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AACE Clinical Guidance

American Association of Clinical Endocrinology Clinical Practice Guideline on Pharmacologic Management of Adults With Dyslipidemia

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ABSTRACT

Objective: To review the evidence and provide updated and new recommendations for the pharmacologic management of adults with dyslipidemia to prevent adverse cardiovascular outcomes. These recommendations are intended for use by clinicians, health care team members, patients, caregivers, and other stakeholders.

Methods: This guideline was developed by a multidisciplinary task force of content experts and guideline methodologists based on systematic reviews of randomized controlled trials or cohort studies from database inception to November 7, 2023. An updated literature search was completed for any additional articles published by May 31, 2024. Clinical questions addressing nonstatin

Abbreviations: AACE, American Association of Clinical Endocrinology; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CAC, coronary artery calcium; CI, confidence interval; COI, conflict of interest; CPG, clinical practice guidelines; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; FDA, U.S. Food and Drug Administration; FRS, Framingham Risk Score; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein a; mAb, monoclonal antibody; MACE, major adverse cardiovascular event; MI, myocardial infarction; MID, minimally important difference; NRI, net reclassification index; OTC, over-the-counter; PCE, Pooled Cohort Equations; PCSK9, proprotein convertase subtilisin/kexin type 9; PICO, population, intervention, comparator, outcome(s); PVD, peripheral vascular disease; RCT, randomized controlled trial; RR, risk ratio; TG, triglyceride; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

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Disclaimer: American Association of Clinical Endocrinology clinical practice guidelines include systematically developed recommendations to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on scientific evidence. In areas of uncertainty, or when clarification is required, expert opinion and professional judgment were applied. This guideline is a working document that reflects the state of the field at the time of publication. Since rapid changes in this area are expected, periodic revisions are inevitable. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision(s) by health care professionals to apply the recommendations provided in this guideline, including prescribing of any medications, must be made in consideration of the recommendations presented, the most recently published prescribing information for medications, local resources, and individual patient circumstances.

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Key Words:
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hypertriglyceridemia
pharmacotherapy

medications and patient-important outcomes were prioritized. The task force assessed the certainty of the evidence and developed recommendations using the Grading of Recommendations Assessment, Development, and Evaluation framework. All recommendations were based on the consideration of the certainty of the evidence across patient-important outcomes, in addition to issues of feasibility, acceptability, equity, and patient preferences and values.

Results: This guideline update includes 13 evidence-based recommendations for the pharmacologic management of adults with dyslipidemia focused on patient-important outcomes of atherosclerotic cardiovascular disease (ASCVD) risk reduction. The task force issued a good practice statement to assess the risk of ASCVD events for primary prevention in adults with dyslipidemia. The task force suggested the use of alirocumab, evolocumab, or bempedoic acid for adults who have ASCVD or who are at increased risk for ASCVD in addition to standard care. The task force suggested against the use of these medications in adults without ASCVD. There was insufficient evidence to recommend for or against the addition of inclisiran. For adults with hypertriglyceridemia and ASCVD or increased risk of ASCVD, the task force suggested the use of eicosapentaenoic acid but not eicosapentaenoic acid plus docosahexaenoic acid and strongly recommended against the use of niacin. There was insufficient evidence for recommendations regarding pharmacologic management in adults with severe hypertriglyceridemia (≥500 mg/dL). The task force suggested a low-density lipoprotein cholesterol treatment goal of <70 mg/dL in adults with dyslipidemia and ASCVD or at increased risk of ASCVD.

Conclusions: Pharmacotherapy is recommended in adults with dyslipidemia to reduce the risk of ASCVD events. There are several effective and safe treatment options for adults with dyslipidemia who have ASCVD or at increased risk of ASCVD who need additional lipid-lowering medications. Shared decision-making discussions are essential to determine the best option for each individual.

Scope and Purpose

Given the high prevalence of dyslipidemia in the global population and the introduction of newer treatment options, the purpose of this clinical practice guideline is to provide practical evidence-based recommendations for nonstatin pharmacotherapies for the management of dyslipidemia. This guideline focuses on critical aspects of risk assessment and the benefits and harms of newer pharmacologic treatment options for adults with dyslipidemia and their impact on individual patient-important atherosclerotic cardiovascular disease (ASCVD)—related outcomes. Clinical topics such as screening, lipid panels, nutrition, physical activity, and statin use are not addressed, but relevant guidance from AACE and others may be referenced to facilitate implementation. The target audience for this guideline are all clinicians and health care team members who care for adults with dyslipidemia. The target population is adults with dyslipidemia. Differing treatment options for specific subgroups of individuals were discussed if evidence was available.

Introduction

The global burden of ASCVD remains high, with more than half a billion people around the world affected, resulting in ≥20.5 million deaths in 2021.[1] More than 800,000 people in the United States die of cardiovascular disease (CVD) each year, accounting for 1 in every 3 deaths.[2] Despite recent substantial decreases in the rates of premature CVD mortality in adults 25 to 64 years of age, heart disease causes 1 in 5 deaths in this age group.[3] CVD mortality in younger adults also substantially impacts health care burden, costs, and the economy. The cost of heart disease including health care services, medicines, and lost productivity was >$252 billion in 2020.[4] At least 25% of these deaths are directly attributed to elevated low-density lipoprotein cholesterol (LDL-C) as the primary but not the only marker of dyslipidemia.[5] LDL-C levels have decreased in recent years, but >76% of adults with ASCVD in the U.S. have LDL-C levels >70 mg/dL and over a quarter of adults without ASCVD had LDL-C levels >130 mg/dL.[6]

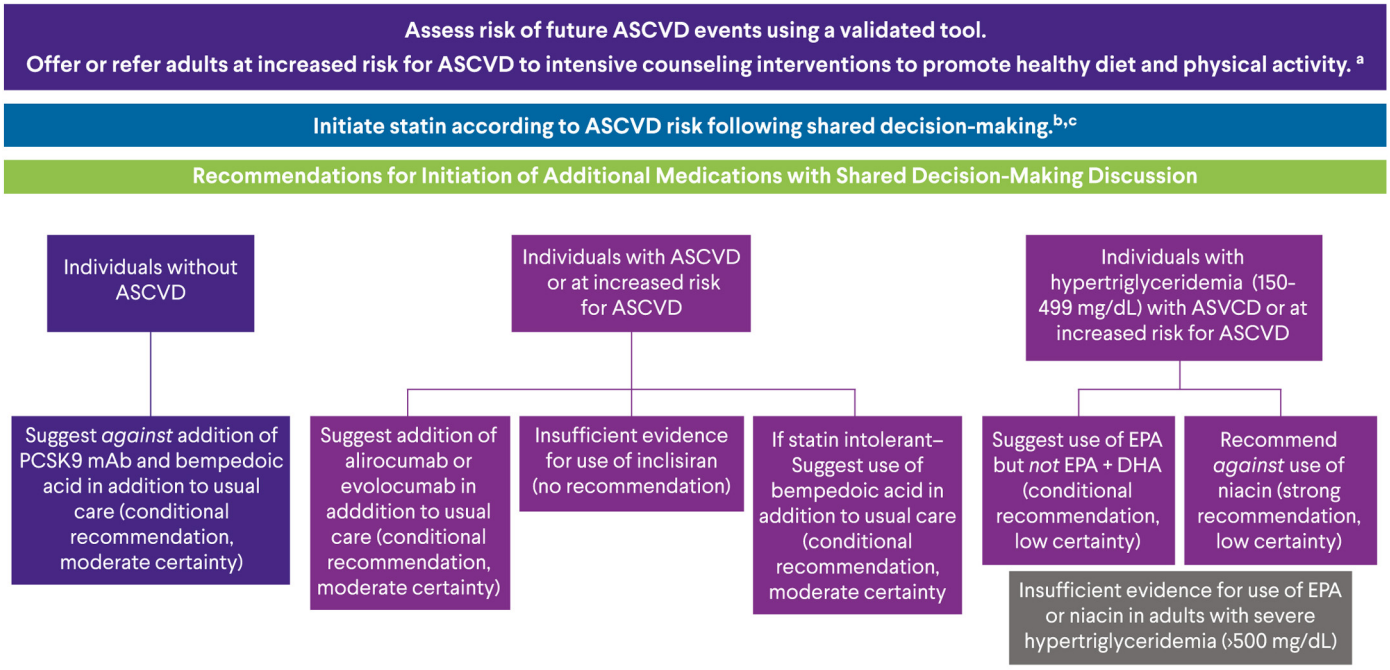
The prevalence of CVD is impacted by social determinants of health and varies by race/ethnicity with Black adults having the highest prevalence of CVD.[7] Inequities in health care access contribute to variations in use of dyslipidemia medications because statin prescriptions vary by race, ethnicity, sex, area poverty level, income level, and insurance coverage.[8,9] While cardiovascular (CV) events are higher in men than women, women experience higher rates of CV-related mortality.[7]

Multiple endocrine disorders are associated with dyslipidemia, with diabetes mellitus (DM) presenting the largest challenge. For persons with DM, CVD is the leading cause of death, contributing to >66% of deaths with as many as 95% of patients with type 2 DM (T2D) having ≥1 abnormal lipid level, for which clinicians need to be able to assess and make treatment recommendations.[10,11] Management of hypertriglyceridemia, particularly severe hypertriglyceridemia, continues to be an important area to address with evidence-based guidance. While lifestyle changes and statin therapy remain the foundations of management for adults with dyslipidemia,[12-14] there are newer data available from an increasing number of CV outcomes trials using agents such as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, icosapent ethyl (IPE), and bempedoic acid (BA).

This 2025 clinical practice guideline serves as a focused update of the 2017 AACE Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease[13] and provides evidence-based recommendations for the pharmacologic management of adults with dyslipidemia by clinicians and their care teams. While this guideline is primarily focused on pharmacotherapy, the task force emphasized the importance of ASCVD risk assessment, including regular screening for dyslipidemia, and nonpharmacologic interventions. Healthy dietary and lifestyle patterns are critical for improvement of patient-important outcomes and successful management of dyslipidemia. The task force supports continual patient-centered discussions on lifestyle patterns and offering or referring adults who are at increased risk for ASCVD to intensive counseling interventions to promote healthy diet and physical activity (Figure).[12] The target populations for the recommendations include adults with dyslipidemia (see Box A for more details).

The recommendations are supported by a rigorous evaluation of the current evidence, which includes consideration of study limitations as well as benefits and harms of different treatment options

Summary of Recommendations: Pharmacotherapy for Adults with Dyslipidemia to Prevent ASCVD Events



AACE suggests treating individuals with ASCVD or increased risk of ASCVD to an LDL-C target of less than 70 mg/dL (conditional recommendation, low certainty). Potential impacts from polypharmacy and the increased costs associated with certain medications should be considered when determining appropriate treatment goals for individual patients.

The 2025 updated recommendations for additional medications were developed using the GRADE framework focused on patient-important outcomes including mortality, ASCVD events, and treatment discontinuations. Current evidence does not show meaningful improvement in prediction of ASCVD risk with the addition of non-traditional risk factors (i.e. CAC score, ApoB, or Lp(a)) to the risk model. Shared decision-making should include a discussion of the benefits and harms of individual medications, costs, resource utilization, and access to healthcare. For specific recommendations related to use of statins, refer to the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan and the 2022 USPSTF Recommendation Statement on Statin Use for Primary Prevention of Cardiovascular Disease.[b,c]

[a] US Preventive Services Task Force. Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Cardiovascular Disease Risk Factors: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(4):367–374. doi:10.1001/jama.2022.10951
[b] Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan—2022 Update. *Endocrine Practice*. 2022;doi:10.1016/j.eprac.2022.08.002
[c] US Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(8):746–753: https://doi.org/10.1001/jama.2022.13044

Fig. Summary of Recommendations: Pharmacotherapy for Adults with Dyslipidemia to Prevent ASCVD Events.

Box A. Who is impacted by these recommendations?

- The guideline recommendations apply to adults 18 years of age and older who have dyslipidemia or hypertriglyceridemia who are receiving standard of care treatment but who are not at goal and may consider additional medications.
- The majority of trials informing the GRADE evidence profiles included adults with ASCVD or at increased risk of ASCVD. Evidence on use of the newer medications for primary prevention was limited.
- For this guideline, the task force considered ASCVD risk to include individuals with known risk factors based on clinical judgment or validated risk assessment tool.
- Dyslipidemia was defined as LDL-C levels greater than 130 mg/dL (3.4 mmol/L) in the general population and greater than 70 mg/dL (1.8 mmol/L) in individuals with ASCVD.
- Hypertriglyceridemia was defined as triglyceride levels above 150 mg/dL (1.7 mmol/L).
- Severe hypertriglyceridemia was defined as triglycerides 500 mg/dL (5.7 mmol/L) or above.

that could support the use of agents for lipid management to improve patient-important outcomes, such as mortality, myocardial infarction (MI), stroke, coronary revascularizations, peripheral vascular disease (PVD) events, and pancreatitis. While many recommendations are consistent with previous guidance provided by AACE and other medical societies,[13,15-18] there are key differences. First, individual patient-oriented outcomes, such as mortality and CVD events, were prioritized over disease-oriented (or intermediate) outcomes, such as lipid levels, allowing for a more robust assessment of the balance of benefits and harms of each pharmacologic agent. Second, the task force considered all domains of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework that highlights the importance of patient preferences and values, acceptability, and equity in development of the recommendations. Third, the task force strongly acknowledged the lack of evidence supporting robust and long-term use of many of the newer and costly treatments. To better understand the long-term potential benefits and harms of these agents, well-done randomized clinical trials are necessary. Finally, the task force highlighted the limited information on appropriate LDL-C targets and the utility of risk calculators and individual risk identifiers in driving evidence-based treatment decisions. In considering the totality of the evidence, the balance of benefits and harms and the roles of patient preferences, values, and access to care, the task force issued one strong recommendation and multiple conditional recommendations that allow for shared decision-making and clinical interpretation.

Methodology

Task Force Composition

This clinical practice guideline was developed by a group of credentialed medical professionals in the fields of endocrinology, lipidology, pharmacology, family medicine, and guideline methodologic specialists. The task force consisted of clinical endocrinologists (S. Patel, chair; K. Wyne, vice-chair; S. Afreen, M. Belalcazar, V. Pulipati, and M. Zilbermint), a clinical pharmacist (J. Marrs), and a family physician (S. Coles).

The evidence team consisted of a staff methodologist (M. Bird), a methodology fellow (C. Peng), and a GRADE expert consultant (S. Sultan). All members provided updated disclosures of interest throughout the development process (Appendix A).

Task Force Empanelment and Conflicts of Interest

The multidisciplinary task force was empaneled following an open call for applications from the AACE membership at large. All task force applicants were required to disclose all relationships and interests according to the 2023 AACE Conflict of Interest (COI) Policy (https://pro.aace.com/about/aace-conflicts-interests-policy). Disclosures were reviewed and applicants were determined to be either ineligible, not conflicted, or conflicted. All AACE task forces are empaneled with a goal of being free from conflict but must have ≥60% members who are not conflicted. The chair of the task force must also be free from conflicts. Applications were then reviewed by an appointed workgroup who considered multiple parameters to ensure diversity, equity, and inclusivity in their recommendations for task force composition.[19] Empanelment workgroups are composed of a member of the Clinical Practice Guidelines (CPG) Oversight Committee, the chair (or designee) of the relevant Disease State Network, and a representative from the Diversity, Equity, and Inclusion Committee. All potential task force members are then approved by the CPG Oversight Committee chair and vice chair and the AACE President.[19,20]

Systematic Review

The evidence review team, with assistance of a medical librarian, conducted several systematic literature searches to inform the GRADE evidence profiles and evidence-to-decision frameworks that support the recommendations for this guideline.

