VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF DYSLIPIDEMIA FOR CARDIOVASCULAR RISK REDUCTION

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They 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 one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical trial 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 clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs nor TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 4.0 – 2020

Prepared by:

The Management of Dyslipidemia for Cardiovascular Risk Reduction Work Group

With support from:

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&
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Version 4.0 – 2020

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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 and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "…on the use of clinical and epidemiological evidence to improve the health of the population…" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.[1] This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with dyslipidemia, thereby leading to improved clinical outcomes.

In 2014, the VA and DoD published a CPG for the Management of Dyslipidemia for Cardiovascular Risk Reduction (2014 VA/DoD Dyslipidemia CPG), which was based on evidence reviewed from January 2010 through February 2014. Since then, a growing body of research has expanded the general knowledge and understanding of dyslipidemia and cardiovascular (CV) risk.

Consequently, a recommendation to update the 2014 VA/DoD Dyslipidemia CPG was initiated in 2019. The system-wide goal of evidence-based guidelines is to improve the patient's health and well-being. To that end, this CPG is intended to guide providers who care for patients with dyslipidemia along management pathways supported by evidence. The expected outcomes of successful implementation of this guideline include:

- Emphasizing the use of patient-centered care using risk factors and event history
- Minimizing preventable complications and morbidity
- Optimizing each individual's health outcomes and improving quality of life
- Assessing the patient's condition and collaborating with the patient, family, and caregivers to determine the optimal treatment

II. Dyslipidemia is Defined by Risk for Cardiovascular Disease

Cardiovascular disease[a] (CVD) is a major cause of morbidity and mortality in the United States (U.S.) and globally.[2,3] Most CVD is caused by atherosclerosis, which is the buildup of plaque (i.e., cholesterol, proteins, calcium, and inflammatory cells) in the walls of arteries. This plaque can narrow the lumen of arteries, limiting the flow of oxygenated blood and increasing the risk of chronic and acute ischemia. If a plaque ruptures within a vital artery, a blood clot forms and may obstruct the flow of oxygenated blood to the heart or brain, resulting in an acute coronary syndrome (ACS), myocardial infarction (MI), or stroke, with potentially irreversible damage to the tissue of the heart or brain.

Control and reduction of CVD risk factors, including high cholesterol levels, 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.

[a] The abbreviation "CVD" will be used throughout this CPG. For the purposes of this guideline, "CVD" includes atherosclerotic cardiovascular disease.

Although serum cholesterol and its components have been well established as independent risk factors for CVD, they contribute only marginally to risk calculators in estimating CVD risk, the principal driver for the management of lipids in the primary prevention of CVD. Aside from familial hypercholesterolemia (FH) and other genetically mediated forms of extreme lipid levels, dyslipidemia has traditionally been defined as one or more of the following: low-density lipoprotein cholesterol (LDL-C) ≥130 milligrams per deciliter (mg/dL), high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, or triglycerides (TGs) ≥200 mg/dL. However, in patients with known CVD or elevated risk for CVD, even "normal" lipids levels warrant intervention for CVD risk reduction.

Treatment of dyslipidemia involves lifestyle changes and lipid-lowering drugs. However, the management of dyslipidemia has shifted away from treating dyslipidemia itself as a discrete entity and moved toward managing dyslipidemia in the context of overall risk for CVD. For this reason, much of our evidence is based on CV risk reduction and does not require lipid levels for inclusion criteria.

This CPG addresses the various treatment and management strategies for managing lipids among patients at risk for CVD morbidity and mortality focusing upon an individual's risk factors and event history.

III. About this Clinical Practice Guideline

This guideline is aimed at efficiently improving dyslipidemia management for CV risk reduction in the VA and DoD. It is intended for use by all VA and DoD healthcare providers.

This CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information available on or before May 16, 2019, and is intended to provide general guidance to the best evidence-based practices (see Appendix A for additional information on the evidence review methodology). While this guideline can assist providers, a CPG's content must always be considered as a recommendation, within the context of a provider's clinical judgment and patient values and preferences. The evolution of medical practice and future scientific research will likely impact these recommendations. After assessing the currently available evidence, the Work Group determined future research topics, which are outlined in applicable discussion sections.

An abbreviated provider summary, patient summary, and pocket card are available at this link: https://www.healthquality.va.gov/guidelines/CD/lipids/.

A. Methods

This document is an update to the 2014 VA/DoD Dyslipidemia CPG. The methodology used in developing the 2020 CPG follows the *Guideline for Guidelines*, a VA and DoD EBPWG document that was updated in January 2019.[4] The *Guideline for Guidelines* can be downloaded from http://www.healthquality.va.gov/policy/index.asp. This document outlines procedures for developing and submitting guidelines, including the identification and assembly of Guideline Champions ("Champions") and other subject matter experts from within the VA and DoD (the "Work Group"). Appendix A provides a detailed description of the guideline development process.

This CPG's Champions and Work Group (see Guideline Work Group) were tasked with developing evidence-based clinical practice recommendations through crafting key questions (KQs) that were the most clinically relevant and important for the management of dyslipidemia. The Champions and Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The scientific evidence published since the 2014 VA/DoD Dyslipidemia CPG informed the new KQs. The Champions assisted in:

- Identifying appropriate disciplines to be included in the Work Group
- Directing and coordinating the Work Group
- Overseeing the guideline development and review processes

The VA Office of Quality and Patient Safety, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the DoD proponent for CPGs, identified three clinical leaders, John R. "Rick" Downs, MD, FACP from the VA and Lt Col Brian Neubauer, MD, MHPE, FACP and COL Patrick G. O'Malley, MD, MPH, FACP from the DoD, as Champions for the 2020 CPG.

The Lewin Team, including The Lewin Group, Anjali Jain Research & Consulting, Duty First Consulting, ECRI, and Sigma Health Consulting, was contracted by the VA and DoD to support the development of this CPG and conduct the systematic evidence review. In January 2019, the contracting officer's representative (COR), leaders from the VA Office of Quality and Patient Safety and the DoD Office of Evidence Based Practice, and the Champions kicked off the guideline development effort. During this teleconference, participants discussed the guideline initiative's scope, the Champions' roles and responsibilities, the project timeline, and the approach for developing and prioritizing specific research questions (i.e., key questions) on which to base a systematic evidence review about the management of patients with dyslipidemia. The specialties and clinical areas of interest included: primary care, cardiology, nursing, clinical pharmacology, internal medicine, family practice, exercise physiology, and dietetics.

The guideline development process for the 2020 CPG update included:

1. Formulating and prioritizing KQs
2. Convening a patient focus group
3. Conducting the systematic evidence review
4. Convening a face-to-face meeting with the CPG Champions and Work Group members to review the evidence, craft evidence-based recommendations, and develop an algorithm
5. Drafting and submitting a final CPG on the management of dyslipidemia to the VA/DoD EBPWG

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses these four domains to assess the strength of each recommendation:[5]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence

- Values and preferences
- 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"). A "Strong" recommendation generally indicates high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar values and preferences, and understood influence of other implications (e.g., resource use, feasibility). If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it generally assigns a "Weak" recommendation. It is important to distinguish GRADE terminology (i.e., "Strong" versus "Weak") from a recommendation's clinical importance. For instance, a "Weak" recommendation indicates the Work Group's assessment of the four domains outlined above. Despite the "Weak" strength supporting the recommendation, it may still be important to the clinical care of a patient with dyslipidemia.

Occasionally, there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure, such as when there is an absence of studies that met evidence review inclusion criteria, or when studies included in the evidence review report had conflicting or inconclusive results.

Using these elements, the strength of each recommendation is presented as part of a continuum:

- Strong for (or "We recommend offering this option …")
- Weak for (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence …")
- Weak against (or "We suggest against offering this option …")
- Strong against (or "We recommend against offering this option …")

The strength of each recommendation can be found in the Recommendations section. For additional information regarding the use of GRADE, see Appendix A.

b. Reconciling 2014 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence, or as scheduled and subject to time-based expirations.[6] For example, the U.S. Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services.[7]

This Work Group developed new and updated recommendations based on the evidence yielded from this CPG's key questions. The Work Group also considered the current applicability of the recommendations

included in the 2014 VA/DoD Dyslipidemia CPG that were not addressed by the KQs in light of evolving practice in today's environment. Accordingly, some of the 2014 VA/DoD Dyslipidemia CPG's recommendations do not appear in this updated CPG.

Recommendation categories were adapted from those used by the National Institute for Health and Care Excellence (NICE).[8,9] These categories and their corresponding definitions were used to account for the ways that older recommendations could have been updated. In short, the categories explain whether the evidence related to a recommendation was systematically reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current care environment and within the scope of the CPG. For additional information regarding these categories and their definitions, see Recommendation Categorization. The 2020 CPG recommendation categories can be found in the Recommendations section. Appendix G outlines the categories for the recommendations carried forward from the 2014 VA/DoD Dyslipidemia CPG.

The Work Group recognized there may be practical reasons for incorporating findings from a previous systematic review (SR), previous recommendations,[10] or recent peer-reviewed publications into an updated CPG. However, because this would not involve an original, comprehensive systematic evidence review, it may introduce bias.

c. Peer Review Process

The CPG was developed through an iterative process (i.e., the Work Group produced multiple drafts). The process for developing the initial draft is detailed in Drafting and Submitting the Final Clinical Practice Guideline.

Once the Champions and Work Group agreed upon a near-final draft of the guideline, the draft was posted for a 14-business-day peer review and comment period. The peer reviewers comprised individuals working within the VA and DoD healthcare systems and experts from relevant outside organizations designated by the Work Group members.

VA and DoD Leadership contacted internal and external peer reviewers to solicit their feedback on the CPG. The Work Group considered all feedback from the peer reviewers. Modifications made throughout the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When developing a CPG, consideration should be given to the values of the patients who are primarily impacted.[11,12] Patients bring perspectives, values, and preferences that often vary from those of providers. Focus groups can help collect qualitative data on the perspectives of patients.

As part of the effort to update this CPG, VA and DoD Leadership held a patient focus group on March 19, 2019, at the Walter Reed National Military Medical Center in Bethesda, MD. The aim of the focus group was to elicit patient perspectives on a set of topics related to their dyslipidemia. The patient focus group comprised a convenience sample of three people. The Work Group acknowledges this sample is not representative of all patients within the VA and DoD healthcare systems and, thus, findings are not generalizable and did not comprise evidence. For more information on the patient focus group and its key concepts, see Appendix E.

C. Conflicts of Interest

The project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 24 months. Verbal affirmations of no COI were further obtained as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., Centers for Medicare & Medicaid Services open payments or ProPublica).

No COIs were identified for the Champions or Work Group. If a project team member had reported a COI (actual or potential), then it would have been reported to the VA and DoD program offices. It would have also been discussed with the Dyslipidemia CPG Champions in tandem with their review of the evidence and development of recommendations. The VA and DoD program offices and the Dyslipidemia CPG Champions would have determined the appropriateness of further action (e.g., restricting participation, removal from the Work Group). If it had been deemed necessary, VA and DoD Leadership and the Champions would have taken action. Disclosure forms are on file with the VA Office of Quality and Patient Safety and available upon request.

D. Scope of this Clinical Practice Guideline

This CPG is designed primarily to assist primary care providers (or other providers as applicable) in managing patients with dyslipidemia for the purpose of CVD risk reduction. This guideline seeks to inform providers with practical evidence-based recommendations for the most common scenarios involving patients at risk for CVD.

a. Populations Included in this Guideline

The patient population of interest for this CPG is patients ≥40 years old and eligible for care in the VA and/or DoD healthcare systems.

b. Populations Excluded from this Guideline

Patients with heart failure with reduced ejection fraction (EF) ≤35%, a limited life expectancy (<5 years), or end-stage renal disease (ESRD) were excluded from most clinical outcome trials. Although some controlled trial data exists exclusively in patients with ESRD and chronic systolic heart failure, the available evidence is comparatively sparse. Additionally, the data that is available show an absence of CV benefit in these populations. A more nuanced review of this evidence can be found on page 10 in the 2014 iteration of the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction under section "Populations Excluded from this Guideline."[13] Our updated systematic evidence review found no new evidence that would alter this position.

Genetic dyslipidemia conditions (e.g., homozygous FH [HoFH], heterozygous FH [HeFH], TGs >500 mg/dL, etc.) were also excluded from the guideline given their uncommon occurrence and sparse clinical trial data. Although younger patients (i.e., <40 years old) are more common in the DoD, this cohort comprises a low short-term risk population that has been excluded from dyslipidemia intervention trials.

Thus, the Work Group was unable to provide evidence-based recommendations for these populations and suggests that providers consider basing treatment decisions for these cohorts on comorbidity, quality of

life, and patient's values and preferences. Such shared and informed decision making should clearly lay out the uncertainty of benefit and known risks associated with pharmacologic treatment.

E. Patient-centered Care

Guideline recommendations are intended to consider a patient's needs and preferences and be patient centered, culturally appropriate, and available to people with limited literacy skills, and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). Regardless of the setting, all patients should be able to access evidence-based care that is appropriate to them. Patient-centered care may decrease patient anxiety, increase trust in providers, and improve treatment adherence.[14-16] Good communication is essential and should be supported by evidence-based information tailored to the patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences. 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.

F. Highlighted Features of this Clinical Practice Guideline

The 2020 edition of the VA/DoD Dyslipidemia CPG is the fourth update to the original CPG. It provides practice recommendations for the management of dyslipidemia.

a. Methodology

Particular strengths of this CPG include adherence to the National Academy of Medicine's (NAM) eight principles of trustworthy guidelines, including the management of COI, interdisciplinary stakeholder involvement, and representation from the broad spectrum of providers engaged in the treatment and management of dyslipidemia.[17] This CPG also uses GRADE methodology, which allows the systematic consideration of factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of the intervention, equity of resource availability, the potential for variation in patient values and preferences, and other considerations (e.g., resource use, subgroup considerations) as appropriate. Applicability of the evidence to VA/DoD populations was also considered. The GRADE methodology allows for explicit recommendations on how primary care providers may improve efficiency in clinic and incorporate patient-centered clinical outcomes. A simple one page algorithm accompanies the guideline and provides an overview of the recommendations in the context of the flow of patient care and to assist with training providers (see the Algorithm section). The algorithm may be used to help facilitate the translation of guideline recommendations into effective practice. Finally, this CPG includes the newest U.S. Food and Drug Administration (FDA) approved dyslipidemia treatments (e.g., bempedoic acid, icosapent ethyl), evaluates use of nutraceuticals and supplements for treatment of dyslipidemia, and has recommendations on practical exercise and the role of cardiac rehabilitation after a CVD event.

b. Treatment Intensity Instead of Lipid Targets

The Work Group carefully considered whether to use target levels for LDL-C but noted that the evidence relating patient-oriented outcomes to LDL-C levels consisted of trial comparisons between therapy intensities. Most often this consisted simply of active treatment versus placebo. Since no study

prospectively evaluated LDL-C goals, the Work Group decided to focus on treatment intensity to match the evidence and simplify point of care decision making.

The Work Group chose to use the common convention of moderate- and high-dose statins. Available statin doses are separated into moderate- and high-dose in Sidebar 3 of the algorithm. The Work Group is using the terms "dose" to represent what has also been called intensity. Both terms appear in the literature.

G. Shared Decision Making

This CPG encourages providers to practice shared decision making. Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now the NAM) report, in 2001.[18] Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or locations of care, especially as differences between risks and benefits become less clear. Providers are encouraged to use shared decision making strategies to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

H. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of 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 for a patient with dyslipidemia. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this guideline. Robust implementation will require wide dissemination through publication in the medical literature, online access, educational programs, and ideally electronic medical record programming in the form of clinical decision support tools at the point of care.

IV. Guideline Work Group

Organization	Name*
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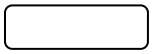
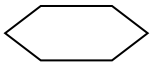
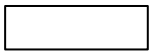
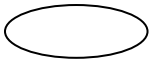
V. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in identifying patients at risk for CVD who are then eligible for management of their dyslipidemia. This algorithm format represents a simplified flow of the management of patients with dyslipidemia and helps foster efficient decision making by providers. It includes:

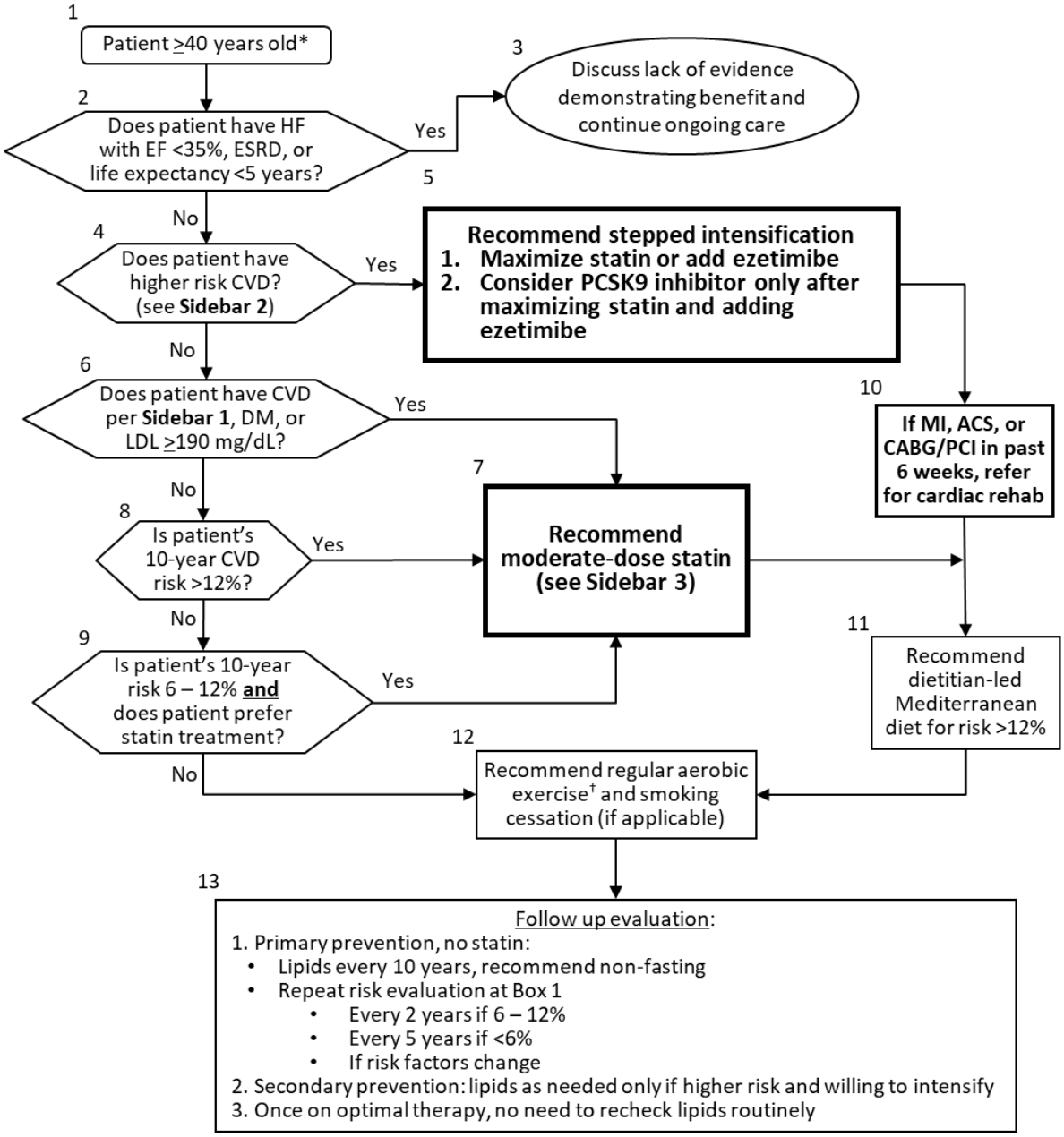
- An ordered sequence of steps of care
- Recommended decision criteria
- Decisions to be considered
- Actions to be taken

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.[19] 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 guideline

Appendix K contains alternative text descriptions of the Algorithm: Management of Dyslipidemia for Cardiovascular Risk Reduction.

Algorithm: Management of Dyslipidemia for Cardiovascular Risk Reduction



* There are no evidence-based recommendations for patients under age 40 because there is no evidence for the benefit of lipid screening and treatment within this age group. In patients younger than 40 years old interested in pursuing lipid testing and management, shared decision making is recommended to discuss the risks and unknown benefit of pharmacotherapy, with therapeutic lifestyle changes being the primary focus of CVD primary prevention.

† Suggest regular aerobic activity of any intensity or duration. Although incremental benefit is associated with increased doses of physical activity, lower doses including leisure time activity (i.e., walking, landscaping, washing dishes) are associated with benefit when compared to mostly sedentary behavior. A provider's considerations when recommending physical activity might include a patient's motivation, functional capacity, and physical activity preferences.

Abbreviations: ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CVD: cardiovascular disease; DM: diabetes mellitus; EF: ejection fraction; ESRD: end-stage renal disease; HF: heart failure; LDL: low-density lipoprotein cholesterol; mg/dL: milligrams per deciliter; MI: myocardial infarction; PCI: percutaneous coronary intervention

Sidebar 1: CVD and Equivalents

- MI or ACS
- CABG/PCI
- Stable CAD (angina or equivalent)
- Atherosclerotic CVA/TIA
- PAD (claudication or AAA)
- Does **not** include asymptomatic incidental finding of potential atherosclerosis (e.g., CAC)

Abbreviations: AAA: abdominal aortic aneurysm; ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAC: coronary artery calcium; CAD: coronary artery disease; CVA: cerebrovascular accident; CVD: cardiovascular disease; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; TIA: transient ischemic attack

Sidebar 2: Higher Risk CVD Patients

- MI or ACS in past 12 months; or
- Recurrent ACS, MI, or CVA; or
- Known CVD (see **Sidebar 1**) and any of the following: currently smoking, DM, PAD, or CABG/PCI

Abbreviations: ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CVA: cerebrovascular accident; CVD: cardiovascular disease; DM: diabetes mellitus; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention

Sidebar 3: Drug Doses

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

- In patients who are intolerant of statins: after washout (e.g., 1 month), re-challenge with same or a different statin or lower dose, and if that fails, a trial of intermittent (nondaily) dosing
- Intensified patient care (e.g., phone calls, emails, patient education, drug regimen simplification) may improve adherence to lipid-lowering medications

‡ Statin doses listed as "moderate" are equivalent to moderate intensity; statin doses listed as "high" are equivalent to high intensity

Abbreviations: BID: twice per day; mg: milligrams; XL: sustained release

VI. Recommendations

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Primary Prevention: Screening and Assessment of Cardiovascular Risk		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
		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
		3.	For cardiovascular risk assessment in primary prevention, we suggest using a 10-year risk calculator.	Weak for	Reviewed, Amended
		4.	We suggest against the routine use of coronary artery calcium testing.	Weak against	Reviewed, Not changed
		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
Pharmacotherapy, Supplements, and Nutraceuticals	*a. Primary Prevention*	6.	For primary prevention, we recommend offering a moderate-dose statin in patients with a ≥12% 10-year cardiovascular risk or low-density lipoprotein cholesterol ≥190 mg/dL or diabetes.	Strong for	Reviewed, New-replaced
		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
		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
		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
		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
	b. Secondary Prevention	11.	For secondary prevention, we recommend using at least a moderate-dose statin.*	Strong for	Reviewed, New-replaced
		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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy, Supplements, and Nutraceuticals (cont.)	*b. Secondary Prevention (cont.)*	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
		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 following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient's values and preferences.	Weak for	Reviewed, New-replaced
	c. Other Medications, Supplements, and Nutraceuticals	15.	For primary or secondary prevention, we recommend against using niacin (i.e., supplements or prescriptions).	Strong against	Reviewed, New-replaced
		16.	For primary or secondary prevention, we suggest against adding fibrates to statins.	Weak against	Reviewed, New-replaced
		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
		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
		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
		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
		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 risks.	Neither for nor against	Reviewed, New-added
	d. Monitoring and Adherence	22.	We suggest against the routine monitoring of lipid levels in patients taking statins.	Weak against	Reviewed, New-replaced
		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
		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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Lifestyle Interventions		25.	For primary and secondary prevention of cardiovascular disease, we suggest a dietitian-led Mediterranean diet.	Weak for	Reviewed, New-replaced
		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
		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

[a] For additional information, see Grading Recommendations.

[b] For additional information, see Recommendation Categorization and Appendix G.

* Statin doses listed as "moderate" are equivalent to moderate intensity; statin doses listed as "high" are equivalent to high intensity

** Higher risk patients include those with (1) MI or ACS in past 12 months; (2) recurrent ACS, MI, or CVA; or (3) established CVD and with additional risk factors (e.g., currently smoking, DM, PAD, or CABG/PCI).

