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Discussion

Highlights of the 2025 American Association of Clinical Endocrinology Clinical Practice Guideline on Pharmacologic Management of Adults With Dyslipidemia

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Heart disease, including atherosclerotic cardiovascular disease (ASCVD) is a leading cause of death worldwide.[1] In the U.S. alone, almost 700 000 people died from heart disease in 2021.[2] In addition to hypertension, diabetes, obesity, smoking, and elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides are associated with metabolic syndrome and heart disease.[1] Recognizing the important role of endocrinologists and the endocrine care team, the American Association of Clinical Endocrinology (AACE) prioritized an update of the 2017 dyslipidemia guideline using the newly adopted Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodological framework. This commentary provides a summary of recent updates to AACE clinical practice guideline (CPG) program and the 2025 focused update on pharmacotherapy for adults with dyslipidemia including hypercholesterolemia and hypertriglyceridemia.[3]

In 2022, AACE adopted a strategic plan with the goals to increase awareness of AACE scientific publications and education to the worldwide endocrine community, the breadth of membership to include the entire endocrine community, the value of engagement in AACE, and the use of AACE education, guidelines, and publications.[4] That same year, the AACE Board of Directors approved adoption of the GRADE methodology for the development of CPGs, updates to an enhanced conflicts of interest policy, and commitment to increased efforts toward diversity, equity, and inclusion of members on every task force.[4] GRADE provides a transparent and systematic framework for development of evidence-based recommendations. It facilitates consideration of the certainty of the evidence, balance of benefits/harms, equity, costs, feasibility, and acceptability of different tests or interventions.[5]

Overview of the 2025 AACE CPG on Pharmacologic Management of Adults With Dyslipidemia

A multidisciplinary task force was empaneled following an open call for applications from AACE membership at large and in accordance with the 2023 AACE conflict of interest policy (https://pro.aace.com/about/aace-conflicts-interests-policy). In addition to the clinical experts, a methodology fellow, an information specialist, and guideline methodologists provided support for completion of systematic reviews and evidence assessments.

With AACE adoption of GRADE, the 2025 AACE dyslipidemia guideline update was developed de novo to implement this method with its transparent and systematic framework for development of recommendations. To further support this standardized process, a focused scope and new format for clinical questions with key identifiers for population, intervention, comparison, outcomes, timing, and setting (PICOTS) laid the foundation for development of the update.

The purpose of the guideline update is to provide practical evidence-based recommendations for the use of nonstatin medications in the management of adults with dyslipidemia. As nutrition, physical activity, and prescription of statins or combination therapy are standard of care, this guideline update focused on newer lipid-lowering medications, including PCSK9 inhibitors, bempedoic acid, and newer omega-3 fatty acid formulations. The 2025 guideline also addressed newer aspects of ASCVD risk assessment and appropriate treatment targets for LDL-C.[3]

The recommendations support shared decision-making between patients and clinicians, including those in endocrinology, cardiology, and primary care. It is important to note that although not included as formal recommendations in the new document, AACE continues to emphasize the need for continual patient-centered discussions on lifestyle patterns and offering or referring

Abbreviations: AACE, American Association of Clinical Endocrinology; ASCVD, atherosclerotic cardiovascular disease; CPG, clinical practice guideline; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LDL-C, low-density lipoprotein cholesterol.

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adults at increased risk for ASCVD to intensive counseling interventions to promote healthy diet and increase physical activity.

Key Differences Between the 2017 and 2025 AACE Dyslipidemia Guidelines

Although many of the 2025 recommendations are consistent with previous AACE clinical guidance and guidance from other medical societies, there are a few key differences in outcomes addressed, assessment of evidence, and development of recommendations. The 2025 guideline focused on "individual" patient-oriented outcomes, such as mortality and cardiovascular events (eg, myocardial infarction and stroke). Disease-oriented (or surrogate) outcomes, such as lipid panel levels, and multipoint cardiovascular composite outcomes were not considered as part of the robust assessment of the balance of benefits and harms of each medication. A side-by-side comparison of recommendations in the 2017 AACE guidelines on management of dyslipidemia is provided in the Table.[6]

In addition to prioritizing individual patient-oriented outcomes, following an in-depth assessment of the certainty of evidence across all outcomes, the 2025 task force made judgments for each GRADE framework domain with particular emphasis on the importance of patient preferences and values, cost, acceptability, and equity in development of the recommendations. By including these additional considerations, the task force acknowledged the current lack of evidence supporting robust and long-term use of many of the newer treatments, particularly the PCSK9 inhibitors. Specifically, there was limited reporting on cardiovascular outcomes with many studies only publishing changes in lipid panel levels.[3] In line with best practice for guideline development, as new information is published, AACE will review and determine whether an update to any of the recommendations is warranted. With limited evidence for the newer omega-3 fatty acid formulations, the task force issued only a conditional recommendation for eicosapentaenoic acid monotherapy for individuals with moderate hypertriglyceridemia. Based on concerns with limited efficacy and increased risk of harms, the task force issued recommendations against the use of eicosapentaenoic acid + docosahexaenoic acid and niacin for individuals with moderate hypertriglyceridemia.[3]

Accurate ASCVD risk assessment is essential for patient-centered shared decision making about treatment. The 2025 guideline supports the use of validated risk assessment tools to assess risk for adults with dyslipidemia.[3] Multiple validated tools are available including the American College of Cardiology/American Heart Association Predicting Risk of cardiovascular disease EVENTs (PREVENT) calculator released in 2024.[7,8] However, there are limited data to support substantial improvement of accurate risk assessment with broad testing for additional risk enhancers, including coronary artery calcium score, apolipoprotein B, and lipoprotein a. This has important implications in practice as many patients may not be able to access or afford these additional tests.

One of the biggest changes from previous AACE guidance is the change in cholesterol treatment target recommendations. The 2025 guideline highlighted the limited evidence to support lower LDL-C treatment targets. The previous 2017 guideline issued a recommendation for lower LDL-C treatment targets (<55 mg/dL) in patients at very high risk for ASCVD.[6] However, this recommendation was informed by a single trial on statin + ezetimibe.[9] Subsequent meta-analyses of numerous trials that used statins and other treatment options did not show a difference in cardiovascular events or mortality. Although it is possible for individuals to obtain very low levels of LDL-C, it usually requires multiple medications or very costly treatments, which can impact health equity. It is also not known how long these levels are maintained and their long-term impact on ASCVD risk, highlighting the need for more research to determine the optimal treatment targets to facilitate robust shared decision making between patients and clinicians. In addition, it is unclear whether extreme lower LDL-C levels (<20 mg/dL) can have some side effects. Therefore, the task force issued a conditional recommendation based on low certainty of evidence for treatment

Table
Comparison of Recent American Association of Clinical Endocrinology Clinical Practice Guidelines on Dyslipidemia

Recommendation topic	2025	Difference from 2017
ASCVD risk assessment using a validated risk assessment tool	Recommends use of validated ASCVD risk assessment tool (good practice statement).	No change
Use of ASCVD risk enhancers (CAC, ApoB, and Lpa)	No recommendation. Current evidence does not support routine addition of nontraditional risk factors to standard risk assessment.	Change in recommendation type and strength
Statins	Statins considered first-line treatment.	No change
PCSK9 mAb	Conditional recommendation for use in persons with or at increased risk for ASCVD.	Change in recommendation strength and level of evidence
Inclisiran	No recommendation; insufficient evidence for outcomes of interest.	Not included
Bempedoic acid	Conditional recommendation for use in persons with ASCVD or at increased risk and statin intolerant.	Not included
EPA	Conditional recommendation for use in persons with or at increased risk for ASCVD; insufficient evidence for individuals with severe hypertriglyceridemia.	Change in recommendation strength and certainty of evidence
EPA + DHA	Conditional recommendation against use in persons with or at increased risk for ASCVD; insufficient evidence for individuals with severe hypertriglyceridemia.	Change in recommendation direction, strength, and certainty of evidence
Niacin	Strong recommendation against use in persons with or at increased risk for ASCVD; insufficient evidence for individuals with severe hypertriglyceridemia.	Change in recommendation direction, strength, and certainty of evidence
Fibrates	Not included	Not prioritized as an intervention due to lack of evidence for outcomes of interest
LDL-C treatment goal	Conditional recommendation for treatment goal of <70 mg/dL in persons with or at increased risk for ASCVD.	Change in recommendation strength, language, and certainty/ of evidence

Abbreviations: ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; Lpa = lipoprotein a; mAb = monoclonal antibody.

targets of LDL-C levels of <70 mg/dL for individuals with ASCVD or at high risk for ASCVD.

Conclusion

AACE's adoption of the GRADE methodology, alongside its updated 2025 AACE dyslipidemia guideline, underscores a commitment to advancing dyslipidemia management in a way that considers patient preferences, cost, and health equity. In addition, it provides recommendations based on the best available evidence. This approach reflects the evolving understanding of ASCVD risk management and the need for ongoing research to establish optimal treatment targets and the need to guide shared decision making for diverse populations, ultimately supporting improved cardiovascular outcomes for a broad patient population.

As a practicing clinical endocrinologist and part of the endocrine team, the availability of trustworthy CPGs that consider the evidence, benefits and harms of treatment, patient-relevant outcomes, and patient preferences and values are paramount to providing patient-centered care of the highest quality.

Disclosure

R.C. reports serving as immediate past chair of the American Association of Clinical Endocrinology CPG Oversight Committee, member of the American Association of Clinical Endocrinology Board of Directors, and in leadership positions at the American Medical Association, Western Endocrine Alliance, American Federation for Medical Research, American College of Physicians, and Endocrine Society.

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