The following clinical questions were addressed:

1. In adults with dyslipidemia, what are the benefits/harms of PCSK9 inhibitors compared with usual care?
2. In adults with dyslipidemia, what are the benefits/harms of BA compared with usual care?
3. In adults with hypertriglyceridemia, what are the benefits and harms of eicosapentaenoic acid (EPA) compared with EPA plus docosahexaenoic acid (DHA)?
4. In adults with hypertriglyceridemia, what are the benefits/harms of extended release niacin compared with nonstatin treatments such as fibrates and EPA?
5. In adults with dyslipidemia, what are the benefits/harms of treating to a lower LDL-C goal (<70 mg/dL) compared with a higher LDL-C goal (≥70 mg/dL)?
6. In adults with dyslipidemia without CVD, does the addition of risk enhancers such as calcium artery calcification scoring, apolipoprotein B (ApoB), or lipoprotein a (Lp[a]) to traditional risk equations provide more accurate risk prediction of future cardiovascular events?

The clinical questions were then developed into the PICO format—population (P), intervention (I), comparison (C), and outcomes (O)—and inclusion and exclusion criteria were developed a priori (Appendix B). The task force focused on pharmacologic treatments for adults ≥18 years of age with elevated LDL-C and/or triglyceride (TG) that were approved by the U.S. Food and Drug Administration (FDA). Dyslipidemia was defined as LDL-C levels >130 mg/dL (3.4 mmol/L) in the general population and >70 mg/dL (1.8 mmol/L) in individuals with CVD. Hypertriglyceridemia was defined as TG levels >150 mg/dL (1.7 mmol/L). Severe hypertriglyceridemia was defined as TG levels ≥500 mg/dL (5.7 mmol/L). Therapeutic options included PCSK9 inhibitors (alirocumab, evolocumab, and inclisiran), BA, EPA, DHA, and niacin. Statins, ezetimibe, and fibrates were considered as part of the comparison or usual care group, or as cointerventions. Recent trial data demonstrated a lack of evidence in support of the use of fibrates, when added to statins, for the prevention of CVD, and the task force only evaluated this class of agents when investigating outcome of pancreatitis in patients with hypertriglyceridemia.

The task force prioritized patient-oriented outcomes for each question, which included mortality, MI, stroke, coronary revascularization, PVD events, pancreatitis, treatment discontinuation due to adverse events, and changes in risk assessment. All outcomes were rated as critical for clinical decision-making except for the outcome of PVD events which was rated as important. To assess imprecision, the task force used a minimally contextualized approach to identify a single threshold (minimally important difference [MID]) for each outcome a priori. The MID was set as the smallest clinically meaningful difference in the absolute risk for each outcome by consensus following a discussion of observed frequencies for each outcome in untreated populations and overall clinical judgment. An absolute risk difference of 5 per 1000 participants was considered clinically meaningful for all outcomes except coronary revascularization, which was given a threshold of 50 coronary revascularizations per 1000 participants. Changes in risk assessment included improvements in the c-statistic for a particular test and risk reclassification. Intermediate or disease-oriented outcomes, such as a reduction in LDL-C or other lipids,

were not included in the evidence profiles. However, lipid levels were discussed in terms of target populations and for areas where data on CV outcomes were not available. The composite endpoint, major adverse cardiovascular events (MACEs), was not considered as an outcome for any of the questions; instead, individual components of this outcome were included to better understand the varying treatment effects.[21] Studies were included if they reported ≥1 CV outcome or treatment discontinuations as part of the efficacy or safety analysis. Studies that only reported lipid values or composite outcomes were excluded from the evidence synthesis. No restrictions were made based on participant number or duration of follow-up. Systematic reviews and randomized controlled trials (RCTs) were prioritized in the searches; however, cohort studies were included for specific questions if RCTs were not available.

A medical librarian aided in the development and execution of the literature searches. PubMed (Medline), Cochrane Database of Systematic Reviews, and clinicaltrials.gov were searched for English-language studies published from database inception until November 7, 2023. The literature search for the risk assessment PICO question was limited to 2018 to present because of the availability of an evidence report from 2018 by the U.S. Preventive Services Task Force.[22] Additional articles were found by hand-searching reference lists of included studies. Inclusion and exclusion criteria and key words are provided in the appendices. Title and abstract screening and full-text review were performed by 2 reviewers using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) against specific inclusion and exclusion criteria based on the PICO elements (Appendix B) for each clinical question. Published systematic reviews were prioritized and used to inform the evidence profiles if considered to be of sufficient quality. Quality of included systematic reviews was assessed using the AMSTAR 2 checklist.[23]

If systematic reviews were not of sufficient quality or did not address the outcomes of interest, the evidence team abstracted data from the relevant RCTs and conducted meta-analyses using Review Manager Web (RevMan Web, version 6.5.2; The Cochrane Collaboration, 2023 available at revman.cochrane.org). A random-effects model was used to calculate summary estimates of effect for pooled event rates across trials. All outcomes of interest were dichotomous and reported as risk ratio (RR) except when odds ratios or hazard ratios were used in the published systematic review. Heterogeneity was assessed using the I^2 statistic. Risk of bias assessments from the included systematic reviews were reviewed by the evidence team and additional or updated risk of bias assessments were conducted using the Cochrane RoB v1 tool.[24] From these literature searches, 9 systematic reviews of 108 RCTs, and 8 cohort studies were included in the evidence supporting the recommendations (see Appendix C for PRISMA diagram). Additional post hoc publications or observational studies were included in the supporting text as appropriate.

An updated literature search was performed before review and approval by AACE leadership to identify any additional RCTs published before May 31, 2024. The literature search resulted in 35 additional studies identified. None of the studies were included in the evidence profile; however, 3 references were added to the clinical considerations section for risk assessment, evolocumab, and BA.

Formulation of Recommendations

The task force followed the AACE CPG development process as published previously.[19] To facilitate review of the evidence for each PICO question, smaller workgroups were formed to review the GRADE evidence profiles as presented by the evidence team. Consensus was obtained from the workgroups on individual ratings of risk of bias, indirectness, inconsistency, and imprecision. Workgroup members then worked with the evidence team to complete draft evidence-to-decision frameworks by providing key input into each judgment resulting in draft recommendation language and justifications. Completed frameworks were presented to the full task force for further discussion and refinement and to achieve consensus for the recommendations. In addition, members were asked to reaffirm consensus and approval of the recommendations after completion of the manuscript.

The task force used GRADE to assess the certainty of evidence across studies for each outcome and the overall strength of each recommendation (Table 1).[25-27] To the extent possible, the task force considered the absolute risk differences for each outcome which were calculated as risk difference per 1000 individuals. A strong recommendation was issued based on high or moderate certainty of evidence where the task force had high confidence in the estimate of effect across outcomes (net benefit/harm) and that most informed individuals would choose the recommended option. A conditional recommendation was used for low to moderate certainty of evidence where the task force had lower confidence in the estimate of effect across outcomes (net benefit/harm) and where individual choice may vary based on values and preferences. No recommendation was made if the evidence was deemed as very low certainty or insufficient to adequately assess the balance of benefits and harms.

The wording of the recommendations reflected the strength and direction of the recommendation, and the certainty of the evidence was listed parenthetically. Summary of Findings tables are provided for each recommendation that outline the magnitude of the effect of the intervention and the certainty in the absolute estimate of effect. In addition, summary language was included in the tables to describe these findings using wording as outlined in Table 2.[28] Guideline recommendations were finalized based on consensus of the task force after completion of GRADE Evidence-to-Decision Frameworks, which enabled consideration of the certainty of the evidence across outcomes in addition to issues of feasibility, acceptability, equity, and patient preferences and values.

Table 1
American Association of Clinical Endocrinology Recommendation Grading System[a]

Recommendation type	Definition	Certainty of the evidence	
Strong: AACE recommends for/against…	High confidence in the estimate of effect across outcomes. Most informed patients would choose the recommended option.	High Moderate	⊕⊕⊕⊕ ⊕⊕⊕◯
Conditional: AACE suggests for/against…	Lower confidence in the estimate of effect across outcomes. Patient choices may vary based on values and preferences.	Moderate Low	⊕⊕⊕◯ ⊕⊕◯◯
No recommendation		Very low Insufficient	⊕◯◯◯
Good practice statement[b]	Ungraded guidance statements	None	

[a] Adapted from GRADE system for assessing the certainty of evidence and developing evidence-based recommendations (Guyatt 2008, Balshem 2011, Alonso-Coello 2016)[25-27].
[b] Consistent with the GRADE methodology, good practice statements will be clear and actionable. Task forces will label good practice statements as ungraded, transparently report judgments that consider benefits and harms, and clearly document rationale of statement to indirect evidence.

Table 2
Example Language for GRADE Summary of Findings Tables

Example magnitude of effect	Wording used to describe the effect for an outcome	Certainty in the estimate of effect	Wording used to describe our certainty in the effect for an outcome
Absolute risk estimate is at or near MID	Trivial increase/decrease in the outcome	High Moderate Low	There is… There is probably.. There may be..
Absolute risk estimate is larger than MID	Small to moderate increase/decrease in the outcome	High Moderate Low	There is… There is probably.. There may be..
Absolute risk difference is substantially larger than MID	Large increase/decrease in the outcome	High Moderate Low	There is… There is probably.. There may be..

Abbreviation: MID = minimally important difference in absolute risk.
Adopted from GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions.[28]

The recommendation statements are listed in Table 3 and shown in Figure. Supporting evidence summaries, an outline of benefits and harms, and clinical considerations are provided for each recommendation. In addition, an overview of the medications included in the guideline is provided in the conclusions section below.

Review Process and Patient Input

Drafts of this clinical practice guideline were reviewed and approved by all task force members, the AACE CPG Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*. In addition, all AACE members were able to provide review and comment on the draft recommendations and supporting summary of findings tables and frameworks during a member comment period of 4 weeks. A patient summary of the recommendations and supporting evidence and judgments was created and reviewed by patient champions from WomenHeart: The National Coalition for Women with Heart Disease. The patient champions provided feedback on the recommendation language, the prioritization of the patient-important outcomes, and judgments made by the task force members. In addition, the patient champions provided input on the accessibility and readability of the summary information and helpfulness in understanding the recommendations and support of shared decision-making. All comments were reviewed and revisions were made where appropriate.

Recommendations

ASCVD Risk Assessment

Recommendation 1. For primary prevention in adults with dyslipidemia, AACE recommends for the use of a validated tool or calculator to predict future risk of ASCVD events as part of shared decision-making around treatment. (Good Practice Statement, ungraded)

Summary of the Evidence

No head-to-head trials were identified from the literature search for this specific question; however, several systematic reviews and cohort studies were identified that reported c-statistics for addition of the specified risk enhancers. Other outcomes were not reported consistently across all studies. There were 7 observational studies and reviews that identified coronary artery calcium (CAC) score, ApoB, or Lp(a) compared with a risk calculator or risk assessment tool.[22,29-34] Individuals in the cohorts were adults (≥50 years of age) without CVD from the United States, Europe, and South Korea. Specific demographics varied by cohort, but in general, most participants were White men. A few cohorts, like the Multi-Ethnic Study of Atherosclerosis, included more diverse participants.[35] A range of risk assessment tools were used in the study calculations including the American College of Cardiology/American Heart Association Pooled Cohort Equations (PCE),[36] the Framingham Risk Score (FRS),[37] Systematic Coronary Risk Estimation,[38] and validated risk factors.

For this PICO question, task force members prioritized the outcomes of risk reclassification and prediction of CV events. There was limited direct evidence for these outcomes and inconsistent reporting across studies; therefore, GRADE evidence profiles were not created. Some studies reported actual or potential individuals whose risk was reclassified along with the net reclassification index (NRI). NRI is used to compare the improvement in risk prediction when adding different biomarkers to an existing risk prediction model. However, NRI can produce high rates of false-positive conclusions or an overestimation of the improvement of risk prediction with the biomarker.[39,40] The calibration slope is another measure used to validate risk prediction models; however, many studies do not calculate nor report the slope correctly by omitting the intercept, which can lead to a slope of 1 which can be interpreted as "good fit."[41] In comparison, c-statistics (change in the receiver operator curve) are more reliable and have been recommended over the NRI for evaluating newer risk prediction models. The task force reviewed the change in c-statistic reported by the different studies for each cohort and risk enhancer. This information was then used to make judgments about the addition of a risk enhancer in improvement of the different risk prediction models using a modified GRADE Evidence-to-Decision Framework (Table 4). Overall, the cohort studies showed c-statistic results for risk calculators (or risk factors) alone with a range of 0.693 to 0.84, which indicates that risk calculators or traditional models are good at predicting future ASCVD events. The addition of a risk enhancer only slightly improved the ability of the different models to predict ASCVD risk. Addition of a CAC score >0 was externally validated in 101 389 participants from 27 cohorts reported in 3 studies.[22,29,30] Across all of the different cohorts, the addition of CAC score increased the c-statistic anywhere from -0.01 to 0.088 compared with the PCE, FRS, or classical risk factors. Overall, it had the most impact of the 3 risk enhancers. The addition of ApoB was externally validated in 2 studies reporting on 4 cohorts with a total of 369 628 individuals.[29,30] The addition of ApoB levels of >100 mg/dL increased the c-statistic within a range of 0.0004 to 0.002 compared with the FRS, Reynolds, PCE, or classical risk factors.[29,30] The addition of Lp(a) was externally validated in >75 000 participants from 11 cohorts reported in 4 different studies.[29,31,32,34] Addition of Lp(a) values >50 mg/dL resulted in an increase of 0 to 0.0164 compared with the PCE or classical risk factors.[29,31,32,34] Based on these results, the task force concluded that the addition of these risk enhancers to a standard and validated risk calculator provided limited improvement in risk prediction. This is consistent with other groups such as the U.S. Preventive Task Force, which

Table 3
Summary of Recommendations

1. For primary prevention in adults with dyslipidemia, AACE recommends for the use of a validated tool or calculator to predict future risk of ASCVD events as part of shared decision-making around treatment. (Good practice statement, ungraded)
   - ASCVD risk assessment is a central component in person-centered management of dyslipidemia. However, there is limited utility in broad application in adding CAC scores, ApoB, and Lp(a) measurements. Additional testing may be considered for individuals at intermediate risk who understand the potential additional costs of testing and still value the risk information ascertained from using CAC score, ApoB, and/or Lp(a) to inform a treatment decision.
2. In adults with dyslipidemia who are on maximally tolerated statins and have ASCVD or are at increased risk for ASCVD but who are not at goal (LDL-C <70 mg/dL), AACE suggests for the use of evolocumab or alirocumab in addition to usual care. (Conditional recommendation, moderate certainty of evidence)
3. In adults with dyslipidemia who do not have ASCVD, AACE suggests *against* the use of evolocumab or alirocumab in addition to usual care. (Conditional recommendation, moderate certainty of evidence)
   - There is currently no direct evidence comparing evolocumab to alirocumab; use of either monoclonal antibody may be considered.
   - Most trial participants were at increased risk for ASCVD or were being treated for secondary prevention. It is unclear if the benefits outweigh the harms for use of these agents in adults at lower risk for ASCVD.
   - The task force considered ASCVD risk to include individuals with known risk factors based on clinical judgment or validated risk assessment tool.
4. There is insufficient evidence to make a recommendation for or against the use of inclisiran in adults with dyslipidemia. (No recommendation, insufficient evidence)
   - Overall, there were very few trials and cardiovascular events, preventing determination of the balance of potential benefits and harms for use of inclisiran in addition to usual care. Adequately powered longer-term cardiovascular outcomes trials are needed.
5. In adults with dyslipidemia who are statin intolerant and have ASCVD or are at increased risk for ASCVD, AACE suggests for the use of bempedoic acid in addition to usual care. (Conditional recommendation, moderate certainty of evidence)
6. In adults with dyslipidemia who do not have ASCVD and who may tolerate other lipid-lowering medications, AACE suggests *against* the use of bempedoic acid in addition to usual care. (Conditional recommendation, moderate certainty of evidence)
   - Patients should be informed that while bempedoic acid may lead to a small reduction in myocardial infarction, there may be a risk of potential harms (gout, cholelithiasis, and tendon rupture); therefore, a shared decision-making approach that includes a discussion about the potential benefits and harms should guide the treatment choice.
   - There was substantial heterogeneity in the trial populations related to the use of other lipid-lowering medications, including some participants taking low-dose statins.
   - Evidence for primary prevention is limited. A secondary analysis from the largest trial showed a potential for benefit in primary prevention; however, the number of individuals was small, and all participants were at high risk for ASCVD.
7. In adults with hypertriglyceridemia (150-499 mg/dL) who have cardiovascular disease or who are at increased risk for ASCVD, AACE suggests for the use of EPA (IPE) in addition to statins. (Conditional recommendation, low certainty of evidence)
8. There is insufficient evidence to recommend for or against the use of EPA (IPE) in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)
   - Patients should be informed that while EPA monotherapy may lead to a small reduction in myocardial infarction, there may be a risk of potential harms (small increased risk of developing atrial fibrillation and major bleeding). Therefore, a shared decision-making approach that includes a discussion about the potential benefits and harms, should guide treatment choice.
   - Individuals with severe hypertriglyceridemia (≥500 mg/dL) were not included in any of the trials. In addition, the trials did not report effects of EPA or IPE monotherapy on pancreatitis.
9. In adults with hypertriglyceridemia (150-499 mg/dL) who have cardiovascular disease or are at increased risk for cardiovascular disease, AACE suggests *against* the use of EPA plus DHA in addition to statin therapy. (Conditional recommendation, low certainty of evidence)
10. There is insufficient evidence to recommend for or against the use of EPA plus DHA in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)
    - Patients should be informed that treatment with doses of ≥1.8 grams per day of EPA plus DHA resulted in no clinically meaningful reduction in cardiovascular events or mortality and that there may be a risk of potential harms (small increased risk of developing atrial fibrillation and major bleeding). Therefore, a shared decision-making approach including a discussion about the potential benefits and harms should guide treatment choice.
    - Individuals with severe hypertriglyceridemia (≥500mg/dL) were not included in any of the trials. Additionally, the trials did not report effects of EPA plus DHA on pancreatitis.
11. In adults with hypertriglyceridemia (150-499 mg/dL) who have ASCVD or are at increased risk for ASCVD, AACE recommends *against* the use of niacin in addition to usual care. (Strong recommendation, low certainty of evidence)
12. There is insufficient evidence to recommend for or against the use of niacin in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)
    - Niacin, in combination with statins, may lead to a trivial reduction in myocardial infarction, but there is a risk of serious potential harms (small to moderate increased risk of infection, bleeding, and hospitalization due to hyperglycemic events).
    - Combination drugs containing niacin and statin are no longer approved by the FDA.
    - Individuals with severe hypertriglyceridemia (≥500 mg/dL) were not included in any of the trials. In addition, the trials did not report effects of EPA (IPE) on pancreatitis.
13. In adults undergoing pharmacotherapy for dyslipidemia who have ASCVD or are at increased risk for ASCVD, AACE suggests for treatment to an LDL-C target of <70 mg/dL. (Conditional recommendation, low certainty of evidence)
    - The 2017 recommendation for lower LDL-C treatment targets (<55 mg/dL) was informed by a single trial on statin plus ezetimibe. Subsequent meta-analyses of numerous trials and multiple types of agents did not show a difference in cardiovascular events or mortality.
    - Clinicians should engage patients in shared decision-making including the trivial to small benefits and trivial adverse effects, costs, patient preferences, and impact on equity with lower treatment targets.

Abbreviations: AACE = American Association of Clinical Endocrinology; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FDA = U.S. Food and Drug Administration; IPE = icosapent ethyl; Lp(a) = lipoprotein a; LDL-C = low-density lipoprotein cholesterol.

issued statements of insufficient evidence for inclusion of nontraditional risk factors in risk assessment and treatment decisions for primary prevention of ASCVD.[22,42]

Benefits and Harms

The task force used a modified GRADE Evidence-to-Decision Framework for addition of risk enhancers to ASCVD risk assessment to discuss potential impacts on different domains including patient values, strength of the association of the risk enhancers and ASCVD risk, potential harms and benefits of additional testing and false positives or false negatives, costs, equity, acceptability, and feasibility (Table 4).

Based on the domains above, the task force judged there to be limited utility in the broad application of adding CAC scores, ApoB, and Lp(a) measurements to a validated risk assessment tool. Risk assessment is a central feature in determining management plans and treatment goals for adults with elevated lipid levels. The

Table 4
Modified GRADE Evidence-to Decision Framework for Addition of Risk Enhancers to ASCVD Risk Assessment

Domain	Discussion
How much do patients value incremental improvement in prediction of their 10-year ASCVD risk?	Patient values and preferences were judged to be variable with potential differences based on a patient's awareness of ASCVD risk and their education level or family history. The task force discussed the potential of more impact for individuals at intermediate risk and determining management and treatment goals.
Strength of association of prognostic indicators and ASCVD risk	The task force judged there to be no clinically impactful change in c-statistic when adding one of the risk enhancers to a standard risk calculator or tool.
Balance of benefits/harms of evaluating additional prognostic indicators (initial testing)	Potential benefits: The task force discussed that providing detailed risk information may increase patient satisfaction/reassurance and increased information for shared decision-making. Potential harms: The task force discussed the increased costs for imaging and blood tests, the additional exposure to radiation for CAC, additional needle sticks for blood work, and extra office visits.
Benefits/harms for downstream treatment or management decision (false positive and false negative) e.g., overtreatment or undertreatment	The task force acknowledged the potential harmful impact of patients and clinicians having a test result without adequate treatment options, the potential for overtreatment and side effects, potential inappropriate treatments; increased patient and clinician anxiety; increased office visits and follow-up. The task force discussed the main benefits being more information to facilitate shared decision-making and the potential for early identification of heart disease in family.
Costs of additional testing	As discussed above, there are definite costs associated with additional testing, although the actual costs vary based on practice setting and insurance coverage. Specifically for CAC, there would be costs for imaging, clinical time to read the image, time off work for patients (potentially including travel), and barriers in access in certain regions. For ApoB and Lp(a), there could be costs for additional laboratory blood draws and if the tests need to be sent to a different location for processing. There may also be additional office visits depending on the timing of the tests.
Equity (bias in algorithms/calculator)	Race bias in many risk calculators may negatively impact results and treatment decisions for some individuals. Additional impacts on equity could result from socioeconomic differences in awareness and desire for testing and access to additional tests. Globally, there will be impacts on different groups of individuals related to regional differences in lipid profiles and access to health care.
Acceptability (clinicians and patients; access)	The task force judged that acceptability would vary for patients and clinicians, depending on patient values and access to care or other resources.
Feasibility (labs, CAC imaging, etc)	As outlined above, the task force judged feasibility to vary as there are documented access issues in rural and under-resourced communities that do not have imaging facilities or equipment or in-house laboratory services for these additional risk enhancers.

Abbreviations: ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; Lp(a) = lipoprotein a.

calculation of an individual's risk is considered standard of care and several risk calculators are embedded in an electronic health record or accessed online as part of the workflow. While several calculators have been validated using the exact or similar cohorts as described above, there is currently no preferential recommendation for one calculator over another. Therefore, the task force issued a good practice statement recommending the use of a validated ASCVD risk assessment tool for determining an individual's 10-year ASCVD risk for persons 40 to 79 years of age.

Clinical Considerations

The risk calculator tool is a particularly important aspect of risk factor assessment, and its greatest utility may be for individuals at intermediate ASCVD risk where the decision to treat or not treat with pharmacologic intervention may be uncertain. This tool should not be used when the decision to offer pharmacologic treatment for an individual is already supported by clinical findings or assessment (secondary prevention, high risk for future ASCVD events, or genetic predisposition) and its applicability is limited in those who have no CV risk factors. The risk calculator tool is best used in shared decision-making between patients and clinicians to decide whether the initiation of lipid-lowering medication could be beneficial in preventing future ASCVD events. Risk calculators should be used to determine ASCVD risk before the initiation of treatment. If a person has not begun pharmacotherapy, repeat calculations can be performed to monitor potential changes in risk while instituting lifestyle changes. Many risk calculators may not be suitable for individuals with familial hypercholesteremia as they can underestimate risk. Additional considerations and screening may be needed to accurately assess risk and determine treatment plans for these patients.[43]

Several risk assessment tools are now available for use, and each of these tools are interchangeable and appropriate for routine care. It is widely acknowledged that there are inherent issues with many clinical algorithms and calculators in their inappropriate use of race.[44] Many medical specialty societies are developing new algorithms that do not include race such as the American Heart Association Predicting Risk of CVD EVENTs (PREVENT) online calculator.[45,46] Instead of race, it uses ZIP code as a better surrogate for social deprivation index (health disparities). In addition, the PREVENT calculator includes measures of kidney function and A1C as part of the risk prediction model.[46] It is also important to recognize the limitations of risk calculators. For example, not every stratum of age is represented and well-validated, and many available risk calculators do not appropriately consider diversity in patient populations, including differences in social determinants of health, race/ethnicity, gender, regionality, and risk related to current or previous health conditions. The PREVENT model was observed to result in lower risk predictions compared with the PCE. However, it is not known which model is more accurate in clinical practice.[47]

In summary, the inclusion of multiple independent risk factors (Lp[a], ApoB, and CAC scores) leads only to incremental improvement and does not provide impactful benefits in assessing risk. However, there may be instances where additional information could be useful to support shared decision-making. For example, a CAC of 0, which may be associated with a reduced risk of CV-related mortality, may support a person at intermediate risk in not starting lipid-lowering medication. In addition, a discordantly elevated ApoB in the face of a modest LDL-C value may be associated with residual risk for ASCVD[48] and may lead to decision to take a statin. However, both examples have limited evidence, and more research is needed. Note there is little utility in repeating the CAC measurement and this should be discouraged as this raises the risk of increased radiation without added benefit.[49] CAC scores may not be reliable in certain individuals, including persons with DM, who are HIV-positive, use nicotine, and are of younger age (<50 years).[16] In addition, many people may not be able to access CAC testing because of location and cost. This is supported by a retrospective analysis of >19 000 patients that observed only a small percentage of individuals from lower socioeconomic areas completing CAC testing after physician or self-referral.[50]

PCSK9 Monoclonal Antibodies

Recommendation 2. In adults with dyslipidemia who are on maximally tolerated statins and have ASCVD or are at increased risk for ASCVD but who are not at goal (LDL-C <70 mg/dL), AACE suggests for the use of evolocumab or alirocumab in addition to usual care. (Conditional recommendation, moderate certainty of evidence)

Recommendation 3. In adults with dyslipidemia who do not have ASCVD and who may tolerate other lipid-lowering medications, AACE suggests *against* the use of evolocumab or alirocumab in addition to usual care. (Conditional recommendation, moderate certainty of evidence)

Summary of the Evidence

The evidence informing the recommendations for evolocumab and alirocumab was derived from a published systematic review of moderate quality.[51] For evolocumab, 17 RCTs were included in the review with 39 381 participants and a weighted mean follow-up of 1.7 years. For alirocumab, there were 22 trials with 27 097 participants and a mean follow-up of 3.1 years. Not all trials contributed events for each outcome as some trials only reported on mortality or CV events as part of their safety analysis. Participants in the included trials comprised adults with LDL-C levels ≥70 mg/dL or as high as 160 mg/dL on statin or on no statin, with or without CVD, with or without heterozygous familial hypercholesterolemia (HeFH) and with or without DM.[51] A small trial (N = 49) with evolocumab in patients with homozygous familial hypercholesterolemia (HoFH) was also included.[52] While all trials were placebo-controlled, participants were continued on other lipid-lowering medications including statins (if tolerated) and ezetimibe as indicated by their CV risk status.

Most of the events used to build the evidence profile and to inform the judgments in the Evidence-to-Decision Framework came from 2 single large RCTs with prespecified CV outcomes: FOURIER (N = 27 594)[53] for evolucumab with a median follow-up of 2.2 years, and ODYSSEY OUTCOMES (N = 18 924)[54] for alirocumab with 2.8 years of median follow-up. Participants in these 2 secondary prevention trials had LDL-C of ≥70 mg/dL on statin with or without ezetimibe at the time of enrollment. In FOURIER, participants had stable CVD (>3 years since their last MI or ischemic stroke) and if randomized to evolocumab received either 140 mg every 2 weeks or 420 mg subcutaneously every 4 weeks.[53] ODYSSEY OUTCOMES enrolled adults with a recent history of acute coronary syndrome (median of 2.6 months since their acute event).[54] Alirocumab was administered at a dose of 75 mg subcutaneously every 2 weeks with adjustments during follow-up to keep the LDL-C in the 25 to 50 mg/dL range. It is important to note that the effects of evolocumab and alirocumab on PVD outcomes were informed by prespecified post hoc analyses from the FOURIER trial for evolocumab and from ODYSSEY OUTCOMES for alirocumab.[55,56]

The summary of the certainty of evidence and magnitude of effects is shown in the Summary of Findings for evolocumab (Table 5) and for alirocumab (Table 6). The full GRADE evidence profile can be found in Appendices E and F.

Overall, there was moderate certainty of evidence for evolocumab based on the lowest level of certainty across the critical outcomes, which included stroke. Based on the summary estimates of effect from the included RCTs, the task force determined that evolocumab does not result in a clinically meaningful difference in the risk of all-cause mortality, CV-related mortality, stroke, coronary revascularization, PVD events, or discontinuation due to adverse events compared with usual care. The addition of evolocumab to usual care leads to a small decrease in risk of MI.

For alirocumab, the certainty of evidence was moderate across all outcomes. The task force determined that it does not result in a clinically meaningful difference in the risk of CV-related mortality, stroke, coronary revascularization, or discontinuation due to adverse effects but does lead to a small decrease in the risk of MI and trivial reductions in PVD events and all-cause mortality when compared with usual care.

Benefits and Harms

CV events with evolocumab and alirocumab were slightly lower than events observed with usual care alone, with the greatest difference of 14 fewer per 1000 participants (95% confidence interval [CI] 18 to 9 fewer) reported for coronary revascularizations in the case of evolocumab and 18 fewer per 1000 participants (95% CI 34 fewer to 4 more) for MI with alirocumab. However, these decreases did not reach the clinically meaningful threshold set by the task force. The absolute risk difference when adding evolocumab to treatment with or without statin for MI was 11 fewer per 1000 participants (95% CI 13 to 7 fewer) and, when adding alirocumab for coronary revascularization, 7 fewer (95% CI 13 to 1 fewer) per 1000 participants. For stroke prevention, the risk difference for evolocumab and alirocumab was similar with 3 fewer events (95% CI 5 to 1 fewer) per 1000 participants. The risk difference for PVD events was 2 fewer events per 1000 participants (95% CI 3 to 1 fewer) with evolocumab and 5 fewer per 1000 participants (95% CI 7 to 2 fewer) with alirocumab. While the addition of alirocumab to usual care led to 6 fewer all-cause deaths per 1000 participants (95% CI 9 to 2 fewer), evolocumab did not result in a clinically meaningful decrease in risk of all-cause or CV mortality rates, ranging from 2 fewer to 4 more deaths. The increase in the number of participants discontinuing treatment due to adverse events was not clinically meaningful for the addition of evolocumab (range from 2 fewer to 4 more) or alirocumab (range from 3 fewer to 7 more) when compared with usual care alone. It is important to note that the rates of events per 1000 participants are not comparable across the 2 PCSK9 inhibitors because the studies providing the evidence for each agent differed in terms of population and duration of follow-up.

The task force judged there to be small desirable effects based on the small decrease observed for MI with the addition of evolocumab and alirocumab compared with placebo. The undesirable effects were based on the number of participants who discontinued treatment due to adverse events, which were judged to be trivial and consisted mainly of local injection site reactions. Overall, the balance of benefits and harms was judged to be small and slightly favored the use of evolocumab or alirocumab in addition to usual care.

Clinical Considerations

Evolocumab and alirocumab are fully human mAbs that bind to PCSK9, a proprotein synthesized mostly in the liver and found in circulation in active form bound to 1 of every 500 to 1000 LDL particles.[57] When an LDL particle containing PCSK9 binds to the LDL receptor it results in the lysosomal degradation of the receptor rather than its recycling to the cell surface. PCSK9 mAbs block the binding of PCSK9 to circulating LDL particles interfering with the degradation of the LDL receptor, thereby increasing LDL-C clearance. Evolocumab and alirocumab are approved by the FDA for use in adults with established CVD and in adults with primary hyperlipidemia, including HeFH and HoFH, to reduce LDL-C.[58,59] Evolocumab also has approval for use in children ≥10 years of age who have HeFH or HoFH. Alirocumab is approved for children with HeFH ≥8 years of age. For adults with dyslipidemia, the approved dosage

Table 5
Summary of Findings: Evolocumab Compared With Usual Care[a] for Adults With Dyslipidemia

Outcomes,[b] mean follow-up 1.7 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with evolocumab		
All-cause mortality	39 381 (17 RCTs)	RR 1.03 (0.90-1.17)	24 per 1000	1 more per 1000 (2 fewer to 4 more)	⨁⨁⨁⨁ High	Evolocumab does not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	38 413 (15 RCTs)	RR 1.04 (0.87-1.23)	14 per 1000	1 more per 1000 (2 fewer to 3 more)	⨁⨁⨁⨁ High	Evolocumab does not result in a clinically meaningful decrease in CV-related mortality.
Myocardial infarction	36 229 (10 RCTs)	RR 0.73 (0.66-0.82)	39 per 1000	11 fewer per 1000 (13 to 7 fewer)	⨁⨁⨁⨁ High	Evolocumab results in a small reduction in myocardial infarction.
Stroke	35 575 (9 RCTs)	RR 0.79 (0.66-0.94)	16 per 1000	3 fewer per 1000 (5 to 1 fewer)	⨁⨁⨁◯ Moderate[d]	Evolocumab probably does not result in a clinically meaningful decrease in stroke.
Coronary revascularization	35 635 (10 RCTs)	RR 0.78 (0.71-0.85)	63 per 1000	14 fewer per 1000 (18 to 9 fewer)	⨁⨁⨁⨁ High	Evolocumab does not result in a clinically meaningful decrease in coronary revascularization.
Discontinuation due to adverse events	33 909 (14 RCTs)	RR 1.03 (0.90-1.17)	16 per 1000	0 fewer per 1000 (2 fewer to 4 more)	⨁⨁⨁⨁ High	Evolocumab does not result in a clinically meaningful increase in discontinuation due to adverse events.
PVD events, median follow-up 2.2 years	27 564 (1 RCT)	HR 0.58 (0.38-0.88)	4 per 1000	2 fewer per 1000 (3 to1 fewer)	⨁⨁⨁⨁ High[e]	Evolocumab does not result in a clinically meaningful reduction in PVD events.

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MID = minimally important difference; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] May include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for PVD events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference. An MID of 5 per 1000 participants was used for all outcomes except coronary revascularization, where an MID was set at 50 per 1000 participants.
[e] Prespecified post hoc analysis and reported in a separate publication.

Table 6
Summary of Findings: Alirocumab Compared With Usual Care[a] for Adults With Dyslipidemia

Outcomes,[b] mean follow-up 3.1 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with alirocumab		
All-cause mortality	27 147 (22 RCTs)	RR 0.83 (0.72-0.95)	33 per 1000	6 fewer per 1000 (9 to 2 fewer)	⨁⨁⨁◯ Moderate[d]	Alirocumab probably results in a trivial decrease in all-cause mortality.
CV-related mortality	26 294 (22 RCTs)	RR 0.86 (0.73-1.02)	23 per 1000	3 fewer per 1000 (6 to 0 fewer)	⨁⨁⨁◯ Moderate[d]	Alirocumab probably does not result in a clinically meaningful decrease in CV-related mortality.
Myocardial infarction	25 326 (14 RCTs)	RR 0.76 (0.54-1.06)	74 per 1000	18 fewer per 1000 (34 fewer to 4 more)	⨁⨁⨁◯ Moderate[d]	Alirocumab probably results in a small reduction in myocardial infarction.
Stroke	24 753 (13 RCTs)	RR 0.75 (0.60-0.95)	13 per 1000	3 fewer per 1000 (5 to 1 fewer)	⨁⨁⨁◯ Moderate[d]	Alirocumab probably does not result in a clinically meaningful decrease in stroke.
Coronary revascularization	24 753 (13 RCTs)	RR 0.90 (0.82-0.98)	74 per 1000	7 fewer per 1000 (13 to 1 fewer)	⨁⨁⨁⨁ High	Alirocumab does not result in a clinically meaningful reduction in coronary revascularization.
Discontinuation due to adverse events	26 999 (19 RCTs)	RR 1.04 (0.93-1.17)	42 per 1000	2 more per 1000 (3 fewer to 7 more)	⨁⨁⨁◯ Moderate[d]	Alirocumab probably does not result in a clinically meaningful increase in discontinuation due to adverse events.
PVD events, median follow-up 2.8 years	18 924 (1 RCT)	HR 0.69 (0.54-0.89)	15 per 1000	5 fewer per 1000 (7 to 2 fewer)	⨁⨁⨁◯ Moderate[d,e]	Alirocumab probably results in a trivial reduction in PVD events.

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] May include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for PVD events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] Prespecified post hoc analysis and reported in a separate publication.

for evolocumab is 140 mg administered as a subcutaneous injection every 2 weeks or 420 mg once monthly. For alirocumab, approved doses are 75 to 150 mg every 2 weeks or 300 mg once per month administered subcutaneously. Dosing may differ for individuals with HeFH and HoFH.

The application of the evidence on the effects of evolocumab and alirocumab on clinical decisions addressing CV outcomes, and particularly mortality, is limited by the relatively short duration of the trials (median <3 years). It is possible that the trivial benefit on overall mortality observed with alirocumab and not with evolocumab could be due to the slightly longer duration of follow-up in the ODYSSEY OUTCOMES trial and/or to the higher risk of the population enrolled in that study when compared with that in FOURIER. Importantly, 70% of trial participants and most of the events for each of the PCSK9 inhibitors from which the evidence was obtained came from one of these 2 phase 3 clinical trials. In an open-label extension of FOURIER,[53] the FOURIER-OLE trial,[60] 6635 participants continued follow-up for a median of 5 additional years, and although a small benefit was seen in CV mortality in those originally randomized to evolocumab compared with those who had received placebo, there was no difference in overall mortality. Studies with longer follow-up will be important to determine impacts on mortality that may differ by underlying risk and potential adverse events with the use of evolocumab and alirocumab over the long term. FOURIER-OLE, with some participants accruing >8 years of follow-up on evolocumab, did not identify concerns for an increased risk of new-onset DM or of hemorrhagic stroke or neurocognitive impairment despite LDL-C levels that remained <40 mg/dL.[60] In addition to the potential for more information related to mortality, longer-term studies may also provide data on CV outcomes, especially PVD events. Data for this outcome are limited with only 2 trials reporting events in the evidence profiles. An additional small study was identified showing improvement in mean and pain-free walking time with evolocumab, but it was of short duration and did not report PVD events.[61]

Currently, there are limited data on the impact of evolocumab and alirocumab across sex/gender or race/ethnicity subgroups; most trial participants were male and White. In this setting, subgroup analysis on primary composite outcomes for evolocumab in FOURIER[53] and for alirocumab in ODYSSEY OUTCOMES[54] did not identify any interactions by age or by sex/gender.[62]

In terms of statin use and CV risk, a 2019 systematic review[51] reported sensitivity analyses that showed no differences in secondary prevention or participants with statin-intolerance compared with the results for the total population. A sensitivity analysis that grouped participants by baseline LDL-C level did show a larger reduction in relative risk for individuals with higher baseline levels (LDL-C ≥100 mg/dL) compared with individuals with lower levels (LDL-C <100 mg/dL).[51] These results are consistent with other published systematic reviews including a high-quality Cochrane Review[63] of phase 3 trials. While head-to-head trials comparing alirocumab and evolocumab directly are not available, a 2021 network meta-analysis found a reduction in the relative risk for all-cause mortality with alirocumab compared with evolocumab.[64] However, there were no differences in relative risk for CV-related mortality, MI, stroke, coronary revascularization, or treatment discontinuation between the 2 antibodies.[64]

Based on the evidence and judgments made in the Evidence-to-Decision Framework (Appendices E and F), the task force determined that both evolocumab and alirocumab probably provide a small benefit on CV events that may be valued by some patients who are at increased risk for CV events or who are unable to tolerate other lipid-lowering medications, leading the task force to issue a conditional recommendation for use of either antibody in addition to usual care for individuals with dyslipidemia who are not at goal (LDL-C <70 mg/dL) who may consider additional medications to reduce ASCVD risk. As outlined above, few participants included in the trials did not have ASCVD and risk categories were not included in outcome reporting, so it is unclear if there are benefits for use of evolocumab or alirocumab for primary prevention or individuals not at increased ASCVD risk. In addition, the costs and required resources were judged to be large for evolocumab and alirocumab based on the cost of medication, requirements for prior authorizations, and the need to have unsuccessfully tried alternative treatments. The task force agreed that there may be a reduction in health equity given potential disparities in ability to afford these medications without insurance coverage and the acknowledged disparities in care for people of color and women.[9,65-68] Therefore, the task force issued a conditional recommendation against the use of evolocumab and alirocumab in individuals who do not have ASCVD and who may tolerate other lipid-lowering medications.

Inclisiran

Recommendation 4. There is insufficient evidence to make a recommendation for or against the use of inclisiran. (No recommendation, insufficient evidence)

Summary of the Evidence

The evidence informing the recommendations for inclisiran was derived from a published systematic review of moderate quality.[69] The systematic review included 4 RCTs, reported in 3 publications, with LDL-C reduction endpoints that also reported CV events or mortality as part of the safety analyses.[70-72] The trials included 4226 participants, with a time of follow-up ranging from 8 to 77 weeks. ORION 1, 9, 10, and 11 were the major trials that contributed to the evidence profile. The latter 3 were phase 3 clinical trials that tested inclisiran at the currently approved dose of 284 mg for a period of 18 months.[70,72]

Participants in the trials included adults at increased risk for CV events who were taking maximally tolerated statin doses, or on no statin due to intolerance, and who had elevated LDL-C levels (≥70 mg/dL if with ASCVD; ≥100 mg/dL if with an ASCVD risk equivalent). Individuals with ASCVD equivalent included those with HeFH, T2D, or a predicted 10-year risk of >20% using FRS for CVD or equivalent. While all trials were placebo-controlled, participants were allowed to continue use of other lipid-lowering medications such as statins (if tolerated) and ezetimibe.

The phase 3 clinical trials contributed to all but 2 of the CV and mortality outcomes of interest (all-cause mortality, CV mortality, stroke, and MI) that were reported as part of their safety analysis. Moreover, the event rates of the reported outcomes of interest were low. None of the trials in the meta-analysis reported incidence of PVD events or coronary revascularization, so these outcomes were not included in the evidence profile.

Overall, there were few trials and events and the CIs included appreciable potential benefit and harm, which led the task force to rate the certainty of evidence as low. Given the uncertainty and limited evidence base, the task force determined there was insufficient evidence at this time to make a recommendation for or against the use of inclisiran. Moreover, the task force awaits the completion of longer-term studies to better understand the impact of inclisiran on CV events and mortality. The summary of the certainty of evidence and magnitude of desirable and undesirable effects are shown in the Summary of Findings table (Table 7 and Appendix G).

Table 7
Summary of Findings: Inclisiran Compared With Usual Care[a] for Adults With Dyslipidemia

Outcomes,[b] follow-up 30-77 weeks	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with inclisiran		
All-cause mortality	3739 (4 RCTs)	OR 1.01 (0.59-1.71)	15 per 1000	0 fewer per 1000 (6 fewer to 10 more)	⨁⨁◯◯ Low[d,e]	Inclisiran may not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	3655 (3 RCTs)	OR 1.11 (0.56-2.23)	8 per 1000	1 more per 1000 (4 fewer to 10 more)	⨁⨁◯◯ Low[d,e]	Inclisiran may not result in a clinically meaningful decrease in CV-related mortality.
Stroke	3174 (2 RCTs)	OR 0.69 (0.11-4.21)	9 per 1000	3 fewer per 1000 (8 fewer to 29 more)	⨁⨁◯◯ Low[d,e,f]	Inclisiran may not result in a clinically meaningful decrease in stroke.
Myocardial infarction	3655 (3 RCTs)	OR 0.85 (0.36-1.98)	23 per 1000	3 fewer per 1000 (14 fewer to 21 more)	⨁⨁◯◯ Low[d,e]	Inclisiran may not result in a clinically meaningful decrease in myocardial infarction.
Discontinuation due to adverse events	3737 (4 RCTs)	OR 1.21 (0.77-1.88)	20 per 1000	4 more per 1000 (4 fewer to 17 more)	⨁⨁◯◯ Low[d,e]	Inclisiran may not result in a clinically meaningful increase in discontinuation due to adverse events.
Coronary revascularization	Not measured					
PVD events	Not measured					

Abbreviations: CI = confidence interval; CV = cardiovascular; OR = odds ratio; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] Usual care may include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The systematic review authors rated the trials as high risk of bias for incomplete reporting and selective reporting of lipid outcomes. The task force judged that these concerns did not apply to this outcome so chose not to rate down for risk of bias.
[e] Rated down 2 levels as there were relatively few events and the CI includes appreciable benefit and harm.
[f] There were few events and 2 studies included for this outcome, leading to the potential for the I^2 value to be overestimated so the task force did not rate down for inconsistency.

Benefits and Harms

The summary of evidence shows no clinically important differences in mortality and CV events with the addition of inclisiran to usual care compared with usual care alone. As shown below, the greatest difference in absolute risk was 3 fewer strokes per 1000 participants (95% CI 8 fewer to 29 more) and 3 fewer MIs per 1000 participants (95% CI 14 fewer to 21 more); however, these decreases are not clinically meaningful. Similarly, the addition of inclisiran made no clinically meaningful difference in all-cause mortality and CV-related mortality with absolute risk rates ranging from 6 fewer but up to 10 more deaths per 1000 individuals. The task force judged the desirable effects to be trivial based on the current data.

The estimate of undesirable effects was derived from the number of participants who discontinued treatment with inclisiran due to adverse events. Adverse events reported in trials included injection site reactions and bronchitis. The task force judged the undesirable effects to be trivial (range from 4 fewer to 17 more treatment discontinuations per 1000 individuals).

Clinical Considerations

Inclisiran is a double-stranded small interfering RNA that blocks PCSK9 production. Its conjugation with *N*-acetyl galactosamine directs its effects to the liver where it leads to the catalytic breakdown of PCSK9 messenger RNA. By inhibiting the synthesis of PCSK9, inclisiran increases the expression of LDL receptors on the hepatocyte cell surface promoting the uptake of LDL-C and reducing circulating LDL-C levels.[73] Inclisiran is approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia, including those with HeFH or ASCVD, who require additional lowering of LDL-C. The recommended dosage is 284 mg administered by a health care professional as a single subcutaneous injection initially, again at 3 months, and then every 6 months thereafter.

The task force regarded the maintenance regimen for inclisiran with twice a year dosing particularly attractive for patients with medication compliance issues. However, it judged the medication to be associated with large costs (see Evidence-to-Decision Framework in Appendix G). Beyond the medication's price, there are supplementary expenses related to staff time for prior authorization, addressing insurance denials and appeals, as well as the stocking and administration of the medication. The lack of access to this medication for uninsured and underinsured Americans and the need to receive doses at a health care facility were judged by task force members to have a potential negative impact on equity.

In all trials, inclisiran reduced LDL-C levels and is approved by the FDA for lowering LDL-C in adults with primary hyperlipidemia who are on medications and require additional lipid-lowering. However, with limited evidence at this time, the task force was unable to determine the balance of CV and mortality benefits over potential harms for use of inclisiran in addition to usual care. Adequately powered longer-term CV outcomes trials are needed to address the question of whether inclisiran, when compared with usual care, reduces CV events and mortality and to further address long-term safety.

Bempedoic Acid

Recommendation 5. In adults with dyslipidemia who are statin-intolerant and have ASCVD or are at increased risk for ASCVD, AACE

suggests for the use of bempedoic acid in addition to usual care. (Conditional recommendation, moderate certainty of evidence)

Recommendation 6. In adults with dyslipidemia who do not have ASCVD and can tolerate other lipid-lowering medications, AACE suggests *against* the use of bempedoic acid in addition to usual care. (Conditional recommendation, moderate certainty of evidence)

Summary of the Evidence

The evidence informing the recommendations for bempedoic acid (BA) was derived from a meta-analysis of 7 RCTs involving 17 924 participants and a length of follow-up ranging from 4 weeks to 3.4 years.[74-80] Populations included in all trials were adults with elevated LDL-C, with or without HeFH, with or without CVD, on maximally tolerated statins. The CLEAR trials assessed the effects of the currently approved bempedoic dose of 180 mg a day.[74,76,78,79] Statin use varied across these trials, ranging from 8%[79] to 99%.[80] The CLEAR Outcomes trial,[79,81] with 13 970 participants, 70% of them with established ASCVD and only 22% on statin therapy, contributed the majority of the events. The following outcomes were assessed: all-cause mortality, CV-related mortality, any MI, any stroke, coronary revascularization, and discontinuation due to adverse events. The outcome of PVD was reported in all trials except one[79] as non-coronary revascularization.

The summary of the certainty of evidence and magnitude of effects is shown in the Summary of Findings table (Table 8). The full GRADE evidence profile can be found in Appendix H.

Overall, there was moderate certainty of evidence based on the critical outcomes of all-cause mortality, stroke, and treatment discontinuation. The outcome of PVD events was rated as low certainty of evidence; however, it was judged as important but not critical for decision-making by the task force.

Benefits and Harms

The Summary of Findings show that there is likely no clinically relevant reduction in all-cause mortality, CVD-related mortality, stroke, or coronary revascularization with use of BA. However, BA results in a small reduction in MI. Absolute risk rates with BA per 1000 participants ranged from 14 fewer to 48 more for all-cause deaths, 4 fewer to 8 more for CV deaths, and 6 fewer to 2 more for strokes. BA resulted in 11 fewer MIs (95% CI 15 to 5 fewer) and 6 fewer PVD events (9 to 0 fewer) per 1000 participants.

The estimate of undesirable effects was derived from the number of participants who discontinued treatment with BA due to adverse events. Examples of adverse events reported in the trials included occurrences of gout, cholelithiasis, and tendon rupture. The absolute risk rate for treatment discontinuation with BA was deemed moderate with 21 more discontinuations due to adverse events per 1000 participants (95% CI 1 to 45 more).

When evaluating the overall evidence, task force members placed more value on the potential decrease in MI and PVD events than on the potential harm from adverse events. The task force judged the balance to favor the use of BA in addition to usual care for adults with elevated LDL-C levels on maximally tolerated statin who have ASCVD or are at high-risk for ASCVD and recommended that those individuals be informed of the potential adverse events.

Table 8
Summary of Findings: Bempedoic Acid Compared With Usual Care[a] for Adults With Dyslipidemia

Outcomes,[b] follow-up 12 weeks to 3.4 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with bempedoic acid		
All-cause mortality	17 865 (6 RCTs)	RR 1.19 (0.73-1.93)	52 per 1000	10 more per 1000 (14 fewer to 48 more)	⨁⨁⨁◯ Moderate[d]	Bempedoic acid probably does not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	17 323 (4 RCTs)	RR 1.05 (0.89-1.24)	32 per 1000	2 more per 1000 (4 fewer to 8 more)	⨁⨁⨁⨁ High	Bempedoic acid does not result in a clinically meaningful decrease in CV-related mortality.
Myocardial infarction	17 383 (5 RCTs)	RR 0.76 (0.65-0.89)	44 per 1000	11 fewer per 1000 (15 to 5 fewer)	⨁⨁⨁⨁ High	Bempedoic acid results in a small reduction in myocardial infarction
Stroke	17 323 (4 RCTs)	RR 0.87 (0.69-1.08)	20 per 1000	3 fewer per 1000 (6 fewer to 2 more)	⨁⨁⨁◯ Moderate[d]	Bempedoic acid probably does not result in a clinically meaningful decrease in stroke.
Coronary revascularization	17 924 (7 RCTs)	RR 0.82 (0.73-0.92)	70 per 1000	13 fewer per 1000 (19 to 6 fewer)	⨁⨁⨁⨁ High	Bempedoic acid does not result in a clinically meaningful reduction in coronary revascularization.
Discontinuation due to adverse events	17 323 (4 RCTs)	RR 1.21 (1.01-1.45)	99 per 1000	21 more per 1000 (1 to 45 more)	⨁⨁⨁◯ Moderate[d]	Bempedoic acid probably results in a moderate increase in discontinuation due to adverse events.
PVD events	3353 (3 RCTs)	RR 0.41 (0.18-0.96)	11 per 1000	6 fewer per 1000 (9 fewer to 0 fewer)	⨁⨁◯◯ Low[e]	Bempedoic acid may result in a trivial decrease in PVD events.

Abbreviations: CI = confidence interval; CV = cardiovascular; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] Usual care may include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] Rated down 2 levels as there were relatively few events and the CI includes appreciable benefit and harm.

Clinical Considerations

BA reduces cholesterol synthesis by inhibiting the action of ATP-citrate lyase, an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase. By blocking cholesterol synthesis, BA increases the expression of LDL receptors and LDL-C clearance. BA is a prodrug that needs to be activated by long-chain acyl-CoA syhetase-1, an enzyme found in liver but not in skeletal muscle.[82] This key activation step directs the effects of the drug away from muscle, potentially reducing the risk of adverse muscular effects. BA received FDA approval for use in adults who have ASCVD or are at increased risk for ASCVD and are unable to take recommended statin therapy to reduce risk of ASCVD events. It is also approved to lower LDL-C in patients with primary hyperlipidemia including HeFH.[83]

Evidence for primary prevention is limited. A secondary analysis from the largest trial showed the potential for benefit in primary prevention; however, the number of individuals was small, and all participants were at high risk for ASCVD.[84] In patients with elevated LDL-C levels with or at increased risk of ASCVD, who may be either unable or unwilling to adhere to the recommended statin doses, BA results in a small decrease in the risk of MI. However, BA also leads to moderate increases in treatment discontinuation because of adverse events. While the task force judged that BA may be a treatment option for some individuals, it acknowledges that there is still some uncertainty regarding how these outcomes will be perceived by both patients and their health care providers and that cost may limit access (Appendix H). Given that the adverse events associated with BA may be potentially serious, a shared decision-making approach should be used to ensure that both patients and providers are fully informed about the benefits and harms of this treatment option.

Treatment of Hypertriglyceridemia

Eicosapentanoic Acid (EPA) and Docosahexanoic Acid (DHA)

Recommendation 7. In adults with hypertriglyceridemia (150-499 mg/dL) who have ASCVD or are at increased risk for ASCVD, AACE suggests for the use of EPA (IPE) in addition to statins. (Conditional recommendation, low certainty of evidence)

Recommendation 8. There is insufficient evidence to recommend for or against the use of EPA (IPE) in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)

Recommendation 9. In adults with hypertriglyceridemia (150-499 mg/dL) who have ASCVD or are at increased risk for ASCVD, AACE suggests *against* the use of EPA plus DHA in addition to statin therapy. (Conditional recommendation, low certainty of evidence)

Recommendation 10. There is insufficient evidence to recommend for or against the use of EPA plus DHA in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)

Summary of the Evidence

No head-to-head trials directly comparing EPA to EPA plus DHA were identified during the systematic literature search. Therefore, the task force split the PICO question to assess the impact on mortality, CV events, and pancreatitis for each intervention separately. The evidence informing the recommendations for EPA and EPA plus DHA was partially derived from a published systematic review.[85] Of the 38 trials included in the full published review, the evidence team conducted meta-analyses that included only trials with populations identified as being specifically at risk for CVD and ≥1 outcome of interest. In addition, only trials that used a dose of EPA or EPA plus DHA of ≥1.8 grams per day were included in the final analysis to more closely mimic doses currently prescribed in practice and eliminate those more akin to over-the-counter (OTC) supplements. The final meta-analysis included 4 trials for EPA alone and 7 trials for EPA plus DHA.

EPA Monotherapy

Overall, 4 trials with 27 255 participants informed the evidence profile comparing the use or addition of EPA with usual care for the outcomes of all-cause mortality, CV-related mortality, MI, stroke, coronary revascularization, and discontinuation due to adverse events.[86-89] No studies reported pancreatitis or PVD events. Usual care may include nutrition and physical activity interventions and other lipid-lowering medications. Not all trials contributed to each outcome as each trial did not report on each identified outcome of interest.

The 4 trials for EPA monotherapy consisted of heterogeneous patient populations. One study included adult patients with coronary artery disease who underwent a percutaneous coronary intervention and were given pitavastatin in addition to EPA or placebo.[87] The second study, JELIS, included adult patients with hypercholesterolemia and mild hypertriglyceridemia who were receiving statin therapy.[86] The third study evaluated the adult population with acute coronary syndrome.[88] All 3 of these studies used the 1.8 grams per day dose of EPA. The last study, REDUCE-IT, evaluated adults with CVD or DM and other risk factors who were receiving statin therapy and had a fasting TG level between 135 and 499 mg/dL (median 216 mg/dL).[89] This study used a 4 g/day dose of IPE versus the 1.8 g/day dose in the other 3 studies. The analysis was predominately weighted on the 2 largest studies, which were JELIS and REDUCE-IT, accounting for >80% of the outcomes of interest.

The summary of the certainty of evidence and magnitude of effect is shown in the Summary of Findings table for EPA monotherapy versus usual care (Table 9). The full GRADE evidence profile is included in Appendix I.

Overall, there was low certainty of evidence for use of EPA monotherapy based on the lowest certainty of evidence across most of the critical outcomes, including all-cause mortality, CV-related mortality, stroke, and discontinuation due to adverse events. The other outcomes of MI and coronary revascularization were rated as moderate certainty of evidence.

Based on the absolute risk estimates derived from the included RCTs, the task force determined that the addition of EPA to statins may not result in a clinically meaningful decrease in all-cause mortality, CV-related mortality, stroke, or coronary revascularization. EPA results in a small decrease in MI. For the treatment discontinuation outcome, 3 trials included this outcome, and the task force determined that EPA may not result in a clinically meaningful increase in discontinuation due to adverse events. However, the use of EPA or IPE may result in increased risks of major bleeding and atrial fibrillation. These risks should be included in a shared decision-making discussion.

EPA Plus DHA

Overall, 7 trials with 14 950 participants informed the evidence profile comparing the use or addition of EPA plus DHA to usual care for the outcomes all-cause mortality, CV-related mortality, MI, stroke, coronary revascularization, and discontinuation due to

Table 9
Summary of Findings: EPA Compared With Usual Care[a] for Adults With Hypertriglyceridemia

Outcomes,[b] follow-up 0.6 to 5 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with EPA		
All-cause mortality	27 255 (4 RCTs)	RR 0.95 (0.74-1.21)	43 per 1000	2 fewer per 1000 (11 fewer to 9 more)	⨁⨁◯◯ Low[d,e]	EPA may not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	27 251 (4 RCTs)	RR 0.83 (0.65-1.07)	18 per 1000	3 fewer per 1000 (6 fewer to 1 more)	⨁⨁◯◯ Low[d,e]	EPA may not result in a clinically meaningful decrease in CV-related mortality.
Myocardial infarction	27 255 (4 RCTs)	RR 0.73 (0.63-0.84)	31 per 1000	8 fewer per 1000 (11 to 5 fewer)	⨁⨁⨁◯ Moderate[d]	EPA probably results in a small reduction in myocardial infarction.
Stroke	27 255 (4 RCTs)	RR 0.83 (0.60-1.18)	22 per 1000	4 fewer per 1000 (9 fewer to 4 more)	⨁⨁◯◯ Low[d,e]	EPA may not result in a clinically meaningful decrease in stroke.
Discontinuation due to adverse events	27 062 (3 RCTs)	RR 1.05 (0.93-1.20)	84 per 1000	4 more per 1000 (6 fewer to 17 more)	⨁⨁◯◯ Low[d,e]	EPA may not result in a clinically meaningful increase in discontinuation due to adverse events.
Coronary revascularization	27 255 (4 RCTs)	RR 0.78 (0.65-0.94)	59 per 1000	13 fewer per 1000 (21 to 4 fewer)	⨁⨁⨁◯ Moderate[d]	EPA probably does not result in a clinically meaningful difference in coronary revascularization.
PVD events	Not reported					
Pancreatitis	Not reported					

Abbreviations: CI = confidence interval; CV = cardiovascular; EPA = eicosapentaenoic acid; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] Usual care may include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] The populations, dose of EPA, and the type of comparison used in the trials varied significantly.

adverse events.[86-92] No studies reported pancreatitis or PVD events. Usual care included nutrition and physical activity interventions and other lipid-lowering medications. Not all trials contributed to each outcome as each trial did not report on each identified outcome of interest.

The 7 trials for EPA plus DHA varied in patient populations. Study populations included patients with combined hyperlipoproteinemia,[90] CAD,[93] symptomatic paroxysmal atrial fibrillation,[94] implanted cardioverter/defibrillators,[92] a recent MI,[95] patients undergoing coronary artery bypass grafting,[91] and patients undergoing statin therapy with high CV risk along with hypertriglyceridemia and low HDL-C levels.[96] Doses of EPA plus DHA ranged from 1.8 to 4 grams per day, with each trial using a different dose of EPA plus DHA.

The summary of the certainty of evidence and magnitude of effect is shown in the summary of findings table for EPA plus DHA versus usual care (Table 10 and Appendix J).

Overall, there was low certainty of evidence for EPA plus DHA, based on the lowest certainty of evidence across the critical outcomes, including all-cause mortality, MI, and stroke. The other outcomes were rated as moderate certainty of evidence.

Based on the absolute risk estimates derived from the included RCTs, the task force determined that EPA plus DHA may not result in a clinically meaningful decrease in all-cause mortality, MI, or stroke. EPA plus DHA probably does not result in a clinically meaningful decrease in CV-related mortality and probably does not result in a clinically meaningful decrease in coronary revascularization. For the treatment discontinuation outcome, only 3 trials provided data for this outcome and the task force determined EPA plus DHA probably results in a moderate increase in discontinuation due to adverse events.

Participants across the 7 studies had a wide range of TG levels, and many trials did not consistently report TG levels. Data specific for adults with severe hypertriglyceridemia were not reported in the included trials. As a result, the task force determined there was insufficient evidence to recommend for or against the use of EPA or EPA plus DHA in adults with severe hypertriglyceridemia (≥500 mg/dL).

Benefits and Harms

EPA

EPA monotherapy added to statin did not demonstrate a clinically meaningful decrease in the risk of all-cause mortality, CV-related mortality, coronary revascularization, or stroke. In addition, EPA monotherapy did not demonstrate a clinically meaningful increase in risk of discontinuation due to adverse events. For all-cause mortality, 4 studies were included with 27 255 participants. The absolute risk difference was 2 fewer deaths per 1000 individuals (95% CI 11 fewer to 9 more). Four trials evaluated CV-related mortality and included 27 251 participants, resulting in an absolute risk of 3 fewer CV-related deaths per 1000 individuals (95% CI 6 fewer to 1 more). Four trials evaluated stroke and included 27 255 participants, resulting in an absolute risk of 4 fewer strokes per 1000 individuals (95% CI 9 fewer to 4 more). Three trials evaluated treatment discontinuation due to adverse events and included 27 062 participants, resulting in an absolute risk of 4 more treatment discontinuations due to adverse events per 1000 individuals (95% CI 6 fewer to 17 more).

Use of EPA monotherapy may result in a small decrease in the risk of MI. Four trials evaluated the MI outcome with EPA alone and included 27 255 participants, resulting in an absolute risk of 8 fewer MIs per 1000 individuals (95% CI 11 fewer to 5 fewer). Rates of discontinuation of treatment were not different in the EPA monotherapy and usual care groups. However, clinical trial data showed an increased risk of atrial fibrillation in patients taking IPE monotherapy and statins, which was mostly observed in individuals with

Table 10
Summary of Findings: EPA plus DHA Compared to Usual Care[a] for Adults with Hypertriglyceridemia

Outcomes,[b] follow-up 1-3.5 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with EPA plus DHA		
All-cause mortality	14 950 (6 RCTs)	RR 1.10 (0.95-1.27)	320 per 1000	32 more per 1000 (16 fewer to 86 more)	⨁⨁◯◯ Low[d,e]	EPA plus DHA may not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	14 003 (4 RCTs)	RR 1.07 (0.90-1.28)	33 per 1000	2 more per 1000 (3 fewer to 9 more)	⨁⨁⨁◯ Moderate[d]	EPA plus DHA probably does not result in a clinically meaningful decrease in CV-related mortality.
Myocardial Infarction	13 142 (2 RCTs)	RR 0.97 (0.81-1.16)	34 per 1000	1 fewer per 1000 (7 fewer to 6 more)	⨁⨁◯◯ Low[d,e]	EPA plus DHA may not result in a clinically meaningful reduction in myocardial infarction.
Stroke	13 415 (2 RCTs)	RR 0.98 (0.38-2.50)	19 per 1000	0 fewer per 1000 (12 fewer to 28 more)	⨁⨁◯◯ Low[d,e]	EPA plus DHA may not result in a clinically meaningful decrease in stroke.
Coronary revascularization	13 378 (2 RCTs)	RR 0.97 (0.83-1.13)	45 per 1000	1 fewer per 1000 (8 fewer to 6 more)	⨁⨁⨁◯ Moderate[d]	EPA plus DHA probably does not result in a clinically meaningful decrease in coronary revascularization.
Discontinuation due to adverse events	14 025 (3 RCTs)	RR 1.36 (1.22-1.51)	76 per 1000	27 more per 1000 (17 more to 39 more)	⨁⨁⨁◯ Moderate[d]	EPA plus DHA probably results in a moderate increase in discontinuation due to adverse events.
PVD events	Not reported					
Pancreatitis	Not reported					

Abbreviations: CI = confidence interval; CV = cardiovascular; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] Usual care may include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] The populations, dose of EPA, and the type of comparison used in the trials varied significantly.

a history of atrial fibrillation.[89] There was also an increase in the risk of bleeding with EPA in addition to statins.[86,87,89]

When evaluating the overall evidence, task force members placed more value on the potential decrease in MI than on the potential harm from adverse events. They judged the balance to favor the use of EPA monotherapy in addition to statins for adults with hypertriglyceridemia and ASCVD or increased risk for ASCVD. The task force recommends that individuals be informed of the potential adverse events before the decision to prescribe EPA or IPE. Adults with severe hypertriglyceridemia were not assessed in the included trials; thus, there is insufficient evidence to make a recommendation for or against the use of EPA monotherapy in this population.

EPA Plus DHA

There was no demonstrated decrease in the risk of all-cause mortality, CV-related mortality, MI, stroke, or coronary revascularization with EPA plus DHA. For all-cause mortality, 6 studies were included with 14 950 participants. The absolute risk difference was 32 more deaths per 1000 individuals (95% CI 16 fewer to 86 more). Four trials evaluated CV-related mortality and included 14 003 participants, resulting in an absolute risk of 2 more CV-related deaths per 1000 individuals (95% CI 3 fewer to 9 more). Two trials evaluated MI and included 13 142 participants, resulting in an absolute risk of 1 fewer MI per 1000 individuals (95% CI 7 fewer to 6 more). Stroke was assessed in 13 415 individuals resulting in absolute risk differences of 12 fewer to 28 more strokes. Coronary revascularization was reported for 13 378 participants resulting in absolute risk differences of 8 fewer to 6 more coronary revascularizations.

There was a demonstrated increase in discontinuation due to adverse effects with EPA plus DHA. Three trials evaluated discontinuation due to adverse effects with EPA plus DHA and included 14 025 participants, resulting in an absolute risk of 27 more discontinuations due to adverse effects per 1000 individuals (95% CI 17 more to 39 more discontinuations due to adverse effects). Similar to EPA (IPE) monotherapy, there was an increased risk of atrial fibrillation with higher doses of the combined EPA plus DHA therapy.[96]

Based on trivial desirable effects (no difference observed) and moderate undesirable effects, the task force judged that the balance did not favor use of EPA plus DHA (≥1.8 g/day) in adults with hypertriglyceridemia, on statins, and with CVD or at risk for CVD. Adults with severe hypertriglyceridemia were not assessed in the included trials, yielding insufficient evidence to make a recommendation for or against use of EPA plus DHA in this population.

Clinical Considerations

EPA monotherapy and EPA plus DHA (doses ≥1.8g/day) have both been used to reduce TG levels in patients with elevated triglycerides, including severe hypertriglyceridemia. Multiple products approved by the FDA are available for EPA (IPE) monotherapy and for combinations of EPA and DHA. There is evidence that these products can be safely used in combination with other lipid-lowering therapies, including statins. In addition, many fish oil products are readily available without a prescription or OTC that include EPA and DHA. These nonprescription products are highly variable relative to the amount of EPA and DHA in them and are not regulated by the FDA. The evaluation of the EPA monotherapy and

combination of EPA plus DHA focused on clinical trials evaluating the available prescription products. These findings should not be applied to products not approved by the FDA or OTC products.

The task force focused on the evaluation of benefits and harms on EPA monotherapy and on the combination of EPA plus DHA, with trials evaluating doses of ≥1.8 g/day approaching recommended prescribing doses in the range of 2 to 4 g/day (Appendices I and J). The interpretation of the recommendations should be grounded in this dosing framework and not applied to doses <1.8 g/day. There are many trials using doses <1.8 g/day and these trials have an even greater variation in study populations and doses used than those constituting the focus of our analysis.

Currently, there are limited data on the impact of EPA monotherapy or EPA plus DHA across sex/gender or race/ethnicity subgroups. The included studies included participants, who were predominantly male, White, and of older age. The demographics other than sex/gender were not reported in many trials, and subgroup analysis was not conducted. The task force judged that the impact on equity is unknown.

Of note, there were no studies evaluating the efficacy of EPA monotherapy or EPA in combination with DHA to prevent pancreatitis in persons with severe hypertriglyceridemia. This is an important area of future clinical study.

It is important to consider and provide counseling to patients on the harms related to EPA and EPA plus DHA, especially given the trivial to small benefits in CV risk and the potential for serious adverse events including atrial fibrillation and major bleeding. There should be increased monitoring for this potential risk, especially in individuals taking anticoagulants or antiplatelet medications. In patients with hepatic impairment who are taking EPA plus DHA, it is recommended to periodically monitor liver function tests. Monitoring LDL-C periodically after a patient is started on EPA plus DHA is indicated as these products may increase LDL-C levels in patients.

Based on the evidence and judgments made in the Evidence-to-Decision Framework (see Appendices I and J), the task force determined that EPA monotherapy treatment for adults with hypertriglyceridemia (150-499 mg/dL) who have CVD or are at increased risk for CVD and taking statins results in a small reduction in MI with some potential adverse effects. Therefore, the task force issued a conditional recommendation for the use of EPA for this population following a shared decision-making discussion with patients about the potential risks of bleeding and atrial fibrillation. In addition, the task force determined that EPA plus DHA in this same population resulted in trivial benefits and moderate adverse effects. Therefore, the task force issued a conditional recommendation against the use of EPA plus DHA for this population. The task force recognizes the paucity of evidence regarding use of EPA alone or in combination with DHA in severe hypertriglyceridemia (≥500 mg/dL). For these individuals, clinicians should conduct shared decision-making when considering EPA monotherapy or EPA plus DHA treatment.

Niacin

Recommendation 11. In adults with hypertriglyceridemia (150-499 mg/dL) who have ASCVD or are at increased risk for ASCVD, AACE recommends *against* the use of niacin in addition to usual care. (Strong recommendation, low certainty of evidence)

Recommendation 12. There is insufficient evidence to recommend for or against the use of niacin in adults with severe hypertriglyceridemia (≥500 mg/dL). (No recommendation, insufficient evidence)

Summary of the Evidence

No head-to-head trials directly comparing niacin to fibrates or EPA were identified during the systematic literature search. Therefore, the task force amended the PICO question to assess the overall evidence for niacin on CV outcomes and pancreatitis in adults with hypertriglyceridemia. The evidence informing the recommendations for niacin was partially derived from a published systematic review.[97] Event rates from trials with ≥1 outcome of interest were abstracted and included in the analysis. Overall, 14 trials with 36 036 participants informed the evidence profile comparing the use or addition of niacin to usual care for the outcomes of all-cause mortality, CV-related mortality, MI, stroke, coronary revascularization, and discontinuation due to adverse events.[98-111] No studies reported pancreatitis or PVD events. Usual care included nutrition and physical activity interventions and/or other lipid-lowering medications. Not all trials contributed to each outcome, as each trial did not report on each identified outcome of interest. The population, dose of niacin, and comparison varied significantly across the trials. In general, participants in the trials included adults with dyslipidemia who have or are at increased risk of ASCVD. Trials included different formulations and doses of niacin and were compared with placebo, ezetimibe, statin, colestipol, diet, or a combination thereof.

Three trials were rated by the systematic review authors as having high risk of bias due to incomplete reporting due to attrition and lack of blinding. Two of the 3 were small trials, contributing few events for some of the outcomes.[103,106] The STOCKHOLM trial was larger with 555 participants.[102] Sensitivity analyses excluding these studies only minimally changed the summary estimate, but the CIs were similar and still crossed the line of no effect. Therefore, the task force did not rate down for risk of bias in their overall assessment.

The summary of the certainty of evidence and magnitude of effect is shown in the Summary of Findings table for niacin versus usual care (Table 11). The full GRADE evidence profile can be viewed in Appendix K.

Overall, there was low certainty of evidence, based on the lowest certainty of evidence across the critical outcomes, including all-cause mortality, CV-related mortality, MI, and stroke. The other outcomes of coronary revascularization and discontinuation of treatment were rated as moderate certainty of evidence.

Based on the absolute risk estimates derived from the included RCTs, the task force determined that niacin may not result in a clinically meaningful decrease in all-cause mortality, CV-related mortality, stroke, or coronary revascularization. Niacin may result in a trivial decrease in MI, though the CI includes both potential benefit and harm. There was a clinically meaningful increase in discontinuation due to adverse events, with an absolute risk difference of 98 more discontinuations anticipated with the use of niacin (39 to 172 more discontinuations) per 1000 individuals compared with usual care.

Participants had a wide range of TG levels across the studies and many trials did not consistently report TG levels. Data specific for adults with severe hypertriglyceridemia were not reported in the included trials. As a result, the task force determined there was insufficient evidence to recommend for or against the use of niacin in adults with severe hypertriglyceridemia (≥500 mg/dL).

Benefits and Harms

There was no demonstrated decrease in the risk of all-cause mortality, CV-related mortality, stroke, or coronary

Table 11
Summary of Findings: Niacin Compared With Usual Care[a] for Adults With Hypertriglyceridemia

Outcomes,[b] follow-up 2-3 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[c]		Certainty of the evidence (GRADE)	What happens
			Risk with usual care	Risk with niacin		
All-cause mortality	36 036 (14 RCTs)	RR 0.96 (0.85-1.08)	89 per 1000	4 fewer per 1000 (13 fewer to 7 more)	⨁⨁◯◯ Low[d,e]	Niacin may not result in a clinically meaningful decrease in all-cause mortality.
CV-related mortality	34 852 (13 RCTs)	RR 0.95 (0.87-1.04)	59 per 1000	3 fewer per 1000 (8 fewer to 2 more)	⨁⨁◯◯ Low[d,e]	Niacin may not result in a clinically meaningful decrease in CV-related mortality.
Myocardial Infarction	34 314 (10 RCTs)	RR 0.89 (0.75-1.05)	55 per 1000	6 fewer per 1000 (14 fewer to 3 more)	⨁⨁◯◯ Low[d,e]	Niacin may result in a trivial decrease in myocardial infarction.
Stroke	35 256 (9 RCTs)	RR 0.93 (0.74-1.18)	46 per 1000	3 fewer per 1000 (12 fewer to 8 more)	⨁⨁◯◯ Low[d,e]	Niacin may not result in a clinically meaningful decrease in stroke.
Coronary revascularization	29 981 (9 RCTs)	RR 0.88 (0.58-1.33)	48 per 1000	6 fewer per 1000 (20 fewer to 16 more)	⨁⨁⨁◯ Moderate[d]	Niacin probably does not result in a clinically meaningful reduction in coronary revascularization.
Discontinuation due to adverse events	31 506 (8 RCTs)	RR 1.60 (1.24-2.05)	164 per 1000	98 more per 1000 (39 to 172 more)	⨁⨁⨁◯ Moderate[d]	Niacin probably results in a large increase in discontinuation due to adverse events.
PVD events	Not reported					
Pancreatitis	Not reported					

Abbreviations: CI = confidence interval; CV = cardiovascular; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] Usual care may include nutrition and physical activity interventions, statins, ezetimibe, or other medications.
[b] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[c] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] The populations, dose of niacin, and the type of comparison used in the trials varied significantly.

revascularization. For all-cause mortality, 14 studies were included with 36 036 participants. The absolute risk difference was 4 fewer deaths per 1000 individuals (95% CI 13 fewer to 7 more). Thirteen trials evaluated CV-related mortality and included 34 852 participants, resulting in an absolute risk of 3 fewer CV-related deaths per 1000 (95% CI 8 fewer to 2 more). Stroke and coronary revascularizations were assessed with 9 RCTs, resulting in absolute risk differences of 3 and 6 fewer, respectively, per 1000 individuals.

Niacin may result in a trivial decrease in MI, though the certainty in the estimate of effect was low due to rating down for indirectness and imprecision. Ten trials were included for this outcome with a duration of follow-up between 2 to 5 years. Absolute risk estimates for a reduction in MI for niacin in addition to usual care was 6 fewer per 1000 individuals (95% CI 14 fewer to 3 more). The FDA issued partial approval for niacin based on the Coronary Drug Project (CDP),[98] which demonstrated a significant decrease in MI. However, the totality of the evidence from all trials included for this outcome suggests trivial or no improvement in the risk of MI.

The absolute risk estimate for adverse events was 98 more discontinuations per 1000 individuals (95% CI 39 to 172 more) which was a large undesirable effect. The larger included trials all demonstrated an increase in flushing and gastrointestinal issues.[98,100,104] These trials also reported an increase in gouty arthritis, liver enzyme elevation and myalgias, and additional musculoskeletal and skin-related issues, increased risk of infection and bleeding, as well as increased incidence in DM and severe hyperglycemic events leading to hospitalizations in persons with DM.[98,100,104,112]

Based on moderate certainty of increased risk of serious adverse events and low certainty of a trivial benefit in reduction of MI, the task force strongly recommended against the use of niacin in usual care of adults with hypertriglyceridemia (150-499 mg/dL).

Clinical Considerations

Niacin has been used to reduce TG levels, LDL-C, and ApoB and to increase HDL-C in patients with dyslipidemia, with the goal of reducing MI and ASCVD. Niacin is typically prescribed in doses of 500 to 2000 mg daily and is contraindicated in persons with active liver disease or unexplained persistent elevations in liver transaminases, active peptic ulcers, or arterial bleeding. Niacin is not used in combination with statins due to increased adverse events. In 2016, the FDA recommended that niacin not be routinely used or combined with statins after trial data showed that the benefit for the combination did not exceed the potential risk for adverse events. It was noted that if niacin was prescribed as monotherapy, the benefits and harms should be discussed with patients (https://www.govinfo.gov/content/pkg/FR-2016-04-18/pdf/2016-08894.pdf).

EPA as monotherapy and fibrates are other options to reduce lipids and ASCVD risk. While no trials have directly compared these medications with niacin, systematic reviews and meta-analyses showed similar small reductions in the risk of MIs and increased risk of adverse events.[113,114] In terms of clinical use, use of EPA with or without DHA is covered above in recommendations 7 through 10. Similar to niacin, the use of fibrates in combination with statins is not recommended. In the 2022 PROMINENT trial, permafibrate was not seen to have any benefit in reducing CV outcomes.[115]

One of the trials in the analysis included a treatment arm with clofibrate.[98] When comparing the niacin and fibrate arms in this single trial, there was a small increase in all-cause mortality (24.4% vs 20.0%), CV-related mortality (21.3% vs 17.3%), and a trivial increase in treatment discontinuations with niacin compared to clofibrate (10.7% vs 10.6%). There was also a trivial decrease in MI and stroke, but the CIs spanned the line of null effect. Of note, this trial focused on clofibrate, which had been discontinued due to adverse effects, recruited participants with a previous MI, and did

not consistently report lipid levels across groups, limiting generalizability and data analysis. Prescriptions for niacin have decreased since 2013, but niacin has been prescribed for individuals with severe hypertriglyceridemia to prevent pancreatitis or those who do not tolerate statins.[116] Of note, there were no studies evaluating the efficacy of niacin to prevent pancreatitis in persons with severe hypertriglyceridemia. This is an important area of future clinical study. Shared decision-making conversations should focus on the lack of evidence supporting use and the significant adverse effects when considering niacin treatment for patients with severe hypertriglyceridemia.

Currently, there are limited data on the impact of niacin across sex/gender or race/ethnicity subgroups. The included studies enrolled participants who were predominantly male, White, and of older age. The demographics other than sex/gender were not reported in many trials, and a subgroup analysis was not conducted. The task force judged the impact on equity is unknown. Based on the evidence and judgments made in the Evidence-to-Decision Framework (see Appendix K), the task force determined that niacin treatment for adults with hypertriglyceridemia (150-499 mg/dL) who have ASCVD or are at increased risk for ASCVD and not taking statins results in low certainty of trivial benefits and moderate certainty of large adverse effects. Therefore, the task force issued a strong recommendation against the use of niacin for individuals with hypertriglyceridemia. The task force recognizes the paucity of evidence regarding the use of niacin in severe hypertriglyceridemia or in patients who are unable to tolerate statins, and that some patients may value the potential trivial reduction in MI or find the side effects of the medication tolerable. Clinicians should conduct shared decision-making when considering niacin treatment.

Treatment Goals for Reduction of LDL-C in Persons With Dyslipidemia

Recommendation 13. In adults undergoing treatment for dyslipidemia who have ASCVD or are at increased risk for ASCVD, AACE suggests for treatment to an LDL-C target of <70 mg/dL. (Conditional recommendation, low certainty of evidence)

Summary of the Evidence

Only 1 trial directly comparing LDL-C treatment goals for adults with dyslipidemia after ischemic stroke or transient ischemic attack was identified during the systematic literature search.[117] The Treat-Stroke-to-Target trial included 2860 patients who had a recent ischemic stroke or transient ischemic attack to a target LDL-C of <70 mg/dL or to a higher target of 90 to 100 mg/dL. While a trivial decrease in the composite MACE outcome was observed, no differences were seen in the individual outcomes of mortality, MI, stroke, or coronary revascularization.[117] The literature search identified 2 systematic reviews that provided information relevant for the PICO question using post hoc analyses of multiple trials.[118,119] One systematic review[118] included 11 studies that had ≥1000 patients and a follow-up longer than 6 months. The authors conducted a post hoc analysis grouping participants in either the active treatment group where mean or median LDL-C was reduced to <70 mg/dL and a less intensive group that did not reach that goal. Studies had different populations, including individuals with and without ASCVD. One trial on treatment not approved by the FDA was excluded from the evidence profile.[120]

In this review,[118] 10 trials with 102 632 participants informed the evidence profile comparing treatment goals of <70 mg/dL compared with a treatment goal of ≥70 mg/dL for the outcomes of all-cause mortality, CV-related mortality, MI, stroke, coronary revascularization. PVD events were not reported by any of the included studies. Study populations were highly variable across the trials and included patients with acute coronary syndromes, without hyperlipidemia but with elevated C-reactive protein, mild to moderate aortic stenosis, increased risk of ASCVD, hyperlipidemia with and without ASCVD, and history of ischemic stroke. Interventions included statin with and without ezetimibe, alirocumab, and evolocumab.

Treatment discontinuations due to adverse events were not reported in the first review of 11 trials. Treatment discontinuations were reported in a separate review that provided the relative risk and absolute risk difference of this outcome in 31 studies.[119] The authors of the larger review did not report event rates and total participants the number of individuals discontinuing treatment were not calculated. Based on the relative risk and absolute risk difference of 0.1% per year observed in the lower LDL-C treatment group, there is probably an increased number of individuals stopping medications in this group.

There was concern of potential risk of bias that accounts for significant methodological variation and that these studies were not designed to answer the question directly. The summary of the certainty of evidence and magnitude of effect is shown in the Summary of Findings table below (Table 12) and in the GRADE evidence profile (Appendix L).

Overall, there was low certainty of evidence based on the lowest certainty of evidence across the critical outcomes, which included all-cause mortality, CV-related mortality, and stroke. The outcomes of MI and coronary revascularization were rated as moderate certainty of evidence.

Based on the absolute risk estimates derived from the included RCTs, the task force determined that achieving an LDL-C level of <70 mg/dL resulted in a trivial decrease in all-cause mortality and CV-related mortality and a moderate decrease in myocardial dysfunction. There was no clinically meaningful decrease in coronary revascularization or stroke. There was a trivial increase in medication discontinuation due to adverse events; however, the absolute risk estimates were not calculated due to incomplete reporting.

Based on a small benefit for MI and potentially trivial harm of medication discontinuation, the task force determined the balance probably favored treating to a target of <70 mg/dL LDL-C. Considerations of polypharmacy and the increased costs associated with certain medications should be considered when determining appropriate treatment goals for individual patients.

Benefits and Harms

There was a trivial decrease in all-cause and CV-related mortality observed in patients who reached a target LDL-C of <70 mg/dL. For the outcomes of all-cause mortality, CV-related mortality, and MI,10 studies were included with 102 623 participants. The anticipated absolute risk difference for all-cause mortality was 5 fewer deaths per 1000 individuals (95% CI 10 fewer to 1 fewer deaths) and for CV-related mortality of 5 fewer deaths per 1000 individuals (95% CI 8 fewer to 1 fewer CV-related deaths). There was a small decrease in the risk of MI with an absolute reduction of 12 fewer MIs per 1000 individuals (95% CI 17 fewer to 6 fewer). Ischemic stroke was evaluated in 9 RCTs with 98 167 participants. The task force determined that there was no clinically meaningful change in risk with a relative risk reduction of 0.77 (95% CI 0.69-0.85) and absolute reduction of 4 fewer per 1000 individuals (95% CI 6 fewer to 3 fewer ischemic strokes).

Relative risks of treatment discontinuation were reported in a separate review that provided relative risks of this outcome in 31 studies.[119] The authors of the review did not report event rates and total participants for this outcome, so absolute risk differences

Table 12
Summary of Findings: Achieved LDL-C <70 mg/dL Compared With ≥70 mg/dL for Adults With Dyslipidemia

Outcomes,[a] range of follow-up 0.5-6 years	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[b]		Certainty of the evidence (GRADE)	What happens
			Risk with ≥70 mg/dL	Risk with <70 mg/dL		
All-cause mortality	102 632 (10 RCTs)	RR 0.90 (0.81-0.99)	54 per 1000	5 fewer per 1000 (10 fewer to 1 fewer)	⨁⨁◯◯ Low[c,d]	A lower treatment goal <70 mg/dL may result in a trivial decrease in all-cause mortality.
CV-related mortality	102 632 (10 RCTs)	RR 0.81 (0.69-0.95)	26 per 1000	5 fewer per 1000 (8 fewer to 1 fewer)	⨁⨁◯◯ Low[c,d]	A lower treatment goal <70 mg/dL may result in a trivial decrease in CV-related mortality.
Myocardial Infarction	102 632 (10 RCTs)	RR 0.80 (0.71-0.89)	59 per 1000	12 fewer per 1000 (17 fewer to 6 fewer)	⨁⨁⨁◯ Moderate[c]	A lower treatment goal <70 mg/dL probably results in a moderate decrease in myocardial infarction.
Stroke	102 632 (10 RCTs)	RR 0.77 (0.69-0.85)	19 per 1000	4 fewer per 1000 (56 fewer to 3 fewer)	⨁⨁◯◯ Low[c,d]	A lower treatment goal <70 mg/dL may not result in a clinically meaningful decrease in stroke.
Coronary revascularization	102 632 (10 RCTs)	RR 0.83 (0.75-0.92)	93 per 1000	16 fewer per 1000 (23 fewer to 7 fewer)	⨁⨁⨁◯ Moderate[c]	A lower treatment goal of <70 mg/dL probably does not result in a clinically meaningful decrease in coronary revascularization.
Discontinuation due to adverse events	Unknown (31 RCTs)	RR 1.08 (1.01-1.16)	2.1%	ARD 0.1% (2.2%-2.1%)	⨁⨁⨁◯ Moderate[c]	A lower treatment goal of <70 mg/dL probably increases the number of individuals discontinuing medication(s).[e]
PVD events	Not reported					

Abbreviations: ARD = absolute risk difference; CI = confidence interval; CV = cardiovascular; MID = minimally important difference; PVD = peripheral vascular disease; RCT = randomized controlled trial; RR = risk ratio.
[a] All outcomes were rated as critical except for peripheral vascular disease events, which were rated as important for clinical decision-making.
[b] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[c] Data are from a study-level analysis that did not account for methodological variation between studies and participants were not stratified by base-line LDL levels or ASCVD risk before analyses.
[d] The CI for the pooled effect estimate crossed the threshold for a clinically important difference.
[e] Missing data on total number of individuals (ARD provided). A minimally important difference of 5 per 1000 participants was used for all outcomes except coronary revascularization where a MID was set at 50 per 1000 participants.

were not calculated. The relative risk demonstrated trivial increase in medical discontinuation because of adverse events with a mean follow-up of 3.7 years. Serious adverse events were reported at 7.4% with a lower LDL-C target compared with 7.5% with a higher LDL-C target and medication discontinuation at 2.2% at a lower target compared with 2.1% at a higher target. The relative risk for discontinuation was 1.08 (95% CI 1.01-1.16). There were no significant differences in myopathy, cancer, myalgias, new onset DM, or elevated aminotransferase levels.

Sensitivity analyses of relative risks were also conducted comparing outcomes for an LDL-C target of <70 mg/dL for primary and secondary prevention. There were no major differences observed between the groups, though most trial participants were being treated for secondary prevention. In all-cause mortality, for example, there was no significant difference in the primary prevention group (RR 0.92 [95% CI 0.77-1.11]) compared with the secondary prevention group (RR 0.89 [95% CI 0.79-1.01]).

Overall, the task force judged that the small desirable effects outweighed the trivial undesirable effects, in favor of suggesting LDL-C treatment target of <70 mg/dL (LDL-C <70 mg/dL) for adults undergoing treatment for dyslipidemia who have ASCVD or are at high risk for ASCVD.

Clinical Considerations

Treatment target goals for LDL-C have been highly debated and there are multiple competing guidelines and recommendations around this topic.[13-18,121,122] Previous AACE guidelines have recommended treating high-risk individuals to a goal of <55mg/dL LDL-C.[13] This 2017 recommendation was based on a single trial (IMPROVE-IT).[123] This double-blind, randomized trial with 18 144 patients compared simvastatin with ezetimibe to simvastatin with placebo for adults with acute coronary syndromes in the preceding 10 days. The study showed a trivial decrease in MACE (hazard ratio 0.94 [95% CI 0.89-0.99]) in participants treated with simvastatin plus ezetimibe who achieved LDL-C levels <55 mg/dL.[123] This decrease was mostly driven by fewer nonfatal MI and ischemic stroke events in the treatment group. No differences were observed in mortality or other CV outcomes. However, in the meta-analysis by Khan et al,[118] there were no statistical differences in the relative risks for mortality or CV outcomes between those individuals who achieved an LDL-C <55 mg/dL and those who did not.

Similarly, the 2019 meta-analysis conducted by Guedeney et al[51] reported pooled event rates for all-cause mortality, CV-mortality, MI, stroke, and discontinuation of treatment based on achieved LDL-C ≤50 mg/dL for individuals using PCSK9 monoclonal antibodies. This review used data from a combination of studies using either alirocumab or evolocumab; individual study data were not reported. The baseline ASCVD risk for individuals in each group was not reported, though most participants had documented ASCVD and were being treated for secondary prevention. Absolute risk differences compared with control groups were calculated and there was no substantial clinical benefit in all-cause mortality, CV-related mortality, MI, or stroke observed in those achieving LDL-C <50 mg/dL. In summary, treatment goals of <55 mg/dL do not appear to provide substantial additional clinical benefit, though a head-to-head clinical trial is needed to fully address this question.

The task force recognized that competing patient values and preferences may impact clinical targets, including potential for increased costs to patients and health care systems to achieve a

lower LDL-C goal with added medications, use of higher priced pharmaceuticals, laboratory testing, and increased number of office visits. There is also a potential for polypharmacy that should be assessed when addressing treatment goals with patients.