A. Screening and Assessment of Cardiovascular Risk

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)**

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, and diabetes mellitus (DM) to calculate 10-year and lifetime CVD risk. 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 five years. For patients whose 10-year CV risk score is 6 – 12%, it is reasonable to repeat CV risk assessment at earlier time intervals to capture patients who may benefit from the initiation of appropriate statin therapy as a change in age alone may alter CV risk score, thus enhancing the provider-patient CVD primary prevention discussion.

This 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.[20,21] Chamnan et al. (2016) evaluated 12,197 patients for CVD event rates utilizing the Framingham Risk Score (FRS). Prediction of CVD events based on the FRS did not change

significantly between the baseline and second visit (mean: 3.7 years).[20] Angelow et al. (2015) evaluated 1,112 patients by estimating CVD risk utilizing the Systematic Coronary Risk Evaluation (SCORE)-Germany prediction model inputting both a 5- or 10-year old total cholesterol (TC) to predict "high CV risk."[21] 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 five-year intervals is sufficiently accurate for primary CVD prevention.[21]

Cardiovascular disease risk assessment models provide a foundation for shared decision making to review the anticipated benefit of preventative 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, and enhance patient participation at checkups. Given the lack of evidence for improved health outcomes, the harms/burdens of CV risk assessment screenings more than every five years outweigh potential benefits.

As this is a *Reviewed*, *Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[20,21] The Work Group's confidence in the quality of the evidence was low. The main study limitations were high attrition rates, differing patient characteristics between those who drop out and those who remained, and a change in lipoprotein measurement methods in one study. Thus, the Work Group decided upon a "Weak against" recommendation.

There is a paucity of evidence about the optimal timing and frequency for CV risk assessment in specific subgroups of patients (i.e., age-, ethnicity-, and comorbidity-based subgroups). More research is needed to evaluate CV risk assessment in specific subgroups and its effect on critical outcomes such as CV mortality.

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)

Discussion

The frequency that providers obtain lipid profiles in their patients varies widely. A systematic review by Perera et al. (2015) found little within-patient change in annual lipid measurements.[22] Test-to-test variations often do not represent a real change in risk. Studies assessing individual cholesterol levels found variation as high as 18% in three successive TC measurements.[21] Frequent testing of lipid profiles may lead to over-diagnosis and an increased number of patients who receive unnecessary treatment. Evidence suggests annual lipid testing, when compared to testing every three years, results in unnecessary treatment in 7 per every 1,000 patients.[22] It is unclear how frequently testing should be conducted to eliminate false positives and false negatives.[23] For primary prevention, Perera et al. (2015) found the true variation from testing exceeds the random variation from repeated testing (signal-to-noise ratio exceeds 1.0) when testing is spaced by 9 – 10 years.[22] Also, cholesterol is a relatively minor contributor to CV risk scores compared to other patient characteristics, which further supports longer testing intervals. Most of the change in CV risk over time is because of the development or change in risk factors (e.g., DM,

blood pressure, age) rather than changes in lipid levels. Individuals who progressed to a higher CVD category over a 10-year timeframe lacked a significant change in their cholesterol.[21]

In addition to limiting the number of patients inappropriately placed on therapy, less frequent testing can decrease patient anxiety about lipid levels. The Work Group encourages provider and patient education regarding the limited utility and potential harms of frequent lipid screening.

The Work Group recognizes there may be situations where patients and providers wish to repeat testing more frequently. For example, a patient may wish to attempt lifestyle changes before starting statin medication. In this case, the change in lipids may provide the information on which to base shared decision making. The common use of this technique is tempered by the limited effect of lipid levels on risk. Alternatively, it may be useful for the provider to posit an improvement in lipid levels and show the limited effect on risk scores to illustrate the reasons for recommending statins.

As this is a *Reviewed, New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[21-23] The Work Group's confidence in the quality of evidence was low. The body of evidence had some limitations (e.g., poor study designs).[21,22] Major concerns about the frequency of lipid testing included cost, judicious use of healthcare resources, and lack of patient benefit from frequent testing. The risk from more frequent lipid panels (i.e., over-diagnosis) outweighed any potential benefit of refining risk assessment, especially given the minor effect of lipid levels on risk score. The Work Group anticipated large variation in patient values and preferences since some expect and/or desire frequent testing. Thus, the Work Group decided upon a "Weak against" recommendation.

More research is needed on the optimal frequency of lipid testing in primary prevention among individuals not on statin therapy.

Recommendation

3. For cardiovascular risk assessment in primary prevention, we suggest using a 10-year risk calculator.
   (Weak for | Reviewed, Amended)

Discussion

Two systematic reviews and 11 model performance studies evaluated various methods to stratify CV risk for primary prevention patients. The equations included the FRS, Pooled Cohort Equations (PCE), version two of the QRISK® cardiovascular disease risk algorithm (QRISK®2), SCORE, Progetto Cuore Score, and Reynolds Risk Score.[24-27] The Veterans Affairs Risk Score for Cardiovascular Disease (VARS-CVD) is an option to calculate a five-year risk using the fully calibrated version to improve the accuracy of the CVD risk estimation.[28] Although several risk calculators exist, the Work Group does not recommend one over another as comparison studies were not evaluated.[26]

Below are the commonly used risk calculators that providers should consider to calculate the 10-year risk and determine the need for lipid-lowering medication. Providers should consider their patient population characteristics when selecting a risk calculator. However, it should be noted that there is a potential for over- or under-estimation of 22 – 24% of CV risk with each risk calculator, which may result in over- or under-treatment.[26] Since every calculator has limited accuracy, providers will inevitably prescribe

medications for patients who may not benefit from pharmacotherapy and withhold medications from patients who may have otherwise benefited from treatment.[27]

- FRS: a tool used to estimate the 10-year risk of having a CV event (not including stroke)[b]
- PCE: a central tool recommended by the American College of Cardiology/American Heart Association (ACC/AHA) based on a 10-year CVD risk estimation from a pooled cohort equation[c]
- VARS-CVD: a five-year risk score calculator only for the VA population using the information available in the VA Electronic Health Record (EHR)[d]

For more information on CVD risk calculators, see Appendix B. Despite the known imprecision of risk calculators, they help identify patients who may benefit the most from treatment for primary prevention with statin therapy.

In clinical practice, providers commonly use the FRS or the PCE to calculate a 10-year CV risk estimation. Evidence supports the use of the revised or updated PCE for African American men and women and those with a history of DM.[27] The revised PCE has higher accuracy than the FRS for CV risk estimates because it considers race and history of DM, while the FRS does not.

As this is a *Reviewed, Amended* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[24-28] The Work Group's confidence in the quality of the evidence was low because of inconsistency, imprecision, and the unknown applicability of risk calculators other than FRS and PCE in the VA/DoD setting. The benefits of using a 10-year risk calculator likely outweigh the harms because they identify high risk patients better than provider judgment alone. The Work Group recognized that under- and over-estimation of CV risk is a concern and may lead to improper prescribing of lipid-lowering medications. However, patients may prefer awareness of their CV risk to make informed decisions. Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed on comparative effectiveness, particularly in terms of the estimation accuracy, of the various CV risk calculators in selected populations.

Recommendation

4. We suggest against the routine use of coronary artery calcium testing.
   (Weak against | Reviewed, Not changed)

Discussion

Coronary artery calcium (CAC) can supplement a 10-year risk calculator to further refine the risk assessment of CVD and the potential need for treatment. The ideal CV risk assessment would correctly reclassify all intermediate risk individuals into a low or high risk category based on future CVD event rates. Individuals at intermediate CV risk have the greatest potential benefit for any test that improves the

[b] The FRS is available at: https://www.thecalculator.co/health/Framingham-Risk-Score-Calculator-for-Coronary-Heart-Disease-745.html

[c] The PCE is available at: https://clincalc.com/cardiology/ascvd/pooledcohort.aspx

[d] The VARS-CVD is available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5561663/

performance of a 10-year risk calculator. However, there is no prospective evidence that additional risk refinement tools improve patient-centered outcomes.

Lin et al. (2018) demonstrated that the addition of CAC to the FRS improved 10-year CVD event prediction by a very small change in the C statistic (change in area under the curve [AUC]: 0.02, 95% confidence interval [CI]: not reported).[29] This systematic review found similar results when CAC was added to the calibrated Pooled Cohort Equation (cPCE) (change in AUC: 0.02, 95% CI: 0.0 – 0.05).[29]

Yeboah et al. (2016) was the largest of the retrospective studies included in Lin et al. related to the addition of CAC testing.[30] It assessed net reclassification improvement by adding CAC to the cPCE within the pre-existing study data from the Multi-Ethnic Study of Atherosclerosis cohort of over 5,000 subjects.[30] When actual patient events were compared with CAC scoring results, 58 patients were correctly reclassified, and 292 patients were incorrectly reclassified. Assuming a statin relative risk reduction of 25% for major adverse cardiac events (MACE), 15 patients who experienced a future event would benefit, whereas the remaining 335 patients would potentially be subjected to risks of treatment without benefit. The Work Group encourages shared decision making on the risks and benefits surrounding the use of CAC for enhancing CV risk assessment.

Prospective studies of CAC screening do show improvement in the net reclassification index.[29] The use of CAC screening may result in overtreatment and unnecessary radiation exposure. No significant benefit in the incidence of MI, CVD, or overall mortality has been demonstrated with the addition of CAC scoring to a traditional risk score. Even in retrospective studies showing a favorable net reclassification index, many more patients were incorrectly reclassified to a higher risk category than were correctly reclassified.[29]

The risk of radiation exposure from CAC scoring is not negligible. Although not included in our systematic evidence review and, thus, not considered in determining the strength of this recommendation, Kim et al. (2009) estimated a single CAC screening at the age of 40 would result in a lifetime excess cancer risk of 9 per 100,000 for males and 28 per 100,000 for females.[31]

As this is a *Reviewed, Not changed* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[29] The Work Group's confidence in the quality of the evidence was low. Other considerations regarding this recommendation include patient preference in understanding the risk and benefits of CAC. Patient values and preferences vary but often align with a desire for more testing. The Work Group encourages a patient-provider conversation regarding the risk of over-diagnosis, cost, and radiation exposure in relation to a very small potential net benefit associated with CAC testing. Thus, the Work Group decided upon a "Weak against" recommendation.

In the absence of individual patient data, it is unclear which patients will benefit from CAC testing. The Work Group recommends prospective studies designed to assess the benefit of adding CAC to traditional risk scoring systems for the prediction of future atherosclerotic CVD endpoints.

Recommendation

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)**

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, all tend to misestimate (i.e., under- or over-estimate) risk.[26,32] In addition, patients and providers remain interested in improving risk prediction for populations identified as intermediate risk by the currently used models.

The use of non-traditional biomarkers to improve the estimation of CV risk assessment has been extensively studied. Non-traditional biomarkers include genetic, serologic, psychosocial, and physiologic markers (e.g., ankle-brachial index [ABI], electrocardiogram [ECG], apolipoproteins [Apo], high-sensitivity C-reactive protein [hsCRP], physical activity, and socioeconomic status). Numerous biomarkers and other variables were assessed in this review, including ABI, lipoprotein(a), Apo A1, Apo B, CAC score, ECG, fibrinogen, HDL-C, N-terminal-pro hormone brain natriuretic peptide (NT-proBNP), hsCRP, physical activity, socioeconomic status, and Apo C3.[29,33-35]

Several biomarkers have demonstrated slight additive predictive risk (e.g., hsCRP, CAC, and ABI); however, the model performance studies that demonstrate these differences are hampered by low or very low quality evidence. Also, the potential clinical impact is unknown. For example, the addition of ABI to either the FRS or PCE improves model discrimination (change in AUC: -0.006 – 0.112 for FRS, 0.01 for PCE) but does not significantly improve calibration or risk reclassification.[29] The addition of hsCRP to either the FRS or PCE results in minimally improved discrimination (changes in AUC: 0 – 0.027).[29] Other than CAC scoring, none of the other risk markers reviewed demonstrated any additive predictive risk value to traditional risk assessment models. No prospective study has shown that incorporating any additional risk marker into CV risk assessment improves outcomes.[29,33-35]

The only theoretical utility of these tests would be for intermediate risk situations where there is uncertainty about the benefit of treatment. There is no prospective evidence to validate any additional risk score method as a means of clarifying intermediate risk. Incorporating additional risk factors in CV risk assessment should occur in the context of a shared decision making framework with a clear discussion about the uncertainty in how lipid management decisions will be affected by the results.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[26,29,32-35] The Work Group's confidence in the quality of evidence was very low. The body of evidence had several limitations (i.e., short follow-up period, low number of outcome events per variable, and lack of adequate statistical reporting).[29,33] Some variation in patient and provider values and preferences is likely since some individuals prefer as much information as possible when determining CVD risk. Other factors influencing this recommendation included resource use (e.g., staffing, time burden), the limited benefit of additive predictive risk, and potential harms from overtreatment. Thus, the Work Group decided upon a "Weak against" recommendation.

B. Pharmacotherapy, Supplements, and Nutraceuticals

a. Primary Prevention

Recommendation

6. For primary prevention, we recommend offering a moderate-dose statin in patients with a ≥12% 10-year cardiovascular risk or low-density lipoprotein cholesterol ≥190 mg/dL or diabetes.
   (Strong for | Reviewed, New-replaced)

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)

Discussion

Evidence suggests moderate-dose statins lower CV mortality, all-cause mortality, and CV events. The largest systematic review, Yebyo et al. (2019), included 40 primary prevention trials (n=94,283).[36] The summary effect size indicated a 20% relative risk reduction in all-cause mortality over one year (number needed to treat [NNT] = 908), an 11% relative risk reduction in CV mortality over one year (NNT=715), and a 26% relative risk reduction in major CV events over one year (NNT=833). A major limitation was the limited follow-up in many trials. This systematic review included a network meta-analysis that did not find a significant difference between statin drugs.[36]

Although the absolute benefit of statin treatment for primary prevention is limited in the general population, the benefit becomes more substantial as time and risk levels increase. Another systematic review of primary prevention trials, Chou et al. (2016), included 19 studies (n=71,344) of adult patients with increased CVD risk and found the same effect of moderate-dose statins (i.e., reducing all-cause mortality, CV mortality and events) but with greater absolute benefits in patients at baseline higher risk.[37] For CV mortality over the 2 to 6 year treatment period of the trials, the NNT was 233; for all-cause mortality over 1 to 6 years, the NNT was 250; and for fatal and non-fatal MI over 2 to 6 years, the NNT was 123. Dedicated studies [38,39] and subgroup analyses show the benefit of statins for primary prevention does not vary with sex, age, race, baseline lipid levels, presence of DM, CKD, or hypertension.[37]

Determining the cardiac risk cutoff to recommend statin treatment is a simplified strategy to most closely resemble the risk profiles of those included in the trials which demonstrated reduction in CV risk. While no studies used CV risk scores as part of the inclusion criteria, the studied populations had a high prevalence of CV risk factors, and some studies showed an increasing absolute benefit of statins with increased baseline CV risk. The 12% threshold we chose most closely resembles the lower limit of risk of populations in the clinical trials for which the benefits clearly outweighed the risks. The major primary prevention trials showed an event rate between 6 – 7.5%. Since these trials lasted 2 to 6 years (roughly equivalent to 12 – 15% ten-year event rate), the Work Group chose a 12% ten-year risk threshold to match the available data.

There are no clinical trials that specifically address the <6% risk category, which would be represented by a control group event rate of approximately 3%. Using the same methodology, only two trials included patients with risks between 6 – 12%, although these trials did include nearly 30,000 patients.[40-43] The Work Group decided to retain the 12% ten-year CV risk score as a threshold for recommending initiation of

treatment with statins in primary prevention along with shared decision making within the 6 – 12% risk range from the 2014 VA/DoD Dyslipidemia CPG.

The addition of patients with an LDL-C level ≥190 mg/dL is intended to include patients with possible familial hypercholesterolemia. In an analysis of the 20-year follow-up of the West of Scotland primary prevention trial, Vallejo-Vaz et al. (2017) demonstrated that patients with LDL-C levels ≥190 mg/dL treated with moderate-dose statins had significant 20-year reductions in CV mortality (3%) and all-cause mortality (5%), more than double the reductions in the population with lower initial LDL-C levels.[44] Thus, this study provided the first prospective evidence on the long-term benefit of moderate-dose statins. Diabetes is similarly maintained as an indication for statin therapy because a systematic review by de Vries et al. (2012) showed a 3% reduction in CV events in diabetics with moderate-dose statins for primary prevention (NNT=34 over four years).[45]

Moderate-dose Statin Safety

While there are known risks associated with the use of moderate-dose statins, most feel these risks are low and that the benefits of statins outweigh these risks in patients at risk for CVD.[40-42,46] It should be noted, however, that most randomized controlled trials (RCTs) of statins did not systematically assess for adverse events routinely. In a systematic review by Chou et al. (2016) of primary prevention RCTs reporting statin-induced adverse events, there was no increased risk for new-onset DM in patients treated with moderate-dose statins versus placebo (relative risk [RR]: 1.05, 95% CI: 0.91 – 1.2).[37] However, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, used a high-dose statin for primary prevention and reported a higher risk for DM than placebo (RR: 1.05, 95% CI: 1.05 — 1.49).[47]

Another systematic review by Engeda et al. (2019) of statins for primary prevention demonstrated a borderline significant increase in DM risk in 78,039 patients from RCTs (RR: 1.11, 95% CI: 1.00 – 1.22) and a significant increase in DM incidence in nearly four million patients from observational studies (RR: 1.55, 95% CI: 1.39 – 1.74).[48] A systematic review by Macedo et al. (2014) of 90 observational studies of all statin doses for primary and secondary prevention showed a trend towards an increased risk for DM that did not reach significance (odds ratio [OR]: 1.31, 95% CI: 0.99 – 1.73).[49] While statins may increase the risk of DM, the risk has not been demonstrated in RCTs of moderate-dose statins. Observational studies suggest a low risk of DM attributable to moderate-dose statins.

Other adverse effects of statins reported in clinical trials may include muscle-related complaints and elevation of liver transaminases. However, in the Chou et al. (2016) systematic review of primary prevention trials, there was no increase in serious adverse events, cancer or fatal cancer, myalgias or elevation of liver transaminases, or the risk for withdrawal because of adverse events.[37] Although there was no increased risk for rhabdomyolysis or myopathy, some trials reported these adverse events. This meta-analysis included all statin doses.[37]

Macedo et al. (2014) reviewed observational studies of statins and found that statin use was not associated with an increased risk of neurologic or psychological effects, eye disorders, or renal impairment.[49] There was a higher incidence of reported myopathy (OR: 2.63, 95% CI: 1.5 – 4.61) and liver transaminase elevation (OR: 1.54, 95% CI: 1.47 – 1.62) with statins in these trials. The observational

studies evaluated were heterogeneous in type and dose of statin, and the meta-analysis suffered from imprecision of the summary effects.[49]

In a systematic review of primary prevention trials by Yebyo et al. (2019), discontinuation of statins for adverse effects was not different than placebo but there was a higher risk for myopathy, hepatic enzyme elevation, and renal dysfunction with statins.[36] Overall, there may be a risk of liver enzyme elevation and myopathy with statins, which appears inconsistent, even among large reviews. While the package inserts for statins continue to recommend baseline liver function testing (LFT), there is no recommendation for routine testing after initiation.

Duration of Statin Therapy

Any recommendation on the optimal duration of statin use beyond that of clinical trials (i.e., about six years) is unknown. Although many trials have studied the legacy effects of statins after completion of the trials, Nayak et al. (2018) demonstrated that after each trial, the proportion of patients taking statins after trial completion were nearly identical (within 4%) between the previous statin and control populations.[50] Instead of demonstrating the continued benefit of statin use during the trial period, these long-term follow-up studies simply demonstrate the continuing advantage of the initial study period for the treatment group. A systematic review by De Vera et al. (2014) found one cohort study that suggested a significant reduction in MI with two years of continuous statin use versus non-continuous use.[51]

As outlined above in Scope of this Clinical Practice Guideline, the CPG applies to patients aged 40 years or older. The Work Group noted that evidence is limited to this population, which is why risk calculators require a minimum age of 40 years old. The Work Group understands there are conditions to consider for primary prevention treatment at younger ages, such as severely elevated LDL-C levels that may suggest a familial hyperlipidemic condition. These cases are challenging because there is no direct evidence to guide providers. Thus, shared decision making about the uncertain benefit and risks is the only recommended strategy for patients younger than age 40 who are interested in lipid testing and management.

Several observational points can inform this decision but are not sufficient for an evidence-based recommendation. Cardiovascular events and mortality are very low in the under 40 age group, and even observational studies of FH do not suggest treatment is necessary. For example, a French registry of HeFH showed that only 7% had a lifetime history of MI, stroke, or peripheral arterial disease (PAD), which increased to 17% when revascularization was included.[52] Including revascularization, 4% of the registry had a CV event before age 40.[52] A Spanish registry showed that of the 15% of HeFH patients with CV event history, only 1.3% were age 40 or under when they had their first event.[53]

While statin therapy is reasonable for patients under age 40, there are no randomized primary prevention trials to demonstrate or quantify benefit. The evidence of the risks of non-continuous statin treatment (see Recommendation 23) suggests the decision to start therapy should be considered lifelong. Because this is a personal decision, shared decision making is even more essential in the absence of direct evidence.

Despite the consistent evidence supporting the use of statins for primary CV event prevention, the NNT is large overall and increases for patients at lower risk. Informing patients of the risks of moderate-dose statins, where the DM risk is questionable and other risks have not been consistently demonstrated in

trials, may be helpful in shared decision making. The low cost of generic statins and convenience of oral daily dosing further support their use.

As these are *Reviewed*, *New-replaced* recommendations, the Work Group systematically reviewed evidence related to this recommendation [36-39,44,48-51] and considered the evidence put forth in the 2014 CPG.[40,42,45,47] The Work Group's confidence in the quality of the evidence for both recommendations was moderate. The body of evidence was primarily limited by study populations with wide variability in CV risk and varied inclusion criteria, leading to the retention of the 12% threshold and 6 – 12% risk range from the 2014 VA/DoD Dyslipidemia CPG. Given the consistent evidence of improvement in CV and all-cause mortality and reduction in MACE with limited harms, the Work Group determined that the benefits of moderate-dose statins outweighed the harms of treatment, but with an absolute improvement that varies based on baseline risk. Thus, the Work Group decided upon a "Strong for" recommendation for Recommendation 6 and a "Weak for" for Recommendation 7.

While the benefits of statins for primary prevention are well proven for higher risk populations (i.e., >12% 10-year risk), determining the risk reduction in lower risk populations is an important research priority.

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)

Discussion

Despite consistent evidence supporting the use of statins for CVD, this CPG's systematic evidence review found no evidence that high-dose statins offer additional benefit over moderate-dose statins in the prevention of CV events or mortality for primary prevention.[36,37] The only major trial that evaluated a high-dose statin for primary prevention was the JUPITER trial, which compared rosuvastatin 20 mg daily to placebo.[47] The JUPITER trial showed comparable changes in patient-centered outcomes to other statins in primary prevention trials.[37] The ASTRONOMER and METEOR trials also included high-dose statins but were much smaller than JUPITER. There are no studies that directly compare high-dose to moderate-dose statins in a primary prevention population.

High-dose Statin Safety

Studies of both primary and secondary prevention suggest that higher statin doses increase the adverse event risk. The most common adverse events of statins are elevated liver enzymes without reports of liver failure and muscle symptoms with rare reports of rhabdomyolysis. A meta-analysis by Silva et al. (2007) showed high-dose simvastatin and atorvastatin are associated with more adverse events (OR: 1.44, 95% CI: 1.33 – 1.55) and more discontinuation due to adverse events (OR: 1.28, 95% CI: 1.18 – 1.39) than lower dosed statins.[54] Moreover, it showed more LFT and creatine kinase (CK) abnormalities in the higher dose group. A meta-analysis of 17 RCTs limited to high-dose atorvastatin, Li et al. (2016), showed a higher risk for liver transaminase elevation (RR: 4.59, 95% CI: 3.26 – 6.48) and discontinuation due to adverse events (RR: 1.29, 95% CI: 1.17 – 1.42) versus placebo or lower dose atorvastatin but no increases in CK, myalgia, or rhabdomyolysis.[55] Although a previous analysis by the Cholesterol Treatment Trialists (CTT) showed that

high-dose statins slightly increase the risk of rhabdomyolysis, this increase was limited to simvastatin at 80 mg daily, which is no longer recommended by the FDA.[56]

A meta-analysis by Engeda et al. (2019) shows that high-dose statins increase the risk of DM compared to placebo with a number needed to harm (NNH) of 208 over four years with no increased risk with lower statin doses.[48] In the JUPITER trial, the NNH for DM was nearly identical to the NNT to reduce all-cause mortality.[47] A meta-analysis by Wang et al. (2017) showed an increase in incident DM with any statin (OR: 1.11, 95% CI: 1.03 – 1.2) with high-dose statins conferring more risk (OR: 1.18, 95% CI: 1.10 – 1.28, NNH=130 over four years).[57] These findings are also supported by a meta-analysis, Preiss et al. (2011), that demonstrated more new-onset DM associated with high statin doses versus lower doses (OR: 1.12, 95% CI: 1.04 – 1.22, NNH=498 over five years).[58]

The effect of high-dose statins on the risk for intracerebral hemorrhage (ICH) is uncertain. While a meta-analysis of seven RCTs by Pandit et al. (2016) showed increased ICH with high-dose statins versus placebo, studies comparing different statin doses were specifically excluded.[59] The results are contradicted by a more comprehensive meta-analysis by McKinney et al. (2012), which did not show an increased risk of ICH (OR: 1.08, 95% CI: 0.88 – 1.32).[60] McKinney et al. (2012) was not included in this CPG's systematic evidence review and, thus, did not impact the strength of this recommendation.

A meta-analysis by Sun et al. (2015) suggested high-dose statins do not increase the risk of cancer.[61] Although not included in our systematic evidence review, a meta-analysis of 27 randomized trials from the CTT Collaborators, Emberson et al. (2012), also showed no increased risk of cancer or cancer mortality.[62]

Summary

The lack of evidence for increased benefit with high-dose statins in primary prevention populations led the Work Group to recommend against increasing statin intensity in primary prevention. Despite the low overall risks of higher statin doses, increased adverse events could lead to more statin discontinuation.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation [36,37,48,55,57,59,61,63] and considered the evidence put forth in the 2014 CPG.[47,56,58] The Work Group did not find direct comparisons of the benefit of high-dose statins compared with moderate-dose statins in a primary prevention population. The literature comparing high- and moderate-dose statins for secondary prevention suggests the increased harms of higher dose statins. Given the lack of evidence of added benefit with higher dose statins, the Work Group determined the increased risks outweigh unproven benefits, although patient preferences may vary significantly on this decision. Thus, the Work Group decided on a "Weak against" recommendation.

More research is needed on the effectiveness of high-dose statins for primary prevention in comparison to moderate-dose statins. This research should consist of direct comparisons between moderate- and high-dose statins in similar populations. These populations should be stratified by CV risk scoring.

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)

Discussion

This CPG's systematic evidence review yielded insufficient evidence related to ezetimibe monotherapy for primary prevention. There was one relevant meta-analysis of 13 trials from the 2014 VA/DoD Dyslipidemia CPG systematic evidence review and a single subsequent trial not included in the meta-analysis.[64,65] All of this evidence compared the addition of ezetimibe to statins with increasing the statin dose in primary prevention patients. Outcomes were limited to patient safety and surrogate outcome measures (e.g., LDL-C lowering).

The Study of Heart and Renal Protection (SHARP) by Baigent et al. (2011) was not included in either the current or previous systematic evidence review and, thus, was not considered in determining the strength of this recommendation.[66] This study evaluated ezetimibe for primary prevention by comparing an ezetimibe-simvastatin combination to placebo in patients with CKD. It found significant reductions in the primary composite outcome of major atherosclerotic events (e.g., non-fatal MI, coronary death, non-hemorrhagic stroke, and any arterial revascularization) in favor of the combination versus placebo (RR: 0.83, 95% CI: 0.74 – 0.94, NNT=48). However, the effect of ezetimibe on clinical outcomes could not be separated from that of statins. Thus, the benefit of ezetimibe alone could not be determined.

The adverse effects of ezetimibe appear to be less than those associated with statins. The systematic review by Mikhailidis et al. (2011) that compared the combination of ezetimibe and a statin to increasing statin doses found that adverse effects were similar in the ezetimibe-statin combination group and the increased statin dose group.[65] However, the included trials were less than four months in length and reviewed outcomes that are neither patient centered nor within the scope of this guideline. In a separate trial evaluating ezetimibe in secondary prevention, Cannon et al. (2015), adverse events were significantly less with ezetimibe-statin combinations than high-dose statins.[67]

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[64] The systematic evidence review did not identify evidence in primary prevention populations for reducing CV events with ezetimibe monotherapy. With the strong evidence for the efficacy of statins for improving outcomes, providers should use statins whenever feasible. The evidence for ezetimibe in primary prevention is limited to surrogate outcomes, and even these are only available in combination with statins. Based on the lack of evidence for ezetimibe's effect on CV risk in primary prevention, either alone or in combination with statins, the Work Group decided upon a "Neither for nor against" recommendation.

This recommendation highlights the research deficits for the use of ezetimibe for primary prevention. Since providers often consider the use of ezetimibe in patients who cannot tolerate statins, the lack of evidence for ezetimibe as monotherapy for primary prevention is a significant knowledge gap. Despite the lack of evidence for significant harm from statins, press coverage is replete with articles suggesting safety concerns with statins. This negative coverage contributes to patient apprehension toward statins, which

was noted by patient focus group participants. If benefit with ezetimibe monotherapy in primary prevention could be proven, providers would have more options.

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)

Discussion

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been studied primarily for secondary prevention of CV events, but trials have included some primary prevention patients. A systematic review by Du et al. (2019) included 10,225 primary prevention patients from studies involving PCSK9 inhibitors with and without statins and failed to demonstrate significant improvements in CV events or mortality.[68] In fact, no important CV outcome showed significant improvement from PCSK9 inhibitors when used for primary prevention. The authors of this review reported they did not have individual trial data, so they could not separate trials that combined primary and secondary prevention.

The FDA approved PCSK9 inhibitors for primary prevention in FH based solely on the effect of lipid parameters in this population. None of the studies were designed to measure CV outcomes. The ODYSSEY LONG TERM trial did perform a post hoc analysis of a combination of secondary prevention and FH patients that showed benefit but did not separate the primary and secondary prevention populations.[69] Because the systematic review of primary prevention patients showed no benefit in any outcome, the Work Group has no basis to recommend PCSK9 inhibitors in any primary prevention population. The high cost of these therapies and unknown long-term safety led the Work Group to recommend against this therapy until a patient-oriented outcome benefit is demonstrated.

Although primary and secondary prevention studies show the short-term adverse effects of PCSK9 inhibitors are limited, the side effects beyond three years are unknown. The most common adverse event is injection site reactions, which occur at a higher rate compared to placebo. However, Schmidt et al. (2017) demonstrated a significant increase in the risk of adverse events, mainly myalgia and influenza, with PCSK9 inhibitors compared to placebo.[70] The primary limitation of studies exploring the safety of PCSK9 inhibitors for primary prevention is their limited follow-up. Unlike the evidence evaluating the effects of statins, which include trials with longer term safety outcomes in secondary prevention, the PCSK9 literature is limited to safety outcomes of up to three years. The possibility of long-term reactions, adverse events, or consequences of prolonged levels of very low LDL-C with these agents are unknown.

PCSK9 inhibitors are extremely expensive and of questionable cost-effectiveness, even in populations where there is evidence of efficacy such as secondary prevention. A systematic review by Korman et al. (2018) included two cost-effectiveness analyses and – even in secondary prevention – found that PCSK9 inhibitors did not meet a willingness to pay (WTP) threshold of $100,000 per additional quality-adjusted life year (QALY).[71] This was reinforced by a later cost-effectiveness analysis by Kazi et al. (2019).[72] Because the evidence of benefit is lacking, the use of PCSK9 inhibitors in primary prevention cannot be justified, especially given the high current cost of these medications.

Despite the dearth of evidence for primary prevention with PCSK9 inhibitors, there is heavy industry marketing and enthusiasm surrounding new therapies, which may influence some patients and providers to consider its use. We therefore felt it was important to make a clear statement against its use until there is more evidence about its risks and benefits.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[68,70-72] The Work Group's confidence in the quality of the evidence was low. The evidence's key limitation was the short duration of follow-up. Indeed, all but one study had a follow-up of fewer than two years. Per GRADE methodology, though, the Work Group determined a "Strong against" recommendation was warranted based on the lack of evidence for reducing CV risk, the unknown long-term adverse event/safety profile in a primary prevention population, and the treatment's prohibitive cost. Thus, the Work Group decided upon a "Strong against" recommendation.

More research on the safety and effectiveness of PCSK9 inhibitors, specifically in the primary prevention populations, is needed. Similar to our recommendations for other primary prevention trials, these studies should use CV risk scores to select patients for treatment. These studies need to be larger and have longer follow-up periods given the lower baseline absolute CVD risk than the secondary prevention trials conducted to date, which will also allow the subgroup analysis that has been performed with statins.

b. Secondary Prevention

Recommendation

11. For secondary prevention, we recommend using at least a moderate-dose statin.
    (Strong for | Reviewed, New-replaced)

Discussion

Secondary prevention is intended to prevent subsequent CVD events in patients with an established clinical diagnosis of CVD. This includes patients with ACS, MI, coronary arteries bypass graft (CABG), percutaneous coronary interventions (PCI), stable obstructive coronary artery disease (CAD) including angina and equivalents, cerebrovascular accident (CVA)/stroke, transient ischemic attack (TIA), and atherosclerotic PAD including claudication or abdominal aortic aneurysm (AAA). Secondary prevention does not include patients with asymptomatic arteriosclerosis, as detected by incidentally reported or measurements of CAC, exercise test, intima-media thickness ultrasound measurement, ABI, or brachial reactivity because there is little evidence on how to best manage the detection of subclinical atherosclerosis. These entities were not specified within the inclusion criteria of clinical trials and the management of subclinical atherosclerosis is beyond the scope of this CPG. The Work Group conceded that revascularizations were not a clear outcome because the indications for these interventions are not well defined, may have regional variation, and their impact on mortality or other important outcomes (e.g., congestive heart failure [CHF]) is uncertain.

This recommendation is supported by three meta-analyses by the CTT Collaborators.[56,73,74] From the CTT meta-analyses, statin use led to a reduction in all-cause mortality, non-fatal MI, coronary death, and non-fatal stroke when compared to placebo control. The trials included in the meta-analyses used primarily fixed, moderate-dose statins (dosing that reduced LDL-C by 30 – 40% from baseline, including simvastatin 20 – 40 mg, pravastatin 40 mg, lovastatin 20 – 80 mg, atorvastatin 10 mg).[56,73,74]

Moderate-dose Statin Safety

There are known, limited harms associated with moderate-dose statins but the benefits of moderate-dose statins for both primary and secondary prevention significantly outweigh the risks.[46] A systematic review and meta-analysis of 90 observational studies in both primary and secondary prevention populations, Macedo et al. (2014), examined the adverse effects of statins and found statin use was not associated with an increased risk of neurologic or psychological effects, eye disorders, or renal impairment in the general population.[49] There was a higher incidence of reported myopathy (OR: 2.63, 95% CI: 1.5 – 4.61), liver transaminase elevation (OR: 1.54, 95% CI: 1.47 – 1.62), and a trend for DM (OR: 1.31, 95% CI: 0.99 – 1.73). The studies were observational in design and heterogeneous, and the meta-analysis suffered from imprecision of the summary effects. Additionally, dose range or mean statin dose was not reported.[49]

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation [49] and considered the evidence put forth in the 2014 CPG.[56,74] The Work Group's confidence in the quality of the evidence was moderate. Although some variation in patient and provider values and preferences is likely, the evidence base clearly demonstrated that the risks/harms were outweighed by the potential benefits (e.g., improved mortality, MI and stroke reduction). Thus, the Work Group decided upon a "Strong for" recommendation.

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)

Discussion

It is understood that the baseline risk for new CVD events is higher in patients treated for secondary prevention than patients treated for primary prevention. However, evidence suggests there are subgroups of patients with established CVD with features or risk factors that further increase their risk for future events. These subgroups include patients with (1) MI or ACS in past 12 months; (2) recurrent ACS, MI, or CVA; or (3) established CVD and with additional risk factors (e.g., currently smoking, DM, PAD, or CABG/PCI). These patients are more likely to benefit from intensified treatment (e.g., maximum dose statins, the addition of ezetimibe to statins, and then the addition of PCSK9 inhibitor to statins plus ezetimibe) to reduce their CV risk. Although there are no prospective studies comparing these higher risk groups to lower risk groups for secondary prevention, subgroup and post hoc analyses demonstrate a greater risk for CVD events in these patients who may benefit from more aggressive treatment.[75,76]

The meta-analysis by de Vries et al. (2014) compared the incidence of major CV and cerebrovascular events between standard-dose statins and placebo (n=4,351) and standard-dose statins with intensive-dose statins (n=4,805) for secondary prevention in patients with DM.[77] There was a statistically significant reduction in major CV and cerebrovascular events in favor of the more intensive statin dose group versus standard dose (RR: 0.91, 95% CI: 0.84 – 0.98).

Another meta-analysis, Koskinas et al. (2018), compared more intensive lipid-lowering therapy (n=76,678) to less intensive therapy.[78] It evaluated 19 clinical trials (n=75,829) conducted primarily in secondary

prevention populations. Of the 15 statin trials, six compared a higher dose statin to a lower or moderate-dose statin. The primary outcome was a composite of major vascular events (e.g., CV death, MI or other ACS, coronary revascularization, and stroke). The high-dose statin therapy reduced events compared to less intensive statin therapy (RR: 0.88, 95% CI: 0.82 – 0.93).

A meta-analysis included in the 2014 VA/DoD Dyslipidemia CPG's systematic evidence review, Preiss et al. (2011), analyzed five studies of moderate- versus high-dose statins.[58] Although its primary objective was to determine the risk for incident DM with high- versus moderate-dose statins, the authors also reported composite CV events, including all-cause mortality, CV death, non-fatal MI, non-fatal stroke and coronary revascularization. Cardiovascular events occurred less often in the high-dose statin group (OR: 0.84, 95% CI: 0.75 – 0.94, NNT=155), resulting in 6.5 fewer CVD events per 1,000 patient-years treated in the high-dose group over a mean follow-up period of 4.9 years. Of the individual CV events, only non-fatal MI (OR: 0.87, 95% CI: 0.79 – 0.95, NNT=58) and coronary revascularization (OR: 0.8, 95% CI: 0.71 – 0.90, NNT=17) were statistically different. The CTT meta-analysis by Baigent et al. (2010) analyzed five trials comparing a high- to moderate-dose statin and demonstrated a statistically significant reduction in any major vascular event (non-fatal MI, coronary heart disease [CHD] death, coronary revascularization, stroke) in favor of the higher dose (unweighted RR: 0.85, 95% CI: 0.82 – 0.89, NNT=125) versus the moderate statin dose.[56]

In these meta-analyses, there was no statistically significant difference in CV or all-cause mortality when comparing high-dose statins to lower dose statins.[56,77,78] The incremental benefit was only statistically significant for a reduction in non-fatal events (e.g., MI, stroke, and revascularization).

High-dose Statin Safety

Studies of both primary and secondary prevention suggest that higher statin doses increase the risk for statin-related adverse events. The most commonly reported adverse events of statins in RCTs are elevated liver enzymes without reports of liver failure and muscle symptoms with rare cases of rhabdomyolysis. A meta-analysis by Silva et al. (2007), which was not identified in the 2014 or 2019 systematic evidence review, showed that high-dose simvastatin and atorvastatin were associated with more adverse events (OR: 1.44, 95% CI: 1.33 – 1.55) and more discontinuation due to adverse events (OR: 1.28, 95% CI: 1.18 – 1.39) than lower dose statins.[54] These interventions were also associated with statistically more LFT and CK abnormalities.

A meta-analysis of 17 RCTs limited to high-dose atorvastatin, Li et al. (2016), showed a higher risk for liver transaminase elevation (RR: 4.59, 95% CI: 3.26 – 6.48) and discontinuation due to adverse events (RR: 1.29, 95% CI: 1.17 – 1.42) versus placebo or lower dose atorvastatin but no significant increase in CK, myalgia, or rhabdomyolysis.[55] Although a previous analysis by the CTT showed that high-dose statins slightly increase the risk of rhabdomyolysis, this increase was limited to simvastatin a dose of 80 mg daily, which is no longer recommended by the FDA.[56]

Diabetes Mellitus

A meta-analysis by Wang et al. (2017) showed an increase in incident DM with any statin (OR: 1.11, 95% CI: 1.03 – 1.2), with high-dose statins conferring more risk (OR: 1.18, 95% CI: 1.10 – 1.28, NNH=130 over four years).[57] Another meta-analysis, Khan et al. (2019), analyzed the association of reducing LDL-C with lipid-lowering drugs and the risk for DM.[79] It included 33 RCTs (n=21 statins, n=12 PCSK9 inhibitors) that

compared more intensive therapy (n=83,123) to less intensive therapy (n=80,565). More intensive therapy was associated with a higher risk for new-onset DM versus less intensive regimens (RR: 1.07, 95% CI: 1.03 – 1.11, p <0.001, no heterogeneity). The increased risk was largely due to a higher rate of new cases of DM with statins (RR: 1.10, 95% CI: 1.05 – 1.15).

A meta-analysis by Preiss et al. (2011) also demonstrated more new-onset DM with high statin doses versus lower doses (OR: 1.12, 95% CI: 1.04 – 1.22, NNH=498 over five years).[58] However, the reduction in CV events with high-dose statins was greater (OR: 0.84, 95% CI: 0.75 – 0.94, NNT=155) than the risk for new-onset DM (OR: 1.12, 95% CI: 1.04 – 1.22, NNH=498 over five years).

Intracranial Hemorrhage

The effect of high-dose statins on the risk for ICH is uncertain. While a meta-analysis of seven RCTs, Pandit et al. (2016), showed increased ICH with high-dose statins versus control, relevant studies comparing different statin doses were excluded.[59] These findings are contradicted by a more comprehensive meta-analysis by McKinney et al. (2012), which did not show an increased risk of ICH (OR: 1.08, 95% CI: 0.88 – 1.32) regardless of the percent reduction in LDL-C or level of LDL-C achieved.[60]

Cancer

A meta-analysis by Sun et al. (2015) suggests high-dose statins do not increase the risk of cancer.[61] Although not included in our systematic evidence review, a meta-analysis of 27 randomized trials from the CTT Collaborators also showed no increased risk of cancer or cancer mortality.[62]

Summary

Patients should be provided an opportunity for a shared, informed decision regarding the harms and benefits of statin therapy; therefore, treatment should be individualized based on CV risk. Use of high-dose statins is associated with a reduction in non-fatal CVD events without demonstrated improvement in mortality, which should be balanced with an increased risk for some adverse events and a higher rate of discontinuation due to adverse events compared to use of moderate statin doses.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation [55,57,59,61,75-79] and considered the evidence put forth in the 2014 CPG.[56,58] The Work Group's confidence in the quality of the evidence was moderate. The Work Group determined the benefits, a reduction in non-fatal CV events and no improved mortality, outweighed the increase in harms, including the risk for new-onset DM. Variation in patient and provider values and preferences is likely since the risk/benefit ratio is not as favorable for high-dose versus moderate-dose statins. Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed to identify the most effective, safe approach for lowering risk for recurrent CVD events, including a comparison between maximizing statin doses and other interventions for secondary prevention. Risk stratification should be prospectively evaluated to identify patients at sufficiently high risk who would most benefit from more aggressive lipid-modifying treatment (e.g., assigning higher weight to risks like DM and PAD versus advanced age or renal impairment).

Recommendation

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)

Discussion

The addition of ezetimibe to moderate-dose statins in higher risk patients for secondary prevention of CV events is supported by two fair quality meta-analyses by Hong et al. (2018) [80] and Zhan et al. (2018) [81] and two fair quality studies of CV risk stratification and benefit of adding ezetimibe to statins using data from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[75,76]

Hong et al. (2018) included seven trials (n=28,191 [7,298 with DM]) comparing a statin plus ezetimibe versus a statin alone or placebo and stratified by the presence of DM.[80] The addition of ezetimibe to statins in patients with DM was associated with a greater reduction in CV events compared to those without DM (pooled RR: 0.84, 95% CI: 0.77 – 0.91 versus pooled RR: 0.93, 95% CI: 0.85 – 1.02, respectively). Zhan et al. (2018) found that ezetimibe added to statins reduced CV event risk versus a statin alone (RR: 0.94, 95% CI: 0.9 – 0.98).[81] Neither analysis showed a change in CV or all-cause mortality.

Two secondary analyses suggest the benefit of ezetimibe is greater in high-risk patients for secondary prevention.[75,76] In Bohula et al. (2017), the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS) Tool was applied to data from IMPROVE-IT to predict which patients may benefit most from the addition of ezetimibe to statins.[75] The TIMI TRS is a nine-point risk stratification tool developed from a large population of patients with atherothrombosis to predict CV death, MI, and ischemic stroke. The nine risk indicators include: CHF, hypertension, aged 75 years and older, DM, prior stroke, prior CABG, PAD, estimated glomerular filtration rate <60 mL/min, and smoking. Based upon number of risk indicators, 45% of patients (n=8,032) were low risk, 30% (n=5,292) were intermediate risk, and 25% (n=4,393) were high risk.

Using the risk prediction tool, patients at high risk (≥3 risk indicators) had a statistically lower incidence of the composite endpoint of CV death, MI, or ischemic stroke in the simvastatin 40 mg plus ezetimibe group versus simvastatin 40 mg alone (33.9% versus 40.2%, respectively, hazard ratio [HR]: 0.81, 95% CI: 0.73 – 0.9, NNT=16) and individual components of the primary endpoint.[75] Patients at intermediate risk (i.e., two risk indicators) and low risk (i.e., 0 – 1 risk indicator) did not show a statistically significant benefit of combination treatment versus statins alone over a period of seven years in IMPROVE-IT.[75]

In another analysis of IMPROVE-IT, Giugliano et al. (2018), examined outcomes based upon the presence of DM.[76] Patients with DM were generally older and women. There were 4,933 patients with DM in IMPROVE-IT, representing 27% of the intervention and control group. In patients with DM, statin plus ezetimibe reduced the seven-year Kaplan-Meier (KM) event rate in the composite endpoint more than statins alone (HR: 0.85, 95% CI: 0.78 – 0.94, NNT=18). In patients without DM, the absolute difference in the primary composite outcome was 0.7% and not statistically different over a seven-year period (HR: 0.98, 95% CI: 0.91 – 1.04). When the authors applied the TRS tool, all patients with DM had a statistically

significant benefit regardless of risk. However, in patients without DM and determined to be at low to intermediate risk based upon the TRS tool, no benefit was observed with combination therapy. There were no differences in CV or all-cause mortality regardless of CV risk.[76]

Safety

The addition of ezetimibe to statins is not associated with a greater risk for hepatic toxicity, cancer, or gallbladder-related conditions, but it is unclear if the risk of myopathy or rhabdomyolysis is increased because of imprecision in the data and low event rates.[76,81]

Summary

The addition of ezetimibe to statins (e.g., simvastatin) reduces CV event endpoints without changing mortality, similar to maximizing the statin dose.[75,76,80,81] The greatest reduction in CV events occurred in patients with DM or in those with three or more risk factors. There is no evidence for an increased risk of cancer, hepatotoxicity, or gallbladder-related diagnoses with the addition of ezetimibe to statins, but the effect on muscle-related complaints is less clear.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[75,76,80,81] The Work Group's confidence in the quality of the evidence was moderate. Based on secondary analyses of the available evidence, the Work Group determined the benefit of adding ezetimibe to statins in patients with DM or in those at higher risk outweighed the risk of harms. Some variation in patient and provider preferences is likely but because of the reduction in non-fatal events, limited harms, ease of use, and generic availability, the Work Group decided upon a "Weak for" recommendation.

More research is needed to identify the most effective, safe approach for lowering risk for recurrent CVD events including a comparison between maximizing statin doses and adding ezetimibe to moderate- and high-dose statins for secondary prevention. Risk stratification should be prospectively evaluated to identify patients at sufficiently high risk who would most benefit from more aggressive lipid-modifying treatment (e.g., assigning higher weight to risks like DM and PAD versus advanced age or renal impairment).

Recommendation

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 following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient's values and preferences.
    (Weak for | Reviewed, New-replaced)

Discussion

In the systematic review of eight trials by Schmidt et al. (2017), PCSK9 inhibitors reduced the risk of CVD events in high-risk patients (OR: 0.86, 95% CI: 0.8 – 0.92) without effecting CV or all-cause mortality. Control treatments varied, including placebo and a statin with or without ezetimibe.[70] The more recent systematic review by Du et al. (2019) found that PCSK9 inhibitors reduced the risk of CV events (RR: 0.84, 95% CI: 0.79 – 0.89), non-fatal MI (RR: 0.83, 95% CI: 0.74 – 0.93), and any type of stroke (RR: 0.75, 95% CI: 0.65 – 0.85), with no effect on mortality.[68]

Short-term (<3 years) safety data for PCSK9 inhibitors suggest no increased risk for new-onset DM,[79,82] no effect on neurocognitive function,[83] and no difference in serious adverse events. The only significant treatment-emergent adverse effect was injection site reactions, which were statistically higher for evolocumab and alirocumab versus control.[82,84,85] The long-term safety of these agents and the effect of prolonged levels of very low LDL-C is unknown. Thus, additional research is needed.

In higher risk patients, there are several approaches that have been proven to reduce non-fatal CVD events compared to moderate-dose statins (see Table 1). However, there is no direct evidence to support the superiority of a single approach for intensification of lipid-lowering therapy between:

a) maximizing statin dose;

b) adding ezetimibe to moderate- or high-dose statin (in patients already on high-dose statins); or

c) adding PCSK9 inhibitors to maximum-dose statin with or without ezetimibe

Table 1. Evidence on Reducing Recurrent CVD Events with Moderate- or High-dose Statins

Clinical Trial	Intervention/Population (Maximize Statin or Add Non-statin)	Results for Primary Composite Endpoint
Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) [86]	Alirocumab added to maximum-dose statin in patients 1 – 12 months after ACS	9.5% versus 11.1% RRR: 15%, NNT=62.6 over 2.8 years
Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) [87]	Evolocumab added to maximum-dose statins with or without ezetimibe in patients with clinically evident ASCVD and one major risk factor or two minor risk factors	9.8% versus 11.3% RRR: 15%, NNT=74 over 2.2 years
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [67]	Ezetimibe added to moderate-dose statins in patients after ACS	32.7% versus 34.7% RRR: 6%, NNT=50 over 6 years
The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22) [88]	Moderate-dose (pravastatin 40 mg) versus high-dose (atorvastatin 80 mg) statin in patients with ACS	22.4% versus 26.3% RRR: 16%, NNT=26 over 24 months
Treating to New Targets (TNT) [89]	Moderate-dose (10 mg) versus high-dose (atorvastatin 80 mg) in patients with stable CAD	8.7% versus 10.9% RRR: 22%, NNT=45 over 4.9 years

Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; mg: milligrams; NNT: number needed to treat; PCSK9: proprotein convertase subtilisin/kexin type 9; RRR: relative risk reduction

Summary

We recommend the combination of maximally tolerated statins and ezetimibe before PCSK9 inhibitors because high-dose statins and ezetimibe have evidence of long-term safety and reduction in CV events. Statins and ezetimibe are also administered orally and are widely available as generic products. In contrast, PCSK9 inhibitors have unknown long-term safety profiles, are administered as subcutaneous injections once or twice a month, are significantly more costly, and require education on proper use while achieving comparable or less relative risk reductions. In patients at higher risk (see Recommendation 12 for a definition) who are already receiving a maximally tolerated statin plus ezetimibe, addition of a PCSK9 inhibitor is suggested to reduce recurrent non-fatal events.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation [68,70,79,82-85] and considered the evidence put forth in the 2014 CPG.[88,89] The Work Group's confidence in the quality of the evidence was moderate. The benefits outweighed the harms and burden. There is likely to be high variation in patient and provider values and preferences because of various factors (e.g., long-term safety has not yet been established, CVD events are reduced but mortality is not impacted, route of administration issues, and high cost, feasibility of use for patients and healthcare systems). Because of these issues, the Work Group decided upon a "Weak for" recommendation centered on a patient's willingness to intensify drug therapy while already receiving a maximally tolerated statin plus ezetimibe.

There is a need for continued investigation of the long-term safety of treatment with PCSK9 inhibitors combined with statins with or without ezetimibe, and the unknown safety of prolonged periods of very low LDL-C levels secondary to this treatment. More research on these topics would be useful:

- What is the optimal combination of lipid-lowering treatments or achieved LDL-C level that will result in the largest reduction in CV events (e.g., whether adding a PCSK9 inhibitor to maximum-dose statins plus ezetimibe versus moderate-dose statins plus ezetimibe results in an incremental benefit in CV risk)?
- What is the comparative effectiveness of a high-dose statin plus ezetimibe, a high-dose statin plus PCSK9 inhibitor, and a high-dose statin plus ezetimibe plus PCSK9 inhibitor (triple therapy) on important CV outcomes in higher risk patients?
- What is the optimal duration of more aggressive treatment in higher risk patients? For example, in a patient with ACS placed on high-dose statins, is the more aggressive treatment continued indefinitely or can some patients have their treatment titrated downward after a period of time?

c. Other Medications, Supplements, and Nutraceuticals

Recommendation

15. For primary or secondary prevention, we recommend against using niacin (i.e., supplements or prescriptions).
    (Strong against | Reviewed, New-replaced)

Discussion

Primary Prevention

In a fair quality SR of five RCTs that evaluated niacin in primary prevention (n=30,310), Keene et al. (2014) noted no patient benefit from niacin. There was no difference in all-cause mortality, non-fatal MI, or stroke.[90] There was evidence of harm, manifested by an increase in infections, gastrointestinal (GI) complications, bleeding, new-onset DM, and DM complications.

Primary and Secondary Prevention

In a fair quality SR of five RCTs in a mix of primary and secondary prevention patients (n=32,966) who used supplements containing therapeutic doses of niacin (2 – 3 grams/day), Schandelmaier et al. (2017) noted no benefits and increased harms.[91] This systematic review noted no difference in CV mortality, all-cause

mortality, non-fatal MI, or stroke. However, side effects resulted in significant flushing, pruritus, GI symptoms, new-onset DM, and more discontinuations.

Secondary Prevention

Finally, in a fair quality systematic review of two RCTs in patients in secondary prevention (n=1,726), Kaur et al. (2014) found no significant differences in CV mortality, all-cause mortality, non-fatal MI, or stroke. It did find significantly higher numbers of niacin discontinuations, dose reductions, and higher incidences of flushing and pruritus.[92]

Summary

The confidence in the quality of evidence was moderate. The evidence demonstrated in multiple populations that harms and burdens outweighed benefits. It is expected patients and providers will find niacin unacceptable and prefer against its use given the significant increase in adverse events (e.g., pruritus, flushing, DM, increased infections) and lack of benefit in clinical outcomes. Based on this data, the FDA removed the approval of combinations of statins with niacin in 2016.[93]

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[90-92] The Work Group's confidence in the quality of the evidence was moderate. Despite decades of niacin use based on the extrapolation that its effects on the lipid profile (i.e., lowering TC, LDL-C, and TGs, and raising HDL-C) would translate into a favorable impact on patient important outcomes, the Work Group determined that the clinical trial data clearly demonstrated in multiple populations that the harms of niacin use outweigh any benefit. Providers and patients are likely to view niacin as unacceptable given the adverse event profile and lack of benefit in clinically important outcomes. Thus, the Work Group decided upon a "Strong against" recommendation. However, the Work Group acknowledges there may be unique patient circumstances where niacin may be clinically appropriate after a shared decision making discussion between provider and patient.

The Work Group had no research recommendations since further research is not likely to change the clinical landscape nor this recommendation.

Recommendation

16. For primary or secondary prevention, we suggest against adding fibrates to statins.
    (Weak against | Reviewed, New-replaced)

Discussion

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 systematic review with 3,502 primary prevention patients, Keene et al. (2014) showed no significant difference in CHD mortality (a subset of CVD mortality) with use of fibrates.[90] In another fair quality systematic review of 3,982 primary prevention patients, Jakob et al. (2016) noted no significant difference in all-cause mortality and major CVD events with fibrates.[94]

The CVD benefits of fibrates added to statins remain unproven for primary prevention based on data from short-term clinical trials. In a systematic review 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 CK at least five times the upper limit of normal (ULN).[95] However, evidence suggests there is some associated risk. Shao et al. (2016) also showed significant increases in LFT transaminases at least three times ULN and a renal safety endpoint of creatinine increase of ≥50%.[95] 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.[96]

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.[97] 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 – 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.[97]

Summary

The Work Group determined the potential for harms outweighed potential benefits. Patient and provider values and preferences likely vary because some might 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 co-pays. Based on this data, the FDA removed the approval of combinations of statins with fenofibrate in 2016.[93]

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation [90,94-96] and considered the evidence put forth in the 2014 CPG.[97] The Work Group's confidence in the quality of the fibrate evidence was low for primary prevention and moderate for secondary prevention. Compared to the niacin data (see Recommendation 15), the fibrate data was less robust and lower quality. Patient and provider preferences likely vary because some patients with high TG may be interested in fibrates. However, the Work Group determined the potential for harm outweighed potential benefits 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.

The Work Group had no research recommendations since further research is not likely to change the clinical landscape nor impact this recommendation.

Recommendation

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)

Discussion

Bempedoic acid is a prodrug that is activated by very-long-chain acyl-CoA synthetase-1 to inhibit ATP-citrate lyase and works upstream of β-hydroxy β-methylglutaryl-coenzyme A. Among patients at risk of CVD who are on statins, intensifying treatment by adding bempedoic acid has not been shown to reduce CVD mortality, all-cause mortality, non-fatal MI, non-fatal stroke, or MACE compared to the placebo group. There were no systematic reviews or meta-analyses that met the inclusion criteria for this CPG's systematic evidence review.

Based on an RCT, Ray et al. (2019), treatment with bempedoic acid in addition to statins did not improve outcomes among patients with atherosclerotic CVD, HeFH, or both.[98] However, these findings were imprecise because of low event rates and the short follow-up (12 months), and the study was limited by high attrition. Evidence suggests a possibility of harm with bempedoic acid, with a non-significant trend toward higher CV (0.4% versus 0.1%) and all-cause mortality (0.9% versus 0.3%) in the treatment group compared to the placebo group. In Ray et al. (2019) there was no significant difference between placebo and bempedoic acid in CVD deaths and all-cause deaths. Adverse effects of bempedoic acid include potentially increased incidence of muscle pain ($p=0.05$) and gout ($p<0.03$), but with lower rates of new-onset or worsening DM ($p=0.02$).[98]

Patient and provider values and preferences could not be determined since bempedoic acid was not on the market at the time of the systematic evidence review. Bempedoic acid received FDA approval in February 2020 and an ongoing clinical outcome trial will be completed in 2022. As a newly released drug, it has an uncertain safety profile and is expensive, compared to effective, safe, and low-priced statins. Given the adverse events and current lack of evidence in reducing CVD outcomes, patient and provider acceptability may be low.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[98] However, there were no systematic reviews or meta-analyses that studied bempedoic acid and our major outcomes of interest. The Work Group's confidence in the quality of the evidence was low. This recommendation is based on one RCT, Ray et al. (2019), which was limited by a short 12-month follow-up and a small number of events. The Work Group also considered the potential harm of adverse events. Patient values and preferences could not be estimated. Finally, the drug will likely be expensive and patient/provider acceptability may be low if the adverse event rate continues to be high. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

There is a need for a larger secondary prevention study of bempedoic acid as an add-on to statins. The study should have longer follow-up and be appropriately powered for adverse events and important clinical outcomes (e.g., fatal and non-fatal stroke, MI, and mortality).

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)

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)

Discussion

Icosapent ethyl is a purified ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). At the time of our systematic evidence review, the body of evidence examining the potential effects of icosapent ethyl on critical CV outcomes was limited to a single randomized trial. 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 icosapent ethyl 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 (NNT=21).[99]

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 atherosclerotic CVD 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. Although beneficial effects in higher risk primary prevention populations might be demonstrated in contemporary studies not captured in this review or with future investigations, the Work Group determined the REDUCE-IT results alone are insufficient to suggest icosapent ethyl for CV risk reduction in patients without a history of CVD.

The results from REDUCE-IT are applicable to many patients classified as high risk by virtue of a history of CVD. However, the inclusion criteria utilized limit its application to part of the secondary prevention population only. Subjects were restricted to those with elevated TG levels (median 216 mg/dL, 90% of patients >150 mg/dL), 90% of whom were on stable doses of moderate- to high-dose statins for at least four weeks before the intervention. As such, the reduction in CVD outcomes by 25% pertain to secondary prevention populations on statin therapy with hypertriglyceridemia. The composite outcome included coronary revascularization, which many deem as a less clinically valid outcome. For some, this might be a cause for concern that positive interpretations of the results are misleading and rendered by outcomes less important to patients. However, a statistically and clinically significant reduction was demonstrated in each of the component endpoints, including vascular death and other patient-important outcomes. 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), further suggesting a potential benefit in patient-oriented outcomes. These beneficial results were balanced by an increased risk of hospitalization for atrial fibrillation (3.1% versus 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 icosapent ethyl treatment arm.[99]

The available evidence for icosapent ethyl has various significant limitations. First, the evidence base is limited to a single RCT without subsequent trials either corroborating or questioning the findings by Bhatt et al. (2019).[99] Further, Bhatt has numerous methodologic flaws that constrain interpretation, including the use of composite endpoints, lack of allocation concealment, conflict of interest concerns related to industry's heavy role, and the potential confounding related to the choice of placebo. In this latter limitation, the Work Group noted a 30% rise in hsCRP in the placebo group during the study period, while a 12% reduction was observed in the icosapent ethyl group. As hsCRP has been implicated in atherogenesis and plaque stability through inflammatory mechanisms, this imbalance in hsCRP 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, which could have reduced the adsorption of the statin therapy patients had been receiving before the trial period. The relatively stable level of LDL-C seen in the icosapent ethyl 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 might not reasonably explain the large differences in CV outcomes observed between treatment groups, loss of statin class effects independent of changes in LDL remain a possible explanation. Furthermore, subgroup analyses demonstrated similar effects on CV outcomes regardless of baseline TG level (including normal levels, defined as <150 mg/dL, for the secondary efficacy endpoint only) and whether TG levels were normalized to <150 mg/dL or not after treatment. This could suggest icosapent ethyl carries metabolic mechanisms other than TG lowering; however, a placebo-related elevation in the CV risk of the control arm unrelated to baseline or post-study TG levels remains a viable explanation.

In addition to the evidence regarding potential beneficial effects and safety concerns with icosapent ethyl, the Work Group considered the drug's high cost and pill burden (i.e., two large pills twice daily) when crafting this recommendation. Both of these factors may be unacceptable for some patients.

As these are *Reviewed*, *New-added* recommendations, the Work Group systematically reviewed evidence related to these recommendations.[99] The Work Group's confidence in the quality of the evidence was moderate. Limitations included a small evidence base (i.e., one clinical trial), unclear allocation concealment, and the potential for confounding related to the choice of placebo. Nonetheless, the study was a large RCT with results that demonstrated a favorable risk-benefit effect on patient outcomes. Given these positive results but significant limitations in the evidence, the Work Group decided upon a "Weak for" recommendation for Recommendation 19. Recommendation 19 is specific to those with a history of CVD, as the REDUCE-IT population primarily consisted of secondary prevention patients (70%). Furthermore, as this CPG's systematic evidence review did not capture primary evidence investigating only or mostly patients without a history of CVD, the Work Group decided upon a separate "Neither for nor against" recommendation for Recommendation 18, which pertains to primary prevention patients. Although a subgroup analysis of primary prevention patients in the REDUCE-IT trial showed no difference in the primary CV endpoint, the Work Group determined such analyses have limitations and should be used for hypothesis generation rather than clinical decision making.

More RCT data is needed on the effectiveness and safety of icosapent ethyl in primary and secondary prevention populations. Use of placebo without mineral oil, and trials composed of mostly primary prevention populations, are needed to more accurately and comprehensively understand the potential effects of icosapent ethyl on CV outcomes.

Recommendation

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)

Discussion

The systematic review by Abdelhamid et al. (2018) evaluated 79 RCTs for the effect of omega-3 supplements on primary and secondary prevention of CVD.[100] 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.[100]

In this systematic review, omega-3 supplementation ranged from 0.5 grams/day to greater than 5 grams/day.[100] Some studies used omega-3 enriched foods, or dietary advice to increase omega-3 consumption, compared to placebo or usual diet. Most studies assessed LCn3 supplementation with capsules, but some used LCn3- or alpha-linolenic acid-rich or enriched foods or dietary advice compared to placebo or usual diet.[100] Omega-3 enriched foods included margarine, juice, bread, walnuts, or other foods. Control groups received olive, corn, sunflower oils, or other types of fats. The duration of studies ranged from 12 – 72 months.[100]

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[100] The Work Group's confidence in the quality of the evidence was moderate. The evidence showed no effect of omega-3 supplements on CV mortality, composite CV events, MI, stroke, or all-cause mortality. There were inconclusive results for the risk of adverse effects, including bleeding and thrombosis, and risk of bias in the RCTs evaluated. Thus, the Work Group decided upon a ''Weak against" recommendation.

Future studies should measure the potential effects of omega-3 supplements on CVD risk factors.

Recommendation

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

Discussion

No studies evaluated the long-term effects 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 systematic review by Hartley et al. (2016) reviewed 23 RCTs and found insufficient evidence of a patient-oriented benefit from fiber supplements.[101] Fourteen RCTs reported information on adverse events.[101] 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. The Work Group's confidence in the quality of evidence for fiber supplements was very low.

Garlic

A systematic review by Sahebkar et al. (2016) reviewed six RCTs and found insufficient evidence of a patient-oriented benefit from garlic supplements.[102] It found garlic supplements were well tolerated with no serious adverse events 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.[103] 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.[102,103]

Ginger

There is no evidence of a patient-oriented benefit from ginger supplements. The systematic review by Zhu et al. (2018) reviewed 12 RCTs and assessed the effects of ginger supplements on Type 2 DM or components of the metabolic syndrome.[104] The evidence was inconclusive for increased adverse events. The Work Group's confidence in the quality of the evidence for ginger was very low.[104]

Green Tea

There is no evidence of a patient-oriented benefit from green tea supplements. The systematic review by Onakpoya et al. (2014) reviewed 20 RCTs and assessed the effectiveness of green tea supplements on blood pressure and lipid parameters.[105] 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.[105]

Red Yeast Rice

There is no evidence of a patient-oriented benefit from red yeast rice supplements. A systematic review by Fogacci et al. (2019) reviewed 53 RCTs and assessed the safety of red yeast rice supplements.[106] These supplements were compared to either a statin or placebo and the follow-up ranged from 1 month – 4.5 years. The authors concluded red rice yeast supplements were safe for use but caution is recommended when used with other medications, especially other cholesterol-lowering agents, due to possible interactions.[107] The Work Group's confidence in the quality of the evidence for red yeast rice was low.

Summary

The National Institutes of Health's Office of Dietary Supplements states that "dietary supplements are products intended to supplement the diet. They are not drugs and therefore are not intended to treat, diagnose, mitigate, prevent, or cure diseases."[108] Dietary supplements do not require FDA premarket review or approval.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[101-106] The Work Group's confidence in the quality of the evidence was very low. The body of evidence did not yield results on the outcomes of CV mortality, all-cause mortality, or CV events. Most studies were short term (i.e., 1 – 6 months). Safety data for fiber, garlic, ginger, and green tea was inconclusive.[101-106] Patient and provider values and preferences likely vary based on

personal beliefs about efficacy and safety and the ability to pay for supplements, which are generally not covered by health plans. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

d. Monitoring and Adherence

Recommendation

22. We suggest against the routine monitoring of lipid levels in patients taking statins.
    (Weak against | Reviewed, New-replaced)

Discussion

Among dyslipidemic patients at high risk of CVD, we suggest against frequently monitoring lipid levels in patients taking statins, except for higher risk secondary prevention in patients for whom therapy could be intensified. No studies included in the systematic evidence review directly compared pharmacologic treatment of high lipid levels by titrating medications to reach target LDL-C or non-HDL-C goals versus fixed-dose treatment based on initial CV risk assessment and standard medication dosing. Therefore, the comparative effectiveness and safety of treating to reach specific LDL-C or non-HDL-C goals versus use of fixed statin doses based on initial CV risk assessment can only be determined indirectly at best.

Several systematic reviews and meta-analyses have evaluated the association between more intensive LDL-C lowering and risk of stroke,[109] CVD,[110-112] and DM,[109,113] but all these reviews evaluated trials that modified treatment intensity instead of targeting LDL-C. They did find that a lower LDL-C level was associated with reduced CVD mortality and any stroke, ischemic stroke, hemorrhagic stroke, or CV event outcomes compared to those that had higher levels (i.e., received placebo or less intensive LDL-lowering treatment). Given that statins reduce LDL-C levels, these results indirectly demonstrate that treatment which reduces LDL levels is better than no treatment or less intensive LDL-lowering treatment (i.e., high intensity treatment is better). The main results are summarized in Table 2, which reports major systematic reviews/meta-analyses on the effect of more intensive lipid-lowering treatment on CVD and DM. Further, the Navarese et al. (2018) meta-analysis suggests that reduction in risk of total and CV mortality was primarily among patients with baseline (or before treatment intensification) LDL-C ≥100 mg/dL.[111] However, all of these analyses were conducted on trials looking at intensification of treatment (not lipid treatment goals) and, as designed, cannot be used to support lipid treatment targets due to indirectness. Evidence also shows a possibility of harm since more intensive LDL-lowering treatment was associated with a higher incidence of new-onset DM.[113]

The 2014 VA/DoD Dyslipidemia CPG recommended against the routine frequent monitoring (i.e., every three or four months) of LDL-C and non-HDL-C goals for the secondary prevention of CVD. Since then, there is evidence supporting the benefits of even lower LDL levels achieved by PCSK9 inhibitors used in patients on statins at continually higher risk (ODYSSEY and FOURIER).[86,87] Yet, a specific LDL-C target or goal at which patients will benefit most from lipid-lowering treatment has not been identified. Since all primary and secondary prevention trials used treatment intensity as inputs, the Work Group determined that treatment intensity provides a more evidence-based input than LDL-C results. However, testing lipid levels is a simple and inexpensive measure of adherence and treatment efficacy. For this reason, the Work Group recommends that monitoring lipid levels in patients taking statins be individualized based on ongoing shared decision making between the patient and the provider rather than routine.

Table 2. Effect of More Intense Lipid Lowering on CVD Outcomes and Diabetes: A Summary of Recent Meta-analyses

Author	Setting and Population	Intervention/Comparator (either placebo or less intense LDL lowering)	Primary Endpoint(s)	Relative Risk	Absolute Risk	Meta-regression (1 mmol/ L↓)
Shin et al. (2019) [109]	RCTs of subjects at risk for stroke	LDL lowering by statins or non-statins (versus placebo or less intense LDL lowering)	Stroke	0.84 (95% CI: 0.78, 0.90)	2.6% versus 3.1%	↓ stroke risk by 23.5% (95% CI: 0.7% – 46.4%, p=0.04)
		LDL-C level: ≤1.3 mmol/L (50 mg/dL) versus higher levels (control)		0.79 (95% CI: 0.68, 0.91)	1.5% versus 1.9%	
		LDL-C level: 1.3 mmol/L (50 mg/dL) to 1.8 mmol/L (70 mg/dL) versus higher levels (control)		0.76 (95% CI: 0.61, 0.93)	1.6% versus 2%	
		LDL-C level: achieved LDL-C level >1.8 mmol/L (70 mg/ dL) versus control		0.88 (95% CI: 0.81, 0.96)	4.2% versus 4.9%	
Silverman et al. (2016) [112]	RCTs of LDL lowering	Different statin and non-statin therapies	MI, CHD, or CVD death			
		Statins				RR: 0.77 (95% CI: 0.71 – 0.84, p <.001)
		Non-statins				RR: 0.75 (95% CI: 0.66 – 0.86, p=.002)
Navarese et al. (2018) [111]	LDL lowering trials with initial low LDL	More intensive compared with less intensive LDL-C lowering, stratified by baseline LDL level	Total and CVD death	0.92 (95% CI: 0.88 – 0.96)	7.08% versus 7.70%	
Sabatine et al. (2018) [110]	LDL lowering trials with initial low LDL	Statins and non-statins	CHD death, MI, ischemic CVA, or CABG/PTCA			RR: 0.79 (95% CI: 0.71 – 0.87, p <.001)
		Statins				RR: 0.78 (95% CI: 0.65 – 0.94)
		Non-statins				RR: 0.79 (95% CI: 0.70 – 0.88)
Cai et al. (2014) [113]	LDL lowering trials with statins	LDL-C level: <1.8 mmol/L (<70 mg/dL)	New-onset diabetes	1.33 (95% CI: 1.14 – 1.56)		
		LDL-C level: 1.8 – 2.59 mmol/L (70 – 100 mg/dL)		1.16 (95% CI: 1.06 – 1.28)		
		LDL-C level: >2.59 mmol/L (>100 mg/dL)		1.01 (95% CI: 0.92 – 1.10)		

Note: LDL levels were converted from mmol/L to mg/dL by multiplying by 38.6

Abbreviations: CABG: coronary artery bypass grafting; CHD: coronary heart disease; CI: confidence interval; CVA: cerebrovascular accident; CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; mg/dL: milligrams per deciliter; MI: myocardial infarction; mmol/L: millimoles per liter; PTCA: percutaneous transluminal coronary angioplasty; RR: relative risk

While the Work Group wishes to emphasize that regular monitoring of lipid levels is not required to monitor therapy effects, there are many reasons a provider may wish to obtain these values. Knowing the LDL level may provide objective data and facilitate shared decision making, identify medication non-adherence, help the provider motivate the patient to follow the treatment regimen, and tailor therapy for patients who are at high risk despite taking statins. Adherence can also be indirectly assessed (e.g., patient report and medication refill frequency).

The Work Group acknowledges providers may measure lipid levels in patients of all ages for the reasons enumerated above, to emphasize the importance of lifestyle changes, or to quantify the effect of positive lifestyle changes. These measurements may also be useful in patients under age 40, for whom these guidelines do not make recommendations given the lack of evidence.

As this is a *Reviewed*, *New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[109-113] The Work Group's confidence in the quality of the evidence was very low. While the evidence does not support setting an LDL-C target or goal for reducing CV events with statins, there is evidence showing that more intense LDL-lowering treatment reduces CV events in secondary prevention patients at higher risk. However, this may be achieved by using a statin dose target rather than an LDL target or by PCSK9 inhibitors. Patient values and preferences likely vary somewhat because patients may expect a cholesterol test and want to know their cholesterol levels. Finally, frequent lipid monitoring has an associated cost (i.e., resources for testing and patient and provider time). Thus, the Work Group decided upon a "Weak against" recommendation.

A direct study evaluating the comparative effectiveness and safety of treating to reach specific LDL-C or non-HDL-C goals versus the use of a fixed-dose statin and based on initial CV risk assessment is needed.

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)

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. A retrospective cohort study by Zhang et al. (2013) examined adherence to statins at one year following statin-related events.[114] Over 6,000 patients who discontinued statins were re-challenged, and over 90% were ultimately able to tolerate a statin. More than 40% were re-challenged with the same statin to which the adverse event was documented. At the 12-month follow-up, 37% of the patients re-challenged with the same statin were taking it at the same or a higher dose. On average, patients were re-challenged with 1.2 unique statins. While not included in the systematic evidence review and, thus, not considered in determining the strength of this recommendation, a second cohort study by Zhang et al. (2017) showed a lower incidence of death and CV events in patients who continued statins after an adverse reaction.[115] The authors examined 28,266 records of patients who had at least one presumed adverse reaction to a statin and found that patients who continued statins after a statin-related adverse event had a 0.9%

absolute risk reduction (ARR) of CV events (95% CI: 0.1 – 1.7%) and 1.2% lower mortality over four years (95% CI: 0.6 – 1.9%).[115]

A retrospective cohort study of 1,605 patient records by Mampuya et al. (2013) evaluated the efficacy of intermittent statin dosing compared to daily dosing and statin discontinuation in patients with confirmed intolerance.[116] In this population, 63.2% of patients tolerated daily statin dosing, 9.3% tolerated intermittent dosing, and 27.5% discontinued statins. Intermittent dosing regimens ranged from once weekly to six days per week. Rosuvastatin was the most commonly used statin in the intermittent group, accounting for 75.2% of statin prescriptions. Both daily and intermittent dosing led to a significantly greater reduction in the surrogate endpoints of TC and LDL-C compared to statin discontinuation, with greater benefit from daily dosing. About 70% of studied patients were taking concomitant lipid-lowering prescription medications and supplements. The intermittent dosing group took a significantly higher rate of supplements compared to the daily dosing group and discontinuation group (52.3% versus 41.4% versus 46.2%, respectively), including red yeast rice, Metamucil®, plant stanols/sterols, omega-3 fatty acids, and coenzyme Q10 (CoQ10). Also, both the intermittent dosing and discontinuation groups had higher rates of niacin and bile acid sequestrant use. There was a non-significant trend toward a decrease in all-cause mortality at eight years for intermittent statin dosing as compared to statin discontinuation, while mortality was similar in intermittent and daily dosing groups.

The most common category of statin-related events is musculoskeletal symptoms, which can be misattributed to statins and may lead to statin discontinuation and a reluctance to restart treatment. A meta-analysis not included in this CPG's systematic evidence review, Riaz et al. (2017), included over 125,000 patients and concluded that rates of myopathy were similar between the statin and placebo group (OR: 1.2, 95% CI: 0.88 – 1.62).[117] The absolute incidence of serious muscle injury (e.g., rhabdomyolysis) is very low and estimated to be about 3.4 per 100,000 person-years.[118] Some risk factors may predispose patients to statin-induced muscle toxicity, including drug-drug interactions, impaired hepatic or renal function, hypothyroidism, advanced age, rheumatologic disorders, vitamin D deficiency, and alcoholism.[56,62,73] Those factors need to be considered when evaluating statin intolerance.

A washout period (i.e., a short-term interruption of a statin), should be implemented to evaluate whether the perceived adverse event is related to a statin. The optimal duration of the washout period was not clear in the available evidence. Based on statin half-lives, an interruption of 2 – 4 weeks is reasonable. Statin treatment then can be reinitiated with the same statin (if symptoms were deemed non-statin related), or with a different statin at recommended intensity (if symptoms resolved after discontinuation). If intolerance persists, providers could consider decreases in dosage. Also, intermittent dosing is an acceptable option in patients with continued tolerance issues. Only in the rare case of a serious adverse event (e.g., rhabdomyolysis) should statins be discontinued.

The Work Group systematically reviewed evidence on the role of vitamin D deficiency in statin-induced myopathy. The confidence in the quality of the two available cohort studies was very low based on a small number of patients and different protocols for vitamin D supplementation.[119,120] Thus, the Work Group was unable to make a recommendation on vitamin D supplementation.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation [114,116,119,120] and considered the evidence put forth in the 2014 CPG.[56] The Work Group's confidence in the quality of the evidence was very low. The evidence was limited by the observational nature of data and outcomes assessment. For almost all patients, there are no significant harms associated with the trial of a different statin or implementation of intermittent dosing, and there is a potential benefit of continuing treatment. Because most agents in the class are available in generic formulations, it is unlikely that switching statins will add a substantial financial burden. With proper education, it is expected that most patients will be amenable to a change in statin or an intermittent dosing schedule. Since statins have the most robust safety and clinical outcome databases of any treatment for dyslipidemia, the Work Group determined any measures that continue statin therapy were preferred over other, less robust interventions. There appeared to be no harms to re-challenging nor intermittent nondaily dosing and statins are associated with improved clinical outcomes. Thus, the Work Group decided upon a "Weak for" recommendation.

Randomized clinical trials that evaluate the relationship between vitamin D replacement or supplementation and statin-induced myopathy are needed.

Recommendation

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)

Discussion

In a systematic review of 35 RCTs (n=925,171), Van Driel et al. (2016) examined strategies to improve patient adherence to lipid-lowering medications.[121] The systematic review found adherence to lipid-lowering medication was improved after intensified patient care. When compared to standard care, these interventions demonstrated significantly better adherence rates and a decrease in cholesterol levels in both the short term (<6 months) and long term (>6 months).

Overall, patients in the intensified care group were twice as likely to be adherent to statin treatment short term, and almost three times as likely to continue treatment long term. Intensified care included drug regimen simplification, patient education and information, intensified patient follow-up with reminders via mail, telephone, and hand-held pill devices, complex behavioral approaches, group sessions, decision support systems, administrative improvements, or large-scale pharmacy-led automated telephone sessions. Intensified care was delivered by different healthcare providers, including pharmacists, nurses, and physicians. Not all interventions among studies included in Van Driel et al. (2016) resulted in positive outcomes. The effect on adherence appeared to depend on the type and quality of the intervention. For instance, Fischer et al. (2014) showed that automated pharmacy-led phone reminders to patients who failed to pick up their prescriptions in eight days after a fill date did not affect the number of abandoned prescriptions.[122] On the other hand, Vollmer et al. (2014) noted increased adherence after automated phone call reminders to patients who were due or overdue for a refill.[123]

According to the Centers for Disease Control and Prevention (CDC), improving medication adherence is a public health priority and could reduce the economic and health burdens of chronic conditions.[124] The

following studies were not included in the systematic evidence review and, thus, were not considered in determining the strength of this recommendation. Rodriguez et al. (2019) estimated adherence to statin therapy is <50% at one year with further decline to <30% after two years.[125] Several sociodemographic characteristics (e.g., patients aged <50 years or >70 years, African American and Hispanic patients, females, patients with low health literacy, and low income) have been associated with lower statin adherence rates.[126] A retrospective cohort analysis of 304,104 patients with prior CVD being treated at the VA showed the risk of mortality was increased by 30% in those with estimated adherence of <50% based on refill history.[125] Conversely, a 10% increase in adherence was found to be associated with a 5% decreased risk of CV-related hospitalizations.[127]

Medication adherence is a complex, multifactorial issue that involves the entire healthcare system. Patient factors negatively impacting adherence may include inadequate understanding of their medical condition, lack of perceived benefit, adverse effects, pill burden, and time lag to benefit. The patient focus group emphasized the need for stronger provider-patient communication and additional education to improve their understanding of treatment.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[121] The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including lack of blinding given the nature of the interventions, significant heterogeneity for short-term adherence, and outcome assessment. There were no harms identified in the systematic review, and there is a significant benefit of improved adherence. Other considerations regarding this recommendation are the cost and availability of resources, such as labor and time commitment. Patient values and preferences were somewhat varied. Because there were no harms identified and given the potential benefits of medication adherence, the Work Group decided upon a "Weak for" recommendation.

C. Lifestyle Interventions

Recommendation

25. For primary and secondary prevention of cardiovascular disease, we suggest a dietitian-led Mediterranean diet.
    (Weak for | Reviewed, New-replaced)

Discussion

A systematic review by Hooper et al. (2015) reviewed 15 RCTs that reduced dietary saturated fat and replaced it with carbohydrate, monounsaturated, or polyunsaturated fat to determine the effect on CVD morbidity and mortality.[128] In eight RCTs, reducing saturated fat did not reduce CVD mortality. A systematic review by Rees et al. (2019) found that a Mediterranean diet reduced composite CV events, stroke, incidence of Type 2 DM, MI, and CV and all-cause mortality and improved the management of dyslipidemia.[129] Wu et al. (2015) conducted a meta-analysis of 18 studies that showed a significant dose-related response between dietary fiber intake and the risk of CHD and concluded that a higher intake of fiber, as in the Mediterranean diet, led to lower risk of CHD morbidity and mortality.[130]

The Mediterranean diet includes a high unsaturated fat/saturated fat ratio, a substantial increase in fiber from plant-based foods (fruits, vegetables, nuts, legumes, and grains), an increased intake of fish,

moderate intake of low-fat dairy products, and a low-to-moderate red wine intake for those who drink alcohol. Moreover, evidence suggests lipid outcomes were improved when a registered dietitian provided medical nutrition therapy for the management of dyslipidemia.[131]

As this is a *Reviewed, New-replaced* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[128,129] The Work Group's confidence in the quality of the evidence was low. With respect to diet, patient values and preferences vary largely. Given the lack of risks and harm related to this diet and the evidence showing improved CV outcomes, the Work Group decided upon a "Weak for" recommendation.

Well-controlled RCTs are needed to evaluate the effectiveness of replacing saturated fat with unsaturated fats to determine the effect on CVD mortality and morbidity.

Recommendation

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)

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, and increases in HDL).[132] 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 Dyslipidemia is Defined by Risk for Cardiovascular Disease). 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 Dyslipidemia CPG) and the updated 2018 PAGA guideline recommend at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic exercise per week.[133] Although randomized trial data are lacking, this CPG's systematic evidence review yielded an expansive body of observational data whose findings align with the established federal PAGA recommendations. These findings from systematic reviews and pooled analyses of observational data [134-136] and other prospective cohort studies [137-141] 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.[136] 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.[136]

Evidence also indicates a possible benefit to activity levels much lower than federal recommendations. A systematic review and meta-analysis of prospective cohort studies by Chastin et al. (2017) 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]) (i.e., writing, walking 2 mph, slow ballroom dancing, golfing with a cart) was approximately twice that of their counterparts.[142] 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).[141] 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 musculoskeletal injuries are not uncommon during exercise.

The Work Group determined the available body of evidence had significant methodologic limitations. No randomized studies were found and, although most were large prospective cohorts whose findings were maintained after multivariable adjustment, 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 on 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 might 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.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[134-142] The Work Group's confidence in the quality of the evidence was very low. The body of evidence had significant methodologic limitations. The potential large benefit on mortality would appear to outweigh the risk of musculoskeletal injury. Although feasibility and resource requirements might be a concern with higher activity levels for some patients, this would not apply to lower intensity activities. Therefore, this recommendation broadens acceptability and feasibility to patients who are unable to achieve the traditional moderate to vigorous intensity physical activity recommendations. Thus, the Work Group decided upon a "Weak for" recommendation.

Research utilizing randomization and more accurate methods of measuring physical activity levels are needed to improve confidence in the effect of physical activity on CV outcomes in both primary and secondary prevention populations.

Recommendation

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)

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.[143-146]

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 systematic review 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).[147] 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. (2017).

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. (2017) found the abovementioned co-variates did not affect any of the CV outcomes with rare exception, such as high adherence.[147] Therefore, the Work Group determined 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, reviewed studies included only patients with CHD (MI event, diagnosis of CAD, CABG, or 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 would anticipate some variability in patient preference and limitations in feasibility related to resource requirements. The Work Group would anticipate 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 resource (i.e., physiotherapists) and equipment requirements of many clinic and community-based programs might limit feasibility in some settings. However, the evidence demonstrated similar CV outcomes with home-based programs, which might have fewer fiscal costs and other resource demands compared to their clinic or community-based counterparts.

As this is a *Reviewed*, *New-added* recommendation, the Work Group systematically reviewed evidence related to this recommendation.[147] The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including significant heterogeneity in exercise interventions and risk of bias in the primary studies. Most of the latter was detection bias because of the inherently problematic nature of blinding in exercise interventions and attrition bias from missing outcomes data. Other considerations regarding this recommendation included the benefits (e.g., improved CV mortality, all-cause mortality, and non-fatal MI). Although data on safety endpoints were not reported, the Work Group determined these benefits outweighed the risk of harm anticipated with exercise interventions, most of which would be minor musculoskeletal injuries. Although variation in patient preference and feasibility is a concern in some settings, the Work Group determined that given the highly favorable risk-benefit ratio for CV mortality, providers and healthcare systems should make strong efforts to motivate their patients and invest in the resources required to provide a cardiac rehabilitation program for their patients. Thus, the Work Group decided upon a "Strong for" recommendation.

More research involving head-to-head comparisons between different exercise components is needed to better ascertain the optimal form of cardiac rehabilitation to improve CV outcomes in patients with CHD and other forms of CVD.

VII. Knowledge Gaps and Recommended Research

Despite the breadth of research on dyslipidemia and the prevention of CVD, the Work Group noted that many patient-oriented questions have not been specifically addressed. In looking towards the next iteration of these guidelines, the Work Group created a ranked list of research priorities.

A. Comparison of Medical Therapies in Primary and Secondary Prevention

a. Primary Prevention

The pool of primary prevention studies using statins almost exclusively employed moderate-dose statins. The JUPITER trial was the only study that employed a high-dose statin.[47] The CV benefit of higher dose statins in JUPITER is consistent with benefits found in other primary prevention trials of moderate-dose statins. Prospective comparisons of different statin intensities might demonstrate an additional benefit of higher statin doses in patients treated for primary prevention.

Similarly, studies of ezetimibe monotherapy and ezetimibe and statin combination therapy showing patient-oriented outcomes in primary prevention are lacking. While similar arguments can be made for bempedoic acid, icosapent ethyl, and PCSK9 inhibitors, their high cost and the large NNT for all therapies in primary prevention limit the potential cost-effectiveness of these medication classes in primary prevention at current prices.

b. Secondary Prevention

Patients with known CVD are at the highest risk of CV events. Since statins and ezetimibe are both generic and have proven benefit in this population when used in combination, the combination should be maximized and serve as the active control for evaluation of added efficacy and safety of newer therapies (bempedoic acid, icosapent ethyl, and PCSK9 inhibitors).

Prospective studies evaluating the benefit of titrating lipid-lowering treatments to achieve specific LDL-C goals (e.g., <50, 70, 100 mg/dL) in patients at higher risk are lacking but would be helpful in determining the need for intensification of treatment to further reduce CV events.

B. Effectiveness of Non-statin Monotherapy for Primary Prevention

Most discontinuation of statin therapy is attributed to presumed statin myopathy. While many patients tolerate the same statin when re-challenged, some are reluctant to resume the same or different statin they presume caused the myalgias, leaving limited evidence-based medication options for primary prevention of CVD in patients who cannot take statins.

There is a need for clinical trials of alternative lipid-lowering agents for CVD risk reduction in primary prevention populations. Current medications suitable for study would be ezetimibe, PCSK9 inhibitors, bempedoic acid, and icosapent ethyl. Because of the low cost of generic ezetimibe, studies of ezetimibe monotherapy for primary prevention would offer the highest potential benefit.

C. Safety of Newer Therapies

The long-term risks of PCSK9 inhibitors and bempedoic acid have not been established, warranting continued surveillance of post-marketing adverse event reports and the persistence of effect on CVD risk reduction in longer term follow-up.

No negative health outcomes have been reported from very low LDL-C levels, including levels ≤50 mg/dL, caused by lipid-lowering drugs in observational studies or post hoc analyses of clinical trials to date. However, if future evidence supports that a minimum threshold LDL-C level is necessary, based upon safety risks, more frequent monitoring may be needed when high intensity treatments are employed.

D. Stratifying Primary Prevention Benefits by Patient Risk Estimates

Primary prevention studies include primarily patients with 10-year CV risk estimates of >12% with smaller numbers between 6 – 12% risk and very few <6%. No primary prevention study has used estimated CV risk as inclusion criteria or provided individual patient predicted cardiac risk data. Future primary prevention studies should include lower risk populations, measure predicted risk, and stratify the randomization procedure (using block randomization) by pretreatment CV risk estimate. We recognize that such a study may be impractical given the extremely large sample size and costs.[148]

E. Prospective Studies to Improve Statin Adherence

The high quality evidence for the benefit of statins for primary and secondary prevention makes adherence a key goal. The limited studies to date suggest that repeated trials of statins increase adherence, but the evidence base is sparse. Both clinic intervention strategies and alterations to prescribing patterns should be evaluated. The efficacy of proposed adjusted statin dosing schedules, such

as intermittent dosing, should be studied with respect to both adherence and patient-oriented outcomes. Studies should verify the washout period that is frequently employed and prospectively evaluate the theoretical reduction in statin-induced myopathy with vitamin D supplementation.

F. Prospective Comparative Study of Risk Prediction Strategies

Among intermediate-risk populations for whom there is less certainty regarding the risk-benefit ratio of statins, some have advocated for tests that further refine risk. To date, the best candidate for such further risk stratification is CAC scoring using ultrafast computed tomography, which has been shown to improve the AUC for diagnosis by about 5% and result in a net reclassification of about 15 – 20% of patients. While more patients will be identified to be at risk for an event, CAC scoring will also falsely label seven patients at high risk for a coronary event for every true high risk patient identified. Only prospective studies that directly compare risk assessment strategies (conventional risk assessment and CAC scoring compared to conventional risk assessment only) as the basis for treatment decisions among primary prevention patients will truly answer this question. Such studies have been proposed and designed but involve very large populations (n=30,000) and a prohibitive cost.[148]

G. Prospective Comparison of Risk Calculators in Varied Populations

The use of electronic medical records (EMR) within large organizations (e.g., VHA, MHS) creates an opportunity to create large prospective data sets. One opportunity is for the EMR to calculate risk scores and longitudinally track patients. These large data sets would help determine the overall accuracy of risk calculators and the effect of sex, ethnicity, and other factors on these risk estimates.

H. Pragmatic, Evidence-based Dietary Studies

Studies of dietary interventions are problematic because of adherence and monitoring issues. The best study would be carefully monitored by a dietitian yet it would be impractical to have every patient pursue a dietitian-led plan. The other issue is the specific elements of the dietary program. This is seen primarily in the low saturated fat dietary intervention, where the replacement of saturated fat with polyunsaturated fat appears beneficial in men only. There is more evidence for the Mediterranean diet, which includes a high level of plant-based foods and low levels of saturated fats (replaced by monounsaturated and polyunsaturated fats). More study of the replacement of saturated fats with polyunsaturated fats alone and large, pragmatic dietary studies could help resolve the issues. There is also a need to study a whole-food, plant-based dietary strategy for CVD risk reduction in primary prevention.

I. Comparative Studies of Cardiac Rehabilitation Programs

While strong evidence supports the use of cardiac rehabilitation programs shortly after coronary events or revascularization procedures, there is little comparison of the elements of these programs. A comparison of different programs could help determine the most cost-effective form of rehabilitation.

Appendix A: Evidence Review Methodology

A. Developing the Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic evidence review on the management of dyslipidemia. These questions, which were developed in consultation with the Lewin Team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [149]

PICOTS Elements	Description
Patients, Population, or Problem	Describes the 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.
Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

Abbreviations: 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 CPG's scope and literature review by prioritizing topics of interest. As a result of resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority and those were included in the review. Table A-2 contains the final set of KQs used to guide this CPG's systematic evidence review.

Once the KQs were finalized, the Work Group prioritized the outcomes they had defined for each KQ based on how important the Work Group judged each outcome to be. Ranking outcomes by their relative importance can help focus attention on those outcomes that are considered most important for clinical decision making when making judgments regarding the overall quality of the evidence to support a recommendation.[150]

Using GRADE methodology, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see

Outcomes); however, only outcomes judged to be critical were used to determine the overall quality of evidence (see Grading Recommendations).

a. Population(s)

- Key Question 1:
  - Individuals previously screened for CVD risk and with risk score below 10 – 20%
- Key Question 2:
  - All adults
- Key Question 3:
  - All adults eligible for primary prevention
- Key Questions 4 – 7, 9 – 12:
  - Specific to adults who are at risk of CVD or already have dyslipidemia
- Key Question 8:
  - Patients who have been taking a statin for 3 or more years for primary or secondary prevention

b. Interventions

- Key Question 1:
  - Repeat CVD risk assessment
- Key Question 2:
  - Lipid lab test
- Key Question 3 – CV risk stratification:
  - Use of risk models (e.g., pooled cohort risk score versus FRS versus biology-based risk assessment). (1) Framingham score, (2) pooled cohort risk score, (3) novel markers
- Key Question 4 – Pharmacotherapy:
  - Statins
  - PCSK9
  - Ezetimibe
  - Bile acid sequestrants
  - Niacin
  - Fibrates
  - Omega-3 fatty acids
  - Bempedoic acid
- Key Question 5 – Treating to goals with pharmacotherapy:
  - LDL goal of <100 mg/dL or <70 mg/dL and non-HDL goal of <130 mg/dL or <100 mg/dL

    - Low HDL or high TGs (150 – 499 mg/dL)
- Key Question 6 – Pharmacotherapy:
    - High dose/intensity statins or ezetimibe, PCSK9 inhibitors, bile acid sequestrant, niacin, fibrate, or fish oils added to statins
    - LDL <70 or <100 and non-HDL <100 or 130 mg/dL
    - Intensified treatment
    - Lower LDL or non-HDL goals
- Key Question 7 – Pharmacotherapy:
    - Statin-Associated Muscle Symptom Clinical Index tool, measurement of CK levels assessment for myalgia and risk factors
    - Alternative day statin therapy
    - Switching to a different statin
    - Lowering the dose
    - Combination therapy after dose reduction or a change in drug
    - Optimize vitamin D status using supplements
    - CoQ-10
- Key Question 8:
    - Stop statin use
- Key Question 9:
    - Lipid interventions (pharmacologic and non-pharmacologic)
- Key Question 10 – Dietary supplements:
    - Omega-3
    - Red yeast rice
    - Soluble fiber
    - Garlic
    - Ginger
    - Plant sterols
    - Green tea
    - Niacin
- Key Question 11:
    - Different dietary therapies (Mediterranean, vegetarian, vegan, low-fat, or DASH diet)
    - Registered dietitian (RD) providing individualized counseling

- Key Question 12 – Physical activity:
  - Resistance training
  - Aerobic exercise (no specification on duration, intensity)

c. Comparators

- Key Question 1:
  - No repeat testing
- Key Question 2:
  - Previous lab test from same individual over varying time frames
- Key Question 3:
  - Usual care
  - No formal stratification
  - Different stratification tool
- Key Question 4:
  - Placebo
  - Another medication class
  - Another medication within the same class
  - A different dose of the same medication
- Key Question 5:
  - Treating without consideration of reaching lipid goal(s) but based on dosage
- Key Question 6:
  - Control (less intense or no added therapy)
  - Higher LDL or non-HDL goals
- Key Question 7:
  - No intervention to improve statin tolerance
- Key Question 8:
  - Continue statin use
- Key Question 9:
  - Usual care (placebo, lower intensity statin; or high intensity statin if add-on comparison such as ezetimibe, PCSK9, fibrate, niacin, etc.)
- Key Question 10:
  - Placebo or different dietary supplement(s)

- Key Question 11:
  - Different dietary therapy or no dietary therapy
  - Different health professional other than an RD
- Key Question 12:
  - No exercise
  - No routine exercise
  - Different type of exercise

d. Outcomes

- Key Question 1:
  - Critical outcomes
    - CV mortality
  - Important outcomes
    - 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, CV mortality, all-cause mortality
    - AMI – fatal or non-fatal
    - Stroke – fatal or non-fatal
    - All-cause mortality
    - Changing risk stratification, reclassification of CV risk
    - Time to crossing to a different treatment threshold
- Key Question 2:
  - Critical outcomes
    - Change in lab value over time
- Key Question 3:
  - Critical outcomes
    - Test characteristics (AUC, specificity, sensitivity, positive predictive value, negative predictive value, etc.)
  - Important outcomes
    - Changing risk stratification, reclassification of CV risk
- Key Questions 4 – 6, 8, 10 – 12:
  - Critical outcomes
    - CV mortality

  - Important outcomes
    - 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, CV mortality, all-cause mortality
    - AMI – fatal or non-fatal
    - Stroke – fatal or non-fatal
    - All-cause mortality
- Key Question 7:
  - Critical outcomes
    - Adherence to lipid therapy medication >85% @ 1 year
  - Important outcomes
    - Changes in lipid levels (total-, LDL-, HDL-cholesterol, non-HDL cholesterol, TGs)
- Key Question 9:
  - Critical outcomes
    - Marginal cost-effectiveness
  - Important outcomes
    - Thresholds of cost-effectiveness for cost, effectiveness, utilities
    - Sensitivity of cost-effectiveness to cost and effectiveness (ARR, RRR)

e. Timing

- Key Question 1:
  - ≥3 years follow-up
- Key Questions 2, 3, 10 – 12:
  - No minimum follow-up
- Key Questions 4 – 6:
  - ≥1 year follow-up
- Key Questions 8, 9:
  - Lifetime horizon

f. Settings

- Outpatient primary care (Key Question 2 also includes laboratory setting)

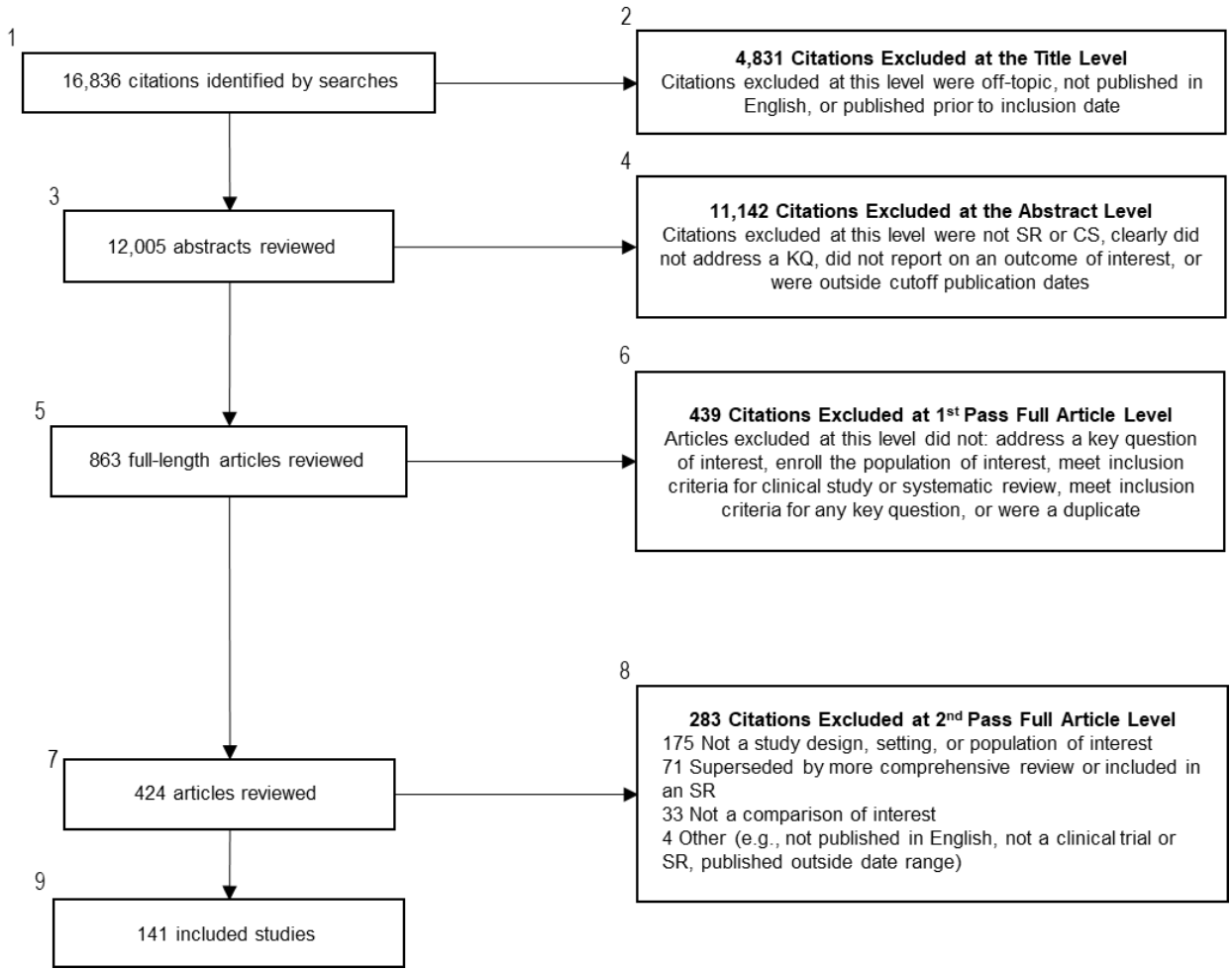
B. Conducting the Systematic Evidence Review

Based on the decisions made by the Champions and Work Group members regarding the scope, the KQs, and the PICOTS statements, the Lewin Team produced a systematic evidence review protocol prior to conducting the review. The protocol was reviewed and approved by the Champions and Work Group members. It described in detail the final set of KQs, the methodology to be used during the systematic evidence review process, and the inclusion/exclusion criteria to be applied to each potential study, including, but not limited to, study type, sample size, and PICOTS criteria.

Extensive literature searches identified 16,836 citations potentially addressing the KQs of interest to this evidence review. Of those, 4,831 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 study inclusion publication date, or not a full-length article). Overall, 12,005 abstracts were reviewed with 11,142 of those being excluded for the following reasons: not a systematic review or an accepted study design (see the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria), did not address a KQ of interest to this review, did not report on an outcome of interest, or published outside cut-off publication dates. A total of 863 full-length articles were reviewed. Of those, 439 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for study design, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 424 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 283 were ultimately excluded. Reasons for their exclusion are presented below in Figure A-1.

Overall, 141 studies addressed one or more of the KQs and were considered as evidence in this review. Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; 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: 16,836 citations identified by searches
    a. Right to Box 2: 4,831 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
    b. Down to Box 3

2. Box 3: 12,005 abstracts reviewed
    a. Right to Box 4: 11,142 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or clinical study, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 863 full-length articles reviewed
    a. Right to Box 6: 439 citations excluded at 1st pass full article level
        i. Articles excluded at this level did not: address a key question of interest, enroll the population of interest, meet inclusion criteria for clinical study or SR, meet inclusion criteria for any key question, or were a duplicate
    b. Down to Box 7
4. Box 7: 424 articles reviewed
    a. Right to Box 8: 283 citations excluded at 2nd pass KQ level
        i. 175 not a study design, setting, or population of interest
        ii. 71 superseded by more comprehensive review or included in an SR
        iii. 33 not a comparison of interest
        iv. 4 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
    b. Down to Box 9
5. Box 9: 141 included studies

Table A-2. Evidence Base for KQs

Question Number	Question	Number of Studies & Type of Studies
1	What is the optimal time to repeat screening for cardiovascular risk, including lipid level and taking into consideration variability of lipid levels over time, on identification of individuals who would benefit from pharmacologic and non-pharmacologic dyslipidemia treatment and on cardiovascular outcomes? Does this vary by age group (20 to 39 years, 40 to 54/64 years, 55/65 to 79 years, 80 years and above), sex, or co-morbid conditions (e.g., diabetes, hypertension, CKD)?	2 cohort studies
2	What is the variability/stability of lipid levels over time?	1 SR, 1 cohort study, and 1 modeling study
3	What is the optimal method to stratify cardiovascular risks, including a combination of classic (e.g., fasting and non-fasting lipid levels, age, sex, smoking history, diabetes, hypertension) and novel (e.g., CAC, IMT, hsCRP, particle size, ABI, coronary CT calcium score, apolipoprotein B, lipoprotein(a), hsCRP, NT proBNP, hs-TnI (high sensitivity troponin I), galectin-3) risk markers or risk calculators, in order to inform pharmacologic and non-pharmacologic treatment for dyslipidemia (e.g., initiating treatment, choice of treatment, or intensity/dosage)?	2 SRs and 11 model performance studies
4	Among patients at risk of CVD, including patients with dyslipidemia, what is the effectiveness (vs. placebo), comparative effectiveness (vs. another medication class, another medication within the same class, a different dose of the same medication), and safety of pharmacotherapy (e.g., statins, PCSK9 inhibitors, ezetimibe, bile acid sequestrant, niacin, fibrate, omega-3, bempedoic acid) on cardiovascular outcomes? Does this vary by patients' age, sex, co-morbid conditions (e.g., diabetes, hypertension, CKD), cardiovascular risk, intolerance to statins, or other patients' characteristics, or for primary vs. secondary prevention?	26 SRs, 2 RCTs, and 5 observational follow-ups of RCT cohorts
5	What is the comparative effectiveness and safety of treating to reach specific LDL-C or non-HDL-C goals or based only on initial cardiovascular risk assessment? Does this vary by patients' age, sex, co-morbid conditions (e.g., diabetes, hypertension, CKD, CHF), cardiovascular risk, intolerance to statins, or other patients' characteristics, or for primary vs. secondary prevention?	4 SRs and 2 RCTs
6	What is the effectiveness and safety of intensifying treatment by adding non-statins (i.e., ezetimibe, PCSK9 inhibitor, bile acid sequestrant, niacin, fibrate or fish oils) to statins, increasing statins dose, or using lower LDL-C or non-HDL-C goals to improve cardiovascular outcomes? Does this vary by patients' age, sex, co-morbid conditions (e.g., diabetes, hypertension, CKD, CHF), cardiovascular risk, intolerance to statins, or other patients' characteristics, or for primary vs. secondary prevention?	25 SRs, 6 RCTs, and 4 open-label extensions of RCTs
7	Among patients at risk of CVD, including patients with dyslipidemia on statin, but who do not tolerate statin well, what is the effectiveness of various strategies (e.g., education, switching statins, use of lower doses, alternate day dosing) to improve patients' tolerance to statins, adherence, or to allow statin dose increase?	1 SR, 1 RCT, and 4 cohort studies
8	What is the safety and efficacy of stopping statins for dyslipidemia among patients who have been on a statin?	2 SRs and 1 RCT
9	What is the cost-effectiveness of various pharmacologic (PCSK9 inhibitors, statins) and non-pharmacologic treatment?	2 SRs and 3 cost-effectiveness studies

Question Number	Question	Number of Studies & Type of Studies
10	What is the effectiveness (vs. placebo), comparative effectiveness (vs. another dietary supplement/nutraceutical), and safety of dietary supplements/nutraceuticals (e.g., Omega-3, red yeast rice, soluble fiber, garlic, ginger, plant sterols, green tea, niacin) on cardiovascular outcomes?	7 SRs and 1 RCT
11	What is the effectiveness (vs. no intervention), comparative effectiveness (vs. a different dietary intervention), and safety of dietary therapy on cardiovascular outcomes? Does this vary by type of dietary therapy (e.g., Mediterranean, vegetarian, vegan, low-fat, or DASH diet), who is delivering the intervention (e.g., RD, or other health professionals), whether the intervention is standardized or individualized, patients' age, sex, co-morbid conditions (e.g., diabetes, hypertension, CKD), cardiovascular risk, or for primary vs. secondary prevention?	2 SRs
12	What is the efficacy and safety of various forms of physical activity, including both aerobic exercise and resistance training, for primary and secondary prevention in patients with dyslipidemia?	3 SRs and 24 cohort studies
	Total Evidence Base	**141 studies (some studies addressed more than 1 KQ)**

Abbreviations: ABI: ankle-brachial index; CAC: coronary artery calcium; CHF: congestive heart failure; CKD: chronic kidney disease; CT: computerized tomography; CVD: cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; HDL-C: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; hs-TnI: high-sensitivity troponin; IMT: intima-media thickness; LDL-C: low-density lipoprotein cholesterol; NT proBNP: N-terminal pro b-type natriuretic peptide; PCSK9: proprotein convertase subtilisin/kexin type 9; RCT: randomized controlled trial; RD: registered dietitian; SR: systematic review; vs.: versus

a. General Criteria for Inclusion in Systematic Review

- Clinical studies or SRs published on or after December 1, 2013, to May 16, 2019. If multiple SRs addressed a KQ, we selected the most recent and/or comprehensive review. SRs were supplemented with clinical studies published after the SR.
- Studies must be published in English.
- Publication must have been a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- SRs 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 GRADE or something compatible (e.g., the one used by the AHRQ Evidence-based Practice Centers). If an existing review did not assess the overall quality of the evidence, evidence from the review must be 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.
- Intervention studies must assess pharmacologic or non-pharmacologic treatment or evaluated the variability of lipid levels over time, effectiveness of CVD risk screening, timing of repeat screening for CVD risk assessment, or risk stratification methods. See Key Question Specific Criteria for additional study designs.
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria).

- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older at risk for CVD.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria

- For KQ 1, SRs of RCTs or comparative observational studies and individual RCTs or comparative observational studies not included in SRs were required.
- For KQ 2, SRs of clinical or lab-based observational repeated measures studies, or individual studies of these designs not included in SRs were required.
- For KQ 3, SRs of RCTs and/or prognostic cohort studies and individual RCTs and prognostic cohort studies not included in SRs were required.
- For KQs 4 and 6, SRs of RCTs (for efficacy or long-term safety) and/or observational cohort/case-control studies (for long-term safety) and individual RCTs (for efficacy or long-term safety) and observational cohort/case-control studies (for long-term safety) not included in SRs were required.
- For KQs 5, 7, 8, 10, and 11, SRs of RCTs and individual RCTs not included in SRs were required.
- For KQ 9, SRs of cost-effectiveness studies and individual cost-effectiveness studies not included in SRs were required.
- For KQ 12, SRs of RCTs and comparative prospective cohort studies and individual RCTs and comparative prospective cohort studies not included in SRs were required.

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 J.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Cochrane Database of Systematic Reviews (Cochrane Reviews)	December 1, 2013, to May 16, 2019	Wiley
Cochrane Central Register of Controlled Trials	December 1, 2013, to May 16, 2019	Wiley
Database of Abstracts of Reviews of Effects	December 1, 2013, to May 16, 2019	Wiley
EMBASE (Excerpta Medica)	December 1, 2013, to May 16, 2019	Elsevier
Health Technology Assessment Database (HTA)	December 1, 2013, to May 16, 2019	Wiley
MEDLINE/PreMEDLINE	December 1, 2013, to May 16, 2019	Elsevier
PsycINFO	December 1, 2013, to May 16, 2019	OvidSP
PubMed (In-process and Publisher records)	December 1, 2013, to May 16, 2019	National Library of Medicine

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one-half day face-to-face meeting of the CPG Champions and Work Group members on August 6 – 9, 2019. These experts were developed and drafted the clinical recommendations for an update to the 2014 VA/DoD Dyslipidemia CPG. Lewin presented findings from the evidence review in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review and asked to categorize and carry forward recommendations from the 2014 VA/DoD Dyslipidemia CPG, modifying the recommendations as necessary. The Work Grop also developed new clinical practice recommendations not presented in the 2014 VA/DoD Dyslipidemia CPG based on the 2019 evidence review. The subject matter experts were divided into three smaller subgroups.

As the Work Group members drafted clinical practice recommendations, they also assigned a rating for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was rated by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations, the Work Group also revised the 2014 VA/DoD Dyslipidemia CPG algorithm to reflect the new and amended recommendations. To update the algorithms, they discussed the available evidence and changes in clinical practice since 2014.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[5]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired

quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as 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?

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 the strength. The evidence review used for the development of recommendations, conducted by ECRI, assessed the confidence in the quality of the evidence base using GRADE methodology and assigned a rating of "High," "Moderate," "Low," or "Very Low." The outcomes judged to be critical were used to determine the overall quality of evidence. Per GRADE, if the quality of evidence differs across the critical outcomes, the lowest quality of evidence for any of the relevant critical outcomes determines the overall quality of the evidence for a recommendation; the overall confidence cannot be higher than the lowest confidence in effect estimates for any outcome that is determined to be critical for clinical decision making.[12,150]

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?

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?

Other implications consider the practicality of the recommendation, including resource 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 may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

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

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	• 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?	• Benefits outweigh harms/burden • Benefits slightly outweigh harms/ burden • Benefits and harms/burden are balanced • Harms/burden slightly outweigh benefits • Harms/burden outweigh benefits
Confidence in the quality of the evidence	• Is there high or moderate quality evidence that answers this question? • What is the overall certainty of this evidence?	• High • Moderate • Low • Very low
Values and preferences	• 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?	• Similar values • Some variation • Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• 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?	• Various considerations

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 combines the four domains.[151] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[5] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength ("Strong" or "Weak")
- Direction ("For" or "Against")

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident in the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong for (or "We recommend offering this option …")
- Weak for (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence …")
- Weak against (or "We suggest against offering this option …")
- Strong against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

A set of recommendation categories was adapted from those used by NICE.[8,9] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2014 VA/DoD Dyslipidemia CPG. The categories and definitions can be found in Table A-5.

Table A-5. 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 that 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 was not changed
	Amended	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment was made
	Deleted	Recommendation from 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, but for which the evidence has not been reviewed
	Amended	Recommendation from 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 previous CPG that has been removed because it was deemed out of scope for the updated CPG

* Adapted from the NICE guideline manual (2012) [8] and Garcia et al. (2014) [9]

Abbreviations: CPG: clinical practice guideline; NICE: National Institute for Health and Care Excellence

b. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not 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 2014 VA/DoD Dyslipidemia 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.

For recommendations carried forward to the updated CPG with a review of the evidence and slightly modified wording, the “Reviewed, Amended” recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive

(i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

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.

c. 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 an updated systematic evidence review. Because of time and budget constraints, the update of the Dyslipidemia CPG could not review all available evidence on the management of dyslipidemia but instead focused its KQs on areas of new or updated scientific research or areas 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 systematic review of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the 2014 VA/DoD Dyslipidemia 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 Dyslipidemia CPG that were carried forward unchanged to the updated version. The category of "Not reviewed, Amended" was used to designate recommendations that were modified from the 2014 VA/DoD Dyslipidemia CPG.

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, and condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2020 version of the guideline are noted in the Recommendations. The categories for the recommendations from the 2014 VA/DoD Dyslipidemia CPG are noted in Appendix G.

F. Drafting and Submitting the Final Clinical Practice Guideline

After the face-to-face meeting, the Champions and Work Group members were assigned to craft discussion sections to support the new recommendations and/or to update discussion sections from the 2014 VA/DoD Dyslipidemia CPG to support the amended "carried forward" recommendations. The Work Group also considered including in this CPG tables, appendices, and other sections from the 2014 VA/DoD Dyslipidemia CPG. During this time, the Champions and Work Group also revised the algorithm.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14 – 20 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.

Draft 3 of the CPG was made available for peer review and comment. This process is described in the section titled Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and patient summary. The final 2020 Dyslipidemia CPG was submitted to the EBPWG in April 2020.

Appendix B: Cardiovascular Disease Risk Calculators

Table B-1. Risk Calculators: Characteristics of Patient Population

		ACC/AHA pooled cohort [152-154]	PCE [27]	SRSRF [24]	VARS-CVD [28]	Framingham [26]
Sample size		24,626	26,689	23,893	1,512,092	360,737
Sex	**Women**	56.4%	14,984	11,032	76,155	171,395
	Men	43.6%	11,905	12,951	1,435,937	189,342
Race	**White**	82.6%	56.1%	18.0%	71.0%	87%
	Black/African American	17.4%	29.4%	82.0%	14.2%	0.0%
	Asian/Pacific Islander	0.0%	0.0%	0.0%	0.0%	0.0%
	American Indians	0.0%	0.0%	0.0%	0.0%	0.0%
	Other	0.0%	0.0%	0.0%	14.6%	13.0%
Age	**Mean**	56.3	57.5	64.2	61.7	59
	Range	40 – 75	40 – 79	45+	45 – 80	40 – 79

Abbreviations: ACA/AHA: American College of Cardiology/American Heart Association; PCE: Pooled Cohort Equations; SRSRF: Self-Reported Stroke Risk Function; VARS-CVD: Veterans Affairs Risk Score for Cardiovascular Disease

Appendix C: Pharmacotherapy

Table C-1. Summary of Statin and Non-statin Pharmacologic Agents*

	Drug Category	Dose	Major Drug Interactions	Adverse Drug Reactions	Notes
Statins	Atorvastatin	10 – 80 mg once daily	Since statins vary in their metabolic pathway, refer to product labeling for drug-drug interactions and statin dose limits	Risk for myalgia, myopathy and, very rarely, rhabdomyolysis. Other risks include diabetes, LFT elevations, and asymptomatic CK elevations.	First line therapy for primary or secondary prevention of CVD
	Rosuvastatin	5 – 40 mg once daily			
	Simvastatin	5 – 40 mg once daily			
	Lovastatin	20 – 80 mg once daily			
	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	Increased incidence of transaminase elevation >3x ULN when combined with statins versus statins alone (1.3% versus 0.4%, respectively)	Generally well tolerated	Benefit for reducing non-fatal CV events in secondary prevention patients in addition to statin
PCSK9 inhibitors	Alirocumab	75 mg once every 2 weeks *OR* 300 mg once every 4 weeks Max: 150 mg every 2 weeks	No known significant interactions	• Injection site reactions (3 – 7%). Adverse reactions with PCSK9 inhibitors reported in RCTs appear to be similar to placebo. • Alirocumab had higher incidence of influenza, bronchitis, myalgia, muscle spasm, sinusitis, cough, and musculoskeletal pain compared to placebo • Evolocumab had a higher incidence of cough, arthralgia, and fatigue	• Benefit for reducing non-fatal CV events in secondary prevention in addition to maximally tolerated statin +/- ezetimibe • It is recommended that patients receive maximally tolerated statins plus ezetimibe prior to adding alirocumab or evolocumab • Limited data on long-term safety
	Evolocumab	140 mg once every 2 weeks *OR* 420 mg once monthly			

	Drug Category	Dose	Major Drug Interactions	Adverse Drug Reactions	Notes
Omega-3 fatty acids	Icosapent ethyl	2 gm twice daily with meals	May enhance antiplatelet and anticoagulation effects. Caution with concomitant agents that increase risk of bleeding.	Arthralgia (2.3%), oropharyngeal pain, peripheral edema, constipation, gout, and atrial fibrillation. Potential for allergic reactions in patients with fish allergy.	• 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 • 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 events was also observed

* Refer to product prescribing insert 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.

Abbreviations: CK: creatine kinase; CV: cardiovascular; CVD: cardiovascular disease; dL: deciliter; gm: grams; LFT: liver function test; mg: milligrams; PCSK9: proprotein convertase subtilisin/kexin type 9; RCT: randomized controlled trial; TG: triglyceride; ULN: upper limit of the normal range

Appendix D: Patient Education on the Mediterranean Diet

Table D-1. Patient Education on the Mediterranean Diet [155]

Eat More	Eat Less
• Fruits and vegetables • Whole grains • Seafood (primarily fatty fish), skinless poultry • Tree nuts, peanuts, nut butters • Legumes • Olive oil • Low-fat milk and cheese • Red wine*	• Red meat • Processed meat • Full-fat milk and cheese • Butter or margarine • Commercial bakery goods • Avoid trans fat

* Providers should consider the risk of recommending alcohol to individual patients.

Appendix E: Patient Focus Group Methods and Findings

A. Methods

As part of the effort to update this CPG, the VA and DoD Leadership held a patient focus group on March 19, 2019, at the Walter Reed National Military Medical Center in Bethesda, MD. The aim of the focus group was to elicit patient perspectives of patients on a set of topics related to their dyslipidemia. The focus group considered a set of topics related to their dyslipidemia, including their treatment plan history, care delivery setting, medications, non-pharmacologic therapies, and the impact of therapy.

VA and DoD Leadership recruited participants for the focus group. Patients were not incentivized for their participation or reimbursed for travel expenses. Three patients participated in the focus group. There were two men and one woman, ranging in age from 50 – 70. One participant receives care at the VA, while the other two receive care from the DoD.

The Dyslipidemia CPG Work Group, with support from Lewin, developed a set of questions to help guide the focus group. The focus group facilitator led the discussion using the previously prepared questions as a general guide to elicit the patient's perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all of the listed questions were addressed.

B. Patient Focus Group Findings

a. Patients stressed the importance of lifestyle changes and felt these were the most important ways to reduce cardiovascular risk and improve their health

- All three participants understood that eating a healthy diet would reduce their CV risk and, for that reason, several implemented comprehensive dietary changes.
- Two participants took supplements that were not recommended by their provider – either in addition to, or instead of, pharmaceuticals.
- Two participants started exercising regularly after learning of their health issues, and they reported feeling better afterward.
- All three participants noted their risk of CVD has not impacted their quality of life.

b. Participants stressed the importance of patient education, fully understanding their CV risk, and learning about the available treatment options. Participants were highly motivated to manage their CV risk.

- All three participants felt that learning of their health risks – CV or otherwise – motivated them to take personal responsibility for their health.
- Participants use various mediums to learn about lipids and CV risk, including websites, family and friends, and providers external to the VA/DoD health care systems.
- Two participants found visual aids that explain the benefits and harms of statins useful, but thought these aids would be confusing in the absence of a provider's explanation.
- All three participants stated they were more likely to adhere to prescribed regimens if they had a strong relationship with their provider. Also, they place a premium on patient-centered care.

c. While all patients have used pharmacologic treatments, they noted various concerns with statins. In addition, they had a general preference for reducing their CV risk via non-pharmacologic treatments.

- All three participants generally did not experience issues regarding adherence to statins. However, some did struggle to take it at the proper time of day.
- Statin side effects varied for the three participants. One participant never had side effects. One participant experienced side effects, but the benefits outweighed the harms. Comparatively, two participants stopped taking statins because of side effects.
- All three participants had tried multiple statins and changed their course of treatment to reduce side effects.

d. Patients had health concerns in addition to their cholesterol and stressed the importance that providers consider comorbidities when managing their cholesterol.

- Two participants are primarily concerned with cholesterol levels and heart health, while another was more concerned with chronic conditions or other diseases posing more immediate barriers to their life.
- Whether dyslipidemia was a patient's primary health care concern depended on their risk levels, comorbidities, and family history.

e. Patients generally find mobile apps and smart devices useful for monitoring their health. Even though not all patients prefer telemedicine and other technology options, providers should be ready to offer these options.

- All three participants use devices (e.g., smartphone, smartwatch) for monitoring their health and some use this modality to share health information with providers.
- One participant communicated with a remote private provider via Skype and enjoys using this method of communication.

f. Despite variability in patient preferences regarding learning their cholesterol levels, patients agreed it was important to hear about the available screening tests. In addition, patients believed it is important that they understand their lipid levels and lipid profile results.

- All three participants have their lipids tested every six months as recommended by their provider.
- All three participants did not feel that fasting lipid testing was burdensome.
- Patient knowledge about lipid profiles varied. One patient used and advocated for providing advanced lipoprotein testing, while two participants were only aware of cholesterol, LDL, and HDL testing.
- All three participants felt that knowing their lipid profile has not made them feel better or worse, or improved their understanding of risk.

Appendix F: Evidence Table

Table F-1. Evidence Table[a,b,c]

Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
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 for	[20,21]	Weak against	Reviewed, Amended
2. For primary prevention in patients not on statin therapy, we suggest against routinely ordering a lipid panel more frequently than every 10 years.	Not applicable	[21-23]	Weak against	Reviewed, New-added
3. For cardiovascular risk assessment in primary prevention, we suggest using a 10-year risk calculator.	Weak for	[24-28]	Weak for	Reviewed, Amended
4. We suggest against the routine use of coronary artery calcium testing.	Weak against	[29] **Additional references**: [30,31]	Weak against	Reviewed, Not changed
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	[26,29,32-35]	Weak against	Reviewed, New-replaced
6. For primary prevention, we recommend offering a moderate-dose statin in patients with a ≥12% 10-year cardiovascular risk or low-density lipoprotein cholesterol ≥190 mg/dL or diabetes.	Weak for, Weak for, Strong for	[36-40,42,44,45,47-51] **Additional references**: [41,43,46,52,53]	Strong for	Reviewed, New-replaced

[a] 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 the 2019 evidence review or included in the evidence base for the 2014 VA/DoD Dyslipidemia CPG. The second set of references in the evidence column ("Additional References") includes references that provide additional information related to the recommendation but which were not systematically identified through a literature review. These references were not included in the evidence base for the recommendation and, therefore, did not influence the strength and direction of the recommendation.

[b] 2020 Strength of Recommendation column: Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[c] 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.

Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
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, Strong for	[36-40,42,44,45,47-51] **Additional references**: [41,43,46,52,53]	Weak for	Reviewed, New-replaced
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.	Strong for	[36,37,47,48,55-59,61,63] **Additional references**: [54,60,62]	Weak against	Reviewed, New-replaced
9. For primary prevention, there is insufficient evidence to recommend for or against using ezetimibe with or without statins.	Strong against	[64] **Additional references**: [65-67]	Neither for nor against	Reviewed, New-replaced
10. For primary prevention, we recommend against offering PCSK9 inhibitors due to unknown long-term safety, inconclusive evidence for benefit, and high cost.	Not applicable	[68,70-72] **Additional references**: [69]	Strong against	Reviewed, New-added
11. For secondary prevention, we recommend using at least a moderate-dose statin.	Strong for	[49,56,74] **Additional references**: [46,73]	Strong for	Reviewed, New-replaced
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	[55-59,61,75-79] **Additional references**: [54,60,62]	Weak for	Reviewed, New-replaced
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	[75,76,80,81]	Weak for	Reviewed, New-replaced
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 following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient's values and preferences.	Strong against	[68,70,79,82-85,88,89] **Additional references**: [67,86,87]	Weak for	Reviewed, New-replaced

Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
15. For primary or secondary prevention, we recommend against using niacin (i.e., supplements or prescriptions).	Strong against	[90-92] **Additional references**: [93]	Strong against	Reviewed, New-replaced
16. For primary or secondary prevention, we suggest against adding fibrates to statins.	Strong against	[90,94-97] **Additional references**: [93]	Weak against	Reviewed, New-replaced
17. There is insufficient evidence to recommend for or against using bempedoic acid with or without statins for either primary or secondary prevention.	Not applicable	[98]	Neither for nor against	Reviewed, New-added
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.	Not applicable	[99]	Neither for nor against	Reviewed, New-added
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.	Not applicable	[99]	Weak for	Reviewed, New-added
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.	Not applicable	[100]	Weak against	Reviewed, New-added
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.	Not applicable	[101-106] **Additional references**: [107,108]	Neither for nor against	Reviewed, New-added
22. We suggest against the routine monitoring of lipid levels in patients taking statins.	Strong against	[109-113] **Additional references**: [86,87]	Weak against	Reviewed, New-replaced
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.	Not applicable	[56,114,116,119,120] **Additional references**: [62,73,115,117,118]	Weak for	Reviewed, New-added
24. We suggest offering intensified patient care (e.g., phone calls, emails, patient education, drug regimen simplification) to improve adherence to lipid-lowering medications.	Not applicable	[121] **Additional references**: [122-127]	Weak for	Reviewed, New-added

Recommendation	2014 Strength of Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
25. For primary and secondary prevention of cardiovascular disease, we suggest a dietitian-led Mediterranean diet.	Weak for, Weak for	[128,129] **Additional references**: [130,131]	Weak for	Reviewed, New-replaced
26. For primary and secondary prevention of cardiovascular disease, we suggest regular aerobic physical activity of any intensity and duration.	Not applicable	[134-142] **Additional references**: [132,133]	Weak for	Reviewed, New-added
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.	Not applicable	[147] **Additional references**: [143-146]	Strong for	Reviewed, New-added

Appendix G: 2014 Recommendation Categorization Table

Table G-1. 2014 Recommendation Categorization Table[a,b,c,d,e,f]

Recommendation Number	Page	2014 Recommendation Text	2014 Strength of Recommendation	Recommendation Category	2020 Recommendation
1	18	We recommend CVD risk screening for men > age 35 and women > age 45, including a lipid profile and a risk calculation.	Strong for	Not reviewed, Deleted	–
2	18	We recommend against routine screening for dyslipidemia outside of the context of a cardiovascular risk assessment.	Strong against	Not reviewed, Deleted	–
3	19	For risk calculation, we suggest a 10-year risk calculator.	Weak for	Reviewed, Amended	Recommendation 3

[a] Recommendation Number column: This indicates the recommendation number of each recommendation within the 2014 VA/DoD Dyslipidemia CPG.
[b] Page column: This indicates the page number of each recommendation within the 2014 VA/DoD Dyslipidemia CPG.
[c] 2014 Recommendation Text column: This contains the wording of each recommendation from the 2014 VA/DoD Dyslipidemia CPG.
[d] 2014 Strength of Recommendation column: The 2014 VA/DoD Dyslipidemia CPG used the GRADE evidence rating system. The strength of recommendations in the 2014 VA/DoD Dyslipidemia CPG were: Strong for, Weak for, Neither for nor against, Weak against, or Strong against. Refer to the Grading Recommendations section for more information.
[e] Recommendation Category column: The Recommendation Category column indicates the way in which each 2014 VA/DoD Dyslipidemia CPG recommendation was updated. Refer to the Recommendation Categorization section for more information.
[f] 2020 Recommendation column: For recommendations that were carried forward to the 2020 VA/DoD Dyslipidemia CPG, this column indicates the new corresponding recommendation(s).

Recommendation Number	Page	2014 Recommendation Text	2014 Strength of Recommendation	Recommendation Category	2020 Recommendation
4	19	We suggest that patients being considered for statin therapy be assessed for other CVD risk factors, including, but not limited to, the following: a. Age (males >35 and females >45) b. Family history of premature coronary artery disease (CAD); definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative c. Current tobacco use/cigarette smoking (or within the last one month) d. Hypertension (systolic blood pressure [SBP] >140 mmHg or diastolic blood pressure [DBP] >90 mmHg confirmed on more than one occasion, or current therapy with anti-hypertensive medications) e. Diabetes mellitus (DM) (See VA/DoD DM CPG, http://www.healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf). A diagnosis of DM is made if any of the following: a) Fasting plasma glucose (FPG) is ≥126 mg/dL on at least two occasions, or b) A single hemoglobin A1c (HbA1c) reading of ≥ 6.5%, confirmed with a FPG ≥126 mg/dL (these tests can be done on the same or different days); or c) HbA1c is ≥ 7% on two occasions using a clinical laboratory methodology standardized to the net splanchnic glucose production (NSGP) (not at the point of care); or d) Symptoms of hyperglycemia and a casual (random) glucose ≥ 200 mg/dL on two occasions. However, casual (random) plasma glucose is not recommended as a routine screening test. f. Level of high density lipoprotein cholesterol (HDL-C) (Less than 40 mg/dL confirmed on more than one occasion) *Modified from the 2006 CPG without an updated systematic review of the evidence.**	Weak for	Not reviewed, Deleted	–
5	21	We suggest against the routine use of high-sensitivity C-reactive protein (hsCRP) testing.	Weak against	Reviewed, New-replaced	Recommendation 5
6	21	We suggest against the routine use of coronary artery calcium (CAC) testing.	Weak against	Reviewed, Not Changed	Recommendation 4

Recommendation Number	Page	2014 Recommendation Text	2014 Strength of Recommendation	Recommendation Category	2020 Recommendation
7	22	We suggest shared decision making regarding pharmacologic treatment for patients with an estimated 10-year CVD risk of 12% or greater that takes into consideration the known minimal harms and substantial benefits of moderate-dose therapy in this group of patients.	Weak for	Reviewed, New-replaced	Recommendation 6
8	22	We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater.	Weak for	Reviewed, New-replaced	Recommendation 6
9	22	We suggest considering a moderate-dose statin for patients with a 10-year CVD risk between 6% and 12% following a discussion of the known minimal harms, benefits derived from limited evidence, and an exploration of the patient's values and preferences.	Weak for	Reviewed, New-replaced	Recommendation 7
10	24	For primary prevention, we recommend a moderate dose statin as the agent of choice to reduce CVD risk if the patient chooses pharmacologic therapy.	Strong for	Reviewed, New-replaced	Recommendations 6 – 8
11	25	For primary prevention in patients who are unable to tolerate statins, we suggest reinforcing adherence to positive lifestyle changes. For patients who prefer to try pharmacotherapy, we suggest considering treatment with gemfibrozil or bile acid sequestrants (BAS), noting that these agents have been associated with only a small CVD risk reduction and studied in limited populations, e.g., males with low density lipoprotein cholesterol (LDL–C) >190 mg/dL.	Weak for	Reviewed, Deleted	–
12	27	We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy.	Weak for	Not reviewed, Deleted	–
13	27	We recommend against routinely measuring LFTs or CK after a moderate dose statin is initiated.	Strong against	Not reviewed, Deleted	–
14	29	In patients with established ASCVD, we recommend use of a moderate-dose statin following a discussion of the minimal harms, substantial benefits, and an exploration of the patient's values and preferences.	Strong for	Reviewed, New-replaced	Recommendation 11
15	29	In patients with ASCVD who are able to tolerate statins, we recommend against the routine use of non-statin lipid lowering drugs (e.g., fibrates, niacin, ezetimibe, omega-3 fatty acids, etc.) either alone as monotherapy or added to statins.	Strong against	Reviewed, New-replaced	Recommendations 9, 14, 15, 16

Recommendation Number	Page	2014 Recommendation Text	2014 Strength of Recommendation	Recommendation Category	2020 Recommendation
16	29	In patients with ASCVD who are unable to tolerate statins, we suggest reinforcing adherence to positive lifestyle changes and suggest offering niacin or gemfibrozil, noting that these agents have been associated with only a small CVD risk reduction and studied in limited populations (e.g., males with low HDL-C).	Weak for	Reviewed, Deleted	–
17	29	We strongly recommend against the routine monitoring of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD.	Strong against	Reviewed, New-replaced	Recommendation 22
18	29	We suggest offering a high-dose statin only in select patient populations (e.g., ACS, multiple uncontrolled risk factors or recurrent CVD events on moderate-dose statin) following a discussion of the added harms, small additional benefits, and an exploration of the patient's values and preferences.	Weak for	Reviewed, New-replaced	Recommendations 12, 13
19	29	We suggest measuring LFTs 4-12 weeks after the initiation of high-dose statin.	Weak for	Reviewed, Deleted	–
20	35	We recommend all adults adopt healthy lifestyles to reduce CVD risk, including: a. Tobacco cessation for all smokers (See 2008 Tobacco Use CPG, http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp) b. Therapeutic Lifestyle Changes (TLC) diet to optimize nutrition (For overweight and/or obese patients, see 2014 Obesity CPG, http://www.healthquality.va.gov/guidelines/CD/obesity/VADoDCPGManagementOfOverweightAndObesityFINAL070714.pdf) c. Optimal physical activity (See 2008 Physical Activity Guidelines for Americans, http://www.health.gov/paguidelines/pdf/paguide.pdf) *Modified from the 2006 CPG without an updated systematic review of the evidence*.	Strong for	Reviewed, Deleted	–
21	37	We suggest offering high-risk patients (see text for definition) a dietitian-monitored Mediterranean diet supplemented with either extra-virgin olive oil (roughly 1 liter per week) or 30 grams (g) of mixed nuts per day (15g of walnuts, 7.5g of hazelnuts, and 7.5g of almonds) for the reduction of CVD events.	Weak for	Reviewed, New-replaced	Recommendation 25

Recommendation Number	Page	2014 Recommendation Text	2014 Strength of Recommendation	Recommendation Category	2020 Recommendation
22	37	We suggest that each patient's diet be individualized based on a nutrition assessment (preferably by a registered dietitian [RD]), other CVD risk factors, other disease conditions, and lifestyle. *Modified from the 2006 CPG without an updated systematic review of the evidence*.	Weak for	Reviewed, Deleted	–
23	38	We recommend treating the common secondary causes of elevated triglycerides (TGs): dietary indiscretion (e.g., refined sugars), alcohol use, hypothyroidism, and hyperglycemia. *Modified from the 2006 CPG without an updated systematic review of the evidence*.	Strong for	Reviewed, Deleted	–
24	39	We suggest for patients with TGs greater than 500 mg/dL a strict diet therapy including avoidance of alcohol, restriction of dietary fat, and avoidance of refined sugars. We suggest for patients with TGs greater than 1000 mg/dL a very low fat diet to reduce chylomicronemia and risk of acute pancreatitis.	Weak for	Reviewed, New-replaced	Recommendation 25
25	40	We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy.	Weak for	Reviewed, Amended	Recommendation 1
26	40	We suggest CVD risk assessment every two years for patients with intermediate CVD risk or with appearance of a new CVD risk factor (e.g., new diagnosis of type 2 diabetes mellitus [DM] or hypertension) and not on statin therapy.	Weak for	Reviewed, Deleted	–

Appendix H: Participant List

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Appendix I: Abbreviation List

Abbreviation	Definition
AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACS	acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
Apo	apolipoproteins
ARR	absolute risk reduction
AUC	area under the curve
BID	twice per day
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CAC	coronary artery calcium
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CI	confidence intervals
CK	creatinine kinase
CKD	chronic kidney disease
COR	contracting officer's representative
cPCE	calibrated Pooled Cohort Equation
CPGs	clinical practice guidelines
CTT	Cholesterol Treatment Trialists
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
dL	deciliter
DM	diabetes mellitus
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
ECG	electrocardiogram
EF	ejection fraction
ESRD	end-stage renal disease
FDA	U.S. Food and Drug Administration
FH	familial hypercholesterolemia
FRS	Framingham Risk Score
g	grams
GI	gastrointestinal

Abbreviation	Definition
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL-C	high-density lipoprotein cholesterol
HEC	Health Executive Committee
HF	heart failure
hsCRP	high-sensitivity C-reactive protein
IOM	Institute of Medicine
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
KQs	key questions
LDL-C	low-density lipoprotein cholesterol
LFT	liver function tests
MACE	major adverse cardiac events
mg	milligrams
MHS	Military Health System
MI	myocardial infarction
NAM	National Academy of Medicine
NICE	National Institute for Health and Care Excellence
NNH	number needed to harm
NNT	number needed to treat
OR	odds ratio
OTC	over-the-counter
PAD	peripheral arterial disease
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PICOTS	the population, intervention, comparison, outcome, timing and setting
RCT	randomized controlled trial
RD	registered dietitian
RRR	relative risk reduction
SR	systematic review
TC	total cholesterol
TGs	triglycerides
TIA	transient ischemic attack
U.K.	United Kingdom
U.S.	United States
ULN	upper limit of the normal range
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

Appendix J: Literature Search Strategy

A. EMBASE with EMBASE.com Syntax

Question	Set #	Concept	Strategy
Question 1 – Time to repeat screening for CV risk (Note: this search builds upon the search for Questions 2 and 3, which include specific terms for CV risk)	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	Screening/risk assessment	'mass screening'/exp OR 'multiphasic screening'/exp OR 'screening test'/exp OR 'risk assessment'/exp OR ((risk or risks) NEAR/4 (stratify or stratifying or stratification or define or defining or predict or prediction or assess* OR classif* OR prioritiz* OR category* OR tier* OR calculat* OR index OR indices OR score OR scores OR marker* OR biomarker* OR profile* OR algorithm* OR factor* OR characteristic*)):ti,ab OR (cardiovascular NEAR/2 risk*)
	#3	Repeat screening/ monitoring	'time factor'/exp OR 'rescreening'/exp OR monitoring/exp OR (rescreen* OR re-screen* OR surveillance OR re-assess* OR monitor* OR ((repeat or repet* or replicat* or redo or "re-do" or rerun or "re-run" or subsequent* or redundant* or re-assess* or reassess* OR "follow up" OR "follow-up") NEAR/4 (test* or screen* OR assess*))):ti,ab
	#4	Outcomes of interest	'cardiovascular disease'/exp/mj/dm_pc 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* OR (cerebrovascular NEXT/1 accident*) OR morbidity OR mortality OR death OR (heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*) OR (heart NEXT/1 infarct*)):ti,ab OR (morbidity OR mortality OR prevent* OR outcome*):ti,ab OR (primary NEXT/1 prevention):ti,ab OR angina:ti,ab
	#5	Combine sets	#1 AND #2 AND #3 AND #4
	#6	Limit to RCTs/SRs/meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#7	Limit to additional study designs	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham):ti,ab OR ((versus OR vs):ti)
	#8	Combine sets	#5 AND (#6 OR #7)
	#9	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 2 – Stability of lipid levels over time	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CVD	'cardiovascular disease'/exp/mj/dm_pc OR 'cardiovascular disease'/de OR 'hypertension'/exp OR 'ischemic heart disease'/exp OR 'heart disease'/de OR 'coronary artery disease'/exp OR 'peripheral vascular disease'/exp OR 'cerebral artery disease'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'cerebrovascular disease'/exp OR 'heart infarction'/exp OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti,de OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti,ab
	#3	Monitoring of lipid levels over time	'lipid blood level'/exp AND (monitoring/exp OR 'time factor'/exp) OR ((cholesteryl* or cholesterol* or lipid* or lipoprotein* or tryglycer* or triaclyglycer* or "HDL-C" or "LDL-C" or "HDL C" or "LDL C" or "non HDL C" or "non-HDL C" or "non-HDL-C") NEAR/5 (level or levels or blood OR value*) NEAR/5 (monitor* OR surveillance OR stable OR stability OR variability OR variable OR "long term" OR "long-term" OR longitud* OR trend*)):ti,ab
	#4	Combine sets	(#1 OR #2) AND #3
	#5	Limit to RCTs/SRs/meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#6	Limit to additional study designs	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham):ti,ab OR ((versus OR vs):ti)
	#7	Combine sets	#4 AND (#5 OR #6)
	#8	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 3 – Methods for risk stratification	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CVD	'cardiovascular disease'/exp/mj OR 'hypertension'/exp/mj OR 'ischemic heart disease'/exp/mj OR 'heart disease'/mj OR 'coronary artery disease'/exp/mj OR 'peripheral vascular disease'/exp/mj OR 'cerebral artery disease'/exp/mj OR 'brain ischemia'/exp/mj OR 'cerebrovascular accident'/exp/mj OR 'cerebrovascular disease'/exp/mj OR 'heart infarction'/exp/mj OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti
	#3	Risk prediction/ stratification	'risk factor'/exp/mj OR 'risk assessment'/exp/mj OR 'cardiovascular risk'/exp/mj OR ((risk or risks) NEAR/4 (stratify or stratifying or stratification or define or defining or predict or prediction or assessment OR classif* OR prioritiz* OR category* OR tier* OR calculat* OR index OR indices OR score OR scores OR marker* OR biomarker* OR profile* OR algorithm* OR factor* OR characteristic*)):ti OR (cardiovascular NEAR/2 risk*):ti
	#4	Risk stratification tools	'lipid analysis'/exp OR 'lipid blood level'/exp OR 'framingham risk score'/exp OR 'ankle brachial index'/exp OR 'coronary artery calcium score'/exp OR 'galectin 3'/exp OR 'c reactive protein'/exp OR 'apolipoprotein b'/exp OR 'lipoprotein a'/exp OR 'arterial wall thickness'/exp OR 'troponin I'/exp OR ((framingham NEXT/2 risk*) OR 'ankle brachial index' OR (coronary NEXT/4 calcium) OR ('c reactive' NEXT/2 protein*) OR 'hs-crp' OR 'hs crp' OR 'hscrp' OR 'ntprobnp' OR 'nt-probnp' OR 'hs-tnl' OR 'hs tnl' OR 'galecton 3' OR 'galecton-3' OR 'pooled cohort' OR (particle NEXT/2 size*) OR (high NEXT/1 sensitiv* NEXT/1 troponin*) OR apolipoprotein* OR lipoprotein* OR (carotid NEXT/1 intima* NEXT/3 thickness*)):ti,ab OR ((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C" OR "non HDL C" OR "non-HDL C" OR "non-HDL-C") NEXT/5 (level OR levels)):ti
	#5	Outcomes of interest	'cardiovascular disease'/exp/mj/dm_pc 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* OR (cerebrovascular NEXT/1 accident*) OR morbidity OR mortality OR death OR (heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*) OR (heart NEXT/1 infarct*)):ti,ab OR (morbidity OR mortality OR prevent* OR outcome*):ti,ab OR (primary NEXT/1 prevention):ti,ab OR angina:ti,ab
	#6	Combine sets – dyslipidemia terms plus CV outcomes	#1 AND #3 AND #4 AND #5
	#7	Combine sets – CV terms without the outcomes string	#2 AND #3 AND #4

Question	Set #	Concept	Strategy
Question 3 – Methods for risk stratification (cont.)	#8	Combine sets	#6 OR #7
	#9	Limit to RCTs/SRs/meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#10	Limit to additional study designs	'latin square design'/de OR 'controlled study'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR 'cohort analysis'/de OR 'follow up'/de OR 'intermethod comparison'/de OR 'parallel design'/de OR 'control group'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'case control study'/exp OR 'major clinical study'/de OR 'evaluation study'/exp OR (cohort* OR longitudinal OR prospective OR retrospective OR "case control" OR compar* OR "control group" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "matched controls" OR placebo* OR random* OR sham):ti,ab OR ((versus OR vs):ti)
	#11	Diagnostic test hedge	'diagnostic test accuracy':de OR 'diagnosis':lnk OR 'differential diagnosis'/exp OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR ('sensitivity' AND 'specficity') OR 'accuracy':de OR 'precision'/exp OR precision OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR ppv OR ((false OR true) NEAR/1 (positive OR negative)) OR diagnos* or PPV OR "receiver operating characteristic" or (area NEXT/1 under NEXT/3 curve) OR AUC or "diagnostic accuracy"
	#12	Combine sets	#8 AND (#9 OR (#10 AND #11))
	#13	Apply limits	See Search Limits at the end of the table
Questions 4, 6, 8, 9 – Pertaining to pharmacologic treatment including cost	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CVD	'cardiovascular disease'/exp/mj/dm_pc OR 'cardiovascular disease'/de OR 'hypertension'/exp OR 'ischemic heart disease'/exp OR 'heart disease'/de OR 'coronary artery disease'/exp OR 'peripheral vascular disease'/exp OR 'cerebral artery disease'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'cerebrovascular disease'/exp OR 'heart infarction'/exp OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti,de OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti,ab
	#3	Pharmacologic treatments: statins	'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp OR 'hypocholesterolemic agent'/exp OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) NEAR/5 reductase):ti OR (HMG NEXT/1 CoA):ti OR (statin* OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin):ti
	#4	Pharmacologic treatments: non-statins	'fibric acid derivative'/exp OR 'gemfibrozil'/exp OR 'hypocholesterolemic agent'/exp OR 'nicotinic acid'/exp OR 'bile acid sequestrant'/exp OR 'ezetimibe'/exp OR 'omega 3 fatty acid'/exp OR (fibrate* OR gemfibrozil OR fenofibrate OR bezafibrate OR (nicotinic NEXT/1 acid*) OR niacin OR (“bile acid” NEXT/1 (sequestrant* OR resin*)) OR ezetimibe OR ((omega* OR marine) NEXT/3 fatty) OR pcsk9 OR “pcsk-9” OR “pcsk 9” OR ((eicosapentaenoic OR docosahexaenoic) NEXT/1 acid*) OR “icosapent ethyl” OR “fish oil”):ti,ab

Question	Set #	Concept	Strategy
Questions 4, 6, 8, 9 – Pertaining to pharmacologic treatment including cost (cont.)	#5	Outcomes of interest	'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* OR (cerebrovascular NEXT/1 accident*) OR morbidity OR mortality OR death OR (heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*) OR (heart NEXT/1 infarct*)):ti,ab OR (morbidity OR mortality OR prevent* OR outcome*):ti,ab OR (secondary NEXT/1 prevention):ti,ab OR (primary NEXT/1 prevention):ti,ab OR angina:ti,ab OR 'adverse event'/exp OR 'side effect'/exp OR 'safety'/de OR ((side NEXT/1 effect*) OR (adverse NEXT/1 event*) OR safe OR safety):ti,ab
		Additional outcome of interest for KQ 8 [change in lipid levels]	((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C") AND (level OR levels OR lower OR low OR reduce OR reduction OR profile* OR target*)).ti,ab
	#6	Combine sets – including outcomes of interest	(#1 OR #2) AND (#3 OR #4) AND #5
	#7	Combine sets – without outcomes of interest	(#1 OR #2) AND (#3 OR #4)
	#8	Limit to RCTs	Randomized controlled trials hedge [see Search Limits at the end of this table]
	#9	Limit to SRs/meta-analyses	systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#10	Limit to cost studies	'health care cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR (cost OR costs OR costly OR costing OR price OR prices OR saving OR savings OR economi* OR financial OR finance* OR pharmacoeconomic* OR QALY or QALYs OR (quality NEXT/1 adjusted NEXT/1 life NEXT/1 year*) or (quality NEXT/1 adjusted life NEXT/1 expectanc*)):ti,ab
	#11	Combine sets	#6 AND (#8 OR #9)
	#12	Combine sets	#7 AND (#9 OR #10)
	#13	Combine sets	#11 OR #12
	#14	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 5 – Pharmacologic treatment to reach specific LDL-C or non-HDL-C goals	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CVD	'cardiovascular disease'/exp/mj/dm_pc OR 'cardiovascular disease'/de OR 'hypertension'/exp OR 'ischemic heart disease'/exp OR 'heart disease'/de OR 'coronary artery disease'/exp OR 'peripheral vascular disease'/exp OR 'cerebral artery disease'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'cerebrovascular disease'/exp OR 'heart infarction'/exp OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti,de OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti,ab
	#3	LDL-C or non-HDL-C goals	(('low density lipoprotein cholesterol level'/exp OR 'high density lipoprotein cholesterol level'/exp) AND (goal OR goals OR target* OR level 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 tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C" OR "non HDL C" OR "non-HDL C" OR "non-HDL-C") NEAR/5 (goal OR goals OR target* OR level OR levels)):ti,ab
	#4	Statins	'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp OR 'hypocholesterolemic agent'/exp OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) NEAR/5 reductase):ti OR (HMG NEXT/1 CoA):ti OR (statin* OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin):ti
	#5	Non-statins	'fibric acid derivative'/exp OR 'gemfibrozil'/exp OR 'hypocholesterolemic agent'/exp OR 'nicotinic acid'/exp OR 'bile acid sequestrant'/exp OR 'ezetimibe'/exp OR 'omega 3 fatty acid'/exp OR (fibrate* OR gemfibrozil OR fenofibrate OR bezafibrate OR (nicotinic NEXT/1 acid*) OR niacin OR ("bile acid" NEXT/1 (sequestrant* OR resin*)) OR ezetimibe OR ((omega* OR marine) NEXT/3 fatty) OR pcsk9 OR "pcsk-9" OR "pcsk 9" OR ((eicosapentaenoic OR docosahexaenoic) NEXT/1 acid*) OR "icosapent ethyl" OR "fish oil"):ti,ab
	#6	Outcomes of interest	'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* OR (cerebrovascular NEXT/1 accident*) OR morbidity OR mortality OR death OR (heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*) OR (heart NEXT/1 infarct*)):ti,ab OR (morbidity OR mortality OR prevent* OR outcome*):ti,ab OR (secondary NEXT/1 prevention):ti,ab OR (primary NEXT/1 prevention):ti,ab OR angina:ti,ab OR ('adverse event'/exp OR 'side effect'/exp OR 'safety'/de OR ((side NEXT/1 effect*) OR (adverse NEXT/1 event*) OR safe OR safety)):ti,ab

Question	Set #	Concept	Strategy
Question 5 – Pharmacologic treatment to reach specific LDL-C or non-HDL-C goals (cont.)	#7	Combine sets	(#1 OR #2) AND #3 AND (#4 OR #5 OR #6)
	#8	RCTs/SRs/Meta-analyses	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#9	Combine sets	#7 AND #8
	#10	Apply limits	See Search Limits at the end of the table
Question 7 – Strategies to improve patient tolerance to statins	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CVD	'cardiovascular disease'/exp/mj/dm_pc OR 'cardiovascular disease'/de OR 'hypertension'/exp OR 'ischemic heart disease'/exp OR 'heart disease'/de OR 'coronary artery disease'/exp OR 'peripheral vascular disease'/exp OR 'cerebral artery disease'/exp OR 'brain ischemia'/exp OR 'cerebrovascular accident'/exp OR 'cerebrovascular disease'/exp OR 'heart infarction'/exp OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti,de OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti,ab
	#3	Statin tolerance/adherence/ substitution (controlled terms)	('hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp OR 'hypocholesterolemic agent'/exp) AND ('medication compliance'/exp OR 'patient compliance'/exp OR 'drug substitution'/exp OR 'drug dose intensification'/exp OR 'drug dose reduction'/exp)
	#4	Statin tolerance/ adherence/ substitution (keywords)	((hydroxymethylglutaryl or hydroxy-methylglutaryl) NEAR/5 reductase*) OR "HMG CoA" or statin* or lovastatin or meglutol or pravastatin or atorvastatin or simvastatin):ti,ab AND (tolerate* or tolerance or adher* or nonadherence* or non-adherence or ((alternat* or low or lower or high or higher or increase or decrease) NEXT/3 dose or dosing or dosag*)):ti,ab
	#5	Combine sets	(#1 OR #2) AND (#3 OR #4)
	#6	RCTs/SRs/Meta-analyses	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#7	Combine sets	#5 AND #6
	#8	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Questions 9, 10, 11, 12 – Pertaining to non-pharmacologic treatment including cost	#1	Dyslipidemia	dyslipidemia/exp OR 'hypercholesterolemia'/exp OR cholesterol/exp OR lipid/de OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia):ti,ab OR ((high OR elevated OR low) NEAR/5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C")):ti,ab
	#2	CV risk	('cardiovascular disease'/exp/mj OR 'hypertension'/exp/mj OR 'ischemic heart disease'/exp/mj OR 'heart disease'/mj OR 'coronary artery disease'/exp/mj OR 'peripheral vascular disease'/exp/mj OR 'cerebral artery disease'/exp/mj OR 'brain ischemia'/exp/mj OR 'cerebrovascular accident'/exp/mj OR 'cerebrovascular disease'/exp/mj OR 'heart infarction'/exp/mj OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) NEAR/5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)):ti OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR stroke* OR (cerebrovascular NEXT/1 accident*)):ti) AND (risk* OR prevent*):ti
	#3	Dietary supplements/ neutraceuticals	'dietary supplement'/exp OR 'plant medicinal product'/exp OR 'omega 3 fatty acid'/exp OR 'vitamin'/de OR garlic/exp OR 'dietary fiber'/exp OR 'ginger'/exp OR 'phytosterol'/exp OR 'ispagula'/exp OR 'tea'/exp OR (((diet OR dietary) NEAR/5 supplement*) OR neutraceutical* OR ((omega* OR marine) NEXT/3 fatty) or "fish oil" OR ((eicosapentaenoic OR docosahexaenoic) NEXT/1 acid*) OR “icosapent ethyl” OR ((diet* OR soluable) NEAR/5 fiber) OR garlic OR ginger OR phytosterol* OR (plant NEXT/2 sterol*) OR (green NEXT/1 tea*) OR niacin* OR psyllium):ti
	#4	Diet therapy	'diet therapy'/exp OR ((Diet or diets or dietary or nutrition) and ("low sodium" or "low fat" or (gluten next/2 free) or "low gluten" or "low carb" or "low carbohydrate" or "low calorie" or vegetarian or vegan or macrobiotic or Mediterranean or DASH)):ti or "diabetic diet":ti or (dietary next/1 approach* NEXT/1 stop NEXT/1 hypertension):ti or diet*:ti
	#5	Exercise	'exercise'/exp OR (aerobics OR dance OR dancing OR exercise* OR fitness OR kinesiotherapy OR "muscle strengthening" OR "physical activity" OR "physical conditioning" OR "plyometric training" OR "resistance training" OR "strength training" OR "tai chi" OR "tai-chi" OR walk* OR "weight lifting" OR yoga OR swim OR swimming OR run OR running OR "weight training"):ti
	#6	Outcomes of interest	'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* OR (cerebrovascular NEXT/1 accident*) OR morbidity OR mortality OR death OR (heart NEXT/1 attack*) OR (myocardial NEXT/1 infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) NEXT/2 event*) OR (heart NEXT/1 infarct*)):ti,ab OR (morbidity OR mortality OR prevent* OR outcome*):ti,ab OR (secondary NEXT/1 prevention):ti,ab OR (primary NEXT/1 prevention):ti,ab OR angina:ti,ab OR ((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C") AND (level OR levels OR lower OR low OR reduce OR reduction OR profile*)):ti,ab OR ('adverse event'/exp OR 'side effect'/exp OR 'safety'/de OR ((side NEXT/1 effect*) OR (adverse NEXT/1 event*) OR safe OR safety):ti,ab
	#7	Combine sets – including outcomes of interest	(#1 OR #2) AND (#3 OR #4 OR #5) AND #6

Question	Set #	Concept	Strategy
Questions 9, 10, 11, 12 – Pertaining to non-pharmacologic treatment including cost (cont.)	#8	Combine sets – without outcomes of interest	(#1 OR #2) AND (#3 OR #4 OR #5)
	#9	Limit to RCTs	Randomized controlled trials hedge [see Search Limits at the end of this table]
	#10	Limit to SRs/Meta-analysis	Systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#11	Limit to cost studies (KQ 9)	'health care cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR (cost OR costs OR costly OR costing OR price OR prices OR saving OR savings OR economi* OR financial OR finance* OR pharmacoeconomic* OR QALY or QALYs OR (quality NEXT/1 adjusted NEXT/1 life NEXT/1 year*) or (quality NEXT/1 adjusted life NEXT/1 expectanc*)):ti,ab
	#12	Combine sets	#7 AND (#9 OR #10)
	#13	Combine sets	#8 AND (#10 OR #11)
	#14	Combine sets	#12 OR #13
	#15	Apply limits	See Search Limits at the end of this table
Search Limits Applied to Each Search		Limit to humans and items published since searches were conducted for 2014 CPG [December 9, 2013]	AND [humans]/lim AND [english]/lim AND [9-12-2013]/sd NOT [2019]/sd
		Exclude conference publications, books, letters, editorials, case studies, etc.	(abstract:nc OR annual:nc OR book/de OR 'case report'/de OR 'case study'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/de OR editorial:it OR erratum/de OR letter:it OR note/de OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/de OR symposium:nc)
		Limit to meta-analyses and SRs	AND ('systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis')
		Limit to RCTs	('randomized controlled trial'/exp OR 'randomization'/de OR 'double blind procedure'/de OR 'single blind procedure'/de OR 'placebo'/de OR 'crossover procedure'/de OR placebo* OR random*:ti,de OR crossover* OR 'cross over' OR ((singl* OR doubl* OR tripl* OR trebl*) AND (blind* OR mask* OR sham*)) OR 'latin square' OR isrtcn* OR actrn* OR (nct* NOT nct))

B. MEDLINE with Ovid Syntax

Question	Set #	Concept	Strategy
Question 1 – Time to repeat screening for CV risk (Note: this search builds upon the search for Questions 2 and 3 which include specific terms for CV risk)	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	Screening/risk assessment	mass screening/ or exp multiphasic screening/ OR risk assessment/ OR ((risk or risks) ADJ4 (stratify or stratifying or stratification or define or defining or predict or prediction or assess* OR classif* OR prioritiz* OR category* OR tier* OR calculat* OR index OR indices OR score OR scores OR marker* OR biomarker* OR profile* OR algorithm* OR factor* OR characteristic*)).ti,ab. OR (cardiovascular ADJ2 risk*)
	#3	Repeat screening/ monitoring	Exp time factors/ OR Monitoring, Physiologic/ OR (rescreen* OR re-screen* OR surveillance OR re-assess* OR monitor* OR ((repeat or repet* or replicat* or redo or "re-do" or rerun or "re-run" or subsequent* or redundant* or re-assess* or reassess*OR "follow up" OR "follow-up") ADJ4 (test* or screen* OR assess*))).ti,ab.
	#4	Outcomes	exp *Cardiovascular Diseases/pc OR exp primary prevention/ OR exp mortality/ OR exp morbidity/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR stroke/ OR exp Angina, Unstable/ OR (stroke* OR (cerebrovascular ADJ accident*) OR morbidity OR mortality OR death OR (heart ADJ attack*) OR (myocardial ADJ infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) ADJ2 event*) OR (heart ADJ infarct*)).ti,ab. OR (morbidity OR mortality OR prevent* OR outcome*).ti,ab. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab. OR angina.ti,ab.
	#5	Combine sets	#1 AND #2 AND #3 AND #4
	#6	Limit to RCTs/SRs/ Meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#7	Limit to additional study designs	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ or exp clinical trial/ or exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/ OR exp case-control studies/ OR follow-up studies/
	#8	Combine sets	#5 AND (#6 OR #7)
	#9	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 2 – Stability of lipid levels over time	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	CVD	exp *Cardiovascular Diseases/pc or cardiovascular diseases/ or heart diseases/ or vascular diseases/ or exp arterial occlusive diseases/ or cerebrovascular disorders/ or exp brain ischemia/ or exp stroke/ or exp myocardial ischemia/ or exp myocardial Infarction/ or exp heart arrest/ or exp hypertension/ or exp peripheral vascular diseases/ or ((heart* or cardio* or cardiac* or coronary or vascular or cerebrovascular or artery or arteries) ADJ5 (disease* or syndrome* or event* or ischem* or ischaem* or plaque*)).ti,ab. or (hyperten* or atherosclero* or arteriosclero* or angina or (Heart ADJ attack*) or (myocardial ADJ infarct*) or stroke* or (cerebrovascular ADJ accident*)).ti,ab.
	#3	Monitoring of lipid levels over time	(Lipids/an,bl,td OR exp Cholesterol/an,bl,td) AND (Exp Monitoring, physiologic/ OR exp lipid analysis/ OR exp lipid metabolism/ OR Exp time factors/) OR ((cholesteryl* or cholesterol* or lipid* or lipoprotein* or tryglycer* or triaclyglycer* or "HDL-C" or "LDL-C" or "HDL C" or "LDL C" or "non HDL C" or "non-HDL C" or "non-HDL-C") ADJ5 (level or levels or blood OR value*) ADJ5 (monitor* OR surveillance OR stable OR stability OR variability OR variable OR "long term" OR "long-term" OR longitud* OR trend*)).ti,ab.
	#4	Combine sets	(#1 OR #2) AND #3
	#5	Limit to RCTs/SRs/ Meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#6	Limit to additional study designs	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ or exp clinical trial/ or exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/ OR exp case-control studies/
	#7	Combine sets	#4 AND (#5 OR #6)
	#8	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 3 – Methods for risk stratification	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	CVD	exp *Cardiovascular Diseases/ OR *heart diseases/ or *vascular diseases/ or exp *arterial occlusive diseases/ or *cerebrovascular disorders/ OR exp *brain ischemia/ or exp *stroke/ or exp *myocardial ischemia/ OR exp *myocardial Infarction/ OR exp *heart arrest/ OR exp *hypertension/ OR exp *peripheral vascular diseases/ OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) ADJ5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)).ti. OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart ADJ attack*) OR (myocardial ADJ infarct*) OR stroke* OR (cerebrovascular ADJ accident*)).ti.
	#3	Risk prediction/stratification	exp *risk factors/ OR exp*risk assessment/ OR ((risk or risks) ADJ4 (stratify or stratifying or stratification or define or defining or predict or prediction or assessment OR classif* OR prioritiz* OR category* OR tier* OR calculat* OR index OR indices OR score OR scores OR marker* OR biomarker* OR profile* OR algorithm* OR factor* OR characteristic*)).ti. OR (cardiovascular ADJ2 risk*).ti.
	#4	Risk stratification tools	Lipids/an,bl OR exp Cholesterol/an,bl OR exp Ankle Brachial Index/ OR exp Galectin 3/ OR C-Reactive Protein/ OR exp Apolipoproteins B/ OR exp Carotid Intima-Media Thickness/ OR c-reactive protein/ or exp Troponin I/ OR ((framingham ADJ2 risk*) OR 'ankle brachial index' OR (coronary ADJ2 calcium) OR ('c reactive' ADJ2 protein*) OR 'hs-crp' OR 'hs crp' OR 'hscrp' OR 'ntprobnp' OR 'nt-probnp' OR 'hs-tnl' OR 'hs tnl' OR 'galecton 3' OR 'galecton-3' OR 'pooled cohort' OR (particle ADJ2 size*) OR (high ADJ sensitiv* ADJ troponin*) OR apolipoprotein* OR lipoprotein* OR (carotid ADJ1 intima* ADJ3 thickness*)).ti,ab. OR ((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C" OR "non HDL C" OR "non-HDL C" OR "non-HDL-C") ADJ5 (level OR levels)).ti.
	#5	Outcomes of interest	exp *Cardiovascular Diseases/pc OR exp primary prevention/ OR exp mortality/ OR exp morbidity/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR stroke/ OR exp Angina, Unstable/ OR (stroke* OR (cerebrovascular ADJ accident*) OR morbidity OR mortality OR death OR (heart ADJ attack*) OR (myocardial ADJ infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) ADJ2 event*) OR (heart ADJ infarct*)).ti,ab. OR (morbidity OR mortality OR prevent* OR outcome*).ti,ab. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab. OR angina.ti,ab.
	#6	Combine sets – dyslipidemia terms plus CV outcomes	#1 AND #3 AND #4 AND #5
	#7	Combine sets – CV terms without the outcomes string	#2 AND #3 AND #4
	#8	Combine sets	#6 OR #7
	#9	Limit to RCTs/SRs/Meta-analysis	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]

Question	Set #	Concept	Strategy
Question 3 – Methods for risk stratification (cont.)	#10	Limit to additional study designs	exp cohort studies/ OR exp longitudinal studies/ OR exp retrospective studies/ OR exp prospective studies OR exp controlled study/ or exp clinical trial/ or exp comparative study/ OR major clinical study/ OR cross-over studies/ or crossover procedure/ or cross over studies/ OR observational study/ OR validation studies/ OR exp case-control studies/ti
	#11	Diagnostic test hedge	exp diagnosis/ or di.fs. or receiver operating characteristic/ or ROC curve/ or (sensitivity/ and specificity/) or accuracy/ or diagnostic accuracy/ or precision or (prediction and forecasting) or likelihood or ((false or true) ADJ (positive or negative)) or predictive value of tests/ or exp diagnostic errors/ or exp diagnostic error/ or diagnostic accuracy/ or positive predictive value or PPV OR (predictive value of tests or receiver operating characteristic or ROC curve or (sensitivity and specificity) or accuracy or diagnostic accuracy or precision or likelihood).de. OR ((false or true) ADJ (positive or negative)).mp.
	#12	Combine sets	#8 AND (#9 OR (#10 AND #11))
	#13	Apply limits	See Search Limits at the end of the table
Questions 4, 6, 8, 9 – Pertaining to pharmacologic treatment including cost	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR exp lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	CVD	exp *Cardiovascular Diseases/pc OR cardiovascular diseases/ or heart diseases/ or vascular diseases/ or exp arterial occlusive diseases/ or cerebrovascular disorders/ OR exp brain ischemia/ or exp stroke/ or exp myocardial ischemia/ OR exp myocardial Infarction/ OR exp heart arrest/ OR exp hypertension/ OR exp peripheral vascular diseases/ OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) ADJ5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)).ti,ab. OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart ADJ attack*) OR (myocardial ADJ infarct*) OR stroke* OR (cerebrovascular ADJ accident*)).ti,ab.
	#3	Pharmacologic treatments: statins	exp Hypolipidemic Agents/ or exp Ezetimibe, Simvastatin Drug Combination/ or exp Anticholesteremic Agents/ or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or ((hydroxymethylglutaryl or hