



VA/DOD CLINICAL PRACTICE GUIDELINE ON LIPID MANAGEMENT FOR CARDIOVASCULAR DISEASE RISK REDUCTION

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DOD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as such, nor should the guidelines be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in each unique clinical situation using a patient-centered approach.

These guidelines are not intended to represent VA or DOD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both, within these guidelines does not guarantee coverage of civilian sector care.

Version 5.0 – 2025

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**The Lipid Management for Cardiovascular Disease Risk Reduction
Work Group**

With support from:

**Office of Quality and Patient Safety, Veterans Health Administration
and
Clinical Quality Improvement Program, Defense Health Agency**

Version 5.0 – 2025

Based on evidence reviewed through January 15, 2025

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DOD) Evidence-Based Practice Work Group (EBPWG) was established in 2004, with a mission to use clinical and epidemiological evidence to improve population health within the Veterans Health Administration (VHA) and Military Health System (MHS) and develop clinical practice guidelines (CPGs) for the VA and DOD populations.⁽¹⁾ The development and updating of VA/DOD CPGs is funded by VA Evidence-Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based guidelines, including this CPG, is to guide providers in lipid management in addition to offering management pathways supported by evidence. This CPG is intended to provide health care providers with a practical framework by which to evaluate, treat, and manage lipids, address the individual needs and preferences of patients, and improve clinical outcomes.

In 2014, the VA and DOD published a CPG for the Management of Dyslipidemia for Cardiovascular Risk Reduction (2014 VA/DOD Lipids CPG), which was based on evidence reviewed from January 2010 through February 2014. This was updated in 2020 using the same process, based on evidence reviewed through May 16, 2019 (2020 VA/DOD Lipids CPG). Since then, a growing body of research has expanded the general knowledge and understanding of the impact of lipid management on cardiovascular (CV) risk. Consequently, a recommendation to update the 2020 VA/DOD Lipids CPG was initiated in October 2024 using published data from May 16, 2019, to January 15, 2025. This updated CPG's use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reflects a more rigorous application of the methodology than previous iterations.⁽²⁾ Therefore, the strength of some recommendations might have been modified because of changes in the quality of the supporting evidence (see [Evidence Quality and Recommendation Strength](#)).

This CPG provides an evidence-based framework for evaluating and managing adult patients, 18 years or older, who are eligible for care in the VA and/or DOD healthcare systems and may benefit from lipid management to lower CV risk. These guidelines were written to emphasize the role of:

- Utilizing patient-centered care;
- Decreasing preventable complications and morbidity;
- Improving health outcomes and quality of life; and
- Using shared decision-making frameworks in patient collaboration efforts.

II. Background

A. Cholesterol as a Marker for Cardiovascular Disease Risk

Cardiovascular disease (CVD) remains the primary cause of mortality in the United States (U.S.). In 2022, heart disease was the primary cause of death at 167 deaths per 100,000 persons, and stroke was fourth at 40 deaths per 100,000 persons.⁽³⁾ Most CVD is caused by atherosclerosis, the buildup of cholesterol-laden plaque in the walls of arteries that limits perfusion and increases ischemia risk. Plaque ruptures within an artery can form blood clots that may obstruct the flow of

oxygenated blood to the heart or brain, resulting in an acute coronary syndrome (ACS) or stroke, with potentially irreversible tissue damage.

Control and reduction of CVD risk factors, including elevated blood pressure, insulin resistance, elevated blood glucose levels, smoking, poor dietary habits, and a sedentary lifestyle, can contribute to a reduction in CVD morbidity and mortality. Low-density lipoprotein cholesterol (LDL-C), measured by the levels of lipoprotein particles that transport cholesterol, serves as a risk marker in the context of numerous patient factors.

Aside from familial hypercholesterolemia (FH) and other genetically mediated forms of extreme lipid levels, dyslipidemia was once defined as one or more of the following: LDL-C ≥ 130 milligrams per deciliter (mg/dL), high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or triglycerides (TGs) ≥ 150 mg/dL. However, in patients with known CVD or elevated risk for CVD, even “normal” lipid levels warrant intervention for CVD risk reduction. Subclinical atherosclerosis (4) can develop in individuals with “normal” lipid levels as demonstrated by imaging studies showing a high prevalence of atherosclerotic plaques in people without other traditional risk factors, suggesting that lipid levels considered normal may still be atherogenic in some individuals. Other factors such as inflammation, endothelial dysfunction, and genetic predisposition, further contribute to CVD risk. See [Appendix K](#) for more information on FH and [Appendix L](#) for information on pharmacogenomic testing.

Accordingly, the management of dyslipidemia has shifted toward managing dyslipidemia in the context of overall risk for CVD. For this reason, lipid level thresholds for treatment vary depending on the risk of CVD. This CPG addresses the various treatment and management strategies for managing lipids among patients at risk for CVD morbidity and mortality, focusing upon either an individual’s risk factors or CV event history. This guideline does not include a comprehensive review of lipid management in the prevention of CVD. The reader should consult other textbooks and review articles for additional information, such as additional risk factors for CVD that impact women and the impact of CVD risk on prolonged medical treatment like hormone therapy.

B. Health-Related Social Needs

Cardiovascular disease, the leading cause of morbidity and mortality worldwide, is profoundly influenced by health-related social needs, including economic, educational, social, healthcare access, and environmental factors.(5-7) Differences in the use of guideline-recommended lipid-lowering therapies, particularly statins, are well-documented across demographic and socioeconomic groups.

Studies demonstrate that Hispanic and Black individuals are less likely to be prescribed statins compared to their White counterparts, even when clinical indications are similar.(7-10) Women are also often under-enrolled in clinical trials and receive lipid-lowering treatment and aggressive therapy at lower rates than men.(9,11,12) Socioeconomic status further influences statin therapy utilization, as individuals from lower-income backgrounds face high medication costs, limited access to healthcare, lower rates of insurance coverage, and reduced therapy adherence.(13) These differences persist among Veterans, which affects CV outcomes.(14-19) Additionally, Veterans from rural areas are more likely to have elevated LDL-C levels compared to those from urban areas.(20)

The limited interventions to address these differences are affected by the under-enrollment of minoritized groups in research.^(6,7) Differences in statin use across various populations cannot be fully explained by clinical factors or socioeconomic status, highlighting the critical role of addressing both conscious and unconscious preconceptions in clinical practice.^(6,14) Doing so is essential to optimizing CV outcomes for all patients.

Achieving optimal, low barrier access to effective pharmacological treatments for all individuals regardless of demographic, geographic, or socioeconomic status is critical. Addressing barriers to statin and other lipid-lowering therapy prescribing and adherence while ensuring optimal, low barrier access can significantly reduce the burden of CVD across patient populations. Key strategies include enhancing provider education to mitigate partiality, increasing the representation of different populations in clinical research, improving provider heterogeneity, implementing policies to improve healthcare access and affordability, and increasing patient-provider trust.^(14,21) By focusing on these areas, the Veterans' healthcare system can move towards more balanced treatment outcomes in lipid management and beyond.

III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available between May 16, 2019, to January 15, 2025. It is intended to provide general guidance on best evidence-based practices (see [Appendix A](#) for additional information on the evidence review methodology). Although this CPG is intended to improve the quality of care and clinical outcomes (see [Introduction](#)), it is not intended to define a standard of care (i.e., mandated or strictly required care).

A. Guideline Audience

This CPG is intended for use by primary care clinicians and other providers in practicing lipid management for CVD risk reduction.

B. Guideline Population

This CPG is intended for adults (18 years or older) with or at risk for CVD who would benefit from lipid management and are eligible for care in the VA and DOD healthcare delivery systems. This includes Veterans and Service Members as well as their eligible adult dependents.

Populations excluded from this guideline due to a lack of evidence or a lack of demonstrated benefit (heart failure with reduced ejection fraction [HFrEF], end-stage renal disease [ESRD]) include individuals with:

- HFrEF $\leq 35\%$;
- Limited life expectancy (<5 years);
- ESRD with or without chronic systolic heart failure; and
- Genetic dyslipidemia conditions (e.g., homozygous FH [HoFH], heterozygous FH [HeFH], TGs >500 mg/dL, etc.).

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline Update

The current document is an update to the 2020 VA/DOD Lipids CPG. The major strength of this CPG is in the coordination and collaboration of the multidisciplinary team, ensuring a broad representation of providers engaged in lipid management. The following significant updates highlight the importance of clinicians reviewing this version of the CPG:

- Updated [Algorithm](#);
- Updated [Sidebars](#); and
- Added 8 new recommendations, reviewed and replaced 4 recommendations, reviewed and amended 6 recommendations, carried over 3 recommendations not changed, carried over 1 recommendation not changed and not reviewed, and carried over 2 recommendations amended but not reviewed from the 2020 VA/DOD Lipids CPG.

Key takeaways

1. Comprehensive lifestyle medicine remains foundational for CV risk reduction. The Mediterranean dietary pattern and increasing physical activity continue to be supported by evidence.
2. In addition to healthy lifestyle changes, moderate-intensity statins remain a core therapy for primary prevention, but other lipid-lowering medications and statin intensities may be effective. For primary prevention, **at least** a moderate-intensity statin is recommended in patients who have diabetes, an LDL-C >190 mg/dL, or a 10-year risk estimate of **10% or greater**.
3. Risk estimation remains essential for guiding treatment decisions. The Predicting Risk of Cardiovascular Disease Events (PREVENT) calculator is now suggested to assess risk for primary prevention. Risk calculations are the starting point for risk estimation and should be considered in the context of additional risk factors and shared decision-making.
4. For primary prevention, a moderate-intensity statin is suggested for adults living with human immunodeficiency virus (HIV) even when the 10-year risk estimate is low.
5. For patients with documented atherosclerotic CVD (ASCVD), a high-intensity statin alone or a moderate-intensity statin combined with ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is suggested.
6. For very high-risk patients with ASCVD, a more intensive approach to medication management is suggested and should include combination therapy comprised of a high-intensity statin with ezetimibe and/or a PCSK9 inhibitor.
7. Coronary artery calcium (CAC) testing is suggested to refine risk and guide management for primary prevention in some patients, especially if there is clinical uncertainty and the calculated risk is intermediate or high.
8. Lipoprotein(a) [Lp(a)] testing is suggested to individualize risk assessment by identifying patients with enhanced risk when elevated.
9. The monoclonal antibody (mAb) PCSK9 inhibitors alirocumab and evolocumab are proven to reduce CV events in patients with ASCVD, but it is still unknown if novel PCSK9

inhibiting medications such as small interfering ribonucleic acid (siRNA) therapies (e.g., inclisiran) and oral small molecules (e.g., lerodalcibep) improve clinical outcomes. Lerodalcibep was not FDA-approved at the time of this writing.

10. We suggest icosapent ethyl in patients with ASCVD and hypertriglyceridemia (i.e., ≥ 150 mg/dL) on maximally tolerated statins.
11. For patients unable to take statins, consider bempedoic acid, ezetimibe, fibrates, or PCSK9 mAb inhibitors.
12. In 2020, we recommended against routinely ordering a lipid panel more frequently than every 10 years for primary prevention in patients not on statin therapy (2020 Recommendation 2), as well as against routinely monitoring lipid levels in patients taking statins (2020 Recommendation 22). This updated CPG removes these recommendations.

The methodology used in developing this CPG reflects a more rigorous application of the GRADE methodology than previous versions. The result is a refined CPG that includes methodologically rigorous, evidence-based recommendations for the management of individuals with or at risk for CVD who would benefit from lipid management.

This CPG also provides expanded recommendations on research needed to strengthen future guidelines.

B. Components of This Guideline

This CPG provides clinical practice recommendations for patients with or at risk for CVD who would benefit from lipid management (see [Recommendations](#)). In addition, the [Algorithm](#) integrates the recommendations in the context of the flow of patient care. This CPG also includes [Research Priorities](#), which list areas the Work Group identified as needing additional research. To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and a quick reference guide, which can be found at <https://www.healthquality.va.gov/index.asp>.

C. Demographic Terminology in This Guideline

The demographic terms used in this guideline are derived from the published literature sources included in the systematic review (SR) and evidence base. The Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and improve clarity and consistency. To accurately present the research evidence on which this CPG is based, the Work Group made every effort to use the same terminology as reported in the published literature base of SRs, clinical trials, and other studies. Consequently, usage of demographic terms in this CPG may vary and appear inconsistent.

V. Guideline Development Team

The VA Evidence-Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Paul Heidenreich, MD, MS, FACC, and Lance Spacek, MD, from VA; and Michael J. Arnold, MD, MHPE, FAAFP, and Brian E. Neubauer, MD, MHPE, FACP, from DOD. The Work Group was comprised of individuals

with the following areas of expertise: cardiology, internal medicine, family medicine, whole health, clinical pharmacy, physical medicine and rehabilitation, endocrinology, physical therapy, and dietetics. [Table 1](#) lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG;
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

Sigma Health Consulting and Duty First Consulting were contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
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VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the Guideline for Guidelines, an internal document of the VA/DOD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DOD CPGs.(22) The Guideline for Guidelines is available at <http://www.healthquality.va.gov/policy/index.asp>. This CPG also aligns with the National Academy of Medicine’s (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(23) [Appendix A](#) provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to

inform the strength of each recommendation (see [Determining Recommendation Strength and Direction](#))(24):

- Balance of desirable and undesirable outcomes;
- Confidence in the quality of the evidence;
- Patient or provider values and preferences; and
- Other implications, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations).

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(25) A *Strong* recommendation generally indicates High or Moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and an understood influence of other implications (e.g., resource use, feasibility). A recommendation’s strength (i.e., *Strong* vs. *Weak*) does not reference its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care).

In some instances, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for a particular therapy or intervention. The way this finding is expressed in the CPG might vary. The Work Group might include a statement among its recommendations acknowledging insufficient evidence for or against a commonly practiced intervention, particularly if it lacks supporting clinical evidence and poses potential risks (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might choose to remain silent in cases where evidence is lacking for a rarely used intervention or when an intervention, despite the absence of recent evidence, is considered the standard of care and has a favorable balance of benefits and harms.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in [Table 2](#). The strength of each recommendation is shown in [Recommendations](#).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

This CPG’s use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the

confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies (e.g., randomized controlled trials [RCTs]) might be inherently more difficult are typically considered lower quality evidence and, in turn, are usually *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted (e.g., RCTs) may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, then the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2,26) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see [Appendix A](#).

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(27) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(28)

Recommendation categories are used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, United Kingdom [UK]).(29,30) [Table 3](#) lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in [Recommendation Categorization](#). The 2025 VA/DOD Lipids CPG recommendation categories can be found in [Recommendations](#). [Appendix C](#) outlines the 2020 VA/DOD Lipids CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions*

Evidence Reviewed	Recommendation Category	Definition
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG and has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made

Evidence Reviewed	Recommendation Category	Definition
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, where the evidence has not been reviewed and the recommendation has not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG, where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012)([29](#)) and Garcia, et al. (2014)([30](#))

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the Guideline for Guidelines.([22](#)) Further, the Guideline for Guidelines refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care)([31](#)) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(22) The disclosure form inquires about relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also asks about any other relationships or activities that could be perceived to have influenced, or give the appearance of potentially influencing, a respondent’s contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and Guideline Development Team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

D. Patient Perspective

When developing a CPG, consideration should be given to patients’ perspectives and experiences, which often differ from those of providers.([26](#)) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DOD Leadership arranged a virtual patient focus group on December 16, 2024. The focus group aimed to gain insights into the perspectives of individuals who received care in the VA and DOD healthcare systems for abnormal lipid levels and incorporated these insights into the CPG, as appropriate. Topics discussed included various interventions participants have used, challenges they have experienced, information they have received regarding their condition and care, and other strategies or resources they have employed to manage lipid levels.

The patient focus group was comprised of a convenience sample of eight participants, which included one woman and seven men. Participants predominantly received care from the VA, with one participant receiving care from the DOD. The length of dyslipidemia treatment ranged widely from as recent as 90 days to as long as 21 years, and most participants reported having a family

history of hypercholesterolemia. The Work Group acknowledges that this convenience sample is not representative of all individuals who have undergone lipid management within the VA and DOD healthcare systems, and thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see [Appendix E](#). Patient focus group participants were provided with the opportunity to review the final draft of this CPG and share additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see [Drafting and Finalizing the Guideline](#). Once the Work Group members completed a near-final draft, they identified individuals from VA and DOD healthcare systems and external organizations generally viewed as experts in their respective fields. The draft was sent to those experts for a 14-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review may be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual healthcare providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care of patients who have or are at risk for CVD and would benefit from lipid management. The Work Group will submit suggested performance metrics for VA and DOD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DOD internal implementation plans and policies. Additionally, implementation will entail wide dissemination through publication in the medical literature, online access to the final CPG, educational programs, and ideally, electronic medical record programming in the form of clinical decision support tools at the point-of-care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

VA and DOD encourage providers to be sensitive to demographic, cultural, and other differences that affect patients' values, needs, and preferences, aimed at treating the condition while also optimizing the individual's overall health and well-being. Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.[\(32,33\)](#) A whole health approach (<https://www.va.gov/wholehealth/>) empowers and equips individuals to meet their personal health and well-being goals. Clear communication is essential and should be supported by evidence-based information tailored to each patient's needs. Guideline recommendations should be applied in a holistic approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. The

focus is using an individual's risk factors and event history to guide the various treatment and management strategies among patients at risk for CVD morbidity and mortality.

B. Shared Decision-Making

This CPG encourages providers to practice shared decision-making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.⁽³⁴⁾ Shared decision-making is emphasized in "Crossing the Quality Chasm," an Institute of Medicine, now NAM, report in 2001 ⁽³⁵⁾ and is a core component of a patient-centered, whole health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, possible outcomes, and levels and/or settings of care, especially where patient heterogeneity in weighing risks and benefits might exist. The VA and DOD have embraced shared decision-making. Providers are encouraged to use shared decision-making to individualize treatment goals and plans based on patient capabilities, needs, values, and preferences.

C. Patients with Co-Occurring Conditions

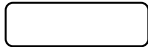

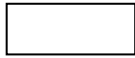

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to lipid management. Many Veterans, Active-Duty Service Members, and their families have one or more co-occurring conditions. Because dyslipidemia is often accompanied by co-occurring conditions, collaborative management with other care providers is often best. Some co-occurring conditions may require early specialist consultation to determine necessary changes in treatment or establish a common understanding of how care should be coordinated.

VIII. Algorithm

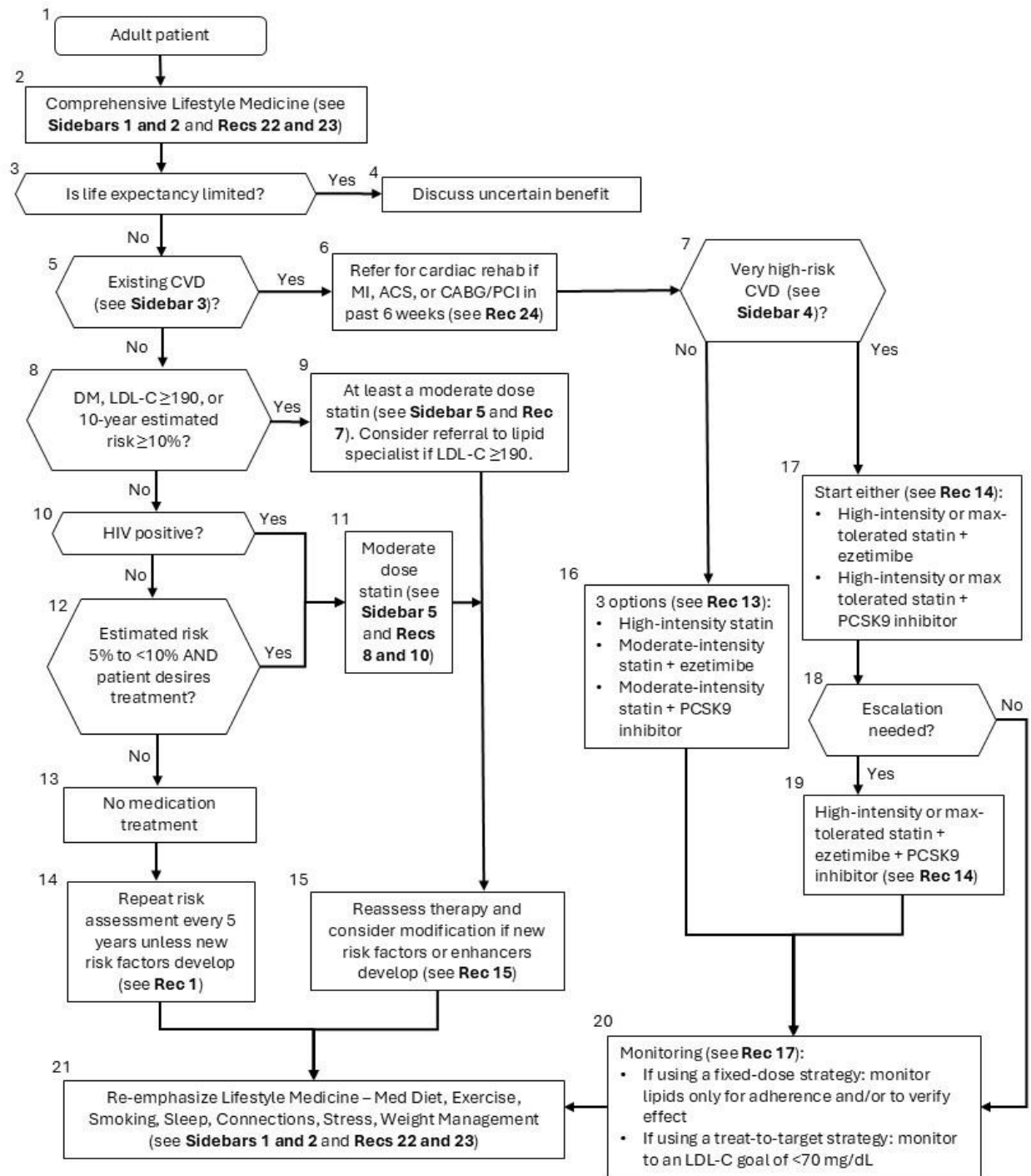
This CPG’s algorithm is designed to facilitate an understanding of the clinical pathway and decision-making process used in lipid management to reduce CVD risk. The algorithm format represents a simplified flow of the management of patients with or at risk for CVD and who would benefit from lipid management, helping to foster efficient decision-making by providers. It includes:

- An ordered sequence of steps of care;
- Recommended observations and examinations;
- Decisions to be considered; and
- Actions to be taken.

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.⁽³⁶⁾ Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered “Yes” or “No”.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the algorithm

Management Algorithm*



* Values for estimated risk are based on the PREVENT risk assessment tool.

Abbreviations: ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CVD: cardiovascular disease; DM: diabetes mellitus; HIV: human immunodeficiency virus; LDL-C: low-density lipoprotein cholesterol; LFTs: liver function tests; Med: Mediterranean; MI: myocardial infarction; PCI: percutaneous coronary intervention; PCSK9: proprotein convertase subtilisin/kexin type 9; Rec: Recommendation; ULN: upper limit of normal

Sidebar 1: Comprehensive Lifestyle Medicine

- Increase physical activity (aerobic and resistance exercise) that maximizes what the patient is willing and able to achieve
 - The stated goals of minutes per week are 150 minutes of moderate-intensity physical activity OR 75 minutes of vigorous-intensity physical activity OR an equivalent combination.
- Choose a healthy dietary pattern (e.g., Mediterranean diet)
- Sleep 7-8 hours/night
- Socialize: forge and embrace social connections
- Quit using tobacco and nicotine
- Minimize alcohol consumption
- Manage stress
- Address overweight and obesity (see VA/DOD Obesity and Overweight CPG)

Sidebar 2: Mediterranean and Other Cardioprotective Diets

Emphasize	Limit
Fruits and vegetables	Added sugar
Whole grains	Sugar-sweetened beverages
Seafood (primarily fatty fish)	Sodium
Skinless poultry	Highly processed foods
Tree nuts, seeds, peanuts, nut butters	Refined carbohydrates
Beans and legumes	Saturated fats
Non-tropical vegetable oils (olive, canola, avocado, etc.)	Tropical vegetable oils (coconut, palm, etc.)
Low-fat dairy products (milk, cheese)	High-fat and processed Meats
	Alcoholic beverages

Sidebar 3: ASCVD (Secondary Prevention)

- MI or ACS
- CABG/PCI
- Stable CAD
- CVA/TIA due to atherosclerosis
- PAD
- Does **not** include asymptomatic atherosclerosis on imaging (e.g., CCTA, CAC, catheterization)

Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CABG: coronary artery bypass grafting; CAC: coronary artery calcium; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CVA: cerebrovascular accident; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; TIA: transient ischemic attack

Sidebar 4: Very High-Risk CVD Patients

- MI or ACS in past 12 months on lipid-lowering therapy; or
- Recurrent ACS, MI, or atherosclerotic CVA on lipid-lowering therapy; or
- ASCVD and LDL-C \geq 70 mg/dL on lipid-lowering therapy

Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CVA: cerebrovascular accident; CVD: cardiovascular disease; dL: deciliter; LDL-C: low-density lipoprotein; mg: milligram; MI: myocardial infarction

Sidebar 5: Statin Intensity

Generic Name	Moderate Intensity	High Intensity
Rosuvastatin	5 – 10 mg	20 – 40 mg
Atorvastatin	10 – 20 mg	40 – 80 mg
Fluvastatin	80 mg (XL) or 40 mg BID	N/A
Lovastatin	40 – 80 mg	N/A
Pitavastatin	1 – 4 mg	N/A
Pravastatin	40 – 80 mg	N/A
Simvastatin	20 – 40 mg	N/A

Intensified patient care (e.g., phone calls, emails, patient education, drug regimen simplification) may improve adherence to lipid-lowering medications.

Abbreviations: BID: twice per day; mg: milligrams; N/A: not applicable; XL: sustained release

Sidebar 6: For Statin Intolerance*

1. Washout period (e.g., 1 month) followed by the same or a different statin; continue other lipid-lowering therapy
2. Lower dose or nondaily dosing (e.g., every other day or 2-3 days per week) of statin (see [Recommendation 18](#))
3. Consider initiating bempedoic acid, ezetimibe, fibrates, or PCSK9 mAb inhibitors in patients unable to take a statin (see [Recommendation 19](#))

*Other groups have described in more detail additional management strategies for statin intolerance; for example: [Management of Statin Intolerance Clinician Factsheet IB 10-1695](#).

Abbreviations: mAb: monoclonal antibody; PCSK9: proprotein convertase subtilisin/kexin type 9

Sidebar 7: Novel Risk Markers

- Suggest checking Lp(a) to identify intrinsic enhanced risk (see [Recommendation 5](#))
- Not recommended to routinely measure CAC in patients with low risk (see [Recommendation 4](#))
- Suggest CAC measurement in patients with intermediate to high risk who question the need for therapy (see [Recommendation 3](#))
- The routine measurement of hs-CRP, ApoB, PRS, TPA, or ABI is not useful to refine risk (see [Recommendation 6](#))

Abbreviations: ABI: ankle brachial index; ApoB: apolipoprotein B; CAC: coronary artery calcium; hs-CRP: high-sensitivity C-reactive protein; Lp(a): lipoprotein(a); PRS: polygenic risk scores; TPA: total carotid plaque area

Sidebar 8: Elevated Triglycerides for Secondary CVD Prevention

- Consider secondary causes of elevated triglycerides*
- If triglycerides are persistently elevated (≥ 150 mg/dL) despite maximally tolerated statin, then consider icosapent ethyl 2 g BID (see [Recommendation 16](#))
- Modify diet

*Secondary causes defined as co-occurring conditions, alcohol intake, and medications that can contribute to elevated triglycerides (e.g., hormones, immune-related, beta blockers, thiazide/loop diuretics, bile acid sequestrants, atypical antipsychotics, isotretinoin).

Abbreviations: BID: twice per day; CVD: cardiovascular disease; dL: deciliter; g: gram; mg: milliliter

IX. Recommendations

The evidence-based clinical practice recommendations listed in the table below were developed using a systematic approach considering four domains as per the GRADE approach (see [Summary of Guideline Development Methodology](#)). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 4. Evidence-Based Clinical Practice Recommendations with Strength and Category

While some of these recommendations may clearly be an element in a particular phase of care, others may require consideration throughout the continuum of care. Of note, the values for estimated 10-year CV risk specified in the recommendations below are based on the PREVENT risk assessment tool.

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
Screening and Assessment of Cardiovascular Risk		1.	For cardiovascular risk assessment in primary prevention, we suggest the PREVENT risk assessment tool.	Weak for	Reviewed, New-replaced
		2.	For primary prevention, in patients over 18 and not on statin therapy who have not developed new cardiovascular risk factors (e.g., diabetes, hypertension, tobacco use), there is insufficient evidence to recommend for or against a specific frequency for cardiovascular disease risk assessment.	Neither for nor against	Reviewed, New-added
		3.	For primary prevention, in patients identified with intermediate to high risk*, we suggest coronary artery calcium testing to improve the accuracy of risk assessment when deemed to affect clinical decision-making.	Weak for	Reviewed, New-added
		4.	For patients with low risk, we suggest against the routine use of coronary artery calcium testing.	Weak against	Reviewed, Not changed
		5.	We suggest measuring lipoprotein(a) [Lp(a)] to identify patients with enhanced risk.	Weak for	Reviewed, New-added
		6.	There is insufficient evidence to recommend for or against the routine use of ankle brachial index (ABI), apolipoprotein B (ApoB), polygenic risk scores (PRS), carotid plaque/total carotid plaque area (TPA), and high-sensitivity C-reactive protein (hs-CRP) for estimating cardiovascular risk.	Neither for nor against	Reviewed, Amended
Pharmacotherapy	Primary Prevention	7.	For primary prevention among patients who have diabetes or 10-year cardiovascular risk $\geq 10\%$ or low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, we recommend using at least a moderate-intensity statin.	Strong for	Reviewed, Amended
		8.	For primary prevention among patients without diabetes who have low-density lipoprotein cholesterol (LDL-C) < 190 mg/dL and a 10-year cardiovascular risk between approximately 5% to less than 10%, we suggest using a moderate-intensity statin.	Weak for	Reviewed, Amended

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b	
Pharmacotherapy (cont.)	Primary Prevention (cont.)	9.	For primary prevention, there is insufficient evidence to recommend for or against icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.	Neither for nor against	Reviewed, Amended	
		10.	For primary prevention in patients with human immunodeficiency virus (HIV), we suggest a moderate-intensity statin that has a low risk of interactions with antiretroviral therapy, even when 10-year risk estimates are low (i.e., $<5\%$).	Weak for	Reviewed, New-added	
		11.	In patients with an indication for statin therapy and elevated baseline aspartate aminotransferase (AST) or alanine transaminase (ALT) less than 3-times the upper limit of normal, we suggest using statins as indicated.	Weak for	Reviewed, New-added	
			12.	For primary or secondary prevention, we suggest against adding fibrates to statins.	Weak against	Reviewed, Not changed
		Secondary Prevention	13.	For secondary prevention, we suggest treating with one of the following ^{**} : <ul style="list-style-type: none"> • High-intensity statin • Moderate-intensity statin with ezetimibe • Moderate-intensity statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. 	Weak for	Reviewed, New-replaced
	14.		For secondary prevention in very high-risk patients [†] , we suggest a combination therapy of one of the following: <ul style="list-style-type: none"> • High-intensity or maximally tolerated statin with ezetimibe • High-intensity or maximally tolerated statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor • High-intensity or maximally tolerated statin with ezetimibe and PCSK9 inhibitor. 	Weak for	Reviewed, New-replaced	
	15.		For patients who achieve a very low low-density lipoprotein value (LDL-C <30 mg/dL) with therapy, we suggest continuing treatment.	Weak for	Reviewed, New-added	
	16.		For secondary prevention, we suggest icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.	Weak for	Reviewed, Amended	
	17.		For secondary prevention, there is insufficient evidence to recommend a treat-to-target strategy (e.g., low-density lipoprotein [LDL-C] <70 mg/dL) over a fixed-dose high-intensity statin strategy.	Neither for nor against	Reviewed, New-added	
	Statin Intolerance		18.	For patients who cannot tolerate a statin, we suggest a washout period followed by a re-challenge with the same or a different statin or lower dose, and if that fails, a trial of intermittent (nondaily) dosing.	Weak for	Reviewed, Not changed

Topic	Sub-topic	#	Recommendation	Strength ^a	Category ^b
		19	For primary and secondary prevention in patients unable to take a statin, we suggest one of the following non-statin: bempedoic acid, ezetimibe, fibrates, or proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9 mAb) inhibitors.	Weak for	Reviewed, New-added
Supplements and Nutraceuticals		20.	There is insufficient evidence to recommend for or against the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce cardiovascular risks.	Neither for nor against	Not reviewed, Not changed
		21.	For primary or secondary prevention, we suggest against the use of omega-3 fatty acids as a dietary supplement or any omega-3 formulation other than icosapent ethyl.	Weak against	Reviewed, Amended
Lifestyle Interventions		22.	For primary and secondary prevention of cardiovascular disease, we suggest a Mediterranean diet.	Weak for	Reviewed, New-replaced
		23.	For primary and secondary prevention, we suggest increasing regular aerobic physical activity that maximizes what the patient is willing and able to achieve.	Weak for	Not reviewed, Amended
		24.	We recommend a structured, exercise-based cardiac rehabilitation program for patients with recent occurrence of coronary heart disease (i.e., myocardial infarction, diagnosis of coronary artery disease, coronary artery bypass grafting, or percutaneous coronary intervention).	Strong for	Not reviewed, Amended

^a For additional information, please refer to [Determining Recommendation Strength and Direction](#).