There is a lack of evidence to determine if there are specific populations, such as older adults, who may have greater risk when an LDL-C target is <70 mg/dL. This is an important area for future research.

There is also limited evidence on the impact of health equity for this recommendation. The task force judged there is the potential to reduce health equity. The majority of the studies in the systematic review[118] included participants who were predominantly male, White, and of older age. The demographics other than sex/gender were not reported in many trials and a subgroup analysis was not conducted. However, the PINNACLE Registry already showed that patients who are younger, female, identify as Black/African American, or have hypertension are less likely to achieve a goal of <70 mg/dL while taking a statin.[124] Further study is needed to determine the impact of lower LDL-C treatment targets on health equity.

Based on the evidence and judgments made in the Evidence-to-Decision Framework (see Appendix L), the task force suggests an LDL-C treatment target of <70 mg/dL (LDL-C <70 mg/dL) for adults undergoing treatment for dyslipidemia who have ASCVD or are at high risk for ASCVD. Low certainty of evidence supports trivial to small benefits and trivial adverse effects. Therefore, the task force issued a conditional recommendation for this treatment target. Clinicians should engage in shared decision-making when determining a treatment target with their patient which discuss the limitations of the evidence, trivial to small benefits, trivial adverse effects, costs, patient preferences, and impact on equity.

Conclusions and Evidence Gaps

Heart disease has remained a major cause of premature mortality (and morbidity) in heavily industrialized nations and has replaced cancer as the number one cause of premature mortality in almost all of these countries.[125] This is now true for both men and women, having replaced breast cancer in the latter group as the major cause of premature mortality.[126] Heart disease is also reported to now become a major factor in disease-related premature death in the rest of the world. Several major risk factors for ASCVD are primarily preventable and can be points of intervention with lifestyle management and pharmacologic agents that have been shown to reduce CV risk in clinical trials. One strong aspect of CV risk is the management of elevated lipids.

In the past 5 decades, several national and international organizations ranging from medical specialty societies to governmental health organizations have developed evidence-based guidelines for the identification, assessment, and treatment of individuals with dyslipidemia. In this update of the 2017 AACE dyslipidemia guideline, the task force used the GRADE methodology and focused on a limited number of key questions to provide guidance on the use of novel lipid-lowering agents as well as controversial areas of the use of fish oil, niacin, and factors for risk assessment. The task force acknowledges that in addition to significant emphasis on enduring changes, with attention to nutrition and physical activity, the use of statins, with and without the use of ezetimibe, remain the cornerstone of lipid management.[13,15]

In this updated 2025 AACE guideline, the task force provided recommendations for the use of novel lipid-lowering agents (PCSK9 inhibitors and BA) to reduce risk of ASCVD. The task force also addressed the impact of omega-3 fatty acids or niacin on important patient outcomes in adults with hypertriglyceridemia. In addition, the task force reviewed available evidence on whether coronary artery calcium, Lp(a), or ApoB improve prediction of future ASCVD events. To aid in implementation of these recommendations, a summary is provided in Figure and Table 3. An overview and comparison of prescribing information for the different nonstatin medications discussed in this guideline is provided in Table 13 below.

For the anti-PCSK9 antibody agents, alirocumab and evolocumab, and BA, the task force issued a conditional recommendation for the addition of these medications in adults with dyslipidemia who have ASCVD or are at increased risk of CV events. For the use of the small interfering RNA therapy inclisiran, there was insufficient evidence to determine the balance of benefit and harm due to a lack of well-powered long-term studies. All the evaluated medications are efficacious in lowering LDL-C, but the impact on mortality and CV events by these agents is limited, resulting in conditional recommendations for use of alirocumab, evolocumab, and BA for adults with or at increased risk for ASCVD.

Currently available evidence for CV outcomes with inclisiran is limited; however, there are ongoing trials that may provide additional information. ORION-4 (NCT03705234) and VICTORION-2 PREVENT (NCT05030428) have anticipated completion dates in 2026 and 2027, respectively. It will be important for these and other trials to provide more robust data for the impact of inclisiran on CV events. Both trials will provide novel information on the effects of inclisiran on urgent coronary revascularization and all-cause death. VICTORION-2 PREVENT will report on major limb adverse events, an outcome deemed by the task force to be clinically important for decision-making.

For all novel therapies there is a lack of representation of individuals from diverse racial and ethnic backgrounds to determine whether there may be different treatment effects or safety considerations, depending on population. Only 15% to 20% of participants in the CV event trials with PCSK9 mAb were non-White. Subgroup analyses in both FOURIER and ODYSSEY OUTCOMES do not show any difference in efficacy among different racial and ethnic groups. While the group sizes were small, the data suggest similar efficacy across subpopulations.[53,54] Given issues with access that affect mostly underserved populations, understanding the impact of these agents on specific outcomes in these populations could support payor policy changes to improve access.

The task force identified management of hypertriglyceridemia, particularly severe hypertriglyceridemia, as an important area for guidance. For the use of fish oils in persons with dyslipidemia and hypertriglyceridemia (150-499 mg/dL), the task force issued a conditional recommendation for the use of EPA but acknowledged the concerns with limited trial data and the potential for increased risk of bleeding and atrial fibrillation. The task force issued a conditional recommendation against the use of EPA plus DHA, as there were no clinically meaningful benefits and the potential for moderate harms. Evidence for the use of niacin in patients with hypertriglyceridemia (150-499 mg/dL) who take statins was also reviewed. Niacin did not provide any substantial reductions in CV events but did result in an increased risk of discontinuation of treatment. The potential side effects observed with niacin include skin and gastrointestinal issues, and the more severe risks of metabolic dysregulation (DM and hyperuricemia), resulting in a strong recommendation against the use of niacin to reduce ASCVD events. There was insufficient evidence for use of these agents in adults with severe hypertriglyceridemia (≥500 mg/dL).

Accurate prediction of future risk of ASCVD events is essential to person-centered care of adults with dyslipidemia. Many guidelines offer options to obtain additional tests to determine levels of nontraditional risk factors such as ApoB, Lp(a), and CAC and include them in a risk prediction model to improve risk prediction,[16,17] especially for individuals in low to intermediate risk categories.

Table 13
Nonstatin Medications Approved by the U.S. Food and Drug Administration for Adults With Dyslipidemia[a]

	Alirocumab	Evolocumab	Inclisiran	Bempedoic acid	EPA	EPA plus DHA	Niacin
Mechanism of action	Fully human mAb that binds PCSK9, interfering with LDL-R degradation, thereby increasing clearance of LDL-C	Fully human mAb that binds PCSK9, interfering with LDL-R degradation, thereby increasing clearance of LDL-C	Small interfering RNA that inhibits synthesis of PCSK9, increasing LDL-R expression and LDL-C clearance	Inhibits adenosine triphosphate-citrate lyase activity, thereby reducing hepatic cholesterol synthesis, increasing LDL-R expression and LDL-C clearance	Reduction in hepatic production of VLDL; pleiotropic effects	Reduction in hepatic production of VLDL; pleiotropic effects	Multiple mechanisms ranging from inhibition of free fatty acid release from adipocytes to inhibition of VLDL secretion by the liver
Delivery	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Oral	Oral	Oral	Oral
Dosing	75-150 mg every 2 weeks or 300 mg monthly	140 mg every 2 weeks or 420 mg monthly	284 mg once, again at 3 months and then every 6 months	180 mg once daily	2 g twice daily with meals	4 g daily or 2 g twice daily	500 mg for 4 weeks and may increase dose 500 mg every 4 weeks with max dose 2 g daily
ASCVD benefit[b]	↓↓MI ↓all-cause mortality	↓↓MI	Insufficient evidence of benefit	↓↓MI	↓↓MI	No evidence of benefit	↓MI
Treatment discontinuation due to adverse events	↑	↑	Insufficient evidence of harm	↑↑	↑	↑↑	↑↑↑
Potential side effect[c]	Nasopharyngitis injection site reactions, influenza	Nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions	Injection site reaction, arthralgia, bronchitis	Hyperuricemia, atrial fibrillation, abdominal pain, anemia, thrombocytosis, back pain, upper respiratory tract infection, tendon rupture	Hemorrhage, atrial flutter/fibrillation, peripheral edema, gout, constipation, musculoskeletal pain, gastrointestinal distress	Dysgeusia, dyspepsia, atrial flutter/ fibrillation, rash, increased liver enzymes	Flushing, GI distress, gout, elevated liver enzyme, myalgia, risk of infection, increase incidence of diabetes mellitus, severe hyperglycemic events leading to hospitalization, rash, musculoskeletal pain
Cautions/ contraindications	Individuals who are allergic to alirocumab or ingredients	Individuals who are allergic to evolocumab or ingredients	Individuals who are allergic to inclisiran or ingredients	Individuals who are allergic to bempedoic acid or ingredients, Pregnancy, breastfeeding	Individuals who are allergic to EPA or IPE or ingredients	Individuals who are allergic to omega 3 fatty acids or ingredients	Individuals who are allergic to niacin, niacinamide, or ingredients; active hepatic disease; active peptic ulcer; arterial hemorrhage
Access/cost[d]	$$$	$$$	$$$, only available at health care facility/ provided in office	$$	$$	$	$

Abbreviations: DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GI = gastrointestinal; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; LDL-R = low-density lipoprotein receptor; mAb = monoclonal antibody; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a] Refer to U.S. Food and Drug Administration fact sheets for additional prescribing information.

[b] Number of arrows represent magnitude of benefit or harm (trivial to large).

[c] Most frequently reported side effects as reported in U.S. Food and Drug Administration prescribing information.

[d] Approximate relative cost indicated by the number of dollar signs. Exact cost will vary based on insurance coverage and pharmacy benefits. All medications are available in community-based pharmacies except for inclisiran, which must be administered in a health care facility.

Large cohort studies were identified in the systematic search; however, outcome reporting was inconsistent. Therefore, we assessed the ability to improve the receiver operating characteristic curve and use the C-statistic as a marker of improvement. Although each of these risk factors led to an improved score, the magnitude of change was very small (the best one was CAC, where the change was positive but not clinically impactful and associated with increased costs and risks). This finding is similar to that of the U.S. Preventive Services Task Force, which found insufficient evidence for the addition of CAC and other nontraditional risk factors in risk assessment.[42] The task force determined that currently available evidence does not support routine assessment above the standard risk assessment tools. However, there may be circumstances where these markers may be useful.

Although newer treatments can regulate LDL-C to very low levels, either as single agents or as combination therapies, clinical trial data are insufficient at this time to determine if lowering LDL-C to <55 mg/dL (and ApoB to <70mg/dL) leads to a reduction in CV mortality rates, whether it is cost-effective or safe to do so. This question is particularly important in patients who are already being treated with statins and are at higher risk of continued ASCVD events. This aspect was further highlighted by a lack of data regarding whether the use of ApoB, compared with LDL-C measurements, would better predict future CV events. Since ApoB-containing particles are the key factors in the initiation and maintenance of atherosclerotic lesions, reporting of this direct assessment of particle numbers in clinical trials is of crucial importance.

PVD events were identified as a priority patient-important outcome for this guideline. However, there is a noticeable absence of clinical trials enrolling patients with PVD events and a lack of reporting on these events as an outcome. PVD is a major manifestation of ASCVD, and there are no data to show that we can clearly state that intensive lipid management in this population has a positive impact, as none of the trials were powered to address this question.

The task force found very few studies that address initiation of lipid management in patients who are >65 years of age (but are otherwise healthy), and where CV risk factor reduction is initiated for the first time. This group certainly has the highest risk of future ASCVD events, but it is not clear whether initiation at this late stage would be impactful.

Triglyceride-lowering has gained some interest because of agents that can lower TG, but there are no clinical trials which show that lowering of triglycerides per se leads to improved CV outcomes. This may speak to the scientific understanding that ApoB-containing particles are more mechanistically involved in the ASCVD process and that TG can manipulate clearance, but it is the particle numbers that determine future risk. Some trials on the use of fibrates and niacin in participants who already take statins have shown lowering of TG levels but do not seem to lower future CV event rates, suggesting that this parameter may not be as critical for lowering ASCVD risk. However, focused trials in this area are needed to address this issue. In addition, given that only 1 trial on EPA has shown a positive outcome (REDUCE-IT), it is imperative for confirmation that this effect is reliable and robust and verifiable by independent trials.

Although very high levels of TG are associated with increased risk of spontaneous pancreatitis, no prospective studies have been reported to date on trials to lower TG using different strategies to see if these can lower future risk of pancreatitis. In addition, while there are publications that show that the risk of pancreatitis increases with almost every increase in TG levels, it is not clear whether this relationship is log-linear or there is a threshold at which the risk is significantly greater. Certainly, the prevailing view is that this risk is considerably increased when the TG are >1000 mg/dL. The task force was aware that therapies blocking ApoC III function are now in clinical trials and advocates that this strategy be compared with an active TG-lowering agent for efficacy.[127]

Statin therapy will continue to remain the cornerstone of lipid management. However, the role of any other pharmacotherapy in the treatment of patients with type 1 DM (T1D) could not be assessed due to lack of data. While most large trials have not actively enrolled patients with T1D, there are 2 small studies demonstrating efficacy and safety of pharmacotherapy, specifically ezetimibe and alirocumab, in people with T1D.[128,129] There are no CV outcomes data in this population and highlight an unmet major need.

Lp(a) is an independent risk factor for CVD, and while its potential for atherogenicity is much higher than for the LDL-C particle, given its relatively lower preponderance in the plasma, it is not clear whether targeting this lipoprotein will be an effective strategy for lowering future ASCVD events, and if select target populations are more suitable for this strategy given there are ethnic variations in this risk factor. The task force is aware of phase 3 clinical trials targeting this specific particle that may identify the specific population that will benefit from intervention.

Interestingly, PCSK9 mAb therapy has been associated with reductions in Lp(a) levels. However, the response is not consistent and appears to be related to baseline levels. If current trials with novel agents specifically targeting Lp(a) confirm a reduction in CV events, the use of PCSK9 inhibitors would need to be further examined in dedicated trials as alternatives for treatment given their dual ability to reduce LDL-C and Lp(a) levels.

Future Research Considerations

As outlined above, this guideline was developed using the best available evidence; however, significant gaps were noted. Research areas that could provide key information on pharmacologic management of adults with dyslipidemia include:

- Safety and efficacy of PCSK9 inhibitors in diverse populations
- Safety and efficacy of initiation of lipid-lowering in an aging population (>75 years of age)
- Safety and efficacy of lipid-lowering in T1D on ASCVD-related outcomes
- Long-term and robust data for inclisiran on patient-important CV outcomes
- Safety and efficacy of newer medications in individuals >65 years of age, individuals who have metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis, and individuals with severe hypertriglyceridemia
- Safety and efficacy of lipid-lowering agents on patient-important CV outcomes in individuals with PVD
- Safety and efficacy in reduction of ASCVD events with newer agents targeting Lp(a), Apo(C), and other proteins involved in lipid metabolism
- Safety and efficacy of lipid-lowering agents on patient-important outcomes in individuals with pancreatitis associated with severe hypertriglyceridemia

Review Process

In addition to a 4-week AACE member comment period, drafts of this clinical practice guideline were reviewed and approved by all task force members, the AACE Clinical Practice Guidelines Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

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Disclosures

Disclosures were obtained, reviewed, and managed according to the AACE Conflicts of Interest Policy updated in 2023 (available at: https://pro.aace.com/about/aace-conflicts-interests-policy). See Appendix A for full list of disclosures.

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AACE reviews and updates or retires its guidance documents 5 years after publication or sooner if significant scientific developments or change in public policy occurs.

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