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 modifications and ongoing LDL-C response to therapy.

If a patient at moderate or intermediate ASCVD risk on a moderate-intensity statin does not achieve a 30% to 49% LDL-C reduction or LDL-C ≥100 mg/dL (or non-HDL-C ≥130 mg/dL), the writing committee recommends consideration of escalation to a high-intensity statin.

As noted in the 2018 AHA/ACC/multisociety cholesterol guideline, some primary prevention patients at higher risk may not wish to take a statin or may not tolerate the recommended intensity of statin therapy.[7] In such patients, it may be reasonable to use LDL-C-lowering drugs that have been proven safe and effective in RCTs, either as monotherapy or combined with a statin. Although limited evidence is available in primary prevention patients, consideration may be given to use of ezetimibe. BAS may be considered as an optional alternative agent for those with ezetimibe intolerance and with triglycerides <300 mg/dL or due to patient preferences, but there is no evidence for a net cardiovascular risk reduction benefit of BAS in addition to statins. These therapies should be considered in the context of a risk discussion that reviews the potential for benefit along with tolerability and safety issues. 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 nonstatin therapy for primary prevention patients with ASCVD risk <20%.

For primary prevention patients aged 40 to 75 years at high (>20%) 10-year estimated ASCVD risk, consideration of high-intensity statin therapy to achieve ≥50% reduction in LDL-C and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) is recommended. The writing committee recommends this greater percent reduction in LDL-C and lower LDL-C threshold because high-risk primary prevention groups have ASCVD event rates that are equivalent to or exceed those observed in many secondary prevention groups. Furthermore, primary prevention trials have demonstrated the benefit and safety of treating higher-risk primary prevention patients to lower LDL-C levels.

If a patient on a high-intensity statin has inadequate lowering of LDL-C, with <50% reduction in LDL-C or LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL), routine clinical assessment and interventions are warranted (see **Section 3.3**). 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 modifications and ongoing LDL-C response to therapy.

In high-risk primary prevention patients, if ≥50% LDL-C reduction or LDL-C ≥70 mg/dL (non-HDL-C ≥100 mg/dL) is not achieved, the addition of ezetimibe may be considered. If ezetimibe is prescribed, clinicians should continue the maximally tolerated statin and continue to monitor for adherence to medications and lifestyle modifications, side effects, and ongoing LDL-C response to therapy.

The writing committee does not routinely recommend PCSK9 mAbs in this patient population, given limited efficacy data and low cost-effectiveness in primary prevention patients on statin therapy. However, see

Section 5.5 for further guidance on implementation of nonstatin therapies in primary prevention patients with extensive subclinical atherosclerosis detected on imaging.

In primary prevention patients aged >75 years, the patient-clinician discussion should consider the limited adequate RCT data to inform these decisions. The writing committee recommends consideration of ASCVD risk in the context of patient goals, competing risks for noncardiovascular disease death, patient frailty, susceptibility to adverse effects, and polypharmacy to derive individual-level recommendations for statin initiation in this highly heterogenous group.

When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy. If there is persistent hypertriglyceridemia (fasting triglycerides ≥150 mg/dL), clinicians should refer to the 2021 ACC ECDP on management of hypertriglyceridemia for further evaluation and management.[48]

5.5. Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥ 190 mg/dL (Figure 6)

For adults aged 40-75 years with a 10-year estimated ASCVD risk of 7.5% to <20% and without diabetes or ASCVD and LDL-C 70-189 mg/dL, particularly in the presence of risk-enhancing factors, the 2018 AHA/ACC/multisociety cholesterol guideline recommends initiation of moderate- or high-intensity statin therapy. For those at 5% to <7.5% 10-year ASCVD risk with additional risk enhancers, initiation of moderate-intensity statin therapy may be reasonable. If, during the clinician-patient discussion, there remains uncertainty about the need to initiate a statin, CAC scoring, which improves risk discrimination and reclassification in such patients, is reasonable to inform this decision.[7] CAC scoring is not recommended routinely in patients with predicted 10-year ASCVD risk <5% because of low yield, nor is it recommended in high-risk patients with risk >20% because of the lack of meaningful downward risk reclassification, even if the CAC score is 0 AU.

For those with a 10-year predicted risk of 5% to <20% and CAC scores of 0 AU, in the absence of diabetes, LDL-C ≥190 mg/dL, a family history of premature coronary heart disease, or active cigarette smoking, it is reasonable to defer statin therapy with a plan for CAC reassessment in 3-5 years.[84]

For those with a CAC score of 1-99 AU and <75th percentile for their age, sex, and race, moderate-intensity statin therapy is reasonable. Titration to high-intensity statin therapy may be considered if the patient achieves <30% LDL-C reduction or LDL-C ≥100 mg/dL.

Data from MESA (Multi-Ethnic Study of Atherosclerosis) identified individuals with a CAC score >100 AU or ≥75th percentile for the patient's age, sex, and race as having a Kaplan-Meier cumulative 10-year incidence of hard ASCVD events of >7.5%,[85] a finding that supports the initiation of moderate- or high-intensity statin therapy.[86]

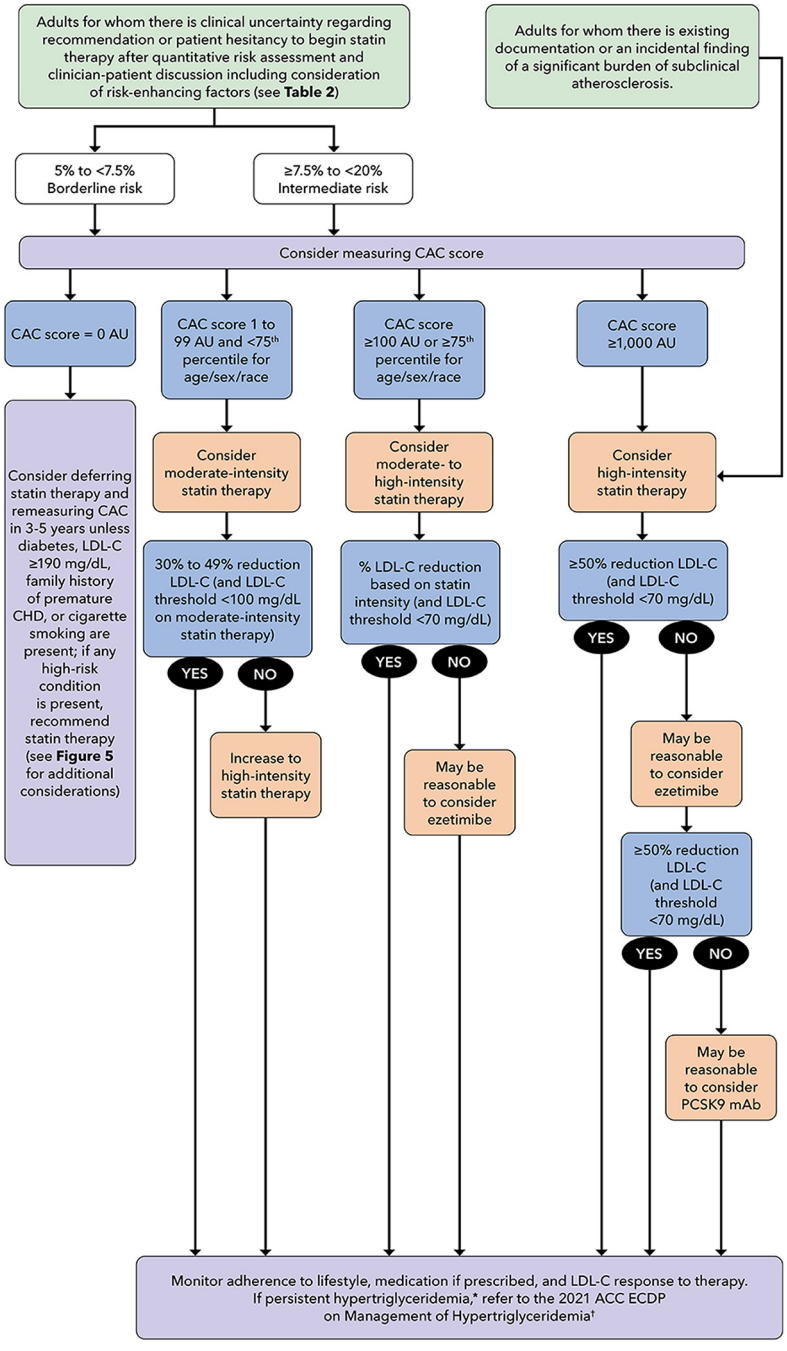
Because ASCVD risk increases in a linear fashion in proportion to an adult's CAC score, there is no absolute score that is universally recognized as either "high "or "very high" risk. However, a CAC score of >300 AU (as in MESA), >400 AU (as in the Heinz Nixdorf Recall Study), or greater than the 75th percentile for their age/sex/race group is associated with a clear upward recalibration of risk for patients with baseline borderline or intermediate predicted risk. Thus, initiation or titration to high-intensity statin therapy may be considered. For such high-risk patients who are on maximally tolerated statin therapy with a <50% LDL-C reduction from baseline or LDL-C ≥70 mg/dL, the addition of ezetimibe may be considered.

For those with CAC scores ≥1,000 AU, data from both the CAC Consortium[87] and MESA[88] demonstrated very high annual clinical ASCVD event rates in individuals not on baseline statin therapy (3.3 per 100 person-years). Based on the high ASCVD risk in such individuals, if maximally tolerated statin and ezetimibe therapy results in inadequate lowering of LDL-C, with <50% LDL-C reduction or LDL-C ≥70 mg/dL, the addition of a PCSK9 mAb may be considered. The writing committee has not provided a recommendation on the use of bempedoic acid or inclisiran due to the absence of cardiovascular outcomes trials for these agents.

The incidental finding of CAC on nongated computed tomographic imaging enhances ASCVD risk prediction.[89,90] The Society of Cardiothoracic Computed Tomography and the Society of Thoracic Radiology Guidelines provide a Class I recommendation for at least qualitative interpretation of CAC (mild, moderate, heavy/severe) on all CT scans of the chest. The presence of moderate or severe calcification generally correlates with a CAC score >100 AU, a guideline-based indication for statin benefit.[89] In many instances, nongated CT scans can be reinterpreted to quantify the CAC score for assistance in decision-making.

When the baseline CAC score is zero before initiation of statin therapy, some investigators favor remeasurement of CAC after 5 to 10 years.[7] However, serial CAC measurement in patients already treated with statin therapy has attenuated utility.[91] Although statins are associated with slower progression of overall coronary atherosclerosis volume and reduction of high-risk plaque features, they increase plaque density and thus increase the CAC score. Increases in Agatston CAC scores caused by statins are generally modest, and very elevated CAC scores

FIGURE 6 Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥190 mg/dL



*Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia. †Refer to the 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.

ASCVD = atherosclerotic cardiovascular disease; AU = Agatston unit; CAC = coronary artery calcium; CHD = coronary heart disease; ECDP = Expert Consensus Decision Pathway; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin 9 monoclonal antibody

(eg, >400 or >1,000) should still be interpreted as indicative of extensive atherosclerosis and prompt aggressive preventive therapies.

When the goals of therapy in the clinician-patient discussion have been achieved, it is reasonable to continue to monitor adherence to lifestyle modifications, medication, and LDL-C response to therapy. If there is persistent hypertriglyceridemia (fasting triglycerides ≥150 mg/dL), clinicians should refer to the 2021 ACC ECDP on management of hypertriglyceridemia for further evaluation and management.

5.6. Adults With Possible Statin-Associated Side Effects (Figure 7)

A systematic approach to evaluation of SASEs is critically important to encourage adherence to evidence-based statin treatment. The most-encountered SASE in clinical practice is statin-associated muscle symptoms, which may occur in 5% to 20% of patients.[7,92] For patients with SASEs who meet evidence-based guideline criteria for statin therapy, avoiding complete discontinuation of statin treatment is strongly recommended. In the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial of patients who discontinued a statin due to SASEs, 90% of the adverse symptom effects experienced with drug therapy can be attributed to what is seen with a blinded placebo. These results suggest that the act of taking a pill may be triggering the anticipated side-effect (the "nocebo" effect). Clinicians should strive to find the highest tolerated statin dose that is as close to the guideline recommendation as possible and work with patients to help understand the nature and severity of symptoms.

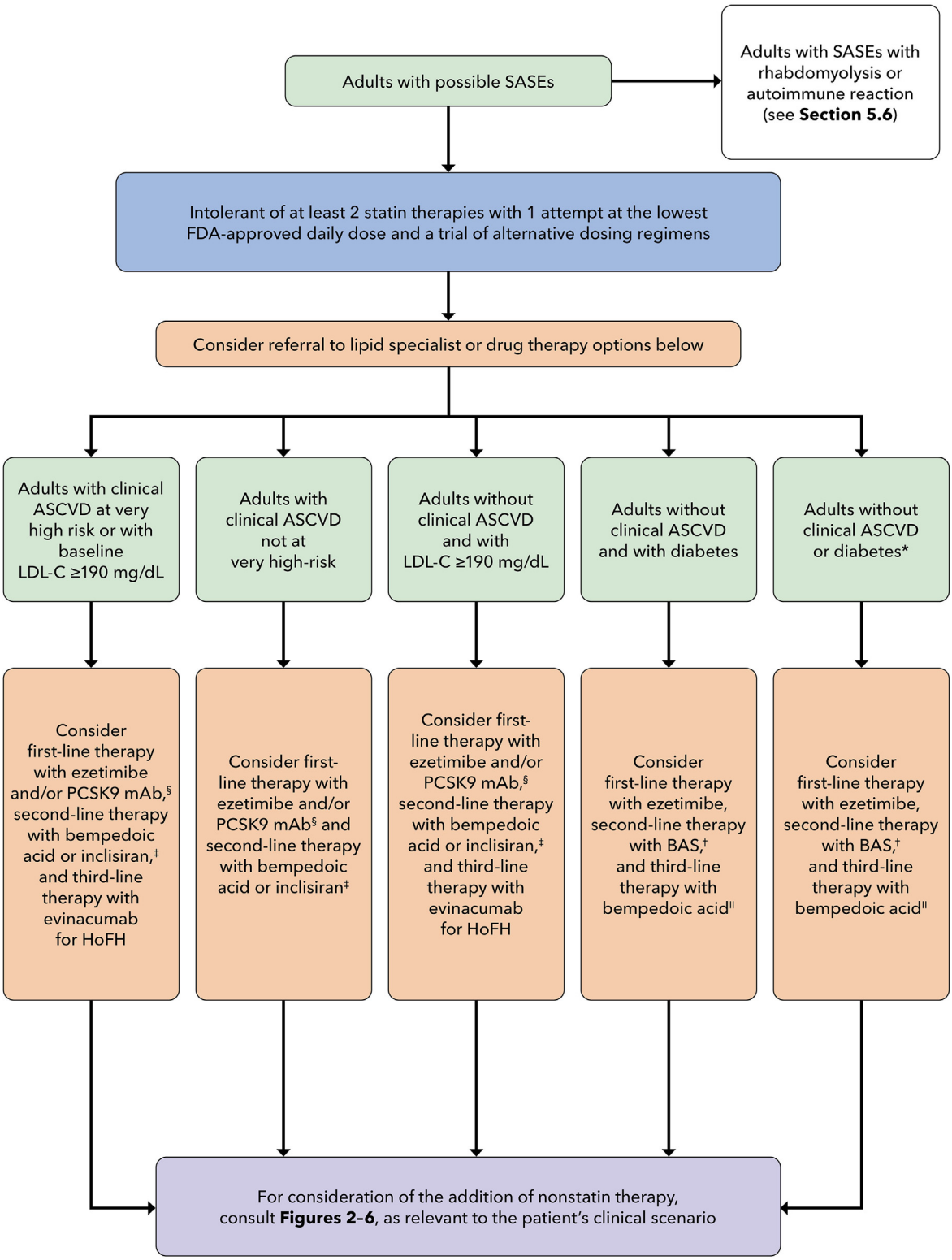
Although statin-associated muscle symptoms may occur while on statin therapy, true complete statin intolerance is uncommon.[93,94] A careful history can help to determine whether symptoms are consistent with statin-related effects, which tend to be symmetric myalgias or weakness in large proximal muscle groups. Other causes of muscle symptoms must be ruled out (eg, 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-associated muscle symptoms. However, these patients may be able to tolerate a lower statin intensity, an alternative statin, or alternative dosing strategies.

The approach to SASEs should include discontinuation of statin therapy until resolution of symptoms and subsequent rechallenge to verify recurrence of muscle-related symptoms.[93] Although there is no 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 recur with rechallenge on at least 2 (and preferably 3) statins, preferably ones that are metabolized by different pathways and have different lipophilicity/hydrophilicity, and one of which is prescribed at the lowest approved dose. The predominantly hydrophilic statins are rosuvastatin and pravastatin, whereas the lipophilic statins include simvastatin, fluvastatin, pitavastatin, lovastatin, and atorvastatin. Although not studied in RCTs nor FDA approved, alternative statin regimens may include alternate-day dosing with a long half-life statin (atorvastatin or rosuvastatin), de-escalation dosing (reducing 40-mg daily dosing to alternating between a 40- and a 20-mg statin every other day), or a lower daily dose (from 40 mg daily to 20 mg daily). The majority of patients who experience SASEs are able to tolerate statin rechallenge with an alternative statin or dose reduction with the same statin.

Nonstatin therapies are not considered to be an alternative to evidence-based statin therapy unless SASEs have been systematically and rigorously evaluated and documented. In patients with clinical ASCVD and possible SASEs who have failed at least 2 (and preferably 3) statins, including a trial of 1 attempt at the lowest approved dose or using alternative statin dosing, or who still have not achieved adequate reduction in LDL-C or non-HDL-C on maximally tolerated statin therapy, a trial of ezetimibe or a PCSK9 mAb may be considered as first-line nonstatin therapy (see Figure 7), depending on the patient's clinical scenario. Second-line therapy options that may be considered are bempedoic acid and inclisiran. Inclisiran may be considered in patients with poor adherence to PCSK9 mAbs, patients with adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. If a patient with ASCVD or baseline LDL-C ≥190 mg/dL has not achieved adequate lowering of LDL-C on maximally tolerated statin therapy with or without ezetimibe, and the patient is considered for prescription of inclisiran, referral should be made to a lipid specialist.

In patients with LDL-C ≥190 mg/dL, with or without clinical ASCVD, who have failed at least 2 (and preferably 3) statins, including a trial of 1 attempt at the lowest approved daily dose or using alternative statin dosing, or who still have not achieved adequate reduction in LDL-C or non-HDL-C on maximally tolerated statin therapy, a trial of either ezetimibe or a PCSK9 mAb may be considered as first-line nonstatin therapy (see Figure 7). Second-

FIGURE 7 Adults With Possible Statin-Associated Side Effects



Continued on the next page

line therapy options that may be considered are bempedoic acid and inclisiran. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs or with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject PCSK9 mAbs. There is currently no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with or without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be used in place of a PCSK9 mAb. If a patient with LDL-C ≥190 mg/dL has not achieved adequate lowering of LDL-C on maximally tolerated statin therapy with or without ezetimibe, and the patient is considered for prescription of inclisiran, referral should be made to a lipid specialist. Third-line therapy options may be considered, including lomitapide, evinacumab, or LDL apheresis in patients with HoFH, but such patients should be managed under the care of a lipid specialist.

For patients without clinical ASCVD or HeFH or HoFH who have possible SASEs and other indications for LDL-C-lowering therapies, the first-line nonstatin therapy should be ezetimibe (see **Figure 7**).

It should be noted that use of CAC assessment may be particularly useful in primary prevention patients with SASEs. A finding of a CAC score of 0 AU in a patient with documented SASEs at borderline or intermediate risk could reinforce a decision to defer lipid-lowering therapy (provided the patient does not have diabetes, heavy current smoking, or a strong family history). Conversely, a finding of a CAC score of ≥100 AU or ≥75th percentile should reinforce efforts to find evidence-based LDL-C-lowering strategies to reduce the ASCVD risk in such a patient.

The 2018 ACC/AHA/multisociety guidelines do not recommend routine measurement of creatine kinase and transaminase levels as they have not been demonstrated to be useful. Rarely, patients treated with statins will present after a few months with proximal muscle weakness and elevated creatine kinase.[95] The presence of anti-hydroxy-methyl-glutaryl coenzyme A reductase autoantibodies and/or necrotizing myopathy on biopsy are used to diagnose statin-associated autoimmune myopathy.[96] Patients diagnosed with statin-associated autoimmune myopathy usually[97] require chronic immunosuppressive therapy and should not be re-exposed to statins. Treatment for these patients may include PCSK9 inhibitors or ezetimibe (see **Figure 7**).[96]

Statin-induced rhabdomyolysis is an extremely rare condition (1.6 per 100,000 patient-years) that causes myonecrosis, in which muscle breakdown is responsible for a massive release of creatine kinase and myoglobin, with resulting myoglobinuria and acute renal failure.[98,99] A comprehensive review and meta-analysis of risk factors associated with statin-induced myopathy and/or rhabdomyolysis included age, sex, diabetes, renal impairment, cardiovascular disease, certain interacting drugs (eg, gemfibrozil), and mutations of the *SLCO1B1* gene, which encodes a liver-specific transporter protein.[100] In patients who have a clear indication for statin therapy but experience severe statin-associated muscle symptoms or rhabdomyolysis, nonstatin therapies should be considered (see **Figure 7**).

5.7. 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.

5.7.1. 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

FIGURE 7 Continued

*May consider BAS as optional alternative agent if ezetimibe-intolerant and triglycerides <300 mg/dL. †Depending on the amount of LDL-C lowering that is desired, clinicians may consider CAC scoring in these patients before alternative therapies, and if the CAC score is 0, may consider deferring lipid-lowering therapy. ‡No outcome studies exist for bempedoic acid or inclisiran. §A PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of their demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. Inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs, adverse effects from both PSCK9 mAbs, or those who may be unable to self-inject. There is currently no evidence for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy with/without ezetimibe or bempedoic acid; therefore, if inclisiran is to be used, it should be in place of a PCSK9 mAb. ‖Due to its demonstrated efficacy and relative safety as monotherapy and in combination with ezetimibe, in the opinion of the writing committee, bempedoic acid may be considered as third-line therapy in high-risk primary prevention patients intolerant of statin therapy.

ASCVD = atherosclerotic cardiovascular disease; FDA = Food and Drug Administration; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody; SASE = statin-associated side effect

ventricular ejection fraction.[101,102] Neither the CORONA nor the GISSI-HF trial demonstrated significant reductions in primary endpoints or major secondary endpoints. However, both trials used low-dose rosuvastatin (10 mg daily) and did not provide evidence regarding potential benefits of higher-dose statin therapy in this setting. 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. A subsequent 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,[103] prompting a change in recommendations for these patients in the 2018 AHA/ACC/multispecialty guidelines. Thus, the writing committee judges that it is reasonable to consider the use of statins in patients with symptomatic heart failure due to ischemic etiology who have reasonable expectation of surviving long enough to achieve benefit from the statin therapy (ie, 3-5 years or more).

A post hoc analysis of IMPROVE-IT identified 9 clinical variables, including heart failure, that may help predict patients with the greatest likelihood of benefit from the addition of ezetimibe to statin therapy following ACS.[8] Thus, for patients with ASCVD and a history of heart failure who achieve inadequate lowering of LDL-C on maximally tolerated statin therapy, the addition of ezetimibe may be reasonable.

In a post hoc analysis of patients with ACS, treatment with the PCSK9 mAb alirocumab failed to show a reduction in major adverse cardiac events in patients with heart failure and was associated with an increase in nonfatal MI. Based on the results of this hypothesis-generating study, the approach to patients with ASCVD and New York Heart Association functional class II-III heart failure due to ischemic heart disease should generally follow the algorithm for patients with ASCVD at very high-risk on statin therapy for secondary prevention, with the exception that no recommendation can be made for the use of a PCSK9 mAb at this time (see **Figure 2A**).

Patients with New York Heart Association functional class II, III, or IV heart failure or whose last known left ventricular ejection fraction was <30% have been excluded from studies with inclisiran[25]; thus, information about clinical outcomes with this agent are lacking for patients with heart failure. Similarly, the CLEAR Outcomes trial of bempedoic acid in patients with ASCVD also excludes patients with severe heart failure.

Decisions about the use of other nonstatin 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.

5.7.2. Patients on Maintenance Hemodialysis

The 2018 AHA/ACC/multisociety cholesterol guideline includes patients with CKD not on dialysis as a higher-risk subset of patients with ASCVD who may merit consideration for more intensive LDL-C lowering with the use of a nonstatin medication, such as ezetimibe (see **Figure 2A**). Similarly, patients with CKD not on dialysis and without ASCVD, on statin therapy for primary prevention, are considered to be at higher risk than the general population (see **Figures 4 and 5**) and have benefit from statin therapy.[104]

However, the issues surrounding the use of statins and nonstatin therapies in patients on maintenance dialysis are less clear and parallel those for patients with symptomatic heart failure. The SHARP (Study of Heart and Renal Protection) trial,[104] which randomized patients with CKD (3,023 on dialysis)[35]; the AURORA trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[105]; and the 4D (Die Deutsche Diabetes Dialyse Studie) trial[106] found no significant benefit for patients on maintenance hemodialysis in any vascular outcomes in the context of their extremely high all-cause mortality rates. For patients who plan to undergo renal transplantation or may have longer expected survival, decisions should be individualized.

Thus, the approach to patients with ASCVD on maintenance dialysis, particularly hemodialysis, should be individualized. Decisions about the use of statins and other nonstatin 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 who are judged to have a potential net benefit from statin therapy and possibly from the addition of nonstatin therapies, the algorithms in **Figure 2B** may apply, except for the use of a PCSK9 mAb, for which no recommendation can be made at this time. Both trials studying the clinical outcomes of PCSK9 mAbs, evolocumab (FOURIER)[5] and alirocumab (ODYESSY Outcomes),[9] excluded patients with severe CKD. However, in a subgroup analysis of FOURIER, relative risk reduction for the primary endpoint was similar for preserved renal function (HR: 0.82; 95% CI: 0.71-0.94), stage 2 CKD (HR: 0.85; 95% CI: 0.77- 0.94), and stage ≥3 CKD (HR: 0.89; 95% CI: 0.76-1.05); $P_{int} = 0.77$.[107] LDL-C lowering and the relative clinical efficacy and safety of evolocumab vs placebo were consistent across CKD groups. Absolute reduction in the composite of CV death, MI, or stroke with evolocumab was numerically greater with more advanced CKD.

Inclisiran has been studied in phase 1 and 2 trials, revealing similar pharmacodynamic effects and safety profiles for patients with normal and impaired renal

function.[108] However, no phase 3 clinical outcome data for inclisiran are available in patients with CKD.

5.7.3. Patients Considering Pregnancy (or Already Pregnant)

Treatment of hypercholesterolemia to reduce ASCVD risk is particularly challenging for at-risk women during the reproductive years. It is generally recommended that women on statin therapy use effective contraception and that statin therapy should be discontinued during conception, pregnancy, and lactation.[109] However, in July 2021, the FDA requested revisions to the information regarding use of statins in pregnancy, removing the contraindication against use in all pregnant patients. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women may not be appropriate. Thus, healthcare professionals and patients may make individual decisions about benefit and risk, especially for those at very high risk of heart attack or stroke. This includes patients with homozygous familial hypercholesterolemia and those who have clinical ASCVD.

Premenopausal women without ASCVD with a baseline LDL-C ≥190 mg/dL often have underlying genetic lipid disorders, particularly HeFH. Women who are currently on lipid-lowering drugs for primary prevention of ASCVD should be advised to discontinue pharmacologic therapy, with the exception of BAS if needed, generally at least 1 month and preferably 3 months before attempted conception or immediately if the patient is already pregnant.[110] Of note, pregnant patients who are managed with BAS should be monitored for vitamin K deficiency. Lipid-lowering therapy may be resumed after completion of breastfeeding.[109]

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 and triglycerides during pregnancy (recognizing that a progressive rise in both LDL-C and triglycerides is physiologic during pregnancy), and be counseled on lifestyle modifications.[111,112]

Patients who have been prescribed lipid-lowering therapy for established clinical ASCVD who are identified as very high risk, including multiple risk factors and/or HoFH, are advised to speak to their healthcare professional to consider ongoing therapeutic needs (including statin therapy) during pregnancy. These patients also should be counseled on intensive lifestyle modifications, and referral to a lipid specialist and RD/RDN is strongly recommended.

Although there were concerns for fetal harm associated with statins, recent large observational studies have not demonstrated evidence of harm to mother or fetus with statin use.[113] The safety of pravastatin has been under study for the prevention of pre-eclampsia in high-risk pregnant women.[114] Statins are known to have pleiotropic effects that may diminish inflammation and oxidative stress, increase angiogenesis, inhibit the coagulation cascade, and protect the endothelium.[115] Human clinical trials are currently in progress to determine whether a hydrophilic statin may be used to prevent pre-eclampsia in high-risk women.

Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.[34] There are no adequate and well-controlled studies of ezetimibe in pregnant women.

According to current prescribing information, bempedoic acid should be discontinued when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.[17] There are no available data on bempedoic acid use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no information regarding the presence of bempedoic acid in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.

Based on data from animal reproduction studies, evinacumab may cause fetal harm when administered to pregnant patients. Available human data are insufficient to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. According to the prescribing information, evinacumab is a human immunoglobulin G4 monoclonal antibody, and human immunoglobulin is known to cross the placental barrier; therefore, evinacumab has the potential to be transmitted from the mother to the developing fetus. A pregnancy test is recommended before starting treatment with evinacumab. An effective method of birth control should be used during treatment and for at least 5 months after the last dose of evinacumab. There are no data on the presence of evinacumab in human or animal milk, its effects on the breastfed infant, or its effects on milk production.

It is recommended that inclisiran be discontinued when pregnancy is recognized.[26] Alternatively, consider the ongoing therapeutic needs of the individual patient. According to the prescribing information, inclisiran may cause fetal harm when administered to pregnant patients based on its mechanism of action. There are no available data on the use of inclisiran in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no information on the presence of inclisiran in human milk, its effects on the breastfed infant, or its effects on milk production.

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 mAbs 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 patients with FH, ASCVD, and pregnancy, LDL apheresis may be considered when LDL-C ≥190 mg/dL.

5.7.4. Race/Ethnicity-based Limitations

The 2018 AHA/ACC/multisociety cholesterol guideline states that it is reasonable for clinicians to consider race and ethnic features that can influence ASCVD risk and to adjust the intensity of statin therapy accordingly.[7] Whereas race and ethnicity are social constructs, patients with genetic backgrounds deriving from some ancestries may have differential risks for SASEs. Higher rosuvastatin plasma levels have been reported in people of Japanese, Chinese, Malay, and Asian-Indian heritage compared with White (typically European ancestry) individuals. ASCVD risk reduction was demonstrated in a large Japanese open-label primary prevention trial of low-intensity pravastatin (10-20 mg daily) vs placebo.[116] The REAL-CAD (High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease) trial provided the first evidence that compared with low-dose statin therapy, high-dose statin therapy has CV outcomes benefits in an Asian population.[117] In this prospective, multicenter, randomized, open-label, blinded endpoint study, 13,054 Japanese patients were assigned to high-dose (4 mg/day) compared with low-dose (1 mg/day) pitavastatin. High-dose pitavastatin significantly reduced cardiovascular events in in these patients with stable coronary artery disease. The 2018 AHA/ACC/multisociety cholesterol guideline reported no differences in sensitivity to statin dosing in Hispanic/Latino-Americans and Black persons/African Americans as compared with non-Hispanic White Americans. Although published studies report similar LDL-C-lowering efficacy of ezetimibe,[7] alirocumab,[118] and evolocumab,[119] regardless of race/ethnicity, minority under-representation is evident in these studies. Thus, the generalizability of the recommendations provided in this document for the use of all statin add-on therapies for individuals from ethnic minorities remains somewhat uncertain.

5.7.5. Patients With Previous Organ Transplantation

Managing dyslipidemias in patients with a history of solid organ transplantation can be particularly challenging. Many of the immunosuppressant medications given to this patient population are associated with dyslipidemia (eg, an increase in total cholesterol, LDL-C, VLDL-C, triglycerides, and HDL-C). Statins are first-line therapy for LDL-C management in these patients. The nonstatins discussed in this ECDP may provide additional LDL-C lowering; however, their use has not been well studied, if at all, in this patient population. Potential drug interactions with the immunosuppressant medications should be considered when selecting any lipid-lowering therapy in patients who have received solid organ transplants. The mechanisms for the interactions with these medications are often multifaceted, involving modulation of cytochrome P450 enzymes and transporter systems for drug metabolism and elimination. Certain combinations of medications will need to be avoided, some will require dosing adjustments, and some will require careful monitoring. For more comprehensive guidance, the reader is referred to a recent review article on the management of dyslipidemia in solid organ transplant recipients and a recent summary of statin-drug interactions and recommendations for statin therapy dose limitations in patients on common cardiovascular medications, including immunosuppressant therapies.[120,121]

5.7.6. 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 writing committee, therefore, urges the need for thoughtful clinician-patient discussion of the potential benefits and harms of statin and nonstatin therapies and patient preferences in the context of the individual patient's clinical situation.

6. CONCLUSIONS

Since the publication of the 2018 AHA/ACC/multisociety cholesterol guidelines, several newer nonstatin agents have demonstrated LDL-C-lowering efficacy, have received FDA approval, and are commercially available for management of at-risk patients. Additional data on higher-risk groups and outcomes in real-world samples have also allowed for refinement of prior recommendations. There are large, ongoing randomized controlled cardiovascular outcomes trials in progress for bempedoic acid and inclisiran. This has resulted in gaps in expert guidance regarding the role of available nonstatin therapies. This ECDP addresses current gaps in care for LDL-C lowering to reduce ASCVD risk and provides recommendations that build on the evidence base established by the 2013 ACC/AHA and 2018 AHA/ACC/multisociety cholesterol guidelines. The algorithms endorse the 4 evidence-based patient management groups identified in the 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 nonstatin 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 newer agents for ASCVD risk reduction.

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KEY WORDS ACC Expert Consensus Decision Pathway, bempedoic acid cardiovascular disease, cholesterol, ezetimibe, inclisiran, LDL dyslipidemia, lipids, PCSK9 inhibitors, statins

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2022 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NONSTATIN THERAPIES FOR LDL-CHOLESTEROL LOWERING IN THE MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

Committee Member	Employment	Consultant	Speakers Bureau	Ownership Interest/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Donald M. Lloyd-Jones (*Chair*)	Northwestern University—Chair, Department of Preventive Medicine; Senior Associate Dean for Clinical and Translational Research; Director, Northwestern University Clinical and Translational Sciences Institute	None	None	None	None	None	None
Pamela B. Morris (*Vice Chair*)	Medical University of South Carolina—Professor of Medicine, Cardiology; Director, Seinsheimer Cardiovascular Health Program; Co-Director, Women's Heart Care	■ Esperion	None	None	None	None	None
Christie M. Ballantyne	Baylor College of Medicine-Chief, Section of Cardiology; Chief Section of Cardiovascular Research; Professor of Medicine	■ Amarin ■ Amgen ■ Esperion ■ Novartis ■ Pfizer Inc. ■ Regeneron	None	None	■ Amgen* ■ Esperion* ■ Novartis*	None	None
Kim K. Birtcher	University of Houston College of Pharmacy—Adjunct Clinical Professor	None	None	None	None	None	None
Ashleigh M. Covington	American College of Cardiology—Team Leader, Clinical Pathways and Roundtables	None	None	None	None	None	None
Sondra M. DePalma	University of Pittsburgh Medical Center Heart and Vascular Institute—American Academy of Physician Associates—Cardiology Physician Assistant; Director, Regulatory & Professional Practice	None	None	None	None	None	None
Margo B. Minissian	Cedars-Sinai Brawerman Institute—Nurse Scientist; Cardiology Nurse Practitioner	■ Regeneron	None	None	None	None	None
Carl E. Orringer	University of Miami Miller School of Medicine—Professor of Medicine, Division of Cardiology	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina, Chapel Hill—Professor of Medicine, Division of Cardiology	None	None	None	None	None	None
Ashley Arana Waring	Medical University of South Carolina—Assistant Professor of Medicine, General Clinical Cardiology	None	None	None	None	None	None
John T. Wilkins		None	None	None	None	None	None

Note: Relevant relationships are highlighted. This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC, a person has a relevant relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document or makes a competing drug or device addressed in the document; or c) the person or a member of the person's household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.
*Significant relationship.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2022 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NONSTATIN THERAPIES FOR LDL-CHOLESTEROL LOWERING IN THE MANAGEMENT OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK

Committee Member	Representation	Institution of Employment	Consultant	Speakers Bureau	Ownership Interest/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Paul L. Douglass	Official Reviewer—Health Equity Task Force	Wellstar Health System—Interventional Cardiologists	None	None	None	NHLBI	■ ACC Health Equity Task Force* ■ Wellstar Health System*	None
Anne C. Goldberg	Content Reviewer—ACC Expert	Washington University—Professor of Medicine	■ AKCEA ■ Esperion ■ IONIS* ■ Novartis Corporation ■ Regeneron	■ NLA* ■ ACC	None	■ Amgen† ■ Arrowhead Pharmaceuticals† ■ IONIS† ■ Novartis Corporation† ■ Regeneron† ■ Sanofi-Aventis†	■ ABIM ■ AHA* ■ The FH Foundation ■ Foundation of the NLA* ■ Merck ■ NLA†	None
Dharam J. Kumbhani	Official Reviewer—Solution Set Oversight Committee	UT Southwestern—Associate Professor of Medicine; Section Chief, Interventional Cardiology	■ ACC*	None	None	None	None	None
Indu G. Poornima	Official Reviewer—Prevention Council	Allegheny Health Network—Director, Section of Preventive Cardiology	None	None	None	None	■ HERITAGE‡ ■ HORIZON, Novartis Corporation‡	None
Michael D. Shapiro	Content Reviewer—ACC Expert	Wake Forest University School of Medicine—Professor of Cardiology and Molecular Medicine	■ Novo Nordisk Inc. ■ Regeneron ■ Amgen Inc. ■ Novartis Corporation	None	None	None	■ ASPC* ■ The FH Foundation* ■ HORIZON, Novartis Corporation‡ ■ PREVENTABLE, NIH‡ ■ VESALIUS, Amgen Inc.‡	None
Neil J. Stone	Official Reviewer—2018 ACC/AHA Multisociety Cholesterol Guidelines	Feinberg School of Medicine, Department of Medicine/Cardiology—Bonow Professor of Medicine	None	None	None	None	None	None
Elisabeth Sulaica	Official Reviewer—Cardiovascular Team Council	None	None	None	None	None	None	None
Salim S. Virani	Content Reviewer—ACC Expert	Michael E. DeBakey VA Medical Center/Baylor College of Medicine— Professor	None	None	None	■ Department of Veterans Affairs† ■ World Heart Federation*	■ ACC† ■ ASPC ■ Continuing Education Company† ■ NLA	None

(continued on the next page)

APPENDIX 2. CONTINUED

Committee Member	Representation	Institution of Employment	Consultant	Speakers Bureau	Ownership Interest/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Barbara S. Wiggins	Content Reviewer—ACC Expert	Medical University of South Carolina	■ Lexi Comp	None	None	None	■ ACC Prevention of Cardiovascular Disease Section Leadership Council* ■ ACC Annual Meeting Committee—Pharmacology Session* ■ Editorial Board—American Journal of Cardiovascular Drugs* ■ ACC Faculty Development Work Group* ■ PERT Consortium Clinical Protocols Committee* ■ ACC Cardiovascular Team PharmD Section* ■ ACC Cardiovascular Management Section Leadership Council*	None

This table represents all relationships of reviewers with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/Guidelines/About-Guidelines-and-Clinical-Documents/Relationships-with-Industry-Policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*No financial benefit.

†Significant relationship.

‡Relationship with this company is limited to enrolling patients in clinical trials. This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the ACC/AHA Disclosure Policy for Writing Committees.

ABIM = American Board of Internal Medicine; ACC = American College of Cardiology; AHA = American Heart Association; ASPC = American Society for Preventive Cardiology; FH = familial hypercholesterolemia; NIH = National Institutes of Health; NLA = National Lipid Association

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APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
ACS = acute coronary syndromes
AHA = American Heart Association
ANGPTL3 = angiopoietin-like protein 3
ASCVD = atherosclerotic cardiovascular disease
AU = Agatston units
BAS = bile acid sequestrant
CAC = coronary artery calcium
CKD = chroic kidney disease
ECDP = Expert Consensus Decision Pathway
FDA = Food and Drug Administration
FH = familial hypercholesterolemia
HDL-C = high-density lipoprotein cholesterol
HeFH = heterozygous familial hypercholesterolemia
HoFH = homozygous familial hypercholesterolemia
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein a
mAb = monoclonal antibody
MI = myocardial infarction
PCSK9 = proprotein convertase subtilisin/kexin type 9
PAD = peripheral artery disease
PCE = Pooled Cohort Equation
RCT = randomized controlled trial
RD/RDN = registered dietitian/registered dietitian nutritionist
RWI = relationships with industry
SASE = statin-associated side effect