^b For additional information, please refer to [Recommendation Categorization](#).

* Read narrative discussion for the definition of intermediate to high risk.

** Listed in alphabetical order.

† Very high-risk patients defined as:

- MI or ACS in the past 12 months on lipid-lowering therapy;
- Recurrent ACS, MI, or atherosclerotic CVA on lipid-lowering therapy; or
- ASCVD and LDL-C \geq 70 mg/dL on lipid-lowering therapy.

A. Screening and Assessment of Cardiovascular Risk

Recommendation

1. For cardiovascular risk assessment in primary prevention, we suggest the PREVENT risk assessment tool.
(Weak for | Reviewed, New-replaced)

Discussion

PREVENT is suggested because recent studies find it to be more accurate than other risk assessment tools. Fifteen studies comparing established and novel risk assessment tools for determining CV risk in primary prevention patients were identified. The tools compared included PREVENT, Pooled Cohort Equation (PCE), and Systematic Coronary Risk Evaluation version 2 (SCORE2). While there are several risk assessment tools, the Work Group suggests that the PREVENT tool be used as the first line estimator based on moderate evidence from retrospective comparisons. There is no current prospective data comparing clinical outcomes between the PREVENT and PCE calculators. Furthermore, future research is needed to define more precise treatment thresholds based on the PREVENT calculator. See [Recommendations 7 and 8](#) for treatment thresholds based on the PREVENT calculator.

The PCE risk estimator, introduced to clinical care in 2013, has been a popular means among providers for determining CVD risk. Though multiple studies have shown, with statistical significance, that the PREVENT tool classifies primary prevention patients into lower risk categories than PCE.[\(37-39\)](#) Potential advantages for using PREVENT include that it can provide a 30-year risk assessment in addition to a 10-year risk assessment in patients aged 30 to 79 years, whereas PCE only provides a 10-year risk assessment in patients aged 40 to 79 years. Health-related social needs are considered in the PREVENT tool where they are not considered in the PCE, while maintaining a race-neutral algorithm that also contributes to its risk assessment accuracy. The PREVENT tool can also be used to assess the risk in primary prevention in patients as young as 30 years old, where PCE requires that a patient be at least 40 years old. The PREVENT calculator requires incorporation of whether or not the patients are on statins and therefore, may be more accurate. The PREVENT tool can also be used to assess a patient's risk for heart failure, coronary heart disease (CHD), and stroke.

While the PREVENT tool has the potential to drastically reduce the number of primary prevention patients on statin therapy based on their risk assessment, there is also potential for the new tool to create "complacency" [\(39\)](#) considering the suggested improved CV health of patients. Heaton et al., 2024 [\(40\)](#) also notes that the PREVENT tool has not yet been widely implemented in clinical practice, creating uncertainty for real-world application. It is still the recommendation of the Work Group that the PREVENT tool be used over other risk assessment tools based on evidence showing positive results. PREVENT can be used to assess the risk of patients being initially evaluated for dyslipidemia as well as those who are already being monitored, with or without statin therapy. The evidence suggests that a patient previously assessed with PCE and started on statin therapy based on the assessed risk may no longer meet criteria for such therapy after being re-assessed with the PREVENT tool. Due to the PREVENT tool requiring the distinction of a patient's statin use, the decision to discontinue such therapy based on a new or different risk assessment would ultimately fall to the provider, with consideration from the patient.

Anderson et al., 2024, speaks to the reduction in statin therapy eligibility for patients assessed with the PREVENT tool compared to PCE,(41) showing a potential reduction in the number of U.S. adults meeting the criteria for primary prevention statin use by 17.3 million. Of those 17 million adults, approximately 4.1 million adults are currently on statin therapy based on an overestimation of risk. A retrospective study by Khan et al., 2024, found that the PREVENT tool is a more accurately calibrated risk assessment tool when directly compared to PCE.(38) When comparing the slopes associated with the predicted risk, the PREVENT tool had a slope “close to 1” whereas PCE had slopes ranging from 0.50 to 0.54, creating an overestimation of about 50% when using PCE.

A retrospective cohort study not included in the evidence base and therefore, not considered in developing this recommendation, Zhou et al., 2025, determined the calibration of the PREVENT tool.(42) Based on the statistical analysis, the PREVENT tool was found to be more accurate at predicting risk than PCE.

The Work Group systematically reviewed evidence related to this recommendation.(37-41) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group’s confidence in the quality of the evidence was Moderate. The body of evidence had some limitations such as retrospective data, lack of long-term follow-up, and lack of evidence showing a direct impact on CV outcomes based on the predictive tool used.(37-41) The benefits of the PREVENT tool, including improved prediction compared to the PCE, outweighed the theoretical harm of statin undertreatment from lower risk estimates. Notably, treatment decisions should be based on accurate prediction and thresholds grounded in the placebo or observed study population risk from clinical trials. Patient values and preferences varied somewhat because patients may not want to participate in reassessment, be taken off a medication they have been using long-term, or commit to taking a new or different medication following reassessment. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

2. For primary prevention, in patients over 18 and not on statin therapy who have not developed new cardiovascular risk factors (e.g., diabetes, hypertension, tobacco use), there is insufficient evidence to recommend for or against a specific frequency for cardiovascular disease risk assessment.

(Neither for nor against | Reviewed, New-added)

Discussion

Cardiovascular risk assessment models are widely used in clinical practice as a strategy for identifying patients who are most likely to benefit from treatment for the primary prevention of CVD. Risk equation models incorporate both modifiable and non-modifiable risk factors including age, sex, ethnicity, blood pressure, tobacco use, cholesterol levels, estimated glomerular filtration rate, body mass index, social vulnerability, and diabetes mellitus (DM) to calculate CVD risk.

The 2020 VA/DOD CPG’s systematic evidence review identified two prospective cohort studies evaluating the timing of repeat screening for CV risk in primary prevention populations based on prediction of CV events or reclassification of CV risk. Chamnan et al., 2016, evaluated 12,197 patients for CVD event rates utilizing the Framingham Risk Score (FRS).(43) Prediction of CVD

events based on the FRS did not change significantly between the baseline visit and a subsequent visit conducted a mean of 3.7 years later. Angelow et al., 2016, evaluated 1,112 patients by estimating CVD risk utilizing the SCORE-Germany prediction model inputting both a 5- or 10-year-old total cholesterol (TC) to predict “high CV risk”.(44) The authors observed only minor changes in TC over time. Moreover, they reported that utilizing 5- or 10-year-old TC levels had high sensitivity and specificity to identify patients at high CV risk and resulted in low misclassification rates. The authors concluded that measuring TC at 5-year intervals is sufficiently accurate for primary CVD prevention. This evidence suggests that the common practice of annual risk assessment may not add value.

Our updated evidence literature review set out to evaluate new CV risk assessment models used over time. An observational study by Gokhale et al., 2024, that included 198,835 patients aimed to study the predictive capability of the QResearch Indicator for CV Risk Algorithm (QRISK) to support decision-making processes regarding CVD prevention in patients with DM.(45) Average follow-up was just over 5 years, and patients with repeated risk evaluations had a negligible improvement in the accuracy of risk prediction.(45)

For primary prevention of CVD in low-risk patients not on statin therapy, frequent cholesterol screening or CV risk assessment is unlikely to reclassify 10-year risk or influence clinical management. In the absence of new CV risk factor development, it is reasonable to perform a CV risk assessment every 5 years.

CVD risk assessment models provide a foundation for shared decision-making to review the anticipated benefit of preventive interventions while minimizing the potential harm from overtreatment. As CV risk scoring influences treatment decisions and frequently involves laboratory testing, excessive monitoring may lead to unnecessary testing and/or treatments. Therefore, avoiding frequent risk assessments has the potential to optimize medical resource use, reduce costs, reduce anxiety, and enhance patient participation at check-ups.

The Work Group systematically reviewed evidence related to this recommendation.(45) Therefore, it is categorized as *Reviewed, New-added*. The Work Group’s confidence in the quality of the evidence was Low. The main study limitations were a lack of data and unblinded outcome assessors. Given the lack of evidence for improved health outcomes, the harms/burdens of conducting CV risk assessment screenings more often than every five years slightly outweigh potential benefits. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

3. For primary prevention, in patients identified with intermediate to high risk*, we suggest coronary artery calcium testing to improve the accuracy of risk assessment when deemed to affect clinical decision-making.
(Weak for | Reviewed, New-added)
4. For patients with low risk, we suggest against the routine use of coronary artery calcium testing.
(Weak against | Reviewed, Not changed)

Discussion

Coronary artery calcium has been suggested to improve the accuracy of 10-year ASCVD risk calculators to further refine the risk assessment of CVD and the potential need for treatment. Unfortunately, reclassification is not accurate or clinically significant in all patient populations. Lin et al., 2018, demonstrated a slight improvement in the accuracy of the PCE when CAC was added, with an improvement to the area under the curve (AUC) of 0.02.[\(46\)](#) In Yeboah et al., 2016, a large retrospective study of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort of over 5,000 subjects, 350 patients were reclassified based on CAC results, with 58 correctly reclassified and 292 incorrectly reclassified.[\(47\)](#) More recently, Bell et al., 2022, an SR of six cohort studies, found that in patients at low risk according to a variety of risk prediction calculators, 0.4%-2.2% were correctly reclassified into the intermediate/high risk category while 2.1%-14.4% were incorrectly reclassified, a more than five-fold incorrect/correct reclassification in those low-risk patients.[\(48\)](#) Therefore, the routine use of CAC screening in primary prevention does not provide sufficient value for risk assessment in the general population.

Bell did, however, demonstrate a benefit in patients at intermediate or higher risk based on the risk equation used. Four of those studies presented reclassification data in comparison to the FRS, with cutoffs for intermediate-to-high versus low-risk of $\pm 6.5\%$ 5-year risk, $\pm 7.5\%$ 10-year risk, and $\pm 10\%$ 10-year risk in two of the studies. A total of 18.9% to 29.3% of intermediate or higher risk patients by risk estimate were correctly reclassified into a lower risk category where only 0.2% to 1.9% were incorrectly reclassified. CAC scoring, then, can help to reclassify up to 1 out of 3 patients into a lower risk category with a false negative risk of less than 2%, limiting the unnecessary use of pharmacotherapy for future CV risk reduction.[\(48\)](#) In the patient who is unwilling to take a statin, knowledge of their CAC score (and where they fall amongst others of their sex and age) can, at a minimum, help reinforce the importance of strict lifestyle improvement and aid in the patient-clinician discussion. It may be enough for some high-risk patients to comply with the recommendation to take a statin now that they understand the amount of calcium in their arteries. In patients who are already willing to take statins, there is less utility to further refining risk and thus, CAC scoring may be superfluous.

While CAC scoring does slightly enhance CV risk assessment, research does not support routine measurement due to the overall low clinical significance and potential for harm. Those harms include radiation exposure, albeit low, cost to the healthcare system that would be required to scan such a large number of patients, time, and inconvenience.

* Read narrative discussion for the definition of intermediate to high risk.

For a patient whose risk estimate recommends statin therapy but is resistant to that therapy, the Work Group's review showed that CAC scoring can be beneficial by reclassifying nearly 1 in 3 patients to low risk with less than a 2% chance of missing a cardiac event. The clinician-patient discussion on CV risk and need for statins can be a challenging one. Patients often have preconceptions about the sometimes-exaggerated harms of statins and a legitimate fear of taking them because of information they have encountered. A CAC score can help facilitate that discussion, in that if it is negative, it can justify deferring therapy.

Based on the relevant studies reviewed in the current CPG evidence base,[\(46-48\)](#) the Work Group provides a *Weak for* recommendation for use of CAC in intermediate- and high-risk patients when it could potentially change management (*Reviewed, New-added*) and a *Weak against* recommendation for routine CAC screening in patients with low risk (*Reviewed, Not changed*). The Work Group's confidence in the quality of the evidence was Moderate.

The body of evidence had some limitations including a small sample size and moderate quality of evidence. There were minor inconsistencies in regards to the definitions of risk used, though not significantly different from the risk definitions provided in this guideline.[\(48\)](#) For routine screening with CAC, the benefits of improved reclassification are outweighed by the potential harm of incorrect reclassification and additional risk of radiation and cost to the healthcare system. In patients at intermediate/high risk in which more information is needed to make a better CV risk prediction prior to prescribing lipid-lowering therapy, the benefits of potentially classifying down, which include less unnecessary statin usage and better patient education, outweigh the potential harms. Patient values and preferences on this topic vary somewhat. Patients generally prefer to have more information when making this decision but tend to come into the discussion with a wide variation in their understanding of the benefits of statins. Thus, the Work Group decided upon a *Weak against* recommendation for routine screening and a *Weak for* recommendation for use of CAC in those intermediate- to high-risk patients in whom CAC results may change management.

Recommendation

5. We suggest measuring lipoprotein(a) [Lp(a)] to identify patients with enhanced risk.
(**Weak for | Reviewed, New-added**)

Discussion

Lp(a) is a unique LDL-C-like particle independently associated with CV risk that has garnered attention as a potential biomarker for refining CV risk estimates. Lp(a) is approximately 90% genetically determined and characterized by particles distinguishable from other LDL-C particles by an additional surface protein called apolipoprotein(a), which is a structural homologue of plasminogen. Increased thrombotic potential rather than atherogenesis may give mechanistic explanation to risk associated with Lp(a), although the underlying pathophysiologic mechanism remains uncertain.

Epidemiological data, genome wide association studies, and mendelian randomization evidence has established Lp(a) as a causal agent for ASCVD.[\(49-54\)](#) However, an Lp(a) threshold of 50 mg/dL (125 nmol/L) has not been shown to improve prediction when incorporated into established risk calculators, such as the American Heart Association and American College of Cardiology (AHA/ACC) PCE.[\(55\)](#) For example, improvement in model discrimination is absent (overall c-

statistic 0.0 for CVD, 0.002 for CHD) or marginal (low-risk subgroup <7.5%; c-statistic +0.024) when Lp(a) is incorporated into the PCE.

Although measures of discrimination are not optimal for assessing models that stratify individuals into risk categories, more effective measures for doing so show similar results.[\(56\)](#) One example is the Net Reclassification Improvement (NRI), a measure that classifies patients into risk categories and then determines how accurately a new model (e.g., model incorporating a novel biomarker) reclassifies patients compared to another model (e.g., the base model). Incorporating Lp(a) (>50 mg/dL) into the PCE improves overall continuous NRI, but the magnitude is marginal (0.0963 for CVD; 0.1248 for CHD) and lower than other markers such as CAC (0.18 to 0.28 for intermediate- to high-risk groups). In conclusion, Lp(a) does not sufficiently refine model-based risk estimates to warrant incorporation directly into the PCE, PREVENT, or other prediction models.

However, absence of model risk refinement does not necessarily render a novel marker void of all clinical utility. Measuring Lp(a) at least once to individualize risk as a risk-enhancer when elevated, without exonerating traditional risk factors when low, is justified by the NRI evidence. In other words, a low Lp(a) value does not negate the risk assessment of traditional risk factors. In the Bhatia study,[\(55\)](#) the component NRI for those destined to not have an event (i.e., “non-events NRI”) was impressive (0.6077; range: 0.0-1.0 for the component) for CVD. This prediction improvement was negated by erroneous prediction in those destined to have an event (i.e., “event NRI”), which rendered the overall NRI unimpressive (0.0963). A viable interpretation of this evidence is that Lp(a) is specific, but not sensitive. As such, Lp(a) is not a “well-rounded” marker that improves prediction when incorporated into an established model; however, when elevated, it identifies the 10-20% of patients with significantly enhanced risk. This interpretation is in keeping with a leading theory that the mechanism undergirding Lp(a) and ASCVD risk is mostly prothrombosis through fibrinolysis inhibition at vulnerable plaques rather than proatherogenic effects.[\(57-60\)](#)

Although not included in our evidence review, additional evidence showed similar patterns in the component NRIs when Lp(a) is incorporated into the AHA/ACC PREVENT risk calculator.[\(61\)](#) Importantly, these improvements were not exclusive to patients with intermediate risk estimates but were also seen across a spectrum of risk as defined by the authors, including low 10-year risk estimates (i.e., <7.5%) and high-risk estimates (i.e., >20%). Additional studies not included in our review have shown improvements in net reclassification to varying degrees when Lp(a) is incorporated into various prediction models.[\(62-65\)](#)

Although statins and healthy lifestyle changes do not lower Lp(a), patients with elevated Lp(a) (e.g., >50 mg/dL or 125 nmol/L) may theoretically offset risk from Lp(a) by more intensive LDL-C lowering with healthy lifestyle changes and LDL-C-lowering medications. Additionally, studies outside the scope of our evidence review have shown some LDL-C lowering treatments, such as apheresis, PCSK9 mAbs (e.g., alirocumab, evolocumab), and PCSK9 siRNAs (e.g., inclisiran), also effectively lower Lp(a) and that patients with higher baseline Lp(a) concentration may derive enhanced benefit from treatment.[\(59\)](#) Novel agents designed to directly lower Lp(a) by various mechanisms have been developed and at the time of this writing their effects on CV outcomes are being studied in phase 3 trials.

There is likely to be some variation in values and preferences when Lp(a) testing is considered. Some patients may experience significant psychological stress knowing their Lp(a) is elevated if targeted therapy is not available or recommended. Some providers may have concerns about the assays used for Lp(a) testing given substantial variability and lack of standardization.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation. (49-51,55) The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including serious risk of bias in many of the studies. The benefits of checking Lp(a) to identify patients with enhanced risk slightly outweigh the potential harm (e.g., false positives, psychological stress, uncertainties regarding therapy). Some variation in patient values and preferences is likely. Other factors influencing this recommendation included Lp(a) assay variability and lack of standardization. Thus, the Work Group decided upon a *Weak for* recommendation to check Lp(a) to improve risk assessment by identifying patients with enhanced risk.

Recommendation

6. There is insufficient evidence to recommend for or against the routine use of ankle brachial index (ABI), apolipoprotein B (ApoB), polygenic risk scores (PRS), carotid plaque/total carotid plaque area (TPA), and high-sensitivity C-reactive protein (hs-CRP) for estimating cardiovascular risk.

(Neither for nor against | Reviewed, Amended)

Discussion

Traditional CV risk assessment relies on the use of multivariate models that integrate data from known risk factors and biomarkers to predict the development of CVD in an individual patient. While numerous models exist, patients and providers continue to seek guidance to improve CV risk prediction.

The use of non-traditional biomarkers to improve the estimation of CV risk has been extensively studied. Non-traditional biomarkers include genetic, serologic, psychosocial, and physiological markers. Numerous biomarkers and other variables were assessed in this review, including ABI, Lp(a), PRS, TPA, ApoB, and hs-CRP. Our review set out to evaluate the comparative accuracy of adding novel risk markers versus using an established risk prediction model alone for prediction of short- and long-term CV risk. Recommendations regarding the role of Lp(a) are discussed above.

Regarding ABI, evidence from one longitudinal cohort study (66) found that, after adjustment for established risk factors, low ABI in a population of patients without known peripheral vascular disease was associated with an increased risk of cardiac or cerebrovascular disease mortality (hazard ratio [HR]: 3.02; 95% confidence interval [CI]: 1.6 to 5.69; p=0.001) as well as all-cause mortality (HR: 2.22; 95% CI: 1.57 to 3.14; p<0.001). In the same study, low ABI was associated with an increased risk of all-cause mortality (HR: 2.22; 95% CI: 1.57 to 3.14; p<0.001). However, the strength of evidence in this study was Low and the quality rating was poor. Moreover, the evidence that the ABI is an accurate screening test in asymptomatic adults is limited. (67) The 2024 AHA/ACC guidelines state, "In patients not at increased risk of PAD [peripheral artery disease] and without history or physical examination findings suggestive of PAD, screening for PAD with the ABI is not recommended." (68)

One fair-quality cohort study (69) found that the addition of TPA to FRS and to CHD risk factors improved model discrimination for incident CHD (AUC: 0.72 and 0.77, respectively) and led to significant change in NRI (0.39). However, the strength of evidence was also Low in this study of a population of patients living in the Reykjavik, Iceland area.

Although there were no RCTs that evaluated the benefit of adding apoB to an established risk prediction model, there are observational studies that demonstrate potential clinical value in using ApoB to augment the standard lipid panel, especially when there is a discordance between LDL-C and ApoB levels.(70) A large cohort study (Marston et al.) showed that the number of ApoB-containing proteins was independently associated with incident MI (adjusted HR per 1 standard deviation: 1.27; 95% CI: 1.15 to 1.40; $p < 0.001$). (71)

Review of the literature included one cohort study that showed no significant association between hs-CRP and incident CHD. Similarly, hs-CRP did not appear to improve model discrimination.(50)

The Work Group reviewed multiple studies that studied the role of PRS in CV risk assessment. The quality of the included studies was poor to fair. Genome-wide association studies have shown that many single nucleotide variants are associated with cardiometabolic diseases.(72) PRS are the weighted summations of these single nucleotide variants. PRS are proposed as tools to improve the prediction of CVD (73) and are increasingly used in large-scale research and direct-to-consumer testing. In a scientific statement on the use of PRS in predicting CVD in July 2022, the AHA acknowledged that the addition of PRS to traditional risk calculators improves their predictive value.(74)

Our review of the literature continues to support the ability of PRS to improve the accuracy of traditional risk calculators. In a cohort study using the UK Biobank resource, Riveros-McKay et al. (75) developed a PRS for CAD which was then combined with PCE or UK QRISK3. This integrated risk tool (IRT) was tested in an additional, independent set of nearly 200,000 UK Biobank individuals. The overall NRI for the IRT (using PCE) was 5.9% (95% CI: 4.7 to 7.0). When individuals were stratified into age-by-sex subgroups, the improvement was larger for all subgroups (range: 8.3% to 15.4%), with the best performance in 40-to-54-year-old men (15.4%; 95% CI: 11.6 to 19.3). Comparable results were found using a different risk tool (QRISK3). Another cohort study assessed the predictive utility of a PRS for CHD in combination with the PCE.(76) The addition of PRS to PCE increased the AUC from 0.759 (95% CI: 0.755 to 0.763) to 0.773 (95% CI: 0.769 to 0.777). The AUC and NRI_{Event} for PRS were higher before the age of 55 years.

The Work Group felt that, although there was evidence for the use of PRS to improve accuracy of traditional risk tools,(75-82) the logistics of using PRS in primary care is challenging. Currently, there are no criteria or established processes for clinical implementation. Criteria for incorporating PRS into clinical care would likely include the potential to reclassify individuals at intermediate risk, estimate potential harms, and provide education surrounding population genetics for clinicians and patients.

In their review of the evidence for the use of novel biomarkers, the Work Group also reviewed the literature on the utility of adding carotid plaque/TPA to the traditional risk models. Both the Gudmundsson and Fuster studies signalled that estimation of the TPA may be predictive of future CV events and/or all-cause mortality.(69,83) For example, in the Fuster study, vascular ultrasound

detected disease in 72% of patients versus 58% by CAC scoring in patients with low risk by FRS. When stratified by FRS groups, the prevalence of multiterritorial atherosclerosis (i.e., CAC and TPA) was 47% in the low-risk group, 69% in the intermediate-risk group, and 81% in the high-risk group. While the prevalence of isolated CAC remained similar in all risk groups (approximately 10%), isolated carotid disease was significantly more prevalent in the low-risk group (25%) and decreased with increasing FRS. After adjustment for CV risk factors (diabetes, smoking, body mass index, lipids, blood pressure) and background medication (lipid-lowering and anti-hypertensive therapies), baseline carotid plaque burden and CAC score were both significantly associated with all-cause mortality (fully adjusted trend HR: 1.23 [95% CI: 1.16 to 1.32] and HR: 1.15 [95% CI: 1.08 to 1.23], respectively; both $p < 0.001$). Because the overall strength of evidence was low for TPA, the Work Group felt that a recommendation of *Neither for nor against* was appropriate. Further RCTs would be important to close this evidence gap.

The theoretical utility of these novel biomarkers would be to refine CV risks for that population of patients who have intermediate risk and where there is uncertainty about the benefit of treatment. Unfortunately, there is no prospective evidence to validate the addition of these non-traditional biomarkers. Therefore, using these non-traditional risk factors in CV risk assessment should occur within the context of a shared decision-making framework, with a focus on whether incorporating these factors will lead to change in lipid management. While most of these tests are considered non-invasive, they may result in increased psychological stress for the patient.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation. ([46](#), [47](#), [49-51](#), [55](#), [66](#), [69](#), [75-86](#)) The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including limited clinical effect, heterogeneity of patient populations, and a short follow-up period. ([49](#), [50](#), [55](#), [76-78](#), [80](#), [81](#), [85](#), [86](#)) The benefits of using additional risk markers when assessing CV risk (e.g., confirmation of risk, avoidance of medication) slightly outweighed the potential harm (e.g., risks and psychological stress associated with the evaluation of incidental findings). Patient values and preferences varied largely. Some individuals prefer as much information as possible when determining CVD risk. Others may have been exposed to direct-to-consumer advertising and have expectations about the value of these tests. Factors influencing this recommendation included resource use (e.g., staffing, time burden), the limited benefit of additive predictive risk, clinical application of PRS, and potential harms from overtreatment. Thus, the Work Group decided upon a *Neither for nor against* recommendation for the routine use of ABI, ApoB, PRS, TPA, and hs-CRP to assess CV risk.

B. Pharmacotherapy

a. Primary Prevention

Recommendation

7. For primary prevention among patients who have diabetes or 10-year cardiovascular risk $\geq 10\%$ or low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, we recommend using **at least** a moderate-intensity statin.
(Strong for | Reviewed, Amended)
8. For primary prevention among patients without diabetes who have low-density lipoprotein cholesterol (LDL-C) < 190 mg/dL and a 10-year cardiovascular risk between approximately 5% to less than 10%, we suggest using a moderate-intensity statin.
(Weak for | Reviewed, Amended)

Discussion

Multiple double-blind RCTs, when combined in meta-analysis, indicate that moderate-intensity statins lower all-cause mortality and CV events. An SR cited in the 2020 VA/DOD Lipids CPG (87) included 40 primary prevention trials (N=94,283) that demonstrated a 20% relative risk reduction in all-cause mortality over one year and a 26% relative risk reduction in major CV events over one year. A recent review confirmed the prior findings and demonstrated a significant reduction in the individual outcomes of stroke and myocardial infarction (MI). (88)

Meta-analyses demonstrate clear benefit without statistically significant harms in most patients receiving a moderate-intensity statin. (88) In the Chou review, statin therapy was not significantly associated with an increased risk of serious adverse events (SAE), myalgias, or elevated alanine transaminase (ALT) level. (88) Statin therapy (primarily moderate-intensity with some high-intensity) was not significantly associated with increased diabetes risk overall, though one individual trial found a significantly increased risk of diabetes with high-intensity statin. (88)

The decision to use a statin is based on risk. The 10-year risk is the commonly used threshold and is the metric produced by calculators, such as the PREVENT calculator that is suggested by this guideline. The baseline 10-year risk was reported in the largest of these primary prevention trials (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER]), (89) which showed a similar relative risk reduction with statin therapy for those above and below the 10-year risk trial average of 10% using the Framingham criteria. Since the PREVENT equations were not available at the time, the trials could not report the 10-year PREVENT risk; however, this can be calculated from the patient population description published for each trial. For the largest primary prevention population, the value is a 7.5% 10-year risk. (89) The lower risk calculated with the PREVENT versus Framingham calculator is consistent with data presented in the [risk assessment recommendations](#), which note that the new PREVENT equations improve accuracy and indicate a lower 10-year risk than older calculators for the same population.

The PREVENT 10-year risk ranged from 8.1% to 11.7% for the next three largest trials, including greater than half of all randomized patients when combined with JUPITER (see [Table 5](#)).

Table 5. PREVENT 10-Year Risk for the Four Largest Primary Prevention Trials*

Primary Prevention Trial	10-Year Risk (Percentage)
JUPITER (89)	7.5%
HOPE-3 (90)	8.1%
ASCOT (91)	11.7%
ALLHAT (92)	11.6%

*Accounts for 58% of subjects in all primary prevention trials. The 10-year risk was obtained by applying the PREVENT risk calculator using the published trial subject characteristics.

Abbreviations: ALLHAT: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ASCOT: Anglo-Scandinavian Cardiac Outcomes; HOPE-3: Heart Outcomes Prevention Evaluation; JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin

We chose the 10% 10-year risk threshold as this value approximated the PREVENT risk estimates of the populations included in the largest primary prevention trials (see [Table 5](#) above). The largest primary prevention trial found a similar relative risk reduction with statin therapy (usually moderate-intensity) for those with a 10-year risk above and below 10%. (89) A strong recommendation is given for those with a 10% risk and above since they have the greater absolute risk reduction. (88) Of note, a primary prevention trial in patients living with HIV noted that a relative benefit appeared to persist at even low levels of risk (<5% 10-year risk). (93) A 5% 10-year risk value is designated as the lower bound in the weak recommendation because it is unclear at what 10-year risk the benefit disappears, especially in patients without the risk enhancement factor of living with HIV.

A recent meta-analysis limited to patients with diabetes confirmed the benefit of moderate- or high-intensity statins. Evidence from 17 RCTs in 1 SR suggested that treatment of patients with diabetes with statins reduces the risk of CV composite outcomes in both primary and secondary prevention when compared to treatment with placebo. (94) The strength of evidence was High.

The recommendations remain ‘Strong’ for higher risk and ‘Weak’ for lower risk patients as in the 2020 VA/DOD Lipids CPG. One revision from the 2020 CPG includes changing the 12% 10-year risk to approximately 10%. This better reflects the PREVENT-calculated 10-year risk of populations from large trials showing a benefit with statins. The phrase “at least a moderate-intensity statin” was added to reflect that some patients received high-intensity statins in the primary prevention trials and that trials have shown greater benefit with greater LDL-C reduction.

Other considerations include the wide availability and very low cost of statin therapy. There is likely wide variation in an individual’s interest in taking a medication to prevent disease. Thus, it is important to have a discussion of expected benefits with each patient (shared decision-making).

Based on the relevant studies reviewed in the prior and current CPG evidence base ([Appendix B](#)), a *Strong for* recommendation is made for those at higher risk and a *Weak for* recommendation is made for those at lower risk. The confidence in the quality of the evidence is High for the higher risk recommendation and Low for the lower risk recommendation. The benefits, which are demonstrated by multiple trials, consistently outweigh the harms of statin therapy. Patient

preferences regarding prevention are likely to vary widely, while the very low cost and wide availability of statin therapy support the recommendations.

The Work Group systematically reviewed evidence related to these recommendations.[\(87-89,93-95\)](#) Therefore, they are both categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was High for Recommendation 7 and Low for Recommendation 8. The body of evidence had some limitations including few studies with long-term follow-up and few patients with very low risk. The benefits of moderate-intensity statin (improved outcomes, reduced total mortality and CV events) outweighed potential harms, which, when analyzed as a group (any adverse event) or individually (e.g., diabetes risk, muscle pain), were not identified as statistically significantly worse with treatment. Patient values and preferences likely vary widely because some patients prefer not to take medications if they feel well. Thus, the Work Group decided upon a *Strong for strength* for Recommendation 7 and a *Weak for strength* for Recommendation 8.

Recommendation

9. For primary prevention, there is insufficient evidence to recommend for or against icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.

(Neither for nor against | Reviewed, Amended)

Discussion

Icosapent ethyl (IPE) is a purified ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). In the prior 2020 VA/DOD Lipids CPG, the only available data on EPA was from a single RCT. In this double-blinded, placebo-controlled trial by Bhatt et al., 2019, Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT), treatment with 4 grams of IPE resulted in a 25% reduction in the primary endpoint defined as a combination of vascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina over 4.9 years (number needed to treat [NNT]=21).[\(96\)](#) The results from REDUCE-IT may not be generalizable to all patients represented in the spectrum of CV risk. Most of the study subjects were high-risk patients as evidenced by 70% of those enrolled having a history of CVD. Although patients without a history of ASCVD were enrolled, primary prevention patients represented a minority of those studied. Further, a subgroup analysis of the primary prevention cohort did not find a difference in CV outcomes.

At the time of our review, there were two new SRs that included trials of omega-3 formulations in primary prevention patients. The Huang 2023 review included trials with a mix of primary and secondary prevention patients with diabetes; there were trials of both EPA only and EPA plus docosahexaenoic acid (DHA).[\(97\)](#) Most trials included in this review did not specify the type of diabetes; the VITAL-HF trial only included type 2 diabetics. This meta-analysis showed that EPA only, and not EPA plus DHA, significantly reduced the risk of CVD in patients with diabetes. Similarly, Irfan 2024 showed a significant decrease in CV events in patients on omega-3 fatty acids and a statin.[\(98\)](#) However, the Work Group did not feel that these results applied to the primary prevention population because the results were largely driven by the REDUCE-IT trial, which was mostly comprised of secondary prevention patients. Furthermore, the data in primary prevention patients is Very low quality per GRADE due to lack of blinding, short follow-up duration (<1 year), and serious imprecision. Additional concerns included a range of different doses between trials and various types of omega-3 fatty oils. Another flaw with these SRs was the

inclusion of the STRENGTH trial for EPA plus DHA, which was stopped early because it did not show a benefit, and it did not help to determine if EPA alone or IPE is beneficial in this population. Finally, the RESPECT-EPA trial was included although it only applies to a secondary prevention population.

When the evidence was reviewed in 2020, the recommendations for IPE came largely from REDUCE-IT, which only had 30% primary prevention patients. Given the limited new evidence in primary prevention for IPE, the potential harm of new atrial fibrillation and bleeding risks, and a Very low to Low strength of evidence, the Work Group agreed on an unchanged recommendation in the *Neither for nor against* category. The Work Group believed there would be some variation in patient preferences, given that there is a U.S. Food and Drug Administration (FDA) approval for the use of IPE in primary prevention, especially those with diabetes; this originated from the primary prevention population which comprised 30% of the study population in REDUCE-IT. The Work Group also felt that there is still a need for more research in this patient population to consider treatment with IPE. Other considerations included resource use like cost and variation in access because of cost.

Although beneficial effects in higher risk primary prevention populations may be demonstrated in future investigations, the Work Group determined the data from the two new SRs analyzed for this CPG, (97,98) along with the previously reviewed REDUCE-IT trial, are insufficient to suggest IPE for CV risk reduction in patients without a history of CVD.

The Work Group systematically reviewed evidence related to this recommendation. (97-99) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations including lack of blinding of participants and personnel, (98,99) short follow-up duration (<1 year), (98) serious imprecision, (98,99) and variability in patient co-occurring conditions and inclusion criteria across studies. (97) The harms/burden of IPE in primary prevention patients slightly outweigh the benefits of CV events. Patient values and preferences vary somewhat because some patients might want to take the drug for an FDA-approved indication while others might be concerned about gastrointestinal (GI) bleeding and hospitalization for atrial fibrillation or atrial flutter. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

10. For primary prevention in patients with human immunodeficiency virus (HIV), we suggest a moderate-intensity statin that has a low risk of interactions with antiretroviral therapy, even when 10-year risk estimates are low (i.e., <5%).

(Weak for | Reviewed, New-added)

Discussion

Concerns regarding risk-enhancing conditions, such as HIV, significantly increasing ASCVD risk has stimulated discussion on whether statin therapy should be considered for primary prevention at lower-than-traditional 10-year risk thresholds. Previous data have not been convincing enough to adjust statin prescribing recommendations despite patients living with HIV having a 2-fold risk of ASCVD, including MI and stroke. (93) However, REPRIEVE, a recent moderate-quality RCT by Grinspoon et al. (93) investigated statin treatment for primary prevention in 7,769 patients living with HIV between 40-75 years old, comparing pitavastatin 4 mg to placebo. This population was

largely lower risk with a median PCE 10-year ASCVD risk of 4.5% (54.3% with a PCE 10-year ASCVD risk of <5%; 78.5% <7.5%; 92.7% <10%). Despite this, the study was stopped early at 5.1 years due to a relative risk reduction in incidence of major adverse cardiac events (MACE) by 35% (4.81 per 1,000 person-years in the pitavastatin group and 7.32 per 1,000 person-years in the placebo group (HR: 0.65; 95% CI: 0.48 to 0.90; p=0.002). The NNT to prevent MACE was 106 over 5 years. There was a small but significant increase in myalgias (2.3% vs. 1.4% [0.49 per 100 person-years vs 0.28 per 100 person-years]) and new diagnosis of DM (5.3% vs. 4% [1.13 per 100 person-years vs. 0.84 per 100 person-years]) but low rates of statin discontinuation due to side effects (1.1% in pitavastatin group and 0.5% in placebo group for myalgias; 0.03% vs. 0.05% for DM).

The Work Group acknowledges that the REPRIEVE RCT included pitavastatin. However, it was felt that the benefit was likely a class effect. Therefore, this recommendation is for use of pravastatin, pitavastatin, or other statins that have a low likelihood of drug-drug interactions with antiretroviral therapy, based on FDA-approved product information (see [Table 6](#)). While there is always the concern for statin discontinuation due to myalgias or other side effects, the overall low risk of side effects and discontinuation of medication in the REPRIEVE study was reassuringly low. It is important to acknowledge the known and real risk of new-onset DM (Number Needed to Harm [NNH]=83 over 5 years). Other patient concerns that will be vital for discussion in patients living with HIV who are already on chronic medical therapy include pill burden and the high potential for drug-drug interactions with statins.

The Work Group systematically reviewed evidence related to this recommendation.⁽⁹³⁾ Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations due to being based on only one moderate-quality RCT and only investigating one type and dose of statin therapy as an intervention. The benefits of moderate-intensity statin with a low risk of interactions with antiretroviral therapy outweighed the potential harms of adverse events, which were low overall (myalgias and new diagnosis of DM). Patient values and preferences varied somewhat due to concerns about pill burden, additional cost, and potential drug-drug interactions. Thus, the Work Group decided upon a *Weak for* recommendation.

Table 6. Risk of Drug-Drug Interaction with Protease Inhibitors

	Suggested Starting Dose*
Low Risk	
- Pitavastatin	4 mg; titrate as needed
- Pravastatin	40 mg; titrate as needed
Moderate Risk	
- Rosuvastatin	10 mg; titrate carefully
- Atorvastatin	10-20 mg; titrate carefully
- Fluvastatin	20 mg; titrate carefully
High Risk	
- Simvastatin	Contraindicated
- Lovastatin	Contraindicated

*Doses are reasonable starting doses; however, antiretroviral therapy varies widely and drug-drug interactions should be carefully reviewed prior to initiation.^(100,101)

Recommendation

11. In patients with an indication for statin therapy and elevated baseline aspartate aminotransferase (AST) or alanine transaminase (ALT) less than 3-times the upper limit of normal, we suggest using statins as indicated.

(Weak for | Reviewed, New-added)

Discussion

Some clinicians may hesitate to initiate a statin if baseline AST or ALT, often referred to as liver function tests (LFTs), are elevated. This reluctance leads to many patients with an indication for statin therapy to not receive statins. A meta-analysis by Masson et al. (102) analyzed 5 RCTs (N=2,548) assessing the effect of statin intensification on liver enzymes in patients with baseline LFTs between 1-3-times the upper limit normal (ULN). They found that there was no statistically significant increase in LFTs (>3x ULN) when comparing more intensive statin-based lipid-lowering therapy to less intensive treatments. Additionally, more intensive statin-based lipid-lowering therapies were associated with further reduction in MACE compared to less intensive therapies. There are several limitations to the Masson meta-analysis that must be considered, including the fact that the specific etiology of LFT elevation was not assessed in 3 out of the 5 studies. Additionally, this meta-analysis did not assess incident DM nor statin discontinuation for adverse effects. However, these data support the safety and efficacy of statins when indicated in patients with mildly elevated baseline LFTs (1-3x ULN).

While mild elevations in LFTs occur in up to 3% of patients treated with statins, clinically apparent drug-induced liver injury is rare.(103) Although not part of our evidence review, an analysis of the Drug-Induced Liver Injury Network found only 22 cases attributed to statins among 1,188 total cases of drug-induced liver injury.(103) Though extremely rare, the possibility of statin-induced liver injury in patients with chronic liver disease may cause some clinicians and patients to avoid statins even when indicated. This may partially explain why only 44% of patients with an indication for a statin and who have metabolic dysfunction-associated steatotic liver disease (MASLD) are prescribed statins.(102)

It is estimated that 10%-20% of the general population has elevated LFTs (104) and the most common cause is MASLD. In the U.S., the prevalence of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) are estimated at 25.6% (105) and 5.8%,(106) respectively. MASH is projected to increase from 5.8% in 2020 to 7.9% in 2025.(106) While MASLD/MASH are not currently known to be independent ASCVD risk-enhancing conditions, type 2 DM is an indication for statin therapy and is an independent risk factor for ASCVD. In patients with type 2 DM, MASLD and MASH are estimated at 70% and 30%-40%, respectively.(107) The increasing incidence of MASLD combined with patient and provider unease for initiating statins in patients with chronic liver disease could lead to a growing number of patients not receiving a safe and effective therapy. Reassuringly, Masson et al. provides data to address these growing concerns.(102) The Work Group acknowledges that there will likely be an increase in laboratory monitoring to provide patient and provider reassurance.

The Work Group systematically reviewed evidence related to this recommendation.(102) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including a relatively small sample size (N=2,549) in 5 trials. The benefits of statin therapy in patients with baseline elevated

LFTs outweighed the potential harm of increased LFTs. Patient values and preferences varied somewhat because some patients may be concerned about pill burden and statin-induced liver injury. Thus, the Work Group decided upon a *Weak for* recommendation.

b. Primary or Secondary Prevention

Recommendation

12. For primary or secondary prevention, we suggest against adding fibrates to statins.
(Weak against | Reviewed, Not changed)

Discussion

A systematic search of the literature identified one SR of 12 trials of fibrates which included primary prevention, secondary prevention, and a mixed population of primary and secondary prevention.[\(108\)](#) Only two of the trials included statins as background therapy, but these trials were not analyzed separately. The findings of this SR do not address the question of additional CV benefit of adding fibrates to statins. Additionally, the systematic literature search did not include the effect of fibrates added to statins in patients with severe hypertriglyceridemia (e.g., ≥ 500 mg/dL) to reduce the risk of pancreatitis. Therefore, the evidence to support this recommendation for reducing CV risk is primarily from the 2020 VA/DOD Lipids CPG evidence review.

Primary Prevention (Fibrate Added to Statin versus Statin Alone)

For primary prevention, fibrates added to statins have not been shown to be beneficial in patient-oriented clinical outcomes. In a fair quality SR with 3,502 primary prevention patients, Keene et al., 2014, showed no significant difference in all-cause mortality, CHD mortality (a subset of CVD mortality), or non-fatal MI with use of fibrates.[\(109\)](#) In another fair quality SR of 3,982 primary prevention patients, Jakob et al., 2016, noted no significant difference in all-cause mortality and major CVD events with fibrates.[\(110\)](#)

In an SR of 12 studies in 5,398 primary prevention patients comparing fenofibrate plus a statin to a statin alone, Shao et al., 2016, found no increase in the important safety endpoints of any adverse event, including a creatinine kinase at least five times the ULN.[\(111\)](#) However, evidence suggests there is some associated risk. Shao et al. also showed significant increases in LFT transaminases at least three times ULN and a renal safety endpoint of creatinine increase of $\geq 50\%$.[\(111\)](#) Although not part of the evidence base, the mechanism for increased serum creatinine with fenofibrate is unknown but may involve altered renal hemodynamics or increased creatinine production rather than direct tubular injury.[\(112\)](#) In an observational study of 1,538 primary prevention patients, Murray et al., 2017, noted no significant differences in cognitive test results between fenofibrate and a statin versus a statin alone.[\(113\)](#)

Secondary Prevention (Fibrate Added to Statin versus Statin Alone)

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 5,518 patients with DM who were receiving open-label simvastatin (80 mg) were randomized to receive fenofibrate or placebo for a mean of 4.7 years.[\(114\)](#) Approximately 36% of patients in each group had experienced a prior CVD event. The primary outcome of the first occurrence of non-fatal MI or stroke or death from CV causes was not different between groups and occurred in 2.2% of patients receiving fenofibrate versus 2.4% of those on placebo (HR: 0.92; 95% CI: 0.79 to 1.08;

p=0.32). Underpowered prespecified subgroup analyses showed possible harm in women (increased CV events) while also showing some decrease in CV events for men with high TGs and low HDL-C.(114)

The ACCORD (114) and Pema-fibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) (115) studies were included in the SR and meta-analysis by Kim et al.,(108) but not included in the 2025 evidence base as separate trials. Evidence from ACCORD was included in the 2020 CPG and did not show a benefit of adding fenofibrate to statins in a mixed population of primary and secondary prevention with DM on MACE. Although the PROMINENT study (115) was not part of the 2025 evidence base, it provides further supporting evidence showing that the addition of pema-fibrate to statins in patients with DM and with or without ASCVD did not reduce MACE compared to statins alone.

The Work Group determined that the potential for harm outweighed potential benefits. Patient and provider values and preferences likely vary because some may use a statin/fenofibrate combination in the high TG, low HDL-C subgroup since benefits may be perceived to outweigh risks. Combination therapy entails a higher pill burden with associated decrements in adherence and additional cost for those with copays. Based on this data, the FDA removed the approval of combinations of statins with fenofibrate in 2016.(116)

As this is a *Reviewed, Not changed* recommendation, the Work Group reviewed evidence related to this recommendation from the SR by Kim et al. (108) and the 2020 VA/DOD Lipids CPG,(109-111,113) as well as considered the evidence put forth in the 2014 VA/DOD Lipids CPG.(114) The Work Group's confidence in the quality of the fibrate evidence was Low for primary prevention and Moderate for secondary prevention. Patient and provider preferences likely vary because some patients with high TGs may be interested in fibrates. However, the Work Group determined that the potential for harm outweighed the lack of evidence for potential benefits for reducing CV risk given the adverse effects on LFTs, serum creatinine, and the possible increase in CV events in women. Given the lack of benefit in both primary and secondary prevention, the Work Group decided upon a *Weak against* recommendation.

c. Secondary Prevention

See [Sidebar 3](#) for the definition of secondary prevention.

Recommendation

13. For secondary prevention, we suggest treating with one of the following**:

- High-intensity statin
- Moderate-intensity statin with ezetimibe
- Moderate-intensity statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

(Weak for | Reviewed, New-replaced)

Discussion

The Work Group reviewed evidence that supports several therapeutic options for improving clinical outcomes. The 2020 VA/DOD Lipids CPG recommended using moderate-intensity statins

** Listed in alphabetical order.

as initial therapy and suggested more intensive therapy only in selected higher risk patients. This recommendation was based on evidence showing a reduction in CV events and mortality with moderate-intensity statins. Evidence also showed incremental benefits with high-intensity statins, but only on non-fatal events, and the benefits were counterbalanced by harms such as new-onset DM. The current evidence demonstrates the consistent benefit of more intensive therapy for reducing non-fatal CV events without significantly increased risk.

High-Intensity Statins

High-intensity statin therapy may improve events and mortality compared to moderate-intensity statins. A meta-analysis that includes 6 trials comparing high-intensity statin therapy to lower-intensity statin therapy and one comparison of bempedoic acid versus placebo demonstrated significant improvements in CV mortality, MACE, MI, and stroke with high-intensity therapy.(117) While this meta-analysis included a total of 115,420 patients, the analysis of concern included 61,786 patients, of which 47,816 involved statin therapy. This was low-quality evidence due to serious study limitations and indirectness. High-intensity statin therapy was also demonstrated to increase the risk of SAEs based on very low-quality evidence due to serious study limitations, inconsistency, and indirectness. The 2020 evidence review included a 2018 meta-analysis of 15 statin trials,(118) including 6 trials with a total of 40,963 patients that compared more intensive versus less intensive statins and showed a reduction in MACE without an improvement in CV or all-cause mortality.

High-intensity statin therapy is associated with an increased risk of adverse events. In our evidence review, this was limited to a nonstatistical increase in the rate of SAEs (relative risk: 1.02; 95% CI: 1.00 to 1.03).(117) Our 2020 evidence review demonstrated a higher odds ratio for adverse events overall and discontinuation due to adverse events.(119) Diabetes is increased with a NNH of over 130 over 4 years compared to lower-intensity statins.(120) Although not included in our evidence review and therefore, not considered in the strength of the recommendation, a recent meta-analysis that included 33 statin trials showed that statins of any intensity may slightly increase the risk of intracranial hemorrhage.(121) Our 2020 analysis did not suggest an increased risk of intracranial hemorrhage or cancer.

Moderate-Intensity Statins and Ezetimibe

There is less evidence for ezetimibe than for PCSK9 inhibitors added to statins in secondary prevention. We did not use one of the references in our review that included only observational studies,(122) with one large study dominating the results. An SR with network meta-analysis,(123) including 3 trials with a total of 21,716 primary and secondary prevention patients, demonstrated that statins and ezetimibe significantly reduce non-fatal MI with an NNT of 91 (95% CI: 59 to 112) and stroke with an NNT of 72 (95% CI: 44 to 334) over 5 years, compared to statins alone in secondary prevention, with similar CV and all-cause mortality. One SR of PCSK9 inhibitors (124) included 7 trials with 2,270 patients that compared PCSK9 inhibitors with ezetimibe as the control and found no difference in MACE, CV mortality, or all-cause mortality between the two therapies.

No increased risk of hepatic toxicity, cancer, or gallbladder related conditions has been demonstrated when ezetimibe is added to statins. Because of low event rates of muscle-related symptoms in clinical trials, the impact of adding ezetimibe is not known.

The evidence for improving CV events with all three of these therapeutic interventions is not clearly different, and the only direct comparative evidence evaluated PCSK9 inhibitors versus ezetimibe and did not demonstrate a clinical difference.⁽¹²⁴⁾ Based on low-quality evidence, high-intensity statins may improve CV mortality, which has not been demonstrated for the other therapies.⁽¹¹⁷⁾ However, high-intensity statins have a higher risk of adverse events, including new onset or worsening diabetes and withdrawal due to adverse events, compared to using moderate-intensity statins with ezetimibe or PCSK9 inhibitors.⁽¹¹⁷⁾ The clinician is best placed to make this decision using shared decision-making with their patients.

Our patient focus group results support the choice inherent in this recommendation. While patients were generally supportive of medications, some patients were very concerned about statin-related adverse effects, suggesting that high-intensity statin therapy is less likely to be accepted as a sole therapeutic option.

When clinicians perform their shared decision-making between these options, patient preference will likely influence the choice of therapy within these unranked options. While patients concerned about statin-related adverse effects may choose to avoid high-intensity statins, other patients who are concerned about the number of medications may prefer a single medication. From the medical system perspective, statins with ezetimibe may be the preferred option due to low cost, high tolerability, and evidence supporting similar clinical benefits when added to statins.

Moderate-Intensity Statins and PCSK9 Inhibitors

PCSK9 inhibitors have primarily been studied as statin add-on therapy. An SR that included a network meta-analysis of 12 studies with 63,795 patients ⁽¹²³⁾ demonstrated that adding PCSK9 inhibitors to statins in patients results in a decrease in non-fatal MI with an NNT of 62 (95% CI: 50 to 91) and non-fatal stroke with an NNT of 48 (95% CI: 35 to 84) over 5 years for secondary prevention. In an SR that included 20 trials and 86,835 patients where only 4 trials with 763 patients did not include a statin as background therapy,⁽¹²⁴⁾ the addition of PCSK9 inhibitors to statins significantly improved MACE, MI, and stroke without improving CV mortality.

Another SR that compared alirocumab to evolocumab with 30 trials and 59,026 patients had similar overall outcomes, with alirocumab reducing MI (relative risk: 0.84; 95% CI: 0.76 to 0.93) and stroke (relative risk: 0.75; 95% CI: 0.59 to 0.94) and evolocumab reducing MI (relative risk: 0.73; 95% CI: 0.65 to 0.82) and stroke (relative risk: 0.79; 95% CI: 0.66 to 0.94). Only alirocumab was associated with an additional significant reduction in all-cause mortality (relative risk: 0.83; 95% CI: 0.73 to 0.95).⁽¹²⁵⁾ This finding may be because the major trial for alirocumab included a higher risk population of patients after an ACS.

Patients may choose to avoid PCSK9 inhibitors due to the need for injection or may favor them due to their greater LDL-C-lowering capabilities despite similar clinical benefits. The cost, potential for injection site reactions, and less frequent biweekly or monthly dosing of PCSK9 inhibitors can have positive or negative effects.

The systematic evidence review did not identify relevant data for inclisiran, an siRNA molecule. Inclisiran works by inhibiting the hepatic production of PCSK9, which results in a significant reduction in circulating LDL-C. Results from several large-scale clinical outcomes trials for

inclisiran are pending at the time of this writing. Refer to [Pharmacology Appendix I](#) for details related to inclisiran.

The Work Group systematically reviewed evidence related to this recommendation. ([117-120, 122-125](#)) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was Low overall, although the evidence for mAb inhibitors (alirocumab or evolocumab) was Moderate. The body of evidence had some limitations, including serious study limitations and indirectness. The benefits of reduction of MACE with limited mortality evidence outweighed the small potential harms of each medication or combination of medications, which are all well-tolerated with limited adverse events. Patient values and preferences varied largely for reasons of convenience, concerns for adverse effects, and preferences for or against infrequent self-injections. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

14. For secondary prevention in very high-risk patients[†], we suggest a combination therapy of one of the following:

- High-intensity or maximally tolerated statin with ezetimibe
- High-intensity or maximally tolerated statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
- High-intensity or maximally tolerated statin with ezetimibe and PCSK9 inhibitor.

(Weak for | Reviewed, New-replaced)

Discussion

In very high-risk patients, there are several pharmacologic approaches that have been proven to further reduce non-fatal CVD events when added to high-intensity or maximally tolerated statins. However, there is no direct evidence to support the superiority of a single approach for intensification of lipid-lowering therapy for reducing CV events.

High-Intensity Statins with Ezetimibe

The addition of ezetimibe to high-intensity or maximally tolerated statin therapy for reducing non-fatal CVD events is supported by one SR and network meta-analysis of 14 studies by Khan et al., 2022. ([123](#)) In their analysis, the addition of ezetimibe to maximally tolerated statins resulted in a statistically lower incidence of MI and stroke versus use of maximally tolerated statins alone. When the data were further analyzed based upon CV risk level (PREDICT risk calculator), patients at high or very high risk benefited from combined therapy, but patients at lower risk had limited to no benefit. Some of the differences in MI or stroke did not meet the minimal important difference defined by the authors. There were no differences in all-cause or CV mortality with addition of ezetimibe to statins. In the SR, patients at very high risk were defined as having established ASCVD or hereditary or familial lipid disorder, while high-risk patients had at least five risk factors or hereditary or familial lipid disorder but no known ASCVD.

[†] Very high-risk patients defined as:

- MI or ACS in the past 12 months on lipid-lowering therapy;
- Recurrent ACS, MI, or atherosclerotic cerebrovascular accident (CVA) on lipid-lowering therapy; or
- ASCVD and LDL-C ≥ 70 mg/dL on lipid-lowering therapy.

The safety of ezetimibe was analyzed in an SR by Wang et al., 2022,(126) involving 48 RCTs with a median follow up of 34 weeks, and 5 observational studies with a median follow up of 282 weeks. The mean proportion of patients receiving statins at baseline was approximately 40%. The authors did not find an association of ezetimibe use with cancer, fracture, neurocognitive events, new-onset DM, discontinuation due to adverse GI events, myalgia, or muscle-related events.

High-Intensity Statins with PCSK9 Inhibitors

The addition of mAb inhibitors of PCSK9 to high-intensity or maximally tolerated statins is supported by one SR and network meta-analysis by Khan et al.(123) This SR identified 14 studies involving patients using ezetimibe or PCSK9 inhibitors with statins to determine the incremental benefit of adding either or both agents to statins. The authors concluded that adding PCSK9 inhibitors to high-intensity or maximally tolerated statins statistically reduced the incidence of MI and stroke. There was no difference in CV or all-cause death with the addition of PCSK9 inhibitors to statins. The incremental benefit of reducing non-fatal events was limited to patients at high or very high risk for CVD events. The definitions used by the authors for separating benefit by baseline CV risk are detailed in the section above, pertaining to use of high-intensity statins combined with ezetimibe.

The safety of PCSK9 mAb inhibitors was determined in an SR and meta-analysis by Li et al., 2022,(127) of 32 trials with a median duration of 40 weeks and a range of 24-146 weeks. Injection site reactions led to discontinuation of therapy in 15 per 1,000 patients over a 5-year period. Compared to placebo, there was no additional risk of new-onset DM, neurocognitive events, cataracts, or GI events. The authors also reported that the use of PCSK9 inhibitors likely does not increase the risk for myalgia, muscle-related events, or other adverse events that may lead to discontinuation of therapy.

High-Intensity Statins with Ezetimibe or PCSK9 Inhibitors

Although PCSK9 mAb inhibitors can reduce LDL-C by a greater magnitude compared to ezetimibe, there is 1 SR with meta-analysis by Khan et al., 2022,(123) and 1 meta-analysis by Ma et al., 2021,(124) that did not show a superior CV benefit of either agent when added to statins. In the SR and network meta-analysis of 14 studies by Khan et al., there were no differences in non-fatal MI or stroke between agents. However, the 95% CIs for direct estimates were wide (MI: 0.6 to 4.34; Stroke: 0.03 to 8.01). In the meta-analysis by Ma et al., 28 studies comparing PCSK9 inhibitors to ezetimibe or placebo were included. While three of the studies were in patients who were not receiving statins, most of the studies evaluated agents added to background therapies including maximally tolerated statins or stable statin doses. In the analysis, no difference in MACE was observed, and secondary analyses did not show differences in individual events including MI, stroke, or CV death between ezetimibe and PCSK9 mAb inhibitors. However, the number of patients in the ezetimibe comparison group was small relative to the PCSK9 inhibitor group.

High-Intensity Statins with Ezetimibe and PCSK9 Inhibitors

The 2025 evidence review was not designed to evaluate the incremental benefit of triple therapy with maximally tolerated statins, ezetimibe, and PCSK9 inhibitors in patients at very high risk or in comparison to dual therapy with maximally tolerated statins and ezetimibe or PCSK9 mAb inhibitors. However, in the SR and network meta-analysis by Khan et al.,(123) the addition of PCSK9 inhibitors to maximally tolerated statins and ezetimibe was associated with a statistically

lower incidence of non-fatal MI and stroke in patients at high or very high risk for CV events (Low certainty of evidence). Interestingly, the addition of ezetimibe to statins combined with PCSK9 inhibitors resulted in a lower number of events versus statins alone, but the differences generally did not meet the minimal important difference for MI and/or stroke outcomes (Low to Moderate certainty of evidence). There was no statistical difference in CV or all-cause mortality with triple therapy.

The 2025 evidence review did not identify evidence evaluating the safety of triple combination therapy with maximally tolerated statins, ezetimibe, and PCSK9 mAb inhibitors. Two large trials evaluating the safety and clinical outcomes of combined therapy with maximally tolerated statins and PCSK9 inhibitors in high-risk patients (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER] ([128](#)) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab [ODYSSEY OUTCOMES] ([129](#))) included patients who were also receiving background therapy with ezetimibe. Although the proportion of patients receiving triple therapy was small ($\leq 3\%$), it is anticipated that the use of triple therapy will cause no additional safety concerns.

In very high-risk patients, we suggest dual combination therapy with high-intensity or maximally tolerated statins and ezetimibe before dual therapy of statins and PCSK9 inhibitors because existing evidence does not support a difference in CV events between ezetimibe and PCSK9 when added to statins. Additionally, statins and ezetimibe are administered orally and are widely available as low-cost generic products. In contrast, PCSK9 mAb inhibitors are administered as subcutaneous injections once or twice a month, are significantly more costly, and require education on proper use while achieving comparable relative risk reductions. Finally, in patients at very high risk who are already receiving a maximally tolerated statin plus ezetimibe and continue to have recurrent events and/or LDL-C is ≥ 70 mg/dL, the addition of a PCSK9 inhibitor is suggested to reduce recurrent non-fatal events.

The systematic evidence review did not identify relevant data for inclisiran, an siRNA molecule. Inclisiran works by inhibiting the hepatic production of PCSK9, which results in a significant reduction in circulating LDL-C. Results from several large-scale clinical outcomes trials for inclisiran are pending at the time of this writing. Refer to [Pharmacology Appendix I](#) for details related to inclisiran.

The Work Group systematically reviewed evidence related to this recommendation. ([123](#), [124](#), [126](#), [127](#)) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including in the SR and network meta-analysis by Khan et al., wherein one trial was open-label and others had missing outcomes or risk of bias. ([123](#)) The benefit of adding ezetimibe or a mAb inhibitor of PCSK9 (alirocumab or evolocumab) to high-intensity or maximally tolerated statin therapy for reducing non-fatal CV events, including MI and stroke, outweighed the potential small risk for harm. Patient values and preferences varied somewhat because some patients may prefer taking less medication, some may prefer oral medications over injectable therapies, and some may be reluctant to maximize statins or other therapies due to the fear of increased risk for adverse events and/or copays. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

15. For patients who achieve a very low low-density lipoprotein value (LDL-C <30 mg/dL) with therapy, we suggest continuing treatment.
(Weak for | Reviewed, New-added)

Discussion

Relevant post hoc analyses illustrate trends in the direction of benefit for continuing treatment for patients who achieve a very low LDL-C value (<30 mg/dL).[\(130-132\)](#) These studies have indicated a reduced risk in composite CV outcomes such as MACE and all-cause mortality. It remains unclear if there is any elevated harm. [\(130-132\)](#)

Harms were inconsistently reported and underpowered in most relevant studies. For instance, new-onset DM risk appeared elevated in patients treated with rosuvastatin at lower LDL-C thresholds compared to atorvastatin, though this was based on a subgroup analysis and did not establish a threshold at which benefit no longer outweighed harm.[\(133\)](#) Similarly, studies on cognitive function found no significant difference in reported decline at very low LDL-C levels but were limited by subjective outcomes and small event rates.[\(130,134\)](#) Of note, the EBBINGHAUS study was not included in the evidence base.

Regarding patient values and preferences, given that benefits are expected to be small for a *very large* reduction in LDL-C compared with a *large* reduction in LDL-C, some patients may feel that any additional benefit might not outweigh the disutility from taking a medication. For instance, some patients may feel achieving LDL-C 40 mg/dL versus 50 mg/dL is inconsequential and does not justify additional pharmacotherapy. Other implications include the financial cost of continuing therapy.

The Work Group systematically reviewed evidence related to this recommendation. This evidence included one SR,[\(135\)](#) one RCT,[\(134\)](#) and four post hoc analyses of three RCTs that compared the impacts of different levels of LDL-C following various lipid-lowering therapies.[\(130-133\)](#) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations. The overall strength of evidence for most outcomes assessed across these studies was rated as Very low primarily due to serious limitations in study design, including the use of per protocol or post hoc subgroup analyses, which restricts the generalizability of the results. While the original RCTs (i.e., ODYSSEY OUTCOMES) were generally well conducted, the analyses used to inform LDL-C threshold effects often excluded early discontinuers or focused on lower-risk populations. Serious indirectness was also present due to comparisons based on achieved LDL-C rather than randomized LDL-C targets. Serious imprecision further limited the strength of evidence for many outcomes due to low event counts and wide CIs. The benefits of secondary prevention slightly outweighed the potential harm, which was small. Patient values and preferences varied largely given that benefits are expected to be small when comparing a very large versus large reduction in LDL-C, and some patients may feel that any additional benefit is below the disutility from taking a medication. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

16. For secondary prevention, we suggest icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.

(Weak for | Reviewed, Amended)

Discussion

Overall, support for this recommendation comes from the REDUCE-IT trial that showed reduced primary composite outcomes in patients with TGs ≥ 150 mg/dL.⁽⁹⁶⁾ Since the last CPG, there is new evidence further supporting IPE in secondary prevention. However, the strength of this new evidence is Very low. The key addition to the data was the Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid (RESPECT-EPA),⁽⁹⁹⁾ which was an unblinded trial in patients with coronary artery disease (CAD) and low EPA/arachidonic acid (AA) ratio and receiving statins, who were randomized to IPE or placebo, and followed for a median of 5 years. Icosapent ethyl showed a trend towards benefit for the primary composite endpoint, but the difference was not statistically significant. The secondary endpoint (sudden cardiac death, fatal and non-fatal MI, unstable angina requiring emergent hospitalization and coronary revascularization, or coronary revascularization) was significantly lower in the IPE group.

In an SR by Irfan et al.,⁽⁹⁸⁾ there were multiple primary outcomes evaluated, including nonfatal and fatal MI or stroke, MACE, revascularization, unstable angina, hospitalization for unstable angina, and CV death. There was a statistically significant reduction in MACE, fatal and nonfatal MI, unstable angina, and hospitalization for unstable angina when omega-3 fatty acids were added to maximally tolerated statins. Other outcomes were not statistically different. Concerns about this SR include results from the REDUCE-IT trial with IPE likely influencing the positive findings and the inclusion of studies using surrogate endpoints (EVAPORATE). There are safety concerns including a higher risk for atrial fibrillation with IPE, as this was seen in both the REDUCE-IT and RESPECT-EPA trials. The Work Group felt that while new data had Very low strength of evidence, it was still in line with the prior data from REDUCE-IT. Of note, the STRENGTH trial, which was included in the Huang et al. SR,⁽⁹⁷⁾ studied the prescription combination DHA/EPA and was stopped early because of no benefit.

The REDUCE-IT trial included both primary and secondary prevention patients; however, since the majority of patients had a history of CVD (70%), the results are more applicable to secondary prevention patients already on a stable dose of a moderate-to-high-intensity statin.⁽⁹⁶⁾ There was a 25% reduction in the primary composite endpoint in patients who received IPE compared to placebo. Additionally, a similar 26% reduction in the secondary composite endpoint of CV death, non-fatal MI, and non-fatal stroke (MACE) was observed (NNT=28). For safety events, there was an increased risk of hospitalization for atrial fibrillation or flutter (3.1% vs. 2.1%; absolute risk increase [ARI]: 1%; NNH=100; p=0.004) and a higher rate of serious bleeding events (ARI: 0.6%; p=0.06) in the IPE treatment arm.⁽⁹⁶⁾

For the REDUCE-IT trial, the Work Group raised concerns regarding the choice of placebo, mineral oil. The Work Group noted a 30% rise in hs-CRP in the placebo group during the study period, while a 12% reduction was observed in the IPE group. As hs-CRP has been implicated in atherogenesis and plaque stability through inflammatory mechanisms, this imbalance in hs-CRP could represent a loss of CV prognostic balance between groups by the study's

conclusion, potentially confounding the results. One potential mechanism is the mineral oil used in the placebo arm, which could have reduced the absorption of the statin therapy patients had been receiving before the trial period. The relatively stable level of LDL-C seen in the IPE group and unexplained 10% rise in the placebo group might indicate a reduction in statin effect in the control arm. Although this relatively small proportional change in LDL-C might not reasonably explain the large differences in CV outcomes observed between treatment groups, reduced statin absorption (independent of LDL-C changes) remains a possible explanation.

Given the limited new evidence in secondary prevention for IPE, the recommendation was largely unchanged from the prior guideline and remains *Weak for*. The Work Group believed there would be some variation in patient preferences. Some patients may be interested in the potential benefit of CV risk reduction with IPE, while others may be concerned with pill burden or the risk of bleeding and atrial fibrillation. Other considerations included resource use like cost and variation to access because of cost.

The Work Group systematically reviewed evidence related to this recommendation.[\(96-99\)](#) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations including lack of blinding of participants and personnel,[\(98,99\)](#) short follow-up duration (<1 year),[\(98\)](#) serious imprecision,[\(98,99\)](#) and variability in patient co-occurring conditions and inclusion criteria across studies.[\(97\)](#) The benefits of IPE in reducing CV events for secondary prevention [\(96,98,99\)](#) slightly outweigh the risk of bleeding and new onset atrial fibrillation/flutter. Patient values and preferences vary somewhat because many patients find personal value in taking "natural" medications like fish oil. However, other patients may be concerned about the bleeding and atrial arrhythmia risk. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

17. For secondary prevention, there is insufficient evidence to recommend a treat-to-target strategy (e.g., low-density lipoprotein [LDL-C] <70 mg/dL) over a fixed-dose high-intensity statin strategy.

(Neither for nor against | Reviewed, New-added)

Discussion

For secondary prevention of CAD, several society CPGs recommend treatment targeting a specific LDL-C goal, usually <70 mg/dL, particularly for patients who are identified as higher risk.[\(136-138\)](#) Some of these guidelines recommend a treat-to-target strategy for primary prevention as well.[\(138\)](#) The evidence for these approaches is largely derived from the extrapolation of data from a handful of RCTs including the Scandinavian Simvastatin Survival Study (4S),[\(139\)](#) IMPROVE-IT,[\(140\)](#) FOURIER,[\(129\)](#) and ODYSSEY OUTCOMES.[\(128\)](#) This approach is limited by the fact that each of these studies compared an intervention (i.e., simvastatin, ezetimibe, evolocumab, or alirocumab) to placebo. None of these studies included LDL-C goal as a specific study endpoint.

Two studies from this evidence review contributed to this recommendation. The LODESTAR study [\(141\)](#) was a randomized, controlled, non-inferiority trial of 4,400 patients with a CAD diagnosis comparing a statin-based treat-to-target strategy to high-intensity statin treatment. The target LDL-C goal was between 50 and 70 mg/dL. This trial demonstrated the non-inferiority of the

treat-to-target approach for the composite outcome of death, MI, stroke, and coronary revascularization. In terms of safety, there were no statistical differences in adverse events including new-onset DM, ESRD, or changes in laboratory values (e.g., aminotransferases, creatinine or creatine kinase elevation) between groups. However, an analysis conducted post-hoc of a composite of events (new-onset DM, ESRD, and elevated laboratory values) showed a statistical benefit in the treat-to-target versus high-intensity statin group. Additionally, patients in the treat-to-target group were less likely to discontinue their statin therapy, though this difference was not statistically significant. This study concluded that a statin-based treat-to-target strategy was non-inferior to a fixed-dose high-intensity statin regimen. The second paper considered in this evidence review is an SR of statin use for the primary prevention of CVD in adults.⁽⁸⁸⁾ This review included 22 RCTs, of which 3 studies compared a limited dose titration strategy of statins to achieve target lipid levels with placebo, and 19 compared a fixed statin dosage to placebo. None of the included studies compared a treat-to-target strategy to a fixed-dose statin. For the 3 studies included in this review that allowed a treat-to-target strategy, there were no significant differences in outcomes, including CV mortality, all-cause mortality, composite CV outcomes, or stroke.

When developing this recommendation, the Work Group considered the benefits and harms of a treat-to-target versus fixed-dose statin strategy. No direct evidence from the patient focus group was available to guide this recommendation. Work Group members felt overall that the benefits of statin therapy, whether using a fixed-dose or treat-to-target strategy, outweighed the harms and burdens of such therapy. The Work Group recognized the likelihood of increased side effects and statin discontinuation in patients on fixed-dose, high-intensity statins.⁽¹⁴¹⁾ There is a paucity of research to draw conclusions regarding acceptability of either strategy among patients.

Implementation of this recommendation brings an interesting question to light, that being, should statin therapy be continued in patients who do not achieve the desired LDL-C goal? The suggestion from our Work Group would be to continue statin therapy in these patients, in addition to implementation of other recommendations included in this CPG for LDL-C therapy, for several reasons. First, clinicians should consider whether there are any analytical issues to be addressed when measuring lipoprotein levels.⁽¹⁴²⁾ In particular, laboratories still using the Friedewald equation to indirectly measure LDL-C levels are prone to error due to the level of TGs present in the sample. This level can vary depending on whether the patient submitted a sample in the fasting state or not. Furthermore, LDL-C levels can display both biological and analytical variability on repeated measurement.⁽¹⁴²⁾ Other important factors to consider include patient compliance with statin therapy and the presence of primary statin resistance and other lipid disorders, such as FH and secondary dyslipidemia.⁽¹⁴²⁾ Clinicians should use discretion to determine if a follow-up lipid panel is warranted to assess patient adherence with therapy and/or responsiveness to the prescribed statin.

The Work Group systematically reviewed evidence related to this recommendation, including an RCT of secondary prevention in patients with CAD ⁽¹⁴¹⁾ and an SR of primary prevention patients.⁽⁸⁸⁾ Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including concerns with randomization, allocation concealment, similarity of groups at baseline, masking of outcome assessors and patients, and loss to follow-up in the SR included in this evidence base.⁽⁸⁸⁾ The benefits of a treat-to-target strategy or a fixed-dose statin strategy on LDL-C

lowering and CV outcomes of interest outweighed the potential harm of side effects. Patient values and preferences varied somewhat because patients may have differential opinions on the need for follow-up laboratory monitoring or the importance of differences in the side effect profile between these two treatment strategies. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

C. Statin Intolerance

Recommendation

18. For patients who cannot tolerate a statin, we suggest a washout period followed by a re-challenge with the same or a different statin or lower dose, and if that fails, a trial of intermittent (nondaily) dosing.

(Weak for | Reviewed, Not changed)

Discussion

Retrospective studies have demonstrated that statins can usually be continued after documentation of a statin-related adverse event and that mortality is improved by continuing the treatment. Zhang et al., 2013,(143) in a retrospective cohort study, examined adherence to statins at one year following statin-related events. In over 6,000 patients who were re-challenged, 92.2% were ultimately able to tolerate a statin. Greater than 40% of those re-challenged were able to tolerate the same statin that was originally discontinued due to adverse effects.(143)

A retrospective cohort study of 1,605 patient records by Mampuya et al., 2013,(144) evaluated the efficacy of intermittent statin dosing compared to daily dosing and statin discontinuation in patients with confirmed intolerance. They evaluated 1,605 patients who were deemed statin intolerant and found that compared to those on a daily statin, those on an intermittent statin had higher levels of LDL-C. However, compared to those not on a statin, intermittent statin dosing resulted in lower LDL-C levels, and there was a non-significant trend toward decreased mortality at 8 years in both the daily dosing and intermittent dosing groups compared to those not on a statin. Rosuvastatin was the most commonly used statin in the intermittent group, accounting for 75.2% of statin prescriptions.

Statin-associated muscle symptoms (SAMS) are the primary reason patients discontinue statin treatment.(145) While not included in this CPG evidence review, Kristiansen et al. (145) evaluated 77 patients with CHD in a double-blinded RCT to evaluate patients who complained of SAMS. The patients had been discharged from two secondary hospitals between 2016 and 2019 after a first or recurrent CHD event. Patients were randomized to a 7-week double-blind treatment with atorvastatin 40 mg/day and placebo in a crossover study design. It was found that rechallenging with high-intensity atorvastatin did not affect the intensity of muscle symptoms. A proportion of patients on placebo were more likely to experience SAMS than those on atorvastatin.

While also not included in the evidence base for this CPG, the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial, a multiple-crossover, 3-arm, double-blind, placebo-controlled study, enrolled participants who had discontinued statin therapy due to adverse events.(146) Many of the participants had previously attempted different statins or dosing of statins. Each underwent a protocol of 4 months each of statin, placebo, and no-tablet months. Daily symptom scores were collected using a smartphone application.(146) Of the 60 participants enrolled, 49 completed the protocol. Authors found no difference in the rate of reported muscle

symptoms or treatment discontinuation between groups. The authors concluded that the majority of symptoms caused by statin tablets were considered nocebo.

This recommendation is consistent with suggestions published by the National Lipid Association in 2022.⁽¹⁴⁷⁾ As this is a *Reviewed, Not changed* recommendation, the Work Group reviewed the related evidence from the prior VA/DOD dyslipidemia guidelines. This included four cohort studies from the 2020 evidence base (^{143,144,148,149}) and one meta-analysis from the 2014 evidence base.⁽¹⁵⁰⁾ No new relevant evidence was found. The Work Group's confidence in the quality of the evidence was Very low. The potential benefits of continuing treatment, including improvement in clinical outcomes, outweighed any potential harms. No significant harm was associated with a trial of a different statin or implementation of intermittent dosing. Per the 2020 VA/DOD Lipids CPG, most patients were amenable to a change in statin or intermittent dosing. Additionally, switching statins will not likely add a substantial financial burden since most agents are available generically. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

19. For primary and secondary prevention in patients unable to take a statin, we suggest one of the following non-statins: bempedoic acid, ezetimibe, fibrates, or proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9 mAb) inhibitors.
(Weak for | Reviewed, New-added)

Discussion

Bempedoic Acid in Statin Intolerant Patients

Bempedoic acid is a prodrug that is activated by very-long-chain acyl-coenzyme A (CoA) synthetase-1 to inhibit adenosine triphosphate (ATP)-citrate lyase and works upstream of β -hydroxy β -methylglutaryl-CoA. In patients who are statin intolerant, bempedoic acid is an option for reducing LDL-C, 4-point MACE (defined as CV death, stroke, unstable angina, or coronary revascularization), 5-point MACE (defined as CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for angina pectoris or unstable angina), and non-fatal AMI. Two SRs with 6 relevant RCTs, Serour et al., 2024,⁽¹⁵¹⁾ and Afzal et al.,⁽¹⁵²⁾ compared bempedoic acid to placebo and found a reduction in 4-point MACE up to 40.6 months. Hamayal et al., 2024,⁽¹⁵³⁾ an SR with 6 RCTs comparing bempedoic acid to placebo, found that bempedoic acid was associated with a reduction in 5-point MACE as well as non-fatal AMI. Goyal et al.,⁽¹⁵⁴⁾ an SR with 5 RCTS, and Afzal et al. ⁽¹⁵²⁾ also found a reduction for non-fatal AMI with bempedoic acid compared to placebo. Notably, the CLEAR Outcomes Trial drove the findings in the SRs and included both populations of primary and secondary prevention. It should also be noted that evidence from 8 RCTs in the Goyal and Afzal SRs ^(152,154) found no difference between bempedoic acid and placebo for CV mortality up to 40.6 months follow-up.

Bempedoic acid is an oral medication taken once daily with a low risk of myalgias. Studies show it has a low risk of discontinuation.⁽¹⁵¹⁾ It is associated with a higher risk of gout, tendon rupture, and increased uric acid and creatine. Caution and potential avoidance of bempedoic acid should be considered in patients with a history of tendon rupture, gout, and/or hyperuricemia. Bempedoic acid is costly given it is new to the market, may require prior authorization, and may not be available at all facilities.

Ezetimibe and PCSK9 Inhibitors in Statin Intolerant Patients

Although direct evidence to support the use of ezetimibe or PCSK9 inhibitors in patients designated as statin intolerant is lacking, inferences can be made from patient populations not treated with statins. An SR and network meta-analysis by Khan et al., 2022,[\(123\)](#) showed that ezetimibe and PCSK9 inhibitors reduced the incidence of non-fatal MI and stroke in secondary prevention patients who were not on statins or other lipid-modifying therapies. While the authors concluded that benefit was limited to high-risk primary and secondary prevention due to a statistical but not clinically important difference for medium-risk primary prevention, the Work Group noted a benefit in medium-risk due to the lower baseline risk.

Evidence for PCSK9 inhibitors versus ezetimibe was mainly driven by indirect comparison, with no trial directly comparing ezetimibe and PCSK9 inhibitor for risk of MI and stroke as primary outcomes. An SR and meta-analysis by Guedeney et al., 2022,[\(155\)](#) looked at 39 RCTs that compared PCSK9 inhibitors (alirocumab and evolocumab) to control (placebo and/or other lipid-lowering drugs) in patients with dyslipidemia and/or established ASCVD. Of the 66,478 patients, 35,896 were treated with a PCSK9 inhibitor in addition to maximally tolerated statin therapy or other adjunct therapy, and 30,582 were treated with placebo or control therapy. Out of the 30 studies, 7 (17.9%) documented that $\leq 20\%$ of the population was not on a statin due to intolerance or the use of the PCSK9 inhibitor as monotherapy. Guedeney et al. found no difference between PCSK9 inhibitors (alirocumab, evolocumab) and control (placebo/ezetimibe) for AMI, stroke, or all-cause mortality up to 48 weeks of follow-up.[\(155\)](#)

Fibrates in Statin Intolerant Patients

As with ezetimibe and PCSK9 inhibitors, direct evidence about fibrates in patients designated as statin intolerant is lacking, but inferences from patients not on statin therapy offer support for fibrates. Two SRs demonstrated an improvement in CV outcomes without improvement in mortality. The first, Khan et al., 2020,[\(156\)](#) sought to relate changes in ApoB with CV outcomes and included two studies looking at treatment with fibrates alone. The studies demonstrated reductions in AMI both as a medication class and with gemfibrozil and fenofibrate separately. The second, Kim et al., 2024,[\(108\)](#) looked at the effect of fibrates and similarly found a reduction in MI and MACE. This second review included studies with fibrates and statins together as well as fibrates alone. The Work Group had already observed that fibrates added to statins do not improve outcomes, and that benefit is exclusive to fibrate-only trials. This was demonstrated in landmark clinical trials included in these reviews, such as FIELD, VA-HIT, Helsinki Heart Study, LEADER, and BIP,[\(157-161\)](#) which covered both primary and secondary prevention. None of these trials specified statin intolerance in their inclusion criteria, and some are old enough to predate the existence of statins. Yet, there remains evidence that fibrates alone reduce nonfatal cardiac events without affecting CV or all-cause mortality in the specific populations studied, despite the lack of benefit when added to statins.

The Work Group systematically reviewed evidence related to this recommendation.[\(108,123,151-156\)](#) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including small sample sizes, confounders in the analysis, and the crossover of individual studies across SRs addressing bempedoic acid. There is limited evidence evaluating or comparing ezetimibe, PCSK9 inhibitors, or fibrates in patients not taking statins or intolerant of statins. Most studies with

ezetimibe and PCSK9 inhibitors included patients who were already on high-intensity statins or maximally tolerated statins. Additionally, most fibrate trials did not specify statin intolerance in their inclusion criteria, and some are old enough to predate the existence of statins. The benefits slightly outweighed harms, including adverse events, cost, and injection risks. Patient values and preferences were similar because the statin intolerance is partially balanced by potential increased risks of bempedoic acid in patients with conditions such as gout and the difficulty of injectables for some patients. Thus, the Work Group decided upon a *Weak for* recommendation.

D. Supplements and Nutraceuticals

Recommendation

20. There is insufficient evidence to recommend for or against the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce cardiovascular risks.

(Neither for nor against | Not reviewed, Not changed)

Discussion

The Work Group did not ask a key question specific to this recommendation; hence, the evidence supporting this recommendation is from the prior VA/DOD Lipids CPG. No studies evaluated the long-term efficacy of fiber, garlic, ginger, green tea, and red yeast rice supplements on CVD morbidity or mortality. Instead, these studies evaluated the safety of these interventions. Most of these studies evaluated these substances in their supplemental form, not as they naturally occur in foods. In foods, these substances may have different effects.

Fiber

The SR by Hartley et al., 2016, reviewed 23 RCTs and found insufficient evidence of a patient-oriented benefit from fiber supplements.[\(162\)](#) Fourteen RCTs reported information on adverse events. In seven studies, GI side effects including flatulence, constipation, nausea, bloating, and diarrhea, were more common in the fiber intervention groups than in control groups, though rates were generally low. Few studies had an intervention duration exceeding 12 weeks. There was a wide variety of fiber sources used with little similarity between groups. While we did not ask a question about supplements during this CPG update, recent evidence seems to indicate that soluble fiber lowers TC and LDL-C with uncertain effects on HDL-C and TGs. Considering the lipid-lowering effects, if used, fiber intake can be slowly increased to avoid the adverse effects that may occur. The Work Group's confidence in the quality of evidence for fiber supplements was Very low.

Garlic

An SR by Sahebkar et al., 2016, reviewed six RCTs and found insufficient evidence of a patient-oriented benefit from garlic supplements.[\(163\)](#) It found that garlic supplements were well tolerated with no SAEs reported. An RCT by Ried et al., 2016, assessed the effect of aged garlic extract on central blood pressure and arterial stiffness in patients with uncontrolled hypertension.[\(164\)](#) There was no statistically significant difference in adverse events for the garlic or placebo group. The Work Group's confidence in the quality of evidence for garlic supplements was Moderate.

Ginger

There is no evidence of a patient-oriented benefit from ginger supplements. The SR by Zhu et al., 2018, reviewed 12 RCTs and assessed the effects of ginger supplements on type 2 DM or

components of metabolic syndrome.(165) The evidence was inconclusive for increased adverse events. The Work Group's confidence in the quality of the evidence for ginger was Very low.

Green Tea

There is no evidence of a patient-oriented benefit from green tea supplements. The SR by Onakpoya et al., 2014, reviewed 20 RCTs and assessed the effectiveness of green tea supplements on blood pressure and lipid parameters.(166) The evidence demonstrated no increased adverse events. The Work Group's confidence in the quality of the evidence for green tea supplements was Very low.

Red Yeast Rice

There is no evidence of a patient-oriented benefit from red yeast rice supplements. An SR by Fogacci et al., 2019, reviewed 53 RCTs and assessed the safety of red yeast rice supplements.(167) These supplements were compared to either a statin or placebo, and the follow-up period ranged from 1 month to 4.5 years. While not included in the evidence base, one recent SR demonstrated a 46% reduction in MACE (95% CI: 34% to 57%) and 38% reduction in mortality (95% CI: 13% to 65%) in about 1,300 patients taking red yeast rice.(168) Red yeast rice is tolerated with a low-dose statin for those who cannot tolerate a high-dose statin.(169) Although the Work Group concluded that red rice yeast supplements are safe for use, caution is recommended when used with other medications, especially other cholesterol-lowering agents, due to possible interactions.(170) For instance, Monacolin K, a compound found in red yeast rice, is homologous to lovastatin. Additionally, red yeast rice side effects include myopathy and transaminitis. The Work Group's confidence in the quality of the evidence for red yeast rice was Low.

The Work Group determined that there was insufficient evidence regarding the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce CV risk. There was no new evidence retrieved for this recommendation and therefore, it is categorized as *Not reviewed, Not changed*. This maintains the same recommendation from the 2020 VA/DOD Lipids CPG. The Work Group's confidence in the quality of the evidence ranged from Moderate for garlic to Low for red yeast rice and Very low for fiber, green tea, and ginger.(162-167) Some variation in patient values and preferences is expected. While some patients may express a preference for dietary supplements, taking these supplements may expose them to potential harms from unregulated ingredients and possibly distract them from taking evidence-based medications proven to reduce their CV risk.(171) Other implications include patients' acceptability of taking "natural" supplements, feasibility due to production and regulation issues, and resource use. Thus, the Work Group decided to carry forward this *Neither for nor against* recommendation.

Recommendation

21. For primary or secondary prevention, we suggest against the use of omega-3 fatty acids as a dietary supplement or any omega-3 formulation other than icosapent ethyl.
(Weak against | Reviewed, Amended)

Discussion

The evidence base for this recommendation consists of an SR by Abdelhamid et al. (172) from the 2020 evidence base and an SR by Irfan et al. (98) from the 2025 evidence base.

Abdelhamid et al. evaluated 79 RCTs for the effect of omega-3 supplements on primary and secondary prevention of CVD.⁽¹⁷²⁾ The evidence showed no statistically significant effect of omega-3 supplementation on CV mortality, composite CV events, MI, stroke, or all-cause mortality. The risk of bias was low for 25 RCTs and moderate to high in the remaining 54 RCTs. In this SR, omega-3 supplementation ranged from 0.5 grams/day to greater than 5 grams/day. Some studies used omega-3 enriched foods or dietary advice to increase omega-3 consumption, compared to placebo or usual diet. Most studies assessed long-chain omega-3 (LCn3) supplementation with capsules, but some used dietary advice or foods rich in/enriched with LCn3 or alpha-linolenic acid compared to placebo or usual diet.⁽¹⁷²⁾ Omega-3 enriched foods included margarine, juice, bread, walnuts, and other foods. Control groups received olive, corn, sunflower oils, or other types of fats. The duration of studies ranged from 12-72 months.

As this is a *Reviewed, Amended* recommendation, the Work Group reviewed more recent evidence related to this recommendation, including the SR by Irfan et al.⁽⁹⁸⁾ This review included 14 trials, some with very small sample sizes, and combined data from EPA-only (JELIS and REDUCE-IT), combination EPA/DHA (STRENGTH), and omega-3 carboxylic acid studies. Irfan et al. suggests that omega-3 fatty acids (combo EPA/DHA) have not been proven to reduce risk when added to statins. The data on the positive effects on MACE and MI with omega-3 fatty acids added to statins versus placebo is mitigated due to including IPE data (the mixing of JELIS, REDUCE-IT, and STRENGTH). Potential harms include new onset atrial fibrillation and bleeding. The evidence base supporting IPE as a regulated FDA-approved medication (preferred to non-FDA regulated formulations of omega-3) is described fully in [Recommendations 9](#) and [16](#).

While fish oils are a popular dietary supplement, we did not find sufficient evidence that they are helpful in reducing CV risk factors unless taken as a standardized, FDA-approved medication (i.e., IPE).

The Work Group systematically reviewed evidence related to this recommendation.^(98,172) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including combining IPE data in the JELIS and REDUCE-IT trials with data from the STRENGTH Trial, which included a mixed EPA/DHA prescription omega-3 product. The harms/burden of omega-3 formulations other than IPE (e.g., potential for new onset atrial fibrillation and potential for bleeding) slightly outweigh benefits. Icosapent ethyl is distinguished from other formulations of omega-3 because it is an FDA-approved medication and therefore, has a standardized formulation. Patient preferences and the ability to pay out-of-pocket may vary widely. For patients who prefer to take fish oil supplements, caution is warranted due to GI-related adverse drug effects and risk for atrial fibrillation, especially with large doses (>4 grams/day). Thus, the Work Group decided upon a *Weak against* recommendation.

E. Lifestyle Interventions

Recommendation

22. For primary and secondary prevention of cardiovascular disease, we suggest a Mediterranean diet.

(Weak for | Reviewed, New-replaced)

Discussion

An SR by Sebastian et al., 2024, reviewed data from 4 clinical trials and found that risk for CV mortality, fatal and non-fatal MI, and stroke were lower for participants that followed a Mediterranean diet.(173) Rees et al., 2020, also reviewed data from 30 RCTs and found that the Mediterranean diet significantly reduced the risk for stroke, and for secondary prevention, demonstrated a relative risk reduction in CV mortality and total mortality.(174) Finally, a meta-analysis by Ge et al., 2020, found that the Mediterranean diet led to a reduction in weight and improvements in CV risk factors.(175) The Mediterranean diet generally includes a high intake of plant-based foods, including fruits and vegetables, cereals and whole-grain breads, beans, nuts, and seeds. In addition, the diet consists of the avoidance of processed foods, limited intake of red meat, higher intake of fish, and a high monosaturated/saturated fat ratio using olive oil as a primary cooking ingredient and/or the consumption of foods high in monounsaturated fats. While registered dietitians are trained to counsel on nutrition, the evidence does not specifically indicate that only a dietitian can recommend following a Mediterranean diet; rather, patients should focus on adopting a Mediterranean diet for overall CV risk reduction.

The Work Group systematically reviewed evidence related to this recommendation.(173-176) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including small, randomized trials, trials outside of the U.S., and the inclusion of plant-based diets. Benefits of the Mediterranean diet included improvements in CV mortality, MACE, stroke, all-cause mortality, weight and CV risk factors, adverse events, and MI, which outweighed the potential harm of potential allergies and costs. Resource use and equity varied due to the cost, additional time required for counseling, and limited access to high-quality, nutritious food. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

23. For primary and secondary prevention, we suggest increasing regular aerobic physical activity that maximizes what the patient is willing and able to achieve.

(Weak for | Not reviewed, Amended)

Discussion

Although the benefits of regular physical activity involve many health domains, its effects on CV risk reduction are commonly cited by clinicians when advocating for lifestyle change to their patients. The biological plausibility that physical activity could improve CV outcomes by positively altering lipid profiles has been well established. Lipids and their various subtypes are established independent CV risk factors, and observational data indicate associations between regular physical activity and the main components of lipids (i.e., reductions in TC and LDL-C, increases in HDL-C).(177) Whether these changes in lipids are mediating the association between physical activity and lower CVD risk is unknown. However, a biological connection is plausible and

although this evidence did not restrict inclusion to patients meeting the traditional definition of dyslipidemia based on lipid levels, we think it is reasonable to extrapolate these data to patients with dyslipidemia defined by CV risk, as we do with statins (see [Cholesterol as a Marker for Cardiovascular Disease Risk](#)). This broader definition of dyslipidemia and the biological plausibility connection warrant consideration of physical activity as a strategy in managing dyslipidemia.

The Work Group recognized that both the 2008 Physical Activity Guidelines for Americans (PAGA) (referenced in the 2014 VA/DOD Lipids CPG) and the updated 2018 PAGA guideline recommend at least 150 minutes of moderate intensity, 75 minutes of vigorous intensity aerobic exercise per week, or an equivalent combination. (178) Although randomized trial data are lacking, the CPG's systematic evidence review yielded an expansive body of observational data whose findings align with the established federal PAGA recommendations. Findings from SRs, pooled analyses of observational data, (179-181) and other prospective cohort studies (182-186) demonstrated an association between recommended physical activity levels and a reduction in CV mortality by 21%-91% and all-cause mortality by 19%-70%. These associations were found in both primary and secondary prevention populations.

However, the body of evidence also suggests CV benefits at various “doses” of physical activity. Based on pooled analysis research of over 600,000 primary prevention patients by Arem et al., 2015, leisure time aerobic physical activity appears to have a dose-response relationship with CV and all-cause mortality. (179) Leisure time activity levels below federal recommendations were associated with a 20% reduction in CV and all-cause mortality compared to no leisure time activity, while activity three to five times the recommended level was associated with a 39% reduction in all-cause mortality and 42% reduction in CV mortality. The dose-response curve demonstrated an upper limit of benefit at three-to-five-times recommended levels, suggesting a ceiling effect on leisure time physical activity benefits. (179)

Evidence also indicates a possible benefit to activity levels much lower than federal recommendations. An SR with meta-analysis of prospective cohort studies by Chastin et al., 2019, showed a 29% reduction in all-cause mortality in primary prevention patients whose time spent daily in light-intensity physical activity (LIPA) (1.5-3 metabolic equivalent of task [METs]) (e.g., writing, walking 2 mph, slow ballroom dancing, golfing with a cart) was approximately twice that of their counterparts. (187) In the Copenhagen City Heart Study, Schnohr et al., 2017, prospectively followed over 12,000 primary prevention patients for over 30 years and found a 24% reduction in CV mortality in patients persistently at “light leisure time physical activity” (2-4 hours LIPA per week) compared to those persistently sedentary (<2 hours LIPA per week). (186) These findings suggest that in patients who are not able to achieve recommended moderate or vigorous activity levels, any movement in daily living during their leisure time might have beneficial effects on CV and all-cause mortality. Safety outcomes were not reported, though the Work Group recognizes that musculoskeletal injuries are not uncommon during exercise.

The Work Group determined that the available body of evidence had significant methodological limitations. No randomized studies were found, and although most were large prospective cohorts whose findings were maintained after multivariable adjustment, an imbalance in unmeasured CV prognostic variables could have impacted outcomes. Additional limitations included reporting bias (i.e., many studies utilized self-reported physical activity levels), potential inaccuracies converting self-reported activity to “accepted” categories, imprecision in the evidence base, and

heterogeneity in exercise interventions. Despite these limitations, the body of evidence on the CVD benefits of exercise indicates a positive association of high magnitude, which was consistently demonstrated across large studies. These positive effects were found for important patient outcomes (e.g., all-cause and CV mortality) in a dose-response relationship.

Although the available evidence provides some support for physical activity to lower CV risk, large variability in patient preferences and resource limitations may limit feasibility. The behavioral change required to exercise can be challenging for many patients and motivation is often mixed. Furthermore, access to gyms or exercise equipment is variable. However, promoting physical activity of lower intensity and duration might mitigate some of these resource and feasibility limitations, especially in lower socioeconomic patients, patients with disabilities, and the elderly with poor physical function.

The Work Group did not systematically review new evidence related to this recommendation. Evidence from the 2020 VA/DOD Lipids CPG was reviewed to carry forward the recommendation.[\(179-187\)](#) Therefore, it is categorized as *Not Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had significant limitations including selection bias, residual confounding in observational study designs, and uncertain validity for some methods used to measure outcomes. The large benefit of aerobic physical activity on CV and all-cause mortality outweighed the small risks of musculoskeletal injury and soreness. Patient values and preferences varied somewhat because some patients may be less motivated to participate in exercise. Access to resources for exercise may be limited for some patients, but this recommendation broadens acceptability and feasibility by promoting the benefits of various exercise configurations as tolerated, including low-intensity leisure time activity. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

24. We recommend a structured, exercise-based cardiac rehabilitation program for patients with recent occurrence of coronary heart disease (i.e., myocardial infarction, diagnosis of coronary artery disease, coronary artery bypass grafting, or percutaneous coronary intervention).

(Strong for | Not reviewed, Amended)

Discussion

Although the benefits of regular physical activity involve many health domains, its effects on CV risk reduction are commonly cited by providers when advocating for lifestyle change to patients. The biological plausibility that physical activity could improve CV outcomes by positively altering lipid profiles is well established. Although not included in this evidence review, cross-sectional and observational data have demonstrated an association between regular physical activity and reductions in TC and LDL-C.[\(188-191\)](#)

A structured, exercise-based cardiac rehabilitation program in patients recently diagnosed with CHD has been found to improve CV mortality, all-cause mortality, and non-fatal MI. Based on the SR and meta-regression analysis of 69 RCTs by Abell et al., 2017, structured cardiac rehabilitation programs with detailed exercise prescription (i.e., frequency, duration, intensity) and follow-up assessments were associated with a 26% reduction (NNT=31) in CV mortality over an average follow-up period of 10 years (range: 3-19 years).[\(192\)](#) This benefit does not apply to

“unstructured” interventions, such as providing general exercise advice (e.g., exercise for 150 minutes per week, walk daily), which were excluded from Abell et al.

As is typical for complex interventions, the formats of the 72 individual exercise programs were highly heterogeneous. There was variability in supervision (supervised versus unsupervised programs), setting (community based, residential, clinic), additional risk factor counseling, individual exercise components (i.e., frequency, intensity, type, duration), and adherence. The meta-regression analysis by Abell et al. found that the above-mentioned covariates did not affect any of the CV outcomes with rare exceptions, such as high adherence.⁽¹⁹²⁾ Therefore, the Work Group determined that the available evidence base does not support a specific cardiac rehabilitation program or exercise component type.

Structured programs of variable format have been shown to reduce critical CV outcomes. Of note, the reviewed studies included only patients with CHD (MI event, diagnosis of CAD, coronary artery bypass grafting [CABG], or percutaneous coronary intervention [PCI]), most of whom began the exercise intervention between 2-8 weeks after the event. Therefore, the Work Group determined that the beneficial effects supported by the evidence are mostly limited to patients with a recent diagnosis or cardiac event. Safety outcomes were not reported in the body of evidence.

Although the evidence base supports a structured cardiac rehabilitation program to lower mortality in patients with CHD, the Work Group anticipates some variability in patient preference and limitations in feasibility related to resource requirements. The Work Group also anticipates that some patients would be more accepting than others of the behavioral changes required to engage in an exercise program; in particular, cardiac rehabilitation programs tend to be of higher intensity. Additionally, the human resources (i.e., physical therapists) and equipment requirements of many clinic- and community-based programs may limit feasibility in some settings. However, the evidence demonstrated similar CV outcomes with home-based programs, which may have fewer fiscal costs and other resource demands compared to their clinic- or community-based counterparts.

The Work Group did not systematically review new evidence related to this recommendation. Evidence from the 2020 VA/DOD Lipids CPG was reviewed to carry forward the recommendation.⁽¹⁹²⁾ Therefore, it is categorized as *Not Reviewed, Amended*. The Work Group’s confidence in the quality of the evidence was Moderate. The body of evidence had some limitations including significant variability of exercise regimens, detection bias in unblinded studies, and attrition bias from missing outcomes data.⁽¹⁹²⁾ The benefits of improved mortality and non-fatal MI outweighed potential harms from musculoskeletal injuries. Patient values and preferences varied somewhat because of differences in motivation and functional capacity to participate in structured exercise programs. Thus, the Work Group decided upon a *Strong for* recommendation.

X. Research Priorities

There are several areas that require more focused research to provide stronger evidence for further recommendation development across the spectrum of care. In summary, the Work Group recommends further research on novel risk markers, risk prediction using risk calculators, statins and other lipid-lowering therapies, lipid thresholds and testing, and non-pharmacologic interventions.

A. Novel Risk Markers

Several research priorities were identified related to risk markers, including studies assessing CAC in a larger, primary prevention patient population, particularly in Active-Duty Service Members. Prospective trials that demonstrate the ability of non-traditional cardiac risk biomarkers to predict CV risk, alone or in combination with traditional risk assessment models, would be beneficial. Additionally, there was a call for studies evaluating the role of Lp(a) in military and Veteran populations to gain greater insights into the utility of using Lp(a) for repeated CVD risk assessments and net reclassifications.

B. Risk Prediction Using Risk Calculators

The research priorities for risk prediction focused primarily on the PREVENT Risk Calculator. Work Group members highlighted the need for prospective studies evaluating the validity of PREVENT to determine its utility in clinical practice, studies to evaluate the optimal timing and frequency of CV risk assessments, studies to define more precise treatment thresholds, and studies in specific subgroups (e.g., age, ethnicity, co-occurring conditions, DM) to better identify high-risk CVD patients. They also desired studies comparing PREVENT versus SCORE2 and those assessing the validity of SCORE2 within a U.S. population.

C. Statins

The need for additional studies on statins was identified as a strong research priority, with specifics noted below:

- Head-to-head trials of a treat-to-target LDL-C strategy vs. fixed-dose high-intensity statin strategy to evaluate CV mortality, all-cause mortality, MI, and stroke
- Additional high-quality studies confirming REPRIEVE findings in patients living with HIV who are at low 10-year ASCVD risk using the same vs. different types of statins, different intensities of statins for optimal dose finding, and alternative non-statin therapies with a low risk of interaction with antiretroviral therapy
- Trials of lipid reduction in individuals over age 75 years

D. Other Lipid-Lowering Therapies

The Work Group emphasized the need for additional evidence on other lipid-lowering therapies, including IPE, bempedoic acid, ezetimibe, and PCSK9 inhibitors. They pinpointed the following areas of interest:

Icosapent Ethyl

- RCTs comparing IPE vs. FDA-approved mixed EPA/DHA product (e.g., Lovaza) to determine if an EPA-only product is superior at reducing MACE
- RCTs assessing IPE in a high-risk primary prevention population

- Studies assessing the importance of the EPA/AA ratio in patient selection for IPE studies
- Studies evaluating whether IPE benefits patients without hypertriglyceridemia
- Studies determining how to best identify patients at highest risk for bleeding and atrial fibrillation/flutter while on IPE

Bempedoic Acid, Ezetimibe, and PCSK9 Inhibitors

- Head-to-head trials between bempedoic acid, ezetimibe, and PCSK9 inhibitors when added to both moderate and high-intensity statins for secondary prevention
- Head-to-head trials between bempedoic acid, ezetimibe, PCSK9 inhibitors, and fibrates in statin intolerant patients
- Large, prospective RCTs comparing dual therapy with high-intensity/maximally tolerated statin with ezetimibe vs. dual therapy with high-intensity/maximally tolerated statin with PCSK9 inhibitor in high-risk patients
- Large, prospective RCTs comparing dual therapy with high-intensity/maximally tolerated statin with ezetimibe or PCSK9 inhibitor vs. triple therapy with statin, ezetimibe, and PCSK9 inhibitor in high- or very high-risk patients
- Anticipate evidence from three ongoing large-scale clinical outcomes trials of inclisiran (ORION-4 secondary prevention [2026]; VICTORIAN-1 PREVENT high-risk primary prevention [after 2027]; and VICTORIAN-2 PREVENT secondary prevention [2027])
- Studies with larger sample sizes that confirm the efficacy and safety of bempedoic acid in diverse populations with different risk profiles

E. Lipid Thresholds and Testing

An observed evidence gap was the determination of a very low LDL-C threshold wherein further reduction is harmful; in particular, larger, well-designed trials that include pre-specified comparisons of randomized groups and patients on intensive lipid-lowering therapy. The Work Group also acknowledged the need for studies that determine the existence of a 10-year risk threshold, below which treatment is ineffective and/or not cost-effective. Furthermore, research on the optimal frequency of lipid testing in primary prevention among individuals not on statin therapy was desired.

F. Non-Pharmacologic Interventions

Work Group members recognized several research priorities focused on non-pharmacologic interventions, encompassing lifestyle interventions and supplements. These include a review of diet intervention studies based in the U.S., a review of clinicians who are most appropriate to provide dietary recommendations, and comparative effectiveness studies of red yeast rice as an add-on option in studies of statin intolerance. There was also a request for additional head-to-head RCTs comparing different exercise components to better ascertain the optimal form of cardiac rehabilitation to improve clinical outcomes in patients with ASCVD. Other studies of interest include those utilizing randomization and more accurate methods of measuring physical activity levels to improve confidence in the effect of physical activity on CV outcomes in both primary and secondary prevention populations. Finally, the Work Group recognized the benefit of studies testing different methods of communicating the tradeoffs of primary prevention treatment to patients when risks and costs are minimal, but benefit is not large (e.g., high NNT).

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DOD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by AHRQ (see [Table A-1](#)).

Table A-1. PICOTS (193)

P	Patients, Population, or Problem	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic/screening test used with the patient or population.
C	Comparison	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
O	Outcome	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
(T)	Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
(S)	Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

The Champions, Work Group, and Evidence Review Team carried out several iterations of this process, each time narrowing the scope of the CPG and literature review by prioritizing the topics of interest. Due to resource constraints, not all developed KQs could be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority to include in the review. [Table A-2](#) contains the final set of KQs used to guide the systematic evidence review for this CPG.

a. Population(s)

The clinical population considered in this SR are adults (aged 18 years or older) with or at risk for CVD who would benefit from lipid management. Most of the KQs focused on this overall clinical population, while the KQs specified below focused on specific subgroups of the clinical population:

- KQ8: Patients with statin associated side effects or who are unwilling or unable to tolerate statin therapy
- KQ9: Patients with low CV risk but with risk-enhancing conditions (HIV, non-alcoholic fatty liver disease [NAFLD], rheumatoid arthritis, systemic lupus erythematosus [SLE], psoriasis, history of pre-eclampsia, history of gestational diabetes, history of gestational hypertension, early menopause [<40 years old])

b. Interventions and Comparators

KQ	Intervention(s)	Comparator(s)
1	<ul style="list-style-type: none"> ■ Repeat cardiovascular disease (CVD) risk assessment 	<ul style="list-style-type: none"> ■ No repeat assessment/first CVD risk assessment ■ Alternative timing and/or frequency of repeat assessment
2	<p><u>Novel risk markers added to established risk prediction models:</u></p> <ul style="list-style-type: none"> ■ Coronary artery calcium (CAC) ■ Lipoprotein(a) [Lp(a)] ■ Apolipoprotein(b) [apo(B)] ■ apo(B) discordance with LDL-C ■ apo(B) discordance with non-HDL-C ■ carotid intima thickness ■ macrophage specific cholesterol efflux capacity ■ high-sensitivity C-reactive protein (hsCRP/hsCRP) ■ polygenic risk scores (PRS) ■ LDL-C subtypes ■ Ankle Brachial Index (ABI) ■ family history ■ “atheroma/coronary plaque morphology” or coronary atherosclerotic plaque activity/characterization assessed by PET-CT (F2DG, Ga-DOTATATE), optical coherence tomography (OCT), coronary CT A (CCTA), intravenous ultrasound (IVUS), intracoronary near infrared spectroscopy (NIRS) ■ Social determinants of health (SDOH indicators/scores, e.g., social deprivation index) ■ Reweighted risk prediction models: <ul style="list-style-type: none"> ○ Predicting Risk of Cardiovascular Events (PREVENT) ○ Electronic Health Record score <p><u>Note:</u> Studies on machine learning were excluded.</p>	<p>Established risk prediction models</p>
3	<p>Novel risk prediction models (PREVENT)</p> <p><u>Note:</u> Only studies evaluating the intervention and comparator for primary prevention purposes were included. Studies focused only on heart failure and atrial fibrillation were excluded. Studies with polygenic risk scores</p>	<p>Established risk prediction models (e.g., Pooled Cohort Equation [PCE], Framingham risk score [FRS], etc.)</p>

KQ	Intervention(s)	Comparator(s)
	were excluded if the tools were unavailable for use in clinical settings.	
4	<ul style="list-style-type: none"> ■ Thresholds for 10- and 30-year risk ■ Modeled risk/benefit inflection point according to 10-year risk estimates ■ Modeled risk/benefit inflection point according to 30-year risk estimates 	Alternative thresholds for either 10- or 30- year risk using either novel (PREVENT >15% over 30 yrs) or established risk calculators (e.g. Framingham and PCE for 30- and 10-year risk, respectively)
5	<ul style="list-style-type: none"> ■ LDL-C ■ Non-HDL-C ■ Apo(B) ■ Apo(B) discordance with LDL-C ■ Apo(B) discordance with HDL-C ■ Lp(a) ■ Hs-CRP 	Gold standard: LDL-C
6	<ul style="list-style-type: none"> ■ Statins ■ Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (small interfering ribonucleic acid [siRNAs] – inclisiran; monoclonal antibodies-, evolocumab, and alirocumab) ■ Ezetimibe ■ Bile acid sequestrants ■ Niacin (not over the counter) ■ Fibrates ■ ATP citrate lyase (ACL) inhibitors (Bempedoic acid) ■ Purified omega-3 fatty acids: Icosapent ethyl (Vascepa), omega-3-acid ethyl esters (Lovaza and generics) ■ Pelacarsen 	Placebo
7	<ul style="list-style-type: none"> ■ High-dose/intensity statins and/or ■ Other agents added to statins: ■ PCSK9 inhibitors (siRNAs – inclisiran; monoclonal antibodies-, evolocumab, alirocumab) ■ Ezetimibe ■ Bile acid sequestrants ■ Niacin (not over the counter) ■ Fibrates ■ ATP Citrate Lyase (ACL) inhibitors- Bempedoic acid ■ Purified omega-3 fatty acids: Icosapent ethyl (Vascepa), omega-3-acid ethyl esters (Lovaza and generics) ■ Pelacarsen 	Less intense statin dose or no added therapy

KQ	Intervention(s)	Comparator(s)
8	<ul style="list-style-type: none"> ■ Alternative or alternate day statin therapy ■ Switching to a different statin ■ Lowering the statin dose ■ Combination therapy with statin after dose reduction or a change in drug ■ Optimize Vitamin D status using supplements ■ Co-enzyme Q10 (CoQ-10) ■ Monotherapy with non-statin or combination of non-statins (e.g., colestipol, cholestyramine, colesevelam, bempedoic acid, ezetimibe, PCSK9 inhibitor or inclisiran) 	<p>No intervention to improve statin tolerance or placebo</p>
9	<ul style="list-style-type: none"> ■ Statins ■ PCSK-9 ■ Ezetimibe ■ Bile acid sequestrants ■ Niacin (exclude non-prescription) ■ Fibrates ■ Omega-3 Fatty Acids (Lovaza and generic Lovaza and icosapent ethyl (Vascepa)) ■ Bempedoic acid ■ Inclisiran 	<ul style="list-style-type: none"> ■ Another medication class, ■ Another medication within the same class, ■ A different dose of the same medication ■ Non-pharmacologic therapies/interventions (e.g., diet, exercise, weight loss, etc.) ■ No medications used to modify lipid levels ■ Placebo
10	<ul style="list-style-type: none"> ■ Treating to goals/targets with pharmacotherapy ■ LDL-C goal/target OR non-HDL-C goal/target OR ApoB goal/target OR Lp(a) goal/target ■ Low HDL-C or high triglycerides (TGs) targets/goals ■ Atheroma morphology or “plaque regression” as a target (using advanced imaging modalities such as OCT, CCTA, IVUS, NIRS) 	<p>Treating without consideration of reaching lipid or imaging goal(s)/target(s) (e.g., treating to total CV risk or “fixed dose” strategies)</p>
11	<p><u>Absolute LDL-C level using standard lipid-lowering pharmacotherapies: (e.g., <50 mg/dL)</u></p> <ul style="list-style-type: none"> ■ Statins ■ PCSK9 ■ Ezetimibe ■ Bile acid sequestrants ■ Niacin 	<p>Different (lower) absolute LDL-C level using standard lipid-lowering pharmacotherapies (e.g., <30 mg/dL)</p>

KQ	Intervention(s)	Comparator(s)
	<ul style="list-style-type: none"> ■ Fibrates ■ Omega-3 Fatty Acids (omega-3-ethyl esters and icosapent ethyl) ■ Bempedoic acid ■ Inclisiran 	
12	<p><u>Different dietary therapies:</u></p> <ul style="list-style-type: none"> ■ Mediterranean ■ Vegetarian ■ Vegan ■ Whole food plant based ■ Low-fat ■ KETO/low carbohydrate ■ Low sodium ■ Low gluten ■ Low-calorie ■ Macrobiotic ■ Diabetic diet ■ Intermittent fasting or daytime restricted eating ■ DASH diet 	Different dietary therapy

c. Outcomes

KQ	Critical Outcome(s)	Important Outcome(s)
1	<ul style="list-style-type: none"> ■ Cardiovascular (CV) mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Changing risk stratification, net reclassification index (NRI) of CV risk ■ Time to crossing to a different treatment threshold
2	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ Test characteristics (AUC/c-statistic/discrimination, specificity, sensitivity, PPV, NPV, goodness of fit/calibration, etc.) ■ Changing risk stratification, net reclassification index (NRI) of CV risk ■ All-cause mortality
3	<ul style="list-style-type: none"> ■ Eligibility for statin therapy 	<ul style="list-style-type: none"> ■ CV mortality ■ All-cause mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina,

KQ	Critical Outcome(s)	Important Outcome(s)
		<p>AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality</p> <ul style="list-style-type: none"> ■ Differences in predicted 10-year risk ■ Projected occurrences of CV events ■ Risk categorization according to established guidelines (e.g., AHA/ACC, USPSTF, VA/DOD)
4	<ul style="list-style-type: none"> ■ Modeled risk/benefit inflection point ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality
5	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ Changing risk stratification, net reclassification index (NRI) of CV risk ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality
6	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Serious adverse events
7	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Time to benefit ■ Serious adverse events
8	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Adherence to lipid therapy medication >85% at 1 year ■ Serious adverse events
9	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Serious adverse events Heart failure

KQ	Critical Outcome(s)	Important Outcome(s)
	stroke, cardiovascular mortality, all-cause mortality	
10	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Time to benefit ■ Serious adverse events
11	<ul style="list-style-type: none"> ■ CV mortality 	<ul style="list-style-type: none"> ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Serious adverse events ■ Cognitive impairment, memory loss, and/or dementia. ■ Increased risk for diabetes mellitus
12	<ul style="list-style-type: none"> ■ CV mortality ■ Composite CV outcomes (as defined as the a priori outcome by individual studies) that could include any of the following: unstable angina, AMI, revascularization, stroke, cardiovascular mortality, all-cause mortality 	<ul style="list-style-type: none"> ■ AMI – fatal or nonfatal ■ Stroke – fatal or nonfatal ■ All-cause mortality ■ Changes in lipid levels ■ Adverse events

d. Timing

KQ	Timing
KQs 2-4, KQ10	No minimum follow-up
KQ1	≥3 years
KQs 5-9, KQs 11-12	≥1 year

e. Setting(s)

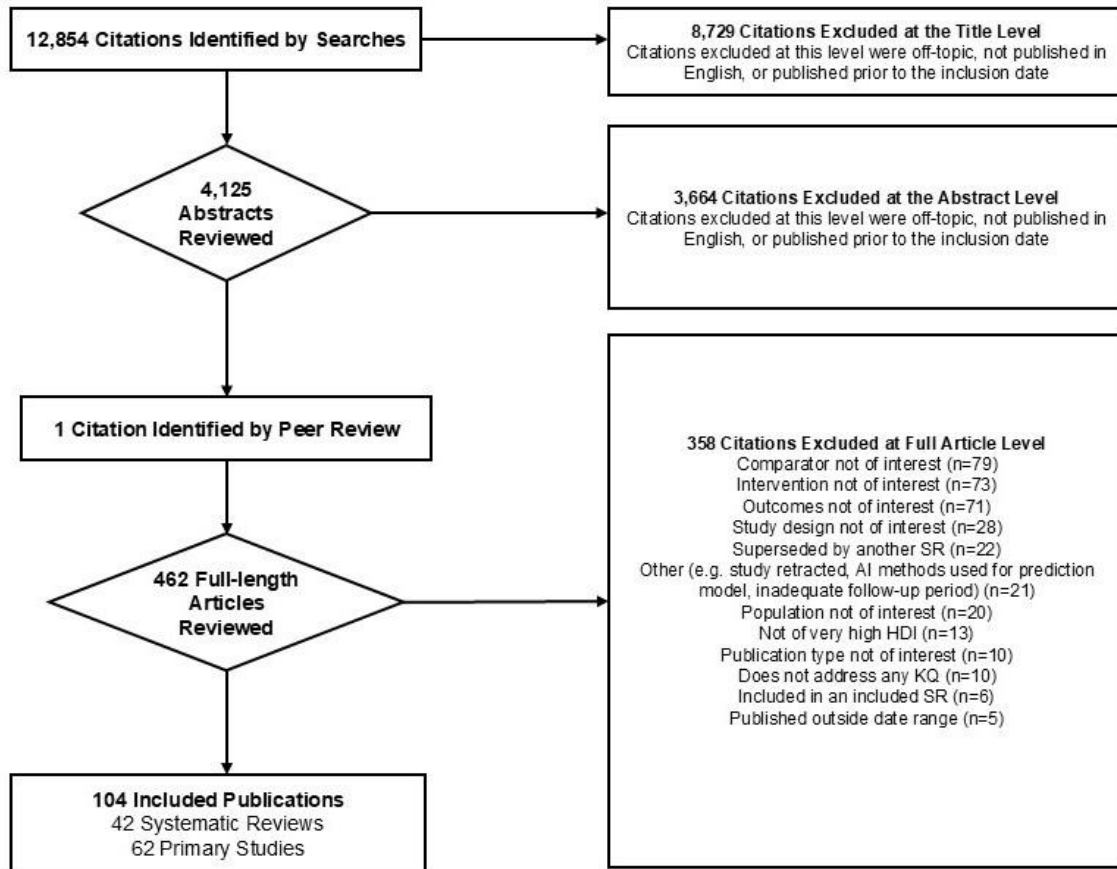
The setting is outpatient primary care for all KQs.

B. Conducting the Systematic Review

Literature searches identified 12,854 citations potentially addressing the KQs of interest for this evidence review. Of these, 8,729 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to the study inclusion publication date, or not a full-length article). A total of 4,125 abstracts were reviewed, with 3,664 excluded at the abstract level for lack of relevance to the CPG topic, not being published in English, or publication prior to the inclusion date. A total of 461 full-length articles were reviewed. Of these, 358 were excluded for the following reasons: comparator not of interest (n=79), intervention not of interest (n=73), outcomes not of interest (n=71), study design not of interest (n=28), superseded by another SR (n=22), population not of interest (n=20), did not address any KQ (n=10), or published outside the date range (n=5). Six full text articles were excluded because they were evidence in an included SR, and an additional 21 full-text articles were excluded for miscellaneous reasons (i.e., study was retracted, artificial intelligence measures were used for prediction models, or inadequate follow-up period). During the CPG Draft 3 review period, an external reviewer identified one additional observational study that was eligible for inclusion under KQ2. This study was retroactively incorporated into this Evidence Synthesis Report. Detailed information on inclusions and exclusions throughout the review process are provided in [Figure A-1](#) below.

Overall, 104 publications addressed one or more of the KQs and were considered as evidence in this review, including 42 systematic reviews and 62 primary studies. [Table A-2](#) indicates the number of studies that addressed each of the questions, with some publications being used for more than one KQ.

Figure A-1. Study Flow Diagram



Abbreviations: AI: artificial intelligence; HDI: human development index; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

[Figure A-1. Study Flow Diagram](#) is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 12,854 citations identified by searches.
 - a. Right to Box 2: 8,729 citations excluded at the title level. Excluded citations were off topic, not published in English, or published prior to inclusion date.
 - b. Down to box 3.
2. Box 3: 4,125 abstracts reviewed.
 - a. Right to Box 4: 3,664 citations excluded at the abstract level. Citations excluded were off topic, not published in English, or published prior to inclusion date.
 - b. Down to Box 5.
3. Box 5: 1 citation identified by peer reviewer.
 - a. Down to Box 6.
4. Box 6: 462 full-length articles reviewed.
 - a. Right to Box 7: 358 citations excluded at full-article level.
 - i. 79 comparator not of interest.
 - ii. 73 intervention not of interest.
 - iii. 71 outcomes not of interest.
 - iv. 28 study design not of interest.
 - v. 22 superseded by another SR.
 - vi. 21 other (e.g., study retracted, AI methods used for prediction model, inadequate follow-up period).
 - vii. 20 population not of interest.
 - viii. 13 not of very high HDI.
 - ix. 10 publication type not of interest.
 - x. 10 does not address any KQ.
 - xi. 6 included in an included SR.
 - xii. 5 published outside date range.
 - b. Down to Box 8.
5. Box 8: 104 included publications (42 systematic reviews and 62 primary studies).

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For primary prevention of cardiovascular disease, how often should screening with cardiovascular risk assessment be performed to identify individuals who would benefit from pharmacologic and non-pharmacologic dyslipidemia treatment?	2 retrospective cohort studies
2	What is the comparative accuracy of adding novel risk marker(s) versus using an established risk prediction model alone for predicting short- and long-term cardiovascular risk?	3 SRs, 2 secondary analyses of RCTs, and 29 cohort studies
3	What are the anticipated changes in treatment eligibility when using novel clinical prediction models (e.g., PREVENT) compared to established clinical prediction models (e.g., PCE)?	8 prospective cohort studies, 1 retrospective cohort study, 5 cross-sectional studies, and 1 modeling study
4	For primary prevention, at what thresholds should lipid-lowering treatment be initiated for 10- and 30-year risk?	1 modeling study
5	How do various lipid markers compare to LDL-C for estimating on-treatment residual risk (e.g., LDL-C, non-HDL-C, ApoB)?	1 secondary analysis of an RCT, 1 secondary analysis of 3 RCTs, and 3 longitudinal cohort studies
6	What is the effectiveness of pharmacotherapy on primary or secondary prevention of cardiovascular outcomes?	16 SRs
7	For primary or secondary prevention, what is the effectiveness and safety of intensifying statins and/or adding non-statins to statins?	9 SRs (7 with MA and 2 with NMA) and 2 RCTs
8	In patients with statin associated side effects or who are unwilling or unable to tolerate statin therapy, do modified statin regimens or other lipid-lowering therapies improve adherence, morbidity, and/or mortality?	5 SRs
9	What are the benefits and harms of statins and other lipid-lowering therapy in patients whose calculated risk is low but who have risk enhancing conditions (e.g., HIV, NAFLD)?	4 SRs and 2 RCTs
10	For primary or secondary prevention, does treating to lipid targets [e.g., LDL-C, non-HDL-C, apoB, Lp(a)] improve morbidity or mortality compared to strategies that do not use targets?	1 SR and 1 RCT
11	For primary and secondary prevention, at what absolute level of LDL-C reduction does harm of treatment outweigh benefit?	1 SR, 1 RCT, and 4 post hoc analyses of 3 RCTs
12	What is the comparative effectiveness of different diets on lipid levels and cardiovascular outcomes?	4 SRs
Total Evidence Base		104 publications* (42 SRs and 62 primary studies)

*Some publications addressed more than one KQ.

Abbreviations: ApoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; KQ: key question; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); MA: meta-analysis; NAFLD: nonalcoholic fatty liver disease; NMA: network meta-analysis; PCE: Pooled Cohort Equations; PREVENT: Predicting Risk of cardiovascular EVENTS; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs of RCTs published on or after May 16, 2019, to January 15, 2025.
- Studies must have been published in English.
- Studies must have focused on lipid screening or management to be included.
- Publication must have been a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, research protocols, and other publications that were not full-length clinical studies were not accepted as evidence.
- Systematic reviews must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) or something compatible (e.g., the tool used by the AHRQ Evidence-based Practice Centers [AHRQ-EPCs]). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review. If multiple SRs addressed a KQ, the most recent and/or comprehensive review was selected.
- RCTs must have had an independent control group. Randomized crossover trials were only included if data from the first period (prior to treatment crossover) was reported separately and an adequate washout period was used.
- Studies must have enrolled at least 20 patients (10 per study group for RCTs and 20 for prospective non-randomized studies) unless otherwise noted. For KQ2, the minimum sample size for studies of polygenic risk scores was 12,000 participants, and the minimum sample size for studies of all other risk factors was 500 participants.
- Studies must have enrolled at least 85% of patients who met the study population criteria. If the patient population fell below this threshold but the relevant population of patients were reported separately, then that study was included.
- To ensure applicability to the VA/DOD healthcare systems and consistency across the CPG program, inclusion of individual studies was limited to very high Human Development Index (HDI) countries with an index ≥ 0.8 where standards of healthcare are comparable (e.g., U.S., Canada, UK, Western Europe, Israel, Japan, Hong Kong, Australia, and New Zealand). Inclusion of SRs was limited to those in which more than half of the included studies were from eligible regions.
 - These regions of interest are listed in Table 1 of the Statistical Annex of the [2023/24 Human Development Report](#) produced by the United Nations Development Program.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

If no RCTs were available to address KQ2 (adding novel risk marker vs. using an established risk prediction model alone), KQ3 (treatment eligibility when using novel clinical prediction

models compared to established), and KQ5 (various lipid markers vs. LDL-C for estimating on-treatment residual risk), prospective, non-randomized comparative studies were included. In the event there was no data identified for these KQs, longitudinal cohort studies were assessed. Similarly, if no SRs of RCTs were available for KQs 2, 3, or 5, SRs of eligible non-RCT designs were used. For KQ2, retrospective, single-center, cohort studies were excluded. Modelling studies were only considered for KQ4 and treated like SRs, with the most comprehensive and highest-quality study chosen.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in [Table A-3](#), below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in [Appendix F](#).

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform/ Provider
Bibliographic Databases	Embase, Medline	May 16, 2019, to January 15, 2025	Elsevier
	PubMed in process	May 16, 2019, to January 15, 2025	PubMed
Name		Date Limits	Platform/ Provider
Gray Literature Databases	Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center Reports	May 16, 2019, to January 15, 2025	AHRQ
	Cochrane Database of Systematic Reviews	May 16, 2019, to January 15, 2025	Cochrane Library
	Veterans Affairs Evidence Synthesis Program (VA ESP)	May 16, 2019, to January 15, 2025	VA ESP

d. Rating the Quality of Individual Studies and the Body of Evidence

Sigma Health Consulting assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.[\(194\)](#)

Next, Sigma Health Consulting assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, or *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program within the Defense Health Agency, Sigma Health Consulting convened a 3.5 day in-person recommendation development meeting from May 6-9, 2025, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, Sigma Health Consulting finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting (see [Determining Recommendation Strength and Direction](#)).

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed the CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Determining Recommendation Strength and Direction

Per GRADE methodology, to assess the quality of the evidence base and assign a grade for the strength for each recommendation, the GRADE system uses the following four domains to assess the strength of each recommendation (24):

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease their strength. The evidence review used for the development of recommendations for lipid management, conducted by Sigma Health Consulting, assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low," or "Very low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

2. Balance of Desirable and Undesirable Outcomes

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid events, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse events, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that most clinicians will offer patients therapeutic or preventive measures if the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?

- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

3. Patient Values and Preferences

“Patient values and preferences” is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values,” “some variation,” or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?
- Are the assumed or identified relative values similar across the target population?

4. Other Implications

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions might not be effective and depending on the societal benchmark for willingness to pay, might not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below ([Table A-4](#)) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgement
Balance of desirable and undesirable outcomes	<ul style="list-style-type: none"> ■ What is the magnitude of the anticipated desirable outcomes? ■ What is the magnitude of the anticipated undesirable outcomes? ■ Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa? 	<ul style="list-style-type: none"> ■ Benefits outweigh harms/burdens ■ Benefits slightly outweigh harms/burdens ■ Benefits and harms/burden are balanced ■ Harms/burden slightly outweigh benefits ■ Harms/burden outweigh benefits
Confidence in the quality of evidence	<ul style="list-style-type: none"> ■ Among the designated critical outcomes, what is the lowest quality of relevant evidence? ■ How unlikely is further research to change the confidence in the estimate of effect? 	<ul style="list-style-type: none"> ■ High ■ Moderate ■ Low ■ Very low
Patient values and preferences	<ul style="list-style-type: none"> ■ Are you confident about the typical values and preferences and are they similar across the target population? ■ What are the patient's values and preferences? ■ Are the assumed or identified relative values similar across the target population? 	<ul style="list-style-type: none"> ■ Similar values ■ Some variation ■ Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	<ul style="list-style-type: none"> ■ Are the resources worth the expected net benefit from the recommendation? ■ What are the costs per resource unit? ■ Is this intervention generally available? ■ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ■ Is there lots of variability in resource requirements across settings? 	<ul style="list-style-type: none"> ■ Various considerations

D. Recommendation Categorization

1. Recommendation Categories and Definitions

For use in the 2025 Lipids CPG, a set of recommendation categories was adapted from those used by the UK's NICE.^(29,30) These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2020 VA/DOD Lipids CPG. The categories and definitions can be found in [Table 3](#).

2. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as “New-added,” “New-replaced,” “Not changed,” “Amended,” or “Deleted.”

“Reviewed, New-added” recommendations were original, new recommendations that were not in the 2020 Lipids CPG. “Reviewed, New-replaced” recommendations were in the previous version

of the guideline but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as “Reviewed, Not changed” were carried forward from the previous version of the CPG unchanged.

Recommendations could have also been designated “Reviewed, Deleted.” These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

3. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a review of the evidence. Due to time and budget constraints, the update of the Lipids CPG could not review all available evidence on lipid management, but instead, focused its KQs on new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated review of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as “Not reviewed.” If evidence had not been reviewed, recommendations could have been categorized as “Not changed,” “Amended,” or “Deleted.”

“Not reviewed, Not changed” recommendations refer to recommendations from the previous version of the Lipids CPG that were carried forward unchanged to the updated version. The category of “Not reviewed, Amended” was used to designate recommendations which were modified from the 2020 VA/DOD Lipids CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as “Not reviewed, Deleted” if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2025 version of the guideline are noted under the [Recommendations](#). The categories for the recommendations from the 2020 VA/DOD Lipids CPG are noted in [Appendix C](#).

E. Drafting and Finalizing the Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2020 VA/DOD Lipids CPG to support the amended “carried forward” recommendations. The Work Group also considered tables, appendices, and other

sections from the 2020 VA/DOD Lipids CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithm, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback for and revise the CPG. Once developed, the first two drafts of the CPG were posted on the Lipids Wiki Website for a period of 10-15 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group, and appropriate revisions were made to the CPG.

Appendix B: Evidence Table

Table B-1. 2025 Lipids Evidence Table ^{a, b, c, d}

#	2025 Recommendation	2020 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
1.	For cardiovascular risk assessment in primary prevention, we suggest the PREVENT risk assessment tool.	Weak for	(37-41) Additional References (42)	Weak for	Reviewed, New-replaced
2.	For primary prevention, in patients over 18 and not on statin therapy who have not developed new cardiovascular risk factors (e.g., diabetes, hypertension, tobacco use), there is insufficient evidence to recommend for or against a specific frequency for cardiovascular disease risk assessment.	N/A	(45) 2020 Evidence (43,44) Additional References None	Neither for nor against	Reviewed, New-added
3.	For primary prevention, in patients identified with intermediate to high risk*, we suggest coronary artery calcium testing to improve the accuracy of risk assessment when deemed to affect clinical decision-making.	N/A	(48) 2020 Evidence (46,47) Additional References None	Weak for	Reviewed, New-added
4.	For patients with low risk, we suggest against the routine use of coronary artery calcium testing.	Weak against		Weak against	Reviewed, Not changed
5.	We suggest measuring lipoprotein(a) [Lp(a)] to identify patients with enhanced risk.	N/A	(49-51,55) Additional References (52-54,56-65)	Weak for	Reviewed, New-added

#	2025 Recommendation	2020 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
6.	There is insufficient evidence to recommend for or against the routine use of ankle brachial index (ABI), apolipoprotein B (ApoB), polygenic risk scores (PRS), carotid plaque/total carotid plaque area (TPA), and high-sensitivity C-reactive protein (hs-CRP) for estimating cardiovascular risk.	Weak against	(49-51,55,66,69,75-86) 2020 Evidence (46,47) Additional References (67,68,70-74)	Neither for nor against	Reviewed, Amended
7.	For primary prevention among patients who have diabetes or 10-year cardiovascular risk $\geq 10\%$ or low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, we recommend using at least a moderate-intensity statin.	Strong for	(88,93,94) 2020 Evidence (87,89,95) Additional References (90-92)	Strong for	Reviewed, Amended
8.	For primary prevention among patients without diabetes who have low-density lipoprotein cholesterol (LDL-C) < 190 mg/dL and a 10-year cardiovascular risk between approximately 5% to less than 10%, we suggest using a moderate-intensity statin.	Weak for		Weak for	Reviewed, Amended
9.	For primary prevention, there is insufficient evidence to recommend for or against icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.	Neither for nor against	(97-99) 2020 Evidence (96) Additional References None	Neither for nor against	Reviewed, Amended
10.	For primary prevention in patients with human immunodeficiency virus (HIV), we suggest a moderate-intensity statin that has a low risk of interactions with antiretroviral therapy, even when 10-year risk estimates are low (i.e., $< 5\%$).	N/A	(93) Additional References (100,101)	Weak for	Reviewed, New-added
11.	In patients with an indication for statin therapy and elevated baseline aspartate aminotransferase	N/A	(102)	Weak for	Reviewed, New-added

#	2025 Recommendation	2020 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
	(AST) or alanine transaminase (ALT) less than 3-times the upper limit of normal, we suggest using statins as indicated.		Additional References (103-107)		
12.	For primary or secondary prevention, we suggest against adding fibrates to statins.	Weak against	(108) 2020 Evidence (109-111,113) 2014 Evidence (114) Additional References (112,115,116)	Weak against	Reviewed, Not changed
13.	For secondary prevention, we suggest treating with one of the following**: <ul style="list-style-type: none"> • High-intensity statin • Moderate-intensity statin with ezetimibe • Moderate-intensity statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. 	Weak for	(117,122-125) 2020 Evidence (118-120) Additional References (121)	Weak for	Reviewed, New-replaced
14.	For secondary prevention in very high-risk patients†, we suggest a combination therapy of one of the following: <ul style="list-style-type: none"> • High-intensity or maximally tolerated statin with ezetimibe • High-intensity or maximally tolerated statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor • High-intensity or maximally tolerated statin with ezetimibe and PCSK9 inhibitor. 	Weak for	(123,124,126,127) Additional References (128,129)	Weak for	Reviewed, New-replaced
15.	For patients who achieve a very low low-density lipoprotein value (LDL-C <30 mg/dL) with therapy, we suggest continuing treatment.	N/A	(130-135) Additional References None	Weak for	Reviewed, New-added

#	2025 Recommendation	2020 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
16.	For secondary prevention, we suggest icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides ≥ 150 mg/dL.	Weak for	(97-99) 2020 Evidence (96) Additional References None	Weak for	Reviewed, Amended
17.	For secondary prevention, there is insufficient evidence to recommend a treat-to-target strategy (e.g., low-density lipoprotein [LDL-C] <70 mg/dL) over a fixed-dose high-intensity statin strategy.	N/A	(88,141) Additional References (128,129,136-140,142)	Neither for nor against	Reviewed, New-added
18.	For patients who cannot tolerate a statin, we suggest a washout period followed by a re-challenge with the same or a different statin or lower dose, and if that fails, a trial of intermittent (nondaily) dosing.	Weak for	2020 Evidence (143,144,148,149) 2014 Evidence (150) Additional References (145-147)	Weak for	Reviewed, Not changed
19.	For primary and secondary prevention in patients unable to take a statin, we suggest one of the following non-statins: bempedoic acid, ezetimibe, fibrates, or proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9 mAb) inhibitors.	N/A	(108,123,151-156) Additional References (157-161)	Weak for	Reviewed, New-added
20.	There is insufficient evidence to recommend for or against the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce cardiovascular risks.	Neither for nor against	2020 Evidence (162-167) Additional References (168-171)	Neither for nor against	Not reviewed, Not changed

#	2025 Recommendation	2020 Strength of Recommendation	Evidence	2025 Strength of Recommendation	2025 Recommendation Category
21.	For primary or secondary prevention, we suggest against the use of omega-3 fatty acids as a dietary supplement or any omega-3 formulation other than icosapent ethyl.	Weak against	(98) 2020 Evidence (172) Additional References None	Weak against	Reviewed, Amended
22.	For primary and secondary prevention of cardiovascular disease, we suggest a Mediterranean diet.	Weak for	(173-176) Additional References None	Weak for	Reviewed, New-replaced
23.	For primary and secondary prevention, we suggest increasing regular aerobic physical activity that maximizes what the patient is willing and able to achieve.	Weak for	2020 Evidence (179-187) Additional References (177,178)	Weak for	Not reviewed, Amended
24.	We recommend a structured, exercise-based cardiac rehabilitation program for patients with recent occurrence of coronary heart disease (i.e., myocardial infarction, diagnosis of coronary artery disease, coronary artery bypass grafting, or percutaneous coronary intervention).	Strong for	2020 Evidence (192) Additional References (188-191)	Strong for	Not reviewed, Amended

^a 2020 Strength of Recommendation column: “N/A” indicates that the 2025 VA/DOD Lipids CPG recommendation was a new recommendation and therefore, does not have an associated 2020 strength of recommendation.

^b Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation but were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

^c 2025 Strength of Recommendation column: The 2025 VA/DOD Lipids CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the [Grading Recommendations](#) section for more information.

^d Recommendation Category column: Refer to the [Recommendation Categorization](#) section for more information on the description of the categorization process and the definition of each category

* Read narrative discussion for the definition of intermediate to high risk.

** Listed in alphabetical order.

† Very high-risk patients defined as: MI or ACS in the past 12 months on lipid-lowering therapy; Recurrent ACS, MI, or atherosclerotic cerebrovascular accident (CVA) on lipid-lowering therapy; or ASCVD and LDL-C \geq 70 mg/dL on lipid-lowering therapy.

Appendix C: 2020 Recommendation Categorization

2020 CPG Recommendation #	2020 Recommendation Text ¹	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category ²	2025 CPG Recommendation Category ³	2025 CPG Recommendation #
1	For primary prevention in patients over age 40 and not on statin therapy who have not developed new cardiovascular risk factors (e.g., diabetes, hypertension, tobacco use), we suggest against offering a cardiovascular disease risk assessment more frequently than every five years.	Weak against	Reviewed, Amended	N/A – Deleted recommendation	
2	For primary prevention in patients not on statin therapy, we suggest against routinely ordering a lipid panel more frequently than every 10 years.	Weak against	Reviewed, New-added	N/A – Deleted recommendation	
3	For cardiovascular risk assessment in primary prevention, we suggest using a 10-year risk calculator.	Weak for	Reviewed, Amended	Reviewed, New-replaced	1
4	We suggest against the routine use of coronary artery calcium testing.	Weak against	Reviewed, Not changed	Reviewed, Not changed	4
5	We suggest against the routine use of additional risk markers (e.g., high-sensitivity C-reactive protein, ankle-brachial index, coronary artery calcium) when assessing cardiovascular risk.	Weak against	Reviewed, New-replaced	Reviewed, Amended	6
6	For primary prevention, we recommend offering a moderate dose statin in patients with a $\geq 12\%$ 10-year cardiovascular risk or low-density lipoprotein cholesterol ≥ 190 mg/dL or diabetes.	Strong for	Reviewed, New-replaced	Reviewed, Amended	7
7	For primary prevention, we suggest offering a moderate-dose statin for patients with a 10-year cardiovascular risk between 6% and 12% following a discussion of risks, limited benefit, and an exploration of the patient's values and preferences.	Weak for	Reviewed, New-replaced	Reviewed, Amended	8

2020 CPG Recommendation #	2020 Recommendation Text ¹	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category ²	2025 CPG Recommendation Category ³	2025 CPG Recommendation #
8	For primary prevention in patients on moderate-dose statins, we suggest against maximizing the statin dose due to the lack of evidence proving added cardiovascular benefits and the risks of higher dose statins.	Weak against	Reviewed, New-replaced	N/A – Deleted recommendation	
9	For primary prevention, there is insufficient evidence to recommend for or against using ezetimibe with or without statins.	Neither for nor against	Reviewed, New-replaced	N/A – Deleted recommendation	
10	For primary prevention, we recommend against offering PCSK9 inhibitors due to unknown long-term safety, inconclusive evidence for benefit, and high cost.	Strong against	Reviewed, New-added	N/A – Deleted recommendation	
11	For secondary prevention, we recommend using at least a moderate-dose statin.	Strong for	Reviewed, New-replaced	N/A – Deleted recommendation	
12	For secondary prevention in higher risk patients who are willing to intensify treatment, we suggest offering high-dose statins for reducing non-fatal cardiovascular events after discussion of the risk of high-dose statins and an exploration of the patient’s values and preferences.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	13
13	For secondary prevention in higher risk patients who are willing to intensify treatment, we suggest adding ezetimibe to either moderate- or high-dose statins for reducing non-fatal cardiovascular events following a discussion of the risks, additional benefits, and an exploration of the patient’s values and preferences.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	13, 14
14	For secondary prevention in higher risk patients who are willing to intensify treatment, we suggest offering a PCSK9 inhibitor in addition to a maximally tolerated statin dose with ezetimibe for reducing non-fatal cardiovascular events	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	14

2020 CPG Recommendation #	2020 Recommendation Text ¹	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category ²	2025 CPG Recommendation Category ³	2025 CPG Recommendation #
	following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient’s values and preferences.				
15	For primary or secondary prevention, we recommend against using niacin (i.e., supplements or prescriptions).	Strong against	Reviewed, New-replaced	N/A – Deleted recommendation	
16	For primary or secondary prevention, we suggest against adding fibrates to statins.	Weak against	Reviewed, New-replaced	Reviewed, Not changed	12
17	There is insufficient evidence to recommend for or against using bempedoic acid with or without statins for either primary or secondary prevention.	Neither for nor against	Reviewed, New-added	N/A – Deleted recommendation	
18	For primary prevention, there is insufficient evidence to recommend for or against icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides.	Neither for nor against	Reviewed, New-added	Reviewed, Amended	9
19	For secondary prevention, we suggest offering icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides >150 mg/dL to reduce cardiovascular morbidity and mortality.	Weak for	Reviewed, New-added	Reviewed, Amended	16
20	For primary or secondary prevention, we suggest against the use of omega-3 fatty acids as a dietary supplement to reduce cardiovascular disease risk.	Weak against	Reviewed, New-added	Reviewed, Amended	21
21	There is insufficient evidence to recommend for or against the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce cardiovascular risk.	Neither for nor against	Reviewed, New-added	Not reviewed, Not changed	20
22	We suggest against the routine monitoring of lipid levels in patients taking statins.	Weak against	Reviewed, New-replaced	N/A – Deleted recommendation	

2020 CPG Recommendation #	2020 Recommendation Text ¹	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category ²	2025 CPG Recommendation Category ³	2025 CPG Recommendation #
23	For patients who cannot tolerate a statin, we suggest a washout period followed by a re-challenge with the same or a different statin or lower dose, and if that fails, a trial of intermittent (nondaily) dosing.	Weak for	Reviewed, New-added	Reviewed, Not changed	18
24	We suggest offering intensified patient care (e.g., phone calls, emails, patient education, drug regimen simplification) to improve adherence to lipid-lowering medications.	Weak for	Reviewed, New-added	N/A – Deleted recommendation	
25	For primary and secondary prevention of cardiovascular disease, we suggest a dietitian-led Mediterranean diet.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	22
26	For primary and secondary prevention of cardiovascular disease, we suggest regular aerobic physical activity of any intensity and duration.	Weak for	Reviewed, New-added	Not reviewed, Amended	23
27	We recommend a structured, exercise-based cardiac rehabilitation program for patients with recent occurrence of coronary heart disease (i.e., myocardial infarction, diagnosis of coronary artery disease, coronary artery bypass grafting, or percutaneous coronary intervention) to reduce cardiovascular morbidity and mortality.	Strong for	Reviewed, New-added	Not reviewed, Amended	24

¹ The 2020 Recommendation Text column contains the wording of each recommendation from the 2020 VA/DOD Lipids CPG

² The Recommendation Category column indicates the way in which each 2020 VA/DOD Lipids CPG recommendation was updated.

³ For recommendations that were carried forward to the 2025 VA/DOD Lipids CPG, this column indicates the new recommendation(s) to which they correspond.

Appendix D: Participant List

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Appendix E: Patient Focus Group Methods and Findings

A. Methods

VA and DOD Leadership recruited eight participants for the focus group with support from the Champions and other Work Group members. The goal of recruitment for this Patient Focus Group was to have a group of engaging, diverse patients receiving VA or DOD healthcare services, who could cogently explain their experience with dyslipidemia. Participants predominantly received care from the VA, with only one individual receiving care from the DOD and another individual who also received care from a civilian provider because a lipid-lowering medication was not covered by the VA formulary. Participants' length of dyslipidemia treatment ranged widely from as recent as 90 days to as long as 21 years. Most participants reported taking statins, and several individuals reported taking bempedoic acid, ezetimibe, and/or a PCSK9 inhibitor. Participants also engaged in lifestyle modifications such as healthier food choices, increased exercise, and specialty diets.

The Work Group, with support from Sigma Health Consulting, identified topics on which participants' input was important to consider in developing the CPG. Sigma Health Consulting developed, and the Work Group approved, an interview guide covering these topics. The focus group facilitator who led the discussion used the guide to elicit participants' perspectives about their treatment and overall care. Not all questions included in the Moderator's Guide for the Dyslipidemia Patient Focus Group were addressed by participants, but because the moderator encouraged conversation between the Patient Focus Group members, most topics were covered.

B. Patient Focus Group Findings

a. Participants acknowledged the benefits of lipid-lowering medications while expressing concern about their long-term use and potential side effects.

- While all participants felt it was very important to manage lipid levels to reduce cardiac risk, there was variation in the perceived value of being on medication.
- Participants emphasized that they do not want to be on medications for the rest of their lives, even if their medications assist with lowering cholesterol.
- Multiple participants highlighted the side effects they experienced while using lipid-lowering pharmacotherapy.

b. Participants recognized the importance of diet and exercise and expressed the need for more information about these interventions.

- Overall, participants did not feel strongly that diet and exercise alone could sufficiently manage lipid levels. However, they recognized that both are important contributors to overall health and heart health.
- Participants requested more information about various aspects of diet and exercise interventions, including impacts on lipid management and the VA's Whole Health Program.

c. Participants valued providers as trusted sources of information while also actively seeking other educational resources.

- Participants agreed that providers were their most trusted sources of information.

- Many participants sought additional information from the Internet to supplement their understanding and were aware of the potential for misinformation.
- Participants appreciated having access to different types of providers, such as clinical pharmacists, dietitians, and CV specialists.

d. Participants expressed that it can be difficult to be compliant with specific interventions since guidance on lipid management is constantly changing.

- Participants were confused by shifting recommendations and discussed the importance of consistent messaging and agreement on optimal solutions.
- Some participants noted that the continually changing landscape of information about different pharmacotherapies and diets can be perplexing.
- Some participants shared their hope that future studies will provide better direction on which interventions should be followed.

e. Participants discussed the value of education regarding the biology and consequences of hypercholesterolemia, available treatment options, and the importance of screening tests.

- Participants emphasized the importance of patient education on the effectiveness of medications and why they should be continued.
- Some participants expressed difficulty with medication compliance due to unclear instructions.
- Participants conveyed the desire for early intervention and screening.

Appendix F: Literature Review Search Terms and Strategy

A. Resources Searched

Sigma’s Information Specialist searched the following databases for relevant information (see [Table F-1](#)).

Table F-1. Databases Searched

Bibliographic Database	Date Limits	Platform/Provider
EMBASE	May 16, 2019, to January 15, 2025	Elsevier
MEDLINE	May 16, 2019, to January 15, 2025	Elsevier
PubMed in process, publisher, PubMed not MEDLINE records	May 16, 2023, to January 15, 2025	National Library of Medicine
Gray Literature Resources	Date Limits	Platform/Provider
Agency for Healthcare Research and Quality (AHRQ)	May 16, 2019, to January 15, 2025	AHRQ
Veterans Affairs Evidence Synthesis Program (VA ESP)	May 16, 2019, to January 15, 2025	VA
Cochrane Library	May 16, 2019, to January 15, 2025	Cochrane Library

B. Search Strategies

The search strategies for bibliographic databases employed combinations of free-text keywords as well as controlled vocabulary terms including, but not limited to, the concepts detailed in Tables F-2 through F-6.

Table F-2. EMBASE and MEDLINE Search Strategy (Embase.com syntax)

Line No.	Concept	Query	Results
KQ1: For primary prevention of cardiovascular disease, how often should screening with cardiovascular risk assessment be performed to identify individuals who would benefit from pharmacologic and non-pharmacologic dyslipidemia treatment?			
#1	Dyslipidemia	'dyslipidemia'/exp/mj OR 'high density lipoprotein cholesterol'/exp/mj OR 'low density lipoprotein cholesterol'/exp/mj OR 'hypercholesterolemia'/exp/mj OR 'lipid'/exp/mj OR ((disorder NEAR/3 lipoprotein):ti) OR ((disorder NEAR/3 'lipid metabolism'):ti) OR dyslipidaemia*:ti OR dyslipidemia*:ti OR dyslipidproteinaemia*:ti OR dyslipidproteinemia*:ti OR (((elevate* OR high* OR low*) NEAR/2 cholesterol):ti) OR hypercholesterolaemia*:ti OR hypercholesterolemia*:ti OR hyperlipaemia:ti OR hyperlipemia:ti OR hyperlipidaemia*:ti OR hyperlipidemia*:ti OR hyperlipdemic:ti OR hyperlipoproteinaemia*:ti OR hyperlipoproteinemia*:ti OR hypertriglyceridaemia*:ti OR hypertriglyceridemia*:ti OR (((elevate* OR high* OR low*) NEAR/2 lipid*:ti) OR	915,466

Line No.	Concept	Query	Results
		lipemia:ti OR lipidaemia:ti OR lipidemia:ti OR lipoprotein*:ti OR (((elevate* OR high* OR low*) NEAR/2 (triacylglycerol* OR triglycer* OR tryglycer*)):ti)	
#2	Cardiovascular risk	'cardiovascular risk'/exp/mj OR ((cardio* NEAR/5 risk*):ab,ti)	317,011
#3	Cardiovascular disease	'brain ischemia'/exp/mj OR 'cardiovascular disease'/mj OR 'cardiovascular disease'/exp/dm_pc OR 'cerebral artery disease'/exp/mj OR 'cerebrovascular accident'/exp/mj OR 'cerebrovascular disease'/exp/mj OR 'coronary artery disease'/exp OR 'heart disease' OR 'heart infarction'/exp OR 'hypertension'/exp OR 'ischemic heart disease'/exp OR 'peripheral vascular disease'/exp OR (((arteries OR artery OR cardiac* OR cardio* OR cerebrovascular OR coronary OR heart* OR vascular) NEAR/5 (disease* OR event* OR ischaem* OR ischem* OR plaque* OR syndrome*)):ti) OR angina:ti OR arteriosclero*:ti OR atherosclero*:ti OR ((cerebrovascular NEXT/1 accident*):ti) OR ((heart NEXT/1 attack*):ti) OR hyperten*:ti OR ((myocardial NEXT/1 infarct*):ti) OR stroke*:ti	4,064,148
#4	Prevention	'prevention'/exp OR prevent*:ti	2,221,022
#5	Screening	'monitoring'/exp OR 'rescreening'/exp OR 'screening test'/exp OR 'time factor'/exp OR 'follow up':ti OR frequen*:ti OR interval*:ti OR monitor*:ti OR 're-assess*':ti OR 're do':ti OR 're-run':ti OR 're-screen*':ti OR reassess*:ti OR redo:ti OR redundant*:ti OR repeat*:ti OR repet*:ti OR rerun:ti OR rescreen*:ti OR screen*:ti OR subsequent*:ti OR surveillance:ti	2,254,986
#6	Risk assessment	'risk'/exp OR ((risk* NEAR/4 (algorithm* OR assess* OR biomarker* OR calculat* OR categor* OR characteristic* OR classif* OR define* OR defining OR determin* OR factor* OR index OR indices OR marker* OR predict* OR prioritiz* OR profile* OR score* OR stratification OR stratify* OR tier*)):ti)	3,393,973
#7	Combine	(#1 OR #2 OR (#3 AND #4)) AND #5 AND #6	37,403
KQ2: What is the comparative accuracy of adding novel risk marker(s) versus using an established risk prediction model alone for predicting short- and long-term cardiovascular risk?			
#8	Novel risk markers	'ankle brachial index'/exp/mj OR 'apolipoprotein b'/exp/mj OR 'coronary artery calcium score'/exp/mj OR 'carotid intima-media thickness'/exp/mj OR 'family history'/exp/mj OR 'genetic risk score'/exp/mj OR 'high sensitivity c reactive protein'/exp/mj OR 'lipoprotein a'/exp/mj OR 'machine learning'/exp/mj OR 'social deprivation index'/exp/mj OR 'social determinants of health'/exp/mj	334,085

Line No.	Concept	Query	Results
		OR ((ankle NEAR/2 brachial):ti) OR 'apo(b)':ti OR apob:ti OR 'apolipoprotein b':ti OR (((cac OR 'coronary artery calcium') NEAR/2 (score* OR test*)):ti) OR ((carotid NEAR/2 intima NEAR/2 thick*):ti) OR 'carotid imt':ti OR (('electronic health record* NEAR/2 score*):ti) OR 'family histor*':ti OR (((genetic* OR polygenic) NEAR/2 (risk* OR score*)):ti) OR hcrp:ti OR 'high sensitivity c reactive protein':ti OR 'hs-crp':ti OR 'hs crp':ti OR 'hs crp':ti OR (('low-density lipoprotein' OR ldl) NEAR/2 (subclass* OR subtype*)):ti) OR 'lipoprotein(a)':ti OR 'lp(a)':ti OR 'machine learning':ti OR ('macrophage specific':ti AND 'cholesterol efflux capacity':ti) OR (((new OR 'non traditional' OR nontraditional OR novel) NEAR/2 (marker* OR model* OR risk*)):ti) OR 'predicting risk of cardiovascular disease events':ti OR ((prevent NEAR/2 (calculator* OR equation* OR model*)):ti) OR (((reweight* OR 're weight*') NEAR/2 (model* OR predict* OR risk*)):ti) OR sdoh:ti OR 'social deprivation index':ti OR 'social determinants of health':ti OR (('plaque morphology'/exp OR ((plaque* NEAR/2 (activit* OR characteriz* OR morpholog*)):ti)) AND ('coronary ct angiography'/exp OR 'optical coherence tomography'/exp OR 'near infrared spectroscopy'/exp OR 'pet-ct scanner'/exp OR ccta:ti OR 'coronary ct angiography':ti OR f2dg:ti OR 'ga-dotatate':ti OR 'intracoronary near infrared spectroscopy':ti OR 'intravenous ultrasound':ti OR ivus:ti OR nirs:ti OR oct:ti OR 'optical coherence tomography':ti OR 'pet-ct':ti))	
#9	Combine	(#2 OR (#3 AND #6)) AND #8	25,478
KQ3: What are the anticipated changes in treatment eligibility when using novel clinical prediction models (e.g., PREVENT) compared to established clinical prediction models (e.g., PCE)?			
#10	PREVENT	'predicting risk of cardiovascular disease events':ab,ti OR ((prevent NEAR/3 (calculator* OR equation* OR model*)):ab,ti)	1,138
#11	Cardiovascular disease or dyslipidemia risk assessment clinical prediction models	'predictive model'/exp/mj OR ((predict* NEAR/3 model*):ab,ti)	273,792
#12	Combine	(#1 OR #2 OR (#3 AND #6)) AND (#10 OR #11)	18,031
KQ4: For primary prevention, at what thresholds should lipid-lowering treatment be initiated for 10- and 30-year risk?			
#13	Thresholds	'risk benefit analysis'/exp/mj OR '10 year':ab,ti OR '30 year':ab,ti OR ((benefit* NEAR/2 risk*):ab,ti) OR 'inflection	699,807

Line No.	Concept	Query	Results
		point*:ab,ti OR 'ten year':ab,ti OR 'thirty year':ab,ti OR threshold*:ab,ti	
#14	Combine concepts	(#1 OR (#3 AND #4)) AND #13	17,334
KQ5: How do various lipid markers compare to LDL-C for estimating on-treatment residual risk (e.g., LDL-C, non-HDL-C, ApoB)?			
#15	Selected lipid markers	'apolipoprotein b'/exp OR 'high sensitivity c reactive protein'/exp OR 'lipoprotein a'/exp OR 'low density lipoprotein'/exp OR 'apo b':ab,ti OR 'apo(b)':ab,ti OR hcrp:ab,ti OR 'high sensitivity c reactive protein':ab,ti OR 'hs-crp':ab,ti OR 'hs crp':ab,ti OR 'hscrp':ab,ti OR ((lipid* NEAR/3 marker*):ab,ti) OR 'low density lipoprotein':ab,ti OR ldlc:ab,ti OR 'ldl-c':ab,ti OR 'lipoprotein(a)':ab,ti OR 'lp(a)':ab,ti OR 'non-hdl-c':ab,ti OR 'non-high density lipoprotein-cholesterol':ab,ti	246,408
#16	On treatment/residual risk	'residual risk'/exp OR (((on-treatment' OR residual* OR treat*) NEAR/5 risk*):ab,ti)	184,552
#17	Combine	#15 AND #16	5,472
KQ6: What is the effectiveness of pharmacotherapy on primary or secondary prevention of cardiovascular outcomes?			
KQ7: For primary or secondary prevention, what is the effectiveness and safety of intensifying statins and/or adding non-statins to statins?			
KQ9: What are the benefits and harms of statins and other lipid-lowering therapy in patients whose calculated risk is low but who have risk enhancing conditions (e.g., HIV, NAFLD)?			
KQ11: For primary and secondary prevention, at what absolute level of LDL-C reduction does harm of treatment outweigh benefit?			
#18	Statins	'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj OR 'hypocholesterolemic agent'/exp/mj OR (((hydroxymethylglutaryl OR 'hydroxy methylglutaryl') NEAR/5 reductase):ti) OR ((hmg NEXT/1 coa):ti) OR atorvastatin:ti OR lovastatin:ti OR meglutol:ti OR pravastatin:ti OR simvastatin:ti OR statin*:ti	95,096
#19	Other pharmacotherapy	'adenosine triphosphate citrate synthase inhibitor'/exp/mj OR 'antisense oligonucleotide'/exp/mj OR 'bile acid sequestrant'/exp/mj OR 'cholesterol ester transfer protein inhibitor'/exp/mj OR 'fibric acid derivative'/exp/mj OR 'icosapentaenoic acid ethyl ester'/exp/mj OR 'monoclonal antibody'/exp/mj OR 'nicotinic acid'/exp/mj OR 'omega 3 acid ethyl ester'/exp/mj OR 'omega 3 fatty acid'/exp/mj OR 'pcsk9 inhibitor'/exp/mj OR 'small interfering rna'/exp/mj OR alirocumab:ti OR (('angiopoietin-like 3':ti OR angptl3:ti) AND inhibitor*:ti) OR (('apolipoprotein a-i':ti OR	418,994

Line No.	Concept	Query	Results
		'apoa-i':ti) AND infus*:ti) OR (('apolipoprotein c3':ti OR apoc3:ti) AND inhibitor*:ti) OR 'bempedoic acid':ti OR 'bile acid sequestrant*':ti OR (('cholesterol ester transfer protein':ti OR cetp:ti) AND inhibit*:ti) OR evolocumab:ti OR ezetimibe:ti OR fibrate*:ti OR 'fibric acid':ti OR icosapent*:ti OR inclisiran:ti OR lerodalcibep:ti OR lovaza:ti OR 'monoclonal antibod*':ti OR muvalaplin:ti OR niacin:ti OR 'nicotinic acid':ti OR obicetrapib:ti OR olpasiran:ti OR 'omega 3':ti OR 'pcsk-9':ti OR pcsk9:ti OR pelacarsen:ti OR plozasiran:ti OR recaticimab:ti OR sirna*:ti OR 'small interfering rna':ti OR 'small molecule inhibitor*':ti OR vascepa:ti OR zerlasiran:ti OR zodasiran:ti	
#20	Outcomes Emtree terms	'adverse event'/exp OR 'all cause mortality'/exp OR 'cardiovascular disease'/exp/dm_pc OR 'cerebrovascular accident'/exp OR 'cognitive defect'/exp OR 'dementia'/exp OR 'diabetes mellitus'/exp OR 'heart infarction'/exp OR 'morbidity'/exp OR 'mortality'/exp OR 'prevention and control'/exp OR 'primary prevention'/exp OR 'treatment outcome'/exp OR 'unstable angina pectoris'/exp OR ((adverse NEAR/2 (event* OR reaction*)):ab,ti) OR angina:ab,ti OR (((cardiac OR coronary OR vascular) NEXT/2 event*):ab,ti) OR ((cerebrovascular NEXT/1 (accident* OR event*)):ab,ti) OR ((cognitive NEAR/2 (defect* OR impair*)):ab,ti) OR death:ab,ti OR dementia:ab,ti OR diabet*:ab,ti OR ((heart NEXT/1 (attack* OR infarct*)):ab,ti) OR ((memor* NEAR/2 (impair* OR loss)):ab,ti) OR morbidity:ab,ti OR mortality:ab,ti OR ((myocardial NEXT/1 infarct*):ab,ti) OR prevent*:ab,ti OR outcome*:ab,ti OR revascularization:ab,ti OR stroke*:ab,ti OR 'time to benefit':ab,ti	14,144,159
#21	Other risk enhancing conditions	'early menopause'/exp/mj OR 'gestational diabetes'/exp/mj OR 'human immunodeficiency virus'/exp/mj OR 'maternal hypertension'/exp/mj OR 'metabolic fatty liver'/exp/mj OR 'nonalcoholic fatty liver'/exp/mj OR 'preeclampsia'/exp/mj OR 'psoriasis'/exp/mj OR 'rheumatoid arthritis'/exp/mj OR 'systemic lupus erythematosus'/exp/mj OR ((gestational NEAR/2 (diabetes OR hypertension)):ti) OR hiv:ti OR 'human immunodeficiency virus':ti OR lupus:ti OR masld:ti OR 'metabolic dysfunction-associated steatotic liver disease':ti OR 'metabolic fatty liver':ti OR nafld:ti OR 'nonalcoholic fatty liver disease':ti OR 'non alcoholic fatty liver disease':ti OR 'pre-eclampsia':ti OR (((early OR premature) NEAR/2 menopause):ti) OR psoriasis:ti OR 'rheumatoid arthritis':ti	816,027
#22	Combine (including KQ9	(#1 OR #3 OR #21) AND (#18 OR #19) AND #20	90,119

Line No.	Concept	Query	Results
	risk enhancing conditions)		
KQ8: In patients with statin associated side effects or who are unwilling or unable to tolerate statin therapy, do modified statin regimens or other lipid-lowering therapies improve adherence, morbidity, and/or mortality?			
#23	Statin tolerance, adherence, substitution	('hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp OR 'hypocholesterolemic agent'/exp) AND ('drug dose intensification'/exp OR 'drug dose reduction'/exp OR 'drug hypersensitivity'/exp OR 'medication compliance'/exp OR 'patient compliance'/exp OR 'drug substitution'/exp)	15,171
#24	Statin tolerance, adherence, substitution	(((((hydroxymethylglutaryl OR 'hydroxy methylglutaryl') NEAR/5 reductase*):ti,ab) OR 'hmg coa':ti,ab OR statin*:ti,ab OR lovastatin:ti,ab OR meglutol:ti,ab OR pravastatin:ti,ab OR atorvastatin:ti,ab OR simvastatin:ti,ab) AND (adher*:ab,ti OR complian*:ab,ti OR 'non-adherence':ab,ti OR intoleran*:ab,ti OR nonadherence*:ab,ti OR persistan*:ab,ti OR toleran*:ab,ti OR tolerat*:ab,ti OR (((alternat* OR decreas* OR high OR higher OR increas* OR low OR lower OR switch*) NEAR/3 (day OR dosag* OR dose* OR dosing)):ab,ti))	20,773
#25	Other interventions	'coenzyme q10':ab,ti OR coq10:ab,ti OR 'vitamin d':ab,ti	133,673
#26	Combine sets	(#1 OR #2 OR #3) AND (#23 OR #24 OR ((#23 OR #24) AND #25))	22,270
KQ10: For primary or secondary prevention, does treating to lipid targets [e.g., LDL-C, non-HDL-C, apoB, Lp(a)] improve morbidity or mortality compared to strategies that do not use targets?			
#27	LDL-C or non-HDL-C goals	('low density lipoprotein cholesterol level'/exp OR 'high density lipoprotein cholesterol level'/exp) AND (goal:ti OR goals:ti OR target*:ti OR level:ti OR levels:ti) OR (('high density lipoprotein cholesterol'/exp OR 'low density lipoprotein cholesterol'/exp) AND 'goal attainment'/exp) OR (((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR triacylglycerol* OR triglycer* OR tryglycer* OR 'hdl-c' OR 'ldl-c' OR 'hdlc' OR 'ldlc' OR 'non hdl c' OR 'non-hdlc' OR nonhdlc) NEAR/5 (goal OR goals OR target* OR level OR levels)):ti) OR (((atheroma* OR plaque*) NEAR/4 (assess* OR imag* OR morphology)):ti) OR 'plaque regression':ti	28,550
#28	Outcomes of interest	'adverse event'/exp OR 'secondary prevention'/exp OR 'primary prevention'/exp OR 'prevention and control'/exp OR 'treatment outcome'/exp OR 'morbidity'/exp OR 'mortality'/exp OR 'all cause mortality'/exp OR 'cerebrovascular accident'/exp OR 'heart infarction'/exp OR 'unstable angina pectoris'/exp OR stroke*:ti,ab OR	12,764,575

Line No.	Concept	Query	Results
		((cerebrovascular NEXT/1 accident*):ti,ab) OR death:ti,ab OR ((heart NEXT/1 attack*):ti,ab) OR ((myocardial NEXT/1 infarct*):ti,ab) OR (((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*):ti,ab) OR ((heart NEXT/1 infarct*):ti,ab) OR morbidity:ti,ab OR mortality:ti,ab OR prevent*:ti,ab OR outcome*:ti,ab OR ((secondary NEXT/1 prevention):ti,ab) OR ((primary NEXT/1 prevention):ti,ab) OR angina:ti,ab OR ((adverse NEXT/1 event*):ti,ab)	
#29	Combine sets	(#1 OR #2 OR #3) AND #27 AND #28	8,921
KQ12: What is the comparative effectiveness of different diets on lipid levels and cardiovascular outcomes?			
#30	Dietary interventions	'diet therapy'/exp/mj OR ((diet*:ti OR nutrition:ti) AND (dash:ti OR 'daytime restricted':ti OR ((gluten NEXT/2 free):ti) OR 'intermittent fast*':ti OR 'low calor*':ti OR 'low carb*':ti OR 'low fat':ti OR 'low gluten':ti OR 'low sodium':ti OR keto:ti OR macrobiotic:ti OR mediterranean:ti OR 'plant based':ti OR vegan:ti OR vegetarian:ti OR 'whole food*':ti)) OR 'diabetic diet':ti OR ((dietary NEXT/1 approach* NEXT/1 stop NEXT/1 hypertension):ti)	138,816
#31	Outcomes of interest Emtree terms	'adverse event'/exp OR 'all cause mortality'/exp OR 'cerebrovascular accident'/exp OR 'heart infarction'/exp OR 'morbidity'/exp OR 'mortality'/exp OR 'prevention and control'/exp OR 'primary prevention'/exp OR 'secondary prevention'/exp OR 'treatment outcome'/exp OR 'unstable angina pectoris'/exp OR ((adverse NEXT/1 event*):ab,ti) OR angina:ab,ti OR (((cardiac OR cerebrovascular OR coronary OR vascular) NEXT/2 event*):ab,ti) OR ((cerebrovascular NEXT/1 accident*):ab,ti) OR ((cholesterol*:ab,ti OR cholesteryl*:ab,ti OR 'hdl-c':ab,ti OR 'hdlc':ab,ti OR lipid*:ab,ti OR lipoprotein*:ab,ti OR triacylglycerol*:ab,ti OR triglycer*:ab,ti OR tryglycer*:ab,ti OR 'ldl-c':ab,ti OR 'ldlc':ab,ti) AND (level*:ab,ti OR low:ab,ti OR lower*:ab,ti OR profile*:ab,ti OR reduc*:ab,ti)) OR death:ab,ti OR ((heart NEXT/1 attack*):ab,ti) OR ((heart NEXT/1 infarct*):ab,ti) OR morbidity:ab,ti OR mortality:ab,ti OR ((myocardial NEXT/1 infarct*):ab,ti) OR outcome*:ab,ti OR prevent*:ab,ti OR stroke*:ab,ti	13,266,500
#32	Combine	(#1 OR #2 OR (#3 AND #6)) AND #30 AND #31	13,882
Combine all KQs			
#33	Combine all KQs	#7 OR #9 OR #12 OR #14 OR #17 OR #22 OR #26 OR #29 OR #32	232,037
Apply limits			

Line No.	Concept	Query	Results
#34	RCTs	#33 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ti,ab OR 'phase iii':ti,ab OR random*:ti,ab OR rct:ti,ab)	43,773
#35	Systematic reviews	#33 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*:ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR databases:ti,ab OR ebSCO*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*:ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*:ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab))	12,249
#36	Nonrandomized studies (KQs 2, 3, 5)	(#9 OR #12 OR #17) AND ('cohort analysis'/exp/mj OR 'comparative study'/exp/mj OR 'longitudinal study'/exp/mj OR 'prospective study'/exp/mj OR cohort*:ti,ab OR compar*:ti,ab OR 'non-random*':ti,ab OR nonrandom*:ti,ab OR prospectiv*:ti,ab)	25,873
#37	Combine RCTs & systematic reviews	#34 OR #35 OR #36	71,108
#38	Combine with expanded lipids & CV risk terms	#37 AND ('dyslipidemia'/exp OR 'high density lipoprotein cholesterol'/exp OR 'low density lipoprotein cholesterol'/exp OR 'hypercholesterolemia'/exp OR 'lipid'/exp OR ((disorder NEAR/3 lipoprotein):ab,ti) OR ((disorder NEAR/3 'lipid metabolism'):ab,ti) OR dyslipidaemia*:ab,ti OR dyslipidemia*:ab,ti OR dyslipidproteinaemia*:ab,ti OR dyslipidproteinemia*:ab,ti OR cholesterol:ab,ti OR hypercholesterolaemia*:ab,ti OR hypercholesterolemia*:ab,ti OR hyperlipaemia:ab,ti OR hyperlipemia:ab,ti OR hyperlipidaemia*:ab,ti OR hyperlipidemia*:ab,ti OR hyperlipidemic:ab,ti OR hyperlipoproteinaemia*:ab,ti OR hyperlipoproteinemia*:ab,ti OR hypertriglyceridaemia*:ab,ti OR hypertriglyceridemia*:ab,ti OR lipid*:ab,ti OR lipemia:ab,ti OR lipidaemia:ab,ti OR lipidemia:ab,ti OR lipoprotein*:ab,ti OR triacylglycerol*:ab,ti OR triglycer*:ab,ti OR tryglycer*:ab,ti OR 'cardiovascular risk'/exp OR ((cardio* NEAR/5 risk*):ab,ti) OR statin*:ab,ti OR (((hydroxymethylglutaryl OR 'hydroxy methylglutaryl') NEAR/5 reductase):ti,ab) OR ((hmg NEXT/1 coa):ti,ab) OR atorvastatin:ti,ab OR lovastatin:ti,ab OR meglutol:ti,ab OR pravastatin:ti,ab OR simvastatin:ti,ab OR alirocumab:ab,ti OR (('angiopoietin-	50,030

Line No.	Concept	Query	Results
		like 3':ab,ti OR angptl3:ab,ti) AND inhibitor*:ab,ti) OR (('apolipoprotein a-i':ab,ti OR 'apoa-i':ab,ti) AND infus*:ab,ti) OR (('apolipoprotein c3':ab,ti OR apoc3:ab,ti) AND inhibitor*:ab,ti) OR 'bempedoic acid':ab,ti OR 'bile acid sequestrant*':ab,ti OR (('cholesterol ester transfer protein':ab,ti OR cetp:ab,ti) AND inhibit*:ab,ti) OR evolocumab:ab,ti OR ezetimibe:ab,ti OR fibrate*:ab,ti OR 'fibric acid':ab,ti OR icosapent*:ab,ti OR inclisiran:ab,ti OR lerodalcibep:ab,ti OR lovaza:ab,ti OR 'monoclonal antibod*':ab,ti OR muvalaplin:ab,ti OR niacin:ab,ti OR 'nicotinic acid':ab,ti OR obicetrapib:ab,ti OR olpasiran:ab,ti OR 'omega 3':ab,ti OR 'pcsk-9':ab,ti OR pcsk9:ab,ti OR pelacarsen:ab,ti OR plozasiran:ab,ti OR recaticimab:ab,ti OR sirna*:ab,ti OR 'small interfering rna':ab,ti OR 'small molecule inhibitor*':ab,ti OR vascepa:ab,ti OR zerlasiran:ab,ti OR zodasiran:ab,ti)	
#39	Date limit	#38 AND [16-05-2019]/sd NOT [16-01-2025]/sd AND [2019-2025]/py	17,891
#40	Remove out of scope publication types	#39 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ab,ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)	12,662
#41	Remove out of scope age ranges	#40 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))	12,223
#42	Remove animal studies	#41 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti))) NOT (human*:ti OR patient*:ti)))	11,766
#43	English language	#42 AND [english]/lim	11,508

Table F-3. PubMed in Process Search Strategy

Search No.	Query	Results
1	(disorder AND "lipid metabolism"[TI]) OR dyslipidaemia*[TI] OR dyslipidemia*[TI] OR cholesterol[TI] OR hypercholesterolaemia*[TI] OR hypercholesterolemia*[TI] OR hyperlipaemia[TI] OR hyperlipemia[TI] OR hyperlipidaemia*[TI] OR hyperlipidemia*[TI] OR hyperlipoproteinaemia*[TI] OR hyperlipoproteinemia*[TI] OR hypertriglyceridaemia*[TI] OR hypertriglyceridemia*[TI] OR lipid* OR lipemia[TI] OR lipidaemia[TI] OR lipidemia[TI] OR lipoprotein*[TI] OR triacylglycerol*[TI] OR triglycer*[TI] OR tryglycer*[TI]	859,141
2	cardio*[TIAB] AND risk*[TIAB]	373,788
3	((arteries[TI] OR artery[TI] OR cardiac*[TI] OR cardio*[TI] OR cerebrovascular[TI] OR coronary[TI] OR heart*[TI] OR vascular[TI]) AND (disease*[TI] OR event*[TI] OR ischaem*[TI] OR ischem*[TI] OR plaque*[TI] OR syndrome*[TI])) OR angina[TI] OR arteriosclero*[TI] OR atherosclero*[TI] OR (cerebrovascular[TI] AND accident*[TI]) OR (heart[TI] AND attack*[TI]) OR hyperten*[TI] OR (myocardial[TI] AND infarct*[TI]) OR stroke*[TI]	867,065
4	prevent*[TI]	361,009
5	"follow up"[TI] OR frequen*[TI] OR interval*[TI] OR monitor*[TI] OR "re-assess*"[TI] OR "re do"[TI] OR "re-run"[TI] OR "re-screen*"[TI] OR reassess*[TI] OR redo[TI] OR redundant*[TI] OR repeat*[TI] OR repet*[TI] OR rerun[TI] OR rescreen*[TI] OR screen*[TI] OR subsequent*[TI] OR surveillance[TI]	891,582
6	risk*[TI] AND (algorithm*[TI] OR assess*[TI] OR biomarker*[TI] OR calculat*[TI] OR categor*[TI] OR characteristic*[TI] OR classific*[TI] OR define*[TI] OR defining[TI] OR determin*[TI] OR factor*[TI] OR index[TI] OR indices[TI] OR marker*[TI] OR predict*[TI] OR prioritiz*[TI] OR profile*[TI] OR score*[TI] OR stratification[TI] OR stratify*[TI] OR tier*[TI])	296,940
7	(#1 OR #2 OR (#3 AND #4)) AND #5 AND #6	1,953
8	#7 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*"[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebSCO*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct*"[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*"[TIAB] OR "web of science"[TIAB])))	42
9	#8 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolesc* [TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*"[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR	39

Search No.	Query	Results
	<p>animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI]))</p>	
10	<p>#9 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*" [TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody*" [TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*" [TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])</p>	39
11	<p>#9 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*" [TIAB] OR (("cholesterol</p>	10

Search No.	Query	Results
	ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
12	(ankle[TI] AND brachial[TI]) OR "apo(b)"[TI] OR apob[TI] OR "apolipoprotein b"[TI] OR ((cac[TI] OR "coronary artery calcium"[TI]) AND (score*[TI] OR test*[TI])) OR (carotid[TI] AND intima[TI] AND thick*[TI]) OR "carotid imt"[TI] OR ("electronic health record*[TI] AND score*[TI]) OR "family histor*[TI] OR ((genetic*[TI] OR polygenic[TI]) AND (risk*[TI] OR score*[TI])) OR hcrp[TI] OR "high sensitivity c reactive protein"[TI] OR "hs-crp"[TI] OR "hs crp"[TI] OR "hscrp"[TI] OR ("low-density lipoprotein"[TI] OR ldl[TI]) AND (subclass*[TI] OR subtype*[TI]) OR "lipoprotein(a)"[TI] OR "lp(a)"[TI] OR "machine learning"[TI] OR ("macrophage specific"[TI] AND "cholesterol efflux capacity"[TI]) OR ((new[TI] OR "non traditional"[TI] OR nontraditional[TI] OR novel[TI]) AND (marker*[TI] OR model*[TI] OR risk*[TI])) OR (prevent[TI] AND (calculator*[TI] OR equation*[TI] OR model*[TI])) OR ((reweight*[TI] OR "re weight*[TI]) AND (model*[TI] OR predict*[TI] OR risk*[TI])) OR sdoh[TI] OR "social deprivation index"[TI] OR "social determinants of health"[TI] OR (plaque*[TI] AND (activit*[TI] OR characteriz*[TI] OR morpholog*[TI]) AND (ccta[TI] OR "coronary ct angiography"[TI])) OR "ga-dotatate"[TI] OR "intracoronary near infrared spectroscopy"[TI] OR "intravenous ultrasound"[TI] OR ivus[TI] OR nirs[TI] OR oct[TI] OR "optical coherence tomography"[TI] OR "pet-ct"[TI]	210,720
13	(#2 OR (#3 AND #6)) AND #12	13,153
14	#13 AND (inprocess[SB] OR publisher[SB] OR pubmednotmedline[SB]) AND ((cohort*[TIAB] OR compar*[TIAB] OR longitudinal[TIAB] OR "non-random*[TIAB] OR nonrandom*[TIAB] OR prospectiv*[TIAB]) OR ("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct*[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*[TIAB] OR "web of science"[TIAB])))	1,264
15	#14 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR	1,213

Search No.	Query	Results
	animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI]))	
16	#15 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*" [TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody*" [TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*" [TIAB] OR vascepa[TIAB] OR zerasiran[TIAB] OR zodasiran[TIAB])	1,147
17	#15 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR	423

Search No.	Query	Results
	((("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB]))	
18	(prevent[TIAB] AND (calculator*[TIAB] OR equation*[TIAB] OR model*[TIAB]))	98,638
19	predict*[TIAB] AND model*[TIAB]	762,792
20	(#1 OR #2 OR (#3 AND #6)) AND (#18 OR #19)	41,745
21	#20 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND ((cohort*[TIAB] OR compar*[TIAB] OR longitudinal[TIAB] OR "non-random*[TIAB] OR nonrandom*[TIAB] OR prospectiv*[TIAB]) OR ("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct*[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*[TIAB] OR "web of science"[TIAB])))	4,050
22	#21 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	3,774
23	#22 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR	3,594

Search No.	Query	Results
	<p>hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR ("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB] OR ("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB] OR ("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB] OR "bempedoic acid"[TIAB] OR "bile acid sequestrant**"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB] OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod**"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor**"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])</p>	
24	<p>#22 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipidemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR ("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB] OR ("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB] OR ("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB] OR "bempedoic acid"[TIAB] OR "bile acid sequestrant**"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB] OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod**"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor**"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])</p>	1,353

Search No.	Query	Results
25	"10 year"[TIAB] OR "30 year"[TIAB] OR (benefit*[TIAB] AND risk*[TIAB]) OR "inflection point"[TIAB] OR "ten year"[TIAB] OR "thirty year"[TIAB] OR threshold*[TIAB]	711,672
26	(#1 OR (#3 AND #4)) AND #25	18,998
27	#26 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct"[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*[TIAB] OR "web of science"[TIAB])))	513
28	#27 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	487
29	#28 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR	434

Search No.	Query	Results
	olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor**"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
30	#28 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipidemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant**"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody**"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor**"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	133
31	"apo b"[TIAB] OR "apo(b)"[TIAB] OR hcrp[TIAB] OR "high sensitivity c reactive protein"[TIAB] OR "hs-crp"[TIAB] OR "hs crp"[TIAB] OR "hscrp"[TIAB] OR (lipid*[TIAB] AND marker*[TIAB]) OR "low density lipoprotein"[TIAB] OR ldlc[TIAB] OR "ldl-c"[TIAB] OR "lipoprotein(a)"[TIAB] OR "lp(a)"[TIAB] OR "non-hdl-c"[TIAB] OR "non-high density lipoprotein-cholesterol"[TIAB]	161,319
32	("on-treatment"[TIAB] OR residual*[TIAB] OR treat*[TIAB]) AND risk*[TIAB]	996,076
33	#31 AND #32	17,828
34	#33 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND ((cohort*[TIAB] OR compar*[TIAB] OR longitudinal[TIAB] OR "non-random**"[TIAB] OR nonrandom*[TIAB] OR prospectiv*[TIAB]) OR ("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy**"[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB]	1,639

Search No.	Query	Results
	OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct"*[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge"*[TIAB] OR "web of science"[TIAB]))))	
35	#34 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age"*[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	1,488
36	#35 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"*[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod"*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"*[TIAB] OR vascepa[TIAB] OR zerasiran[TIAB] OR zodasiran[TIAB])	1,407
37	#35 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR	439

Search No.	Query	Results
	hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipidemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant**"[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody**"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor**"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
38	"hydroxymethylglutaryl coenzyme a reductase inhibitor"[TI] OR "hypocholesterolemic agent"[TI] OR ((hydroxymethylglutaryl[TI] OR "hydroxy methylglutaryl"[TI]) AND reductase[TI]) OR (hmg[TI] AND coa[TI]) OR atorvastatin[TI] OR lovastatin[TI] OR meglutol[TI] OR pravastatin[TI] OR simvastatin[TI] OR statin*[TI]	34,827
39	alirocumab[TI] OR (("angiopoietin-like 3"[TI] OR angptl3[TI]) AND inhibitor*[TI]) OR (("apolipoprotein a-i"[TI] OR "apoa-i"[TI]) AND infus*[TI]) OR (("apolipoprotein c3"[TI] OR apoc3[TI]) AND inhibitor*[TI]) OR "bempedoic acid"[TI] OR "bile acid sequestrant**"[TI] OR (("cholesterol ester transfer protein"[TI] OR cetp[TI]) AND inhibit*[TI]) OR evolocumab[TI] OR ezetimibe[TI] OR fibrate*[TI] OR "fibric acid"[TI] OR icosapent*[TI] OR inclisiran[TI] OR lerodalcibep[TI] OR lovaza[TI] OR "monoclonal antibody**"[TI] OR muvalaplin[TI] OR niacin[TI] OR "nicotinic acid"[TI] OR obicetrapib[TI] OR olpasiran[TI] OR "omega 3"[TI] OR "pcsk-9"[TI] OR pcsk9[TI] OR pelacarsen[TI] OR plozasiran[TI] OR recaticimab[TI] OR sirna*[TI] OR "small interfering rna"[TI] OR "small molecule inhibitor**"[TI] OR vascepa[TI] OR zerlasiran[TI] OR zodasiran[TI]	87,764
40	(adverse[TIAB] AND (event*[TIAB] OR reaction*[TIAB])) OR angina[TIAB] OR ((cardiac[TIAB] OR coronary[TIAB] OR vascular[TIAB]) AND event*[TIAB]) OR (cerebrovascular[TIAB] AND (accident*[TIAB] OR event*[TIAB])) OR (cognitive[TIAB] AND (defect*[TIAB] OR impair*[TIAB])) OR death[TIAB] OR dementia[TIAB] OR diabet*[TIAB] OR (heart[TIAB] AND (attack*[TIAB] OR infarct*[TIAB])) OR (memor* AND (impair*[TIAB] OR	7,105,693

Search No.	Query	Results
	loss[TIAB]) OR morbidity[TIAB] OR mortality[TIAB] OR (myocardial[TIAB] AND infarct*[TIAB]) OR prevent*[TIAB] OR outcome*[TIAB] OR revascularization[TIAB] OR stroke*[TIAB] OR "time to benefit"[TIAB]	
41	(gestational[TI] AND (diabetes[TI] OR hypertension[TI])) OR hiv[TI] OR "human immunodeficiency virus"[TI] OR lupus[TI] OR masld[TI] OR "metabolic dysfunction-associated steatotic liver disease"[TI] OR "metabolic fatty liver"[TI] OR nafld[TI] OR "nonalcoholic fatty liver disease"[TI] OR "non alcoholic fatty liver disease"[TI] OR "pre-eclampsia"[TI] OR ((early[TI] OR premature[TI]) AND menopause[TI]) OR psoriasis[TI] OR "rheumatoid arthritis"[TI]	477,834
42	(#1 OR #3 OR #41) AND (#38 OR #39) AND #40	13,201
43	#42 AND (inprocess[<i>sb</i>] OR publisher[<i>sb</i>] OR pubmednotmedline[<i>sb</i>]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*" [TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct*" [TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*" [TIAB] OR "web of science"[TIAB])))	471
44	#43 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*" [TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	451
45	#44 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl" [TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR	451

Search No.	Query	Results
	(("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerasiran[TIAB] OR zodasiran[TIAB])	
46	#44 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerasiran[TIAB] OR zodasiran[TIAB])	111
47	("hydroxymethylglutaryl coenzyme a reductase inhibitor"[TIAB] OR "hypocholesterolemic agent"[TIAB]) AND (drug*[TIAB] OR dose*[TIAB] OR dosage*[TIAB]) AND (intensif*[TIAB] OR reduc[TIAB] hypersensitiv*[TIAB] OR compliance[TIAB] OR substitut*[TIAB])	4
48	(hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR "hmg coa"[TIAB] OR statin*[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR atorvastatin[TIAB] OR simvastatin[TIAB]) AND	20,437

Search No.	Query	Results
	((adher*[TIAB] OR complian*[TIAB] OR hypersensitiv*[TIAB] OR "non-adherence"[TIAB] OR intoleran*[TIAB] OR nonadherence*[TIAB] OR persistan*[TIAB] OR toleran*[TIAB] OR tolerat*[TIAB]) OR ((alternat*[TIAB] OR decreas*[TIAB] OR high[TIAB] OR higher[TIAB] OR increas*[TIAB] OR low[TIAB] OR lower[TIAB] OR switch*[TIAB]) AND (day[TIAB] OR dosag*[TIAB] OR dose*[TIAB] OR dosing[TIAB])))	
49	"coenzyme q10"[TIAB] OR coq10[TIAB] OR "vitamin d"[TIAB]	89,441
50	(#1 OR #2 OR #3) AND (#47 OR #48 OR ((#47 OR #48) AND #49))	13,113
51	#50 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*" [TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebSCO*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct*" [TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge*" [TIAB] OR "web of science"[TIAB])))	398
52	#51 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age*" [TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	374
53	#52 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipidemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl" [TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i" [TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*" [TIAB] OR ("cholesterol	374

Search No.	Query	Results
	ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
54	#52 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR ("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB] OR ("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB] OR ("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB] OR "bempedoic acid"[TIAB] OR "bile acid sequestrant*[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibod*[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor*[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	77
55	(("low density lipoprotein cholesterol level"[TI] OR "high density lipoprotein cholesterol level"[TI]) AND (goal[TI] OR goals[TI] OR target*[TI] OR level[TI] OR levels[TI])) OR (("high density lipoprotein cholesterol"[TI] OR "low density lipoprotein cholesterol"[TI]) AND "goal attainment"[TI]) OR ((cholesteryl*[TI] OR cholesterol*[TI] OR lipid*[TI] OR lipoprotein*[TI] OR triacylglycerol*[TI] OR triglycer*[TI] OR tryglycer*[TI] OR "hdl-c"[TI] OR "ldl-c"[TI] OR "hdlc"[TI] OR "ldlc"[TI] OR "non hdl c"[TI] OR "non-hdlc"[TI] OR nonhdlc[TI]) AND (goal[TI] OR goals[TI] OR target*[TI] OR level[TI] OR levels[TI])) OR ((atheroma*[TI] OR plaque*[TI]) AND (assess*[TI] OR imag*[TI] OR morphology[TI])) OR "plaque regression"[TI]	2,050

Search No.	Query	Results
56	stroke*[TIAB] OR "cerebrovascular accident"*[TIAB] OR death[TIAB] OR "heart attack"*[TIAB] OR "myocardial infarct"*[TIAB] OR ((vascular[TIAB] OR cardiac[TIAB] OR coronary[TIAB] OR cerebrovascular[TIAB]) AND event*[TIAB]) OR "heart infarct"*[TIAB] OR morbidity[TIAB] OR mortality[TIAB] OR prevent*[TIAB] OR outcome*[TIAB] OR "secondary prevention"[TIAB] OR "primary prevention"[TIAB] OR angina[TIAB] OR "adverse event"*[TIAB]	719,885
57	(#1 OR #2 OR #3) AND #55 AND #56	727
58	#57 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy"*[TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct"*[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge"*[TIAB] OR "web of science"[TIAB])))	43
59	#58 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age"*[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	43
60	#59 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"*[TIAB] OR (("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR	43

Search No.	Query	Results
	evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
61	#59 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR ("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR ("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR ("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	43
62	((diet*[TI] OR nutrition[TI]) AND (dash[TI] OR "daytime restricted"[TI] OR "gluten free"[TI] OR "intermittent fast"[TI] OR "low calori"[TI] OR "low carb"[TI] OR "low fat"[TI] OR "low gluten"[TI] OR "low sodium"[TI] OR keto[TI] OR macrobiotic[TI] OR mediterranean[TI] OR "plant based"[TI] OR vegan[TI] OR vegetarian[TI] OR "whole food"[TI])) OR "diabetic diet"[TI] OR "diet therapy"[TI] OR "dietary approach* to stop hypertension"[TI]	14,089
63	"adverse event"[TIAB] OR angina[TIAB] OR ((cardiac[TIAB] OR cerebrovascular[TIAB] OR coronary[TIAB] OR vascular[TIAB]) AND event*[TIAB]) OR "cerebrovascular accident"[TIAB] OR ((cholesterol*[TIAB] OR cholesteryl*[TIAB] OR "hdl-c"[TIAB] OR "hdlc"[TIAB] OR lipid*[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR	6,655,797

Search No.	Query	Results
	tryglycer*[TIAB] OR "ldl-c"[TIAB] OR "ldlc"[TIAB]) AND (level*[TIAB] OR low[TIAB] OR lower*[TIAB] OR profile*[TIAB] OR reduc*[TIAB])) OR death[TIAB] OR "heart attack"[TIAB] OR "heart infarct"[TIAB] OR morbidity[TIAB] OR mortality[TIAB] OR "myocardial infarct"[TIAB] OR outcome*[TIAB] OR prevent*[TIAB] OR stroke*[TIAB]	
64	(#1 OR #2 OR (#3 AND #6)) AND #62 AND #63	2,587
65	#64 AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND (("phase 3"[TIAB] OR "phase iii"[TIAB] OR random*[TIAB] OR rct[TIAB]) OR (systematic*[TI] OR cochrane*[TIAB] OR metaanaly*[TIAB] OR "meta analy*" [TIAB] OR (search*[TIAB] AND (cinahl*[TIAB] OR databases[TIAB] OR ebsco*[TIAB] OR embase*[TIAB] OR psychinfo*[TIAB] OR psycinfo*[TIAB] OR "science direct"[TIAB] OR sciencedirect*[TIAB] OR scopus*[TIAB] OR systematic*[TIAB] OR "web of knowledge"[TIAB] OR "web of science"[TIAB])))	125
66	#65 NOT (("case report"[TI] OR comment[TI] OR "conference proceeding"[TIAB] OR editorial[TI] OR letter[TI]) OR ((adolescen*[TI] OR babies[TI] OR baby[TI] OR boys[TI] OR child*[TI] OR girls[TI] OR infancy[TI] OR infant*[TI] OR juvenile*[TI] OR neonat*[TI] OR newborn*[TI] OR nurser*[TI] OR paediatric*[TI] OR pediatric*[TI] OR preschool*[TI] OR "school age"[TI] OR schoolchildren*[TI] OR teen*[TI] OR toddler*[TI] OR youth*[TI]) NOT (adult*[TI] OR men[TI] OR women[TI])) OR (((animal[TI] OR animals[TI] OR canine*[TI] OR dog[TI] OR dogs[TI] OR feline[TI] OR hamster*[TI] OR lamb[TI] OR lambs[TI] OR mice[TI] OR monkey[TI] OR monkeys[TI] OR mouse[TI] OR murine[TI] OR pig[TI] OR piglet*[TI] OR pigs[TI] OR porcine[TI] OR primate*[TI] OR rabbit*[TI] OR rat[TI] OR rats[TI] OR rodent*[TI] OR sheep*[TI] OR swine[TI] OR veterinar*[TI] OR (vitro[TI] NOT vivo[TI])) NOT (human*[TI] OR patient*[TI])))	117
67	#66 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB]	116

Search No.	Query	Results
	OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	
68	#66 AND (dyslipidaemia*[TIAB] OR dyslipidemia*[TIAB] OR cholesterol[TIAB] OR hypercholesterolaemia*[TIAB] OR hypercholesterolemia*[TIAB] OR hyperlipaemia[TIAB] OR hyperlipemia[TIAB] OR hyperlipidaemia*[TIAB] OR hyperlipidemia*[TIAB] OR hyperlipdemic[TIAB] OR hyperlipoproteinaemia*[TIAB] OR hyperlipoproteinemia*[TIAB] OR hypertriglyceridaemia*[TIAB] OR hypertriglyceridemia*[TIAB] OR lipid*[TIAB] OR lipemia[TIAB] OR lipidaemia[TIAB] OR lipidemia[TIAB] OR lipoprotein*[TIAB] OR triacylglycerol*[TIAB] OR triglycer*[TIAB] OR tryglycer*[TIAB] OR (cardio*[TIAB] AND risk*[TIAB]) OR statin*[TIAB] OR hydroxymethylglutaryl[TIAB] OR "hydroxy methylglutaryl"[TIAB] OR atorvastatin[TIAB] OR lovastatin[TIAB] OR meglutol[TIAB] OR pravastatin[TIAB] OR simvastatin[TIAB] OR alirocumab[TIAB] OR (("angiopoietin-like 3"[TIAB] OR angptl3[TIAB]) AND inhibitor*[TIAB]) OR (("apolipoprotein a-i"[TIAB] OR "apoa-i"[TIAB]) AND infus*[TIAB]) OR (("apolipoprotein c3"[TIAB] OR apoc3[TIAB]) AND inhibitor*[TIAB]) OR "bempedoic acid"[TIAB] OR "bile acid sequestrant"[TIAB] OR ("cholesterol ester transfer protein"[TIAB] OR cetp[TIAB]) AND inhibit*[TIAB]) OR evolocumab[TIAB] OR ezetimibe[TIAB] OR fibrate*[TIAB] OR "fibric acid"[TIAB] OR icosapent*[TIAB] OR inclisiran[TIAB] OR lerodalcibep[TIAB] OR lovaza[TIAB] OR "monoclonal antibody"[TIAB] OR muvalaplin[TIAB] OR niacin[TIAB] OR "nicotinic acid"[TIAB] OR obicetrapib[TIAB] OR olpasiran[TIAB] OR "omega 3"[TIAB] OR "pcsk-9"[TIAB] OR pcsk9[TIAB] OR pelacarsen[TIAB] OR plozasiran[TIAB] OR recaticimab[TIAB] OR sirna*[TIAB] OR "small interfering rna"[TIAB] OR "small molecule inhibitor"[TIAB] OR vascepa[TIAB] OR zerlasiran[TIAB] OR zodasiran[TIAB])	37

Table F-4. AHRQ EPC Reports Search Strategy

Query
dyslipidemia [Search by keyword]
lipid [Search by keyword]
statin [Search by keyword]
cardiovascular risk [Search by keyword]

Table F-5. VA ESP Reports Search Strategy

Query
dyslipidemia [Search ALL ESP Reports]
lipid [Search ALL ESP Reports]
statin [Search ALL ESP Reports]
cardiovascular risk [Search ALL ESP Reports]
hypercholesterolemia [Search ALL ESP Reports]
lipoprotein [Search ALL ESP Reports]

Table F-6. Cochrane Library Search Strategy

Line No.	Query	Results
#1	dyslipidaemia* OR dyslipidemia* OR cholesterol OR hypercholesterolaemia* OR hypercholesterolemia* OR hyperlipaemia OR hyperlipemia OR hyperlipidaemia* OR hyperlipidemia* OR hyperlipoproteinaemia* OR hyperlipoproteinemia* OR hypertriglyceridaemia* OR hypertriglyceridemia* OR lipid* OR lipemia OR lipidaemia OR lipidemia OR lipoprotein* OR triacylglycerol* OR triglycer* OR tryglycer* in Record Title OR cardio* AND risk* in Record Title OR atorvastatin OR lovastatin OR meglutol OR pravastatin OR simvastatin OR statin* in Record Title - (Word variations have been searched)	18*

*12 results selected (references focused on infants/children excluded); 4 unique references identified after deduplicating against previously identified references.

Appendix G. Alternative Text Description of Algorithm

The following outline narratively describes the [Management Algorithm](#). An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the [Algorithm](#) section. The sidebars referenced within these outlines can also be found in the [Algorithm](#) section.

Management Algorithm

1. The Management Algorithm begins with Box 1, in the shape of a rounded rectangle: “Adult patient”
2. Box 1 connects to Box 2, in the shape of a rectangle: “Comprehensive Lifestyle Medicine (see **Sidebars 1 and 2** and **Recs 22 and 23**)”
3. Box 2 connects to Box 3, in the shape of hexagon, asks the question: “Is life expectancy limited?”
 - a. If the answer is “Yes” to Box 3, then Box 4, in the shape of a rectangle: “Discuss uncertain benefit”
 - b. If the answer is “No” to Box 3, then Box 5, in the shape of a hexagon, asks the question: “Existing CVD? (See **Sidebar 3**)”
 - i. If the answer is “Yes” to Box 5, then Box 6, in the shape of a rectangle: “Refer for cardiac rehab if MI, ACS, or CABG/PCI in past 6 weeks (see **Rec 24**)”
 - ii. If the answer is “No” to Box 5, then Box 8, in the shape of a hexagon, asks the question: “DM, LDL-C \geq 190, or 10-year estimated risk \geq 10%?”
 1. If the answer is “Yes” to Box 8, then Box 9, in the shape of a rectangle: “At least a moderate dose statin (see **Sidebar 5** and **Rec 7**). Consider referral to lipid specialist if LDL-C \geq 190.”
 - a. Box 9 connects to Box 15, in the shape of a rectangle: “Reassess therapy and consider modification if new risk factors or enhancers develop (see **Rec 15**)”
 - b. Box 15 connects to Box 21, in the shape of a rectangle: “Re-emphasize Lifestyle Medicine – Med Diet, Exercise, Smoking, Sleep, Connections, Stress, Weight Management (see **Sidebars 1 and 2** and **Recs 22 and 23**)”
 2. If the answer is “No” to Box 8, then Box 10, in the shape of a hexagon, asks the question: “HIV positive?”
 - a. If the answer is “Yes” to Box 10, then Box 11, in the shape of a rectangle: “Moderate dose statin (see **Sidebar 5** and **Recs 8 and 10**)”
 - i. Box 11 connects to Box 15, in the shape of a rectangle: “Reassess therapy and consider modification if new risk factors or enhancers develop (see **Rec 15**)”
 - ii. Box 15 connects to Box 21, in the shape of a rectangle: “Re-emphasize Lifestyle Medicine – Med Diet, Exercise, Smoking, Sleep, Connections, Stress, Weight Management (see **Sidebars 1 and 2** and **Recs 22 and 23**)”

6. Box 20 connects to Box 21, in the shape of a rectangle: “Re-emphasize Lifestyle Medicine – Med Diet, Exercise, Smoking, Sleep, Connections, Stress, Weight Management (see **Sidebars 1 and 2** and **Recs 22 and 23**)”

Appendix H. CVD Risk Calculators

The Anderson et al., 2024, cross-sectional study, [\(41\)](#) conducted from December 2023 through January 2024, compared the new 2023 PREVENT CV risk calculator to the 2013 PCE. The following table provides the results of this study. In the 3,785-participant sample, the mean age was 55.7 years, 15.7% of participants had diabetes, 15.5% reported that they were currently smoking, and 20.7% reported that they were currently on statin therapy. Authors calculated the risk for each participant in this sample using both equations, finding that the PREVENT tool estimated a significantly lower 10-year risk for ASCVD when compared to the PCE tool.

Table H-1. PREVENT vs. PCE 10-Year ASCVD Risk Estimate [\(41\)](#)

Patient Characteristics		%
Sample size		3,785 adults
Sex	Women	52.5%
	Men	47.5%
Race	White	66.7%
	Non-Hispanic Black/African American	10.2%
	Non-Hispanic Asian	5.3%
	Mexican Americans	7.0%
	Other Hispanic	6.9%
Age	Mean	55.7 years
	Range	40-75 years
10-Year ASCVD Risk (PREVENT vs. PCE)		4.3% vs. 8.0%
Eligibility for Primary Prevention Statin Therapy (PREVENT vs. PCE)		28.3 million adults vs. 45.5 million adults

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; PREVENT: Predicting Risk of Cardiovascular Disease Events; PCE: Pooled Cohort Equation

Appendix I. Pharmacotherapy

Table C-1. Summary of Pharmacologic Agents*

Consult agency formulary for availability.

Drug Class	Drug	Dose	Mean % LDL-C Reduction+	Major Drug Interactions	Adverse Drug Reactions	Notes
Statins	Atorvastatin	10 – 80 mg once daily	Moderate-dose intensity: 30 to <50%	Since statins vary in their metabolic pathway, refer to product labeling for drug-drug interactions and use in special populations (e.g., Asian patients) regarding statin dosage guidance and dose limits.	Risk for myalgia, myopathy and, very rarely, rhabdomyolysis. Other risks include new onset diabetes (primarily with higher doses), LFT elevation, and asymptomatic CK elevation.	<ul style="list-style-type: none"> • First line therapy for primary or secondary prevention of CVD. • True statin intolerance is uncommon. Evaluation of previous statin use, and retreatment should be strongly considered to reduce CV risk (except for patients with life-threatening adverse events, e.g., rhabdomyolysis). Intermittent dosing regimen may be considered (see Recommendation 18). • Statins, particularly longer-acting statins (e.g., rosuvastatin, atorvastatin), may be taken any time of day.
	Rosuvastatin	5 – 40 mg once daily	High-dose intensity: ≥50%			
	Simvastatin	5 – 40 mg once daily				
	Lovastatin	20 – 80 mg once daily	High-intensity statins: Atorvastatin 40-80 mg Rosuvastatin 20-40 mg			
	Pravastatin	10 – 80 mg once daily				
	Fluvastatin	20 – 80 mg per day				
	Pitavastatin	1 – 4 mg once daily				
Cholesterol absorption inhibitors	Ezetimibe	10 mg once daily	<p>Monotherapy: 18-20%</p> <p>Combined with statins: additional 12-15% (up to 20%)</p>	Increased incidence of transaminase elevation >3x ULN when combined with statins vs. statins alone (1.3% vs. 0.4%, respectively)	Generally well tolerated	<ul style="list-style-type: none"> • Benefit for reducing non-fatal CV events in secondary prevention when added to statins (IMPROVE-IT Trial). • Available as a combination product with simvastatin.

Drug Class	Drug	Dose	Mean % LDL-C Reduction+	Major Drug Interactions	Adverse Drug Reactions	Notes
PCSK9 inhibitors (Monoclonal Antibody or mAb)	Alirocumab	75 mg once every 2 weeks OR 300 mg once every 4 weeks Max: 150 mg every 2 weeks	50 to >60%	No known significant interactions.	Generally well tolerated. Injection site reactions (3-7%) reported more often than placebo in clinical trials. Other adverse reactions with PCSK9 inhibitors were similar to placebo.	<ul style="list-style-type: none"> Benefit for reducing non-fatal CV events in secondary prevention when added to maximally tolerated statin +/- ezetimibe (ODYSSEY Outcomes and FOURIER trials). Self-administered as SQ injection.
	Evolocumab	140 mg once every 2 weeks OR 420 mg once monthly				
Adenosine triphosphate-citrate lyase inhibitor	Bempedoic acid	180 mg once daily	Monotherapy: 21-23% Combined with statins: 12-17% Combined with ezetimibe: 36%	Avoid concomitant use with >20 mg simvastatin or >40 mg pravastatin.	In CLEAR Outcomes, the following adverse events occurred more often with bempedoic acid vs. placebo, respectively: <u>LFT elevation:</u> 4.5 vs. 3% <u>Renal impairment:</u> 11.5 vs. 8.6% <u>Tendon rupture:</u> 1.2 vs. 0.9% <u>Hyperuricemia:</u> 10.9 vs. 5.6% <u>Gout:</u> 3.1 vs. 2.1%	<ul style="list-style-type: none"> Benefit in reducing CV events in patients with statin intolerance (In the CLEAR Outcomes trial, 30% of patients did not have established CVD but were at high risk). Available as a combination product with ezetimibe 10 mg.

Drug Class	Drug	Dose	Mean % LDL-C Reduction+	Major Drug Interactions	Adverse Drug Reactions	Notes
					<p><u>Cholelithiasis:</u> 2.2 vs. 1.2%</p> <p>Caution should be used in patients who might be at greater risk for these events.</p>	
Icosapent Ethyl	Icosapent ethyl	2 g twice daily with meals	N/A	May enhance antiplatelet and anticoagulation effects. Use caution with concomitant agents that increase risk of bleeding.	<p>Arthralgia (2.3%), oropharyngeal pain, peripheral edema, constipation, gout, and atrial fibrillation. Potential for allergic reactions in patients with fish allergy.</p>	<ul style="list-style-type: none"> • Benefit for reduction of CV mortality and morbidity in patients treated for secondary prevention on statins with persistently elevated TG (>150 mg/dL); evidence is limited to one RCT (REDUCE-IT Trial). • Experts have suggested a confirmatory trial be completed to confirm the results since the mineral oil placebo arm in the REDUCE-IT trial led to increases in LDL-C and inflammatory markers (e.g., hs-CRP) which may have amplified the magnitude of the findings. • Hospitalization for atrial fibrillation or flutter was statistically higher with icosapent and a non-significant trend towards a higher incidence of hospitalization for serious bleeding

Drug Class	Drug	Dose	Mean % LDL-C Reduction+	Major Drug Interactions	Adverse Drug Reactions	Notes
						events was also observed.
Small Interfering RNA (siRNA) agent	Inclisiran	284 mg once, at 3 months, and then every 6 months	40% to >50%	No known interactions	Injection site reactions (2% placebo vs. 8% inclisiran), arthralgia (4% placebo vs. 5% inclisiran), bronchitis (3% placebo vs. 4 % inclisiran)	<ul style="list-style-type: none"> Ongoing outcomes trials: ORION 4: secondary prevention trial, potential for results in 2026 VICTORION-1 PREVENT: primary prevention trial; expected after 2027 VICTORION-2 PREVENT: secondary prevention trial; expected completion date is 2027 Should be reserved for patients who cannot use a PCSK9 mAb inhibitor. Do not use in combination with PCSK9 mAb inhibitor. Administered SQ by a healthcare professional.

* Refer to product labeling for more information regarding use restrictions, dose modification, dosing in special populations (e.g., renal or liver impairment, advanced age, pregnancy, etc.), drug-drug interactions, and adverse events.

+ Mean percent LDL-C lowering are estimates, individual response may vary.

Abbreviations: CK: creatine kinase; CV: cardiovascular; CVD: cardiovascular disease; dL: deciliter; gm: grams; DM: diabetes mellitus; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low density lipoprotein cholesterol; LFT: liver function test; mAb: monoclonal antibody; mg: milligrams; PCSK9: proprotein convertase subtilisin/kexin type 9; RCT: randomized controlled trial; SQ: subcutaneous, TG: triglyceride; ULN: upper limit of the normal range

Appendix J. Lifestyle Medicine Interventions

Lifestyle interventions, including a healthy diet and adequate physical activity, play a pivotal role in CV risk reduction in persons with and without CVD.([195-197](#))

A. Physical Activity

Increasing the level of physical activity can be done with limited resources and can prove beneficial in the management of lipid profiles.([197,198](#)) Large-scale epidemiological studies consistently demonstrate that routine physical activity increases HDL-C levels and decreases CV risk.([199-202](#)) These benefits accrue from aerobic activity, resistance exercise, or a combination of both.([195,198](#))

Modes of aerobic activity can include walking, running, gardening, cycling, swimming, in-person or virtual exercise classes, or nearly any movement that increases respiratory rate. Regular aerobic activity is recommended for both primary and secondary prevention of CVD.([202](#)) Cardiovascular risk reduction has been observed in routine aerobic activity with decreases in TC, TG, LDL-C, and very-low LDL-C, and an increase in HDL-C.([198,202](#)) A total of 150 minutes of moderate intensity, 75 minutes of vigorous intensity physical activity, or an equivalent combination of the two intensities per week is associated with a reduction in CV mortality by 21-91% and all-cause mortality by 19-70%.([177,202](#))

Aerobic activity is also foundational in cardiac rehabilitation programs and is strongly recommended for reducing morbidity and mortality for persons who had a recent occurrence of CHD (i.e., MI, diagnosis of CAD, CABG, or PCI).(a href="#">192,202)

Resistance exercise can be performed using free weights, bands, weight machines, and body weight resisted exercises. This form of exercise promotes adaptations of muscles, commonly noted in hypertrophy, and an increase in metabolism. Resistance exercise favorably changes the lipid profile by elevating HDL-C. A 2024 SR and meta-analysis reported that combined aerobic and resistance exercise is most favorable in dyslipidemia management for those without CVD, as compared to resistance or aerobic activity alone. The lipid profiles improved when participation in resistance, aerobic, or combined training occurred at a median frequency of 3 bouts per week and a duration of 3 weeks or more.([198](#))

Engaging in routine physical activity has been shown to be safe for most individuals. Exercise at light to moderate levels, such walking or gardening, is associated with a low risk of musculoskeletal injury and unwanted CV events. Moreover, a gradual increase in activity overtime, especially in low level or inactive individuals, provides additional risk reduction. Adults may successfully adopt a more active lifestyle when there are identified benefits that have personal value to the individual. These may include health benefits associated with physical activity, the opportunity to enjoy recreational activities in a social setting, improved personal appearance or energy, the ability to help a friend or family member be more active, and a greater opportunity to live independently in the community for older adults Following the identification of personal benefits, setting goals connected to those personal benefits and having a graduated approach to physical activity can assist in helping adults become and stay physically active.([178](#))

B. Diet

Table J-1. Patient Education on the Mediterranean and Other Cardioprotective Diets

Eat More	Eat Less
<ul style="list-style-type: none"> • Fruits and vegetables • Whole grains • Seafood (primarily fatty fish) • Skinless poultry • Tree nuts, seeds, peanuts, nut butters • Beans and legumes • Non-tropical vegetable oils (olive, canola, avocado, etc.) • Low-fat dairy products (milk, cheese) 	<ul style="list-style-type: none"> • Added sugar • Sugar-sweetened beverages • Sodium • Highly processed foods • Refined carbohydrates • Saturated fats • Tropical vegetable oils (coconut, palm, etc.) • High-fat and processed meats • Alcoholic beverages

While a new U.S. Surgeon General advisory risk was issued sharing how alcohol increases cancer risk, it is generally understood that red wine, in limited amounts, is healthy for the heart and can reduce CV risk. Resveratrol, a polyphenolic antioxidant compound, is thought to be the compound specifically found in red wine and red grape juice that is known to contribute to CV risk reduction. Providers should consider the risk of recommending alcohol to individual patients.

Appendix K. Familial Hypercholesterolemia

Severe hypercholesterolemia is characterized by LDL-C greater than the 90th percentile for age and sex (i.e., >190 mg/dL) and is associated with elevated CV risk compared to patients with normal or milder elevations. Patients with FH have severely elevated LDL-C that follows a Mendelian inheritance pattern of large effect genetic variants in any of the following: *LDL-R*, *PCSK9*, or *APOB*. The severity of LDL-C elevation is contingent on whether one (i.e., HeFH) or both (i.e., HoFH) copies of the effected gene harbor an abnormal allele. The incidence of HeFH is approximately 1 in 250 people whereas HoFH is estimated to occur in 1 in 300,000 people. Patients with HoFH often have very severe elevations of LDL-C (e.g., >400 mg/dL), symptomatic CVD early in life (e.g., before the age of 20 years), a family history of severe hypercholesterolemia or premature CVD, and abnormal exam findings such as corneal arcus and xanthomata involving the skin and/or tendons. Patients with HeFH may have a history of premature CVD, but events typically occur later in life compared to patients with HoFH. The diagnosis of FH can be made on clinical grounds or by genetic testing. Commonly cited diagnostic criteria for FH include the Dutch Lipid Clinic Network Criteria and the American Heart Association Clinical Classification of Familial Hypercholesterolemia.

Table K-1. The Dutch Lipid Clinic Network Criteria*

Criteria	Points
Family History	
First degree relative with premature coronary and/or vascular disease or LDL-C >95 th percentile for age and sex	1
Children aged <18 years with LDL-C >95 th percentile for age and sex or first-degree relative with tendon xanthomas and/or arcus cornealis	2
Personal history of premature ASCVD	
Coronary heart disease	2
Cerebral or peripheral vascular disease	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age <45 years	4
Plasma levels of LDL-C	
LDL-C >325 mg/dL	8
LDL-C 251-325 mg/dL	5
LDL-C 191-250 mg/dL	3
LDL-C 155-190 mg/dL	1
Molecular genetic testing	
Pathogenic variants in <i>LDL-R</i> , <i>APOB</i> , or <i>PCSK9</i>	8

*Choose the highest score within each diagnostic group and use the sum of all groups to classify: FH is considered present if a total score is >8 points; probable FH if score is 6 to 8 points; possible FH if score is 3 to 5 points; if the score is 0 to 2 points, FH is unlikely.

Adapted from Ballantyne, Christi. "Clinical Lipidology: A Companion to Braunwald's Heart Disease, Third Edition". Chapter 34, page 323. Copyright 2024.

Abbreviations: ApoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; dL: deciliter; LDL-C: low-density lipoprotein cholesterol; LDL-R: low-density lipoprotein receptor; mg: milligram; PCSK9: proprotein convertase subtilisin/kexin type 9

Table K-2. The American Heart Association Clinical Classification of FH (203)

ICD-10 Category	Clinical Criteria	Genetic Testing
Heterozygous FH	<ul style="list-style-type: none"> LDL-C \geq160 mg/dL for children and \geq190 mg/dL for adults and one first-degree relative similarly affected or with premature coronary disease or with positive genetic testing for FH-causing disease 	<ul style="list-style-type: none"> Pathogenic variant in <i>LDL-R</i>, <i>PCSK9</i>, or <i>APOB</i>. Presence of mutations in two different genes (<i>LDL-R</i>, <i>PCSK9</i>, or <i>APOB</i>) and LDL-C-lowering genetic variant
Homozygous FH	<ul style="list-style-type: none"> LDL-C \geq400 mg/dL and one or both parents with clinically or genetically diagnosed FH If LDL-C $>$560 mg/dl or LDL-C $>$400 mg/dL with aortic valve disease or xanthomas at $<$20 years of age, homozygous FH is highly likely 	<ul style="list-style-type: none"> Two pathogenic variants at <i>LDL-R</i>, <i>PCSK9</i>, or <i>APOB</i> Homozygotes will occasionally have LDL-C $<$400 mg/dL

Abbreviations: ApoB: apolipoprotein B; dL: deciliter; FH: familial hypercholesterolemia; ICD-10: International Classification of Diseases, 10th Revision; LDL-C: low-density lipoprotein cholesterol; LDL-R: low-density lipoprotein receptor; mg: milligram; PCSK9: proprotein convertase subtilisin/kexin type 9

Most professional societies do not recommend routine genetic testing in patients with suspected FH because genetic testing rarely changes clinical management.(204,205) The intensity of treatment should be guided by LDL-C and global risk rather than a patient's genotype. In some cases, genetic testing may be warranted to inform decisions about cascade screening of family members or to improve motivation and patient adherence with treatment plans. All patients with FH benefit from vigorous lifestyle modifications and LDL-lowering therapy. More intensive medical management with LDL-C-lowering therapies and other comprehensive care decisions in collaboration with a lipid specialist is advisable in most cases. Cascade screening of family members with a lipid profile and/or genetic testing is a cost-effect method for identifying patients with FH. Clinicians should recommend that patients with FH inform their family members of their diagnosis. If genetic testing for the patient or family members is pursued, then collaboration with a genetic counselor can support informed decision-making and clinical interpretation of results.

Appendix L: Pharmacogenomic Testing

A. Pharmacogenomics in Dyslipidemia

Pharmacogenomics (PGx) utilizes genetic information to predict an individual's response to medications.(206) By identifying gene variants associated with specific drug responses, PGx enables personalized medicine, optimizing drug selection and dosing to enhance efficacy and minimize adverse effects.(207) Within the VA, the National Pharmacogenomics Program (NPP) facilitates PGx testing for Veterans, offering insights into medications commonly prescribed in this population.(208) This PGx testing aids healthcare providers in tailoring treatment plans to individual genetic profiles, potentially improving therapeutic outcomes.

B. The Role of Pharmacogenomics in Lipid Management

Lipid-lowering therapy, particularly statins, is a cornerstone of CVD prevention. However, patient responses to statins vary, with some experiencing reduced efficacy or significant adverse effects.(209) Pharmacogenomic testing enables personalized medicine, predicting systemic exposure (drug concentration in the blood), optimizing drug selection and dosing to enhance efficacy and minimize muscle adverse effects.(207) Although definitive RCTs are lacking, evolving evidence support the potential benefits of a genotype-guided approach to lipid-lowering therapy.(210,211) With the VA expanding PGx testing and growing observational evidence highlighting its clinical relevance,(212) there is a need for clear guidance to help providers effectively integrate PGx testing into dyslipidemia management. By integrating PGx insights into lipid management, clinicians can potentially make informed decisions to enhance patient adherence and outcomes.

Pharmacogenomics can lead to personalized medication choices and dosages for which PGx testing is available, as well as reduce the risk of adverse drug reactions. Statin-associated musculoskeletal symptoms (SAMS) are the leading cause of statin discontinuation.(209) In patients on statins for lipid management, PGx testing can be part of an overall strategy to find more tolerable statin options in patients experiencing SAMS.(213) PGx testing can identify if a patient has genetic variations affecting statin metabolism and may be a useful tool when selecting a statin or statin dose for rechallenge.(214) While all statins are impacted there are statin-specific effects where some statins like simvastatin and atorvastatin are more impacted by SLCO1B1 than others like pravastatin, rosuvastatin, and fluvastatin. Key genetic variants influencing statin metabolism include: SLCO1B1: Variants in this transporter gene can reduce statin uptake into the liver, increasing systemic drug levels and the risk of SAMS;(215) ABCG2: Genetic alterations in this transporter may affect statin clearance, leading to increased drug exposure and potential toxicity;(216) and CYP2C9: This enzyme is involved in the metabolism of certain statins, and genetic variations can influence drug breakdown rates, impacting efficacy and safety.(217) Genetic variations in the ABCG2 transporter most significantly affect the clearance and exposure of rosuvastatin and atorvastatin, with rosuvastatin being the most affected statin for which dosing recommendations are available, and the primary statin metabolized by the CYP2C9 enzyme is Fluvastatin (75%), while rosuvastatin is minimally (<10%) metabolized by it.

C. Implementing Pharmacogenomic Testing in Clinical Practice

Guidelines have been published on the consequences of genetic variations and recommended adjustments in patients experiencing SAMS. (218,219) Although large-scale randomized trials are still needed, emerging observational studies suggest that genotype-guided statin therapy can enhance treatment tolerability and adherence. (220) Given the VA's implementation of PGx testing and growing evidence supporting its use, (221) clinicians should consider the following approaches when managing dyslipidemia:

- Engage in shared decision-making with the patient before ordering PGx testing, explaining the purpose, potential benefits, and limitations of the test. (147)
- Utilize PGx testing for patients who experience SAMS to identify potential genetic contributors. (222)
- Review and discuss PGx results with the patient, highlighting how the findings inform the next trial of statin therapy and setting expectations for benefits and risks. (223)
- Adjust statin selection or dosing based on genetic findings to reduce adverse effects and optimize lipid control. (147,224)
- Refer to established guidelines, such as those provided in the VA clinician guide for PGx testing (206) or the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, (218) for evidence-based recommendations on genotype-driven statin therapy adjustments.

A practical table from the VA clinician's guide for PGx testing is below. (206)

To summarize, PGx has the potential to revolutionize lipid management by enabling personalized statin therapy. As the VA continues to expand PGx testing, providers should incorporate genetic insights into clinical decision-making to enhance patient outcomes. Ongoing research and integration of PGx into routine practice will further refine lipid management strategies, ensuring safer and more effective treatments for Veterans.

Table L-1. Therapeutic Consequences of Variable *SLCO1B1* Function and Recommended Adjustments for Patients Experiencing SAMS

<i>SLCO1B1</i> function	Therapeutic consequence	Recommendation for high-intensity statin therapy [†]	Recommendation for moderate-intensity statin therapy [†]
Increased or normal function	Typical myopathy risk/statin exposure	Prescribe desired starting dose and adjust based on disease-specific guidelines	
Decreased or possible decreased function	<ul style="list-style-type: none"> ↑ Plasma concentrations compared to normal function ↑ Risk of toxicity/SAMS compared to normal function 	Risk of SAMS <ul style="list-style-type: none"> • Lowest: rosuvastatin 20 mg • Moderate: atorvastatin 40 mg, rosuvastatin 40 mg • Highest: atorvastatin 80 mg 	Risk of SAMS <ul style="list-style-type: none"> • Lowest: atorvastatin 10-20 mg, pitavastatin 1 mg, pravastatin 40 mg, rosuvastatin 5-10 mg • Moderate: fluvastatin 80 mg, pitavastatin 2 mg, pravastatin 80 mg • Highest: lovastatin 40-80 mg, pitavastatin 4 mg, simvastatin 20-40 mg
Poor function	<ul style="list-style-type: none"> ↑↑ Plasma concentrations compared to normal/decreased function ↑↑ Risk of toxicity/SAMS compared to normal/decreased function 	Risk of SAMS <ul style="list-style-type: none"> • Lowest: rosuvastatin 20 mg • Highest: atorvastatin 40-80 mg, rosuvastatin 40 mg 	Risk of SAMS <ul style="list-style-type: none"> • Lowest: atorvastatin 10-20 mg, pitavastatin 1 mg, pravastatin 40 mg, rosuvastatin 5-10 mg • Moderate: fluvastatin 80 mg, pravastatin 80 mg • Highest: lovastatin 40-80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg

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See CPIC guidelines (<https://cpicpgx.org/guidelines/>) for recommended dosing for combined *SLCO1B1* and *ABCG2* (rosuvastatin) or *SLCO1B1* and *CYP2C9* (fluvastatin) results or consult your PGx Clinical Pharmacist Practitioner.

[†] High-intensity statin therapy, as defined by the ACC/AHA, is statin therapy with a ≥50% LDL-C-lowering effect. Moderate-intensity statin therapy is defined as statin therapy with a 30-49% LDL-C-lowering effect.

Appendix M: Abbreviation List

Abbreviation	Definition
AA	arachidonic acid
AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACA	atherosclerotic cerebrovascular accident
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACL	ATP citrate lyase
ACS	acute coronary syndrome
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AHRQ-EPCs	AHRQ Evidence-Based Practice Centers
AI	artificial intelligence
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ALT	alanine transaminase
AMI	acute myocardial infarction
Apo	apolipoprotein
ApoB	apolipoprotein B
ARI	absolute risk increase
ASCOT	Anglo-Scandinavian Cardiac Outcomes
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BID	twice per day
BP	blood pressure
CABG	coronary artery bypass grafting
CAC	coronary artery calcium
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK	creatinine kinase
CoA	coenzyme A
CoQ-10	coenzyme Q10
COR	contracting officer's representative
cPCE	calibrated Pooled Cohort Equation
CPG	clinical practice guideline
CRP	c-reactive protein
CT	computed tomography
CTT	Cholesterol Treatment Trialists
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension

Abbreviation	Definition
DHA	docosahexaenoic acid
dL	deciliter
DM	diabetes mellitus
DOD	Department of Defense
EBPWG	Evidence-Based Practice Guideline Work Group
EPA	eicosapentaenoic acid
ESRD	end-stage renal disease
FDA	U.S. Food and Drug Administration
FH	familial hypercholesterolemia
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
FRS	Framingham Risk Score
g	grams
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDI	Human Development Index
HDL-C	high-density lipoprotein cholesterol
HEC	Health Executive Committee
HeFH	heterozygous familial hypercholesterolemia
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia
HOPE-3	Heart Outcomes Prevention Evaluation
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICD-10	International Classification of Diseases, 10th Revision
IOM	Institute of Medicine
IPE	icosapent ethyl
IRT	integrated risk tool
IV	intravenous
IVUS	intravenous ultrasound
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
KQ	key question
LCn3	long-chain omega-3
LDL-C	low-density lipoprotein cholesterol
LDL-R	low-density lipoprotein receptor
LFT	liver function test
LIPA	light-intensity physical activity
Lp(a)	Lipoprotein(a)
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent of task
mg	milligrams
MHS	Military Health System

Abbreviation	Definition
MI	myocardial infarction
MID	minimal important difference
ML	machine learning
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NAM	National Academy of Medicine
NICE	National Institute for Health and Care Excellence
NIRS	near infrared spectroscopy
NNH	number needed to harm
NNT	number needed to treat
NPP	National Pharmacogenomics Program (VA)
NPV	negative predictive value
NRI	net reclassification index
OCT	optical coherence tomography
OR	odds ratio
PAGA	Physical Activity Guidelines for Americans
PAD	peripheral arterial disease
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PGx	pharmacogenomic
PICOTS	population, intervention, comparison, outcome, timing, and setting
PPV	positive predictive value
PREVENT	Predicting Risk of cardiovascular EVENTS
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes
PRS	polygenic risk score
QRISK	QRResearch Indicator for Cardiovascular Risk Algorithm
RCT	randomized controlled trial
SAE	serious adverse events
SAMS	statin-associated muscle symptoms
SAMSON	Self-Assessment Method for Statin Side-effects or Nocebo
SCORE	Systematic Coronary Risk Evaluation
siRNA	small interfering ribonucleic acid
SR	systematic review
SQ	subcutaneous
TC	total cholesterol
TG	triglycerides
TIA	transient ischemic attack
TPA	total carotid plaque area
U.S.	United States
ULN	upper limit of normal range
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VA ESP	Veterans Affairs Evidence Synthesis Program
VARS-CVD	Veterans Affairs Risk Score for Cardiovascular Disease
VHA	Veterans Health Administration
XL	sustained release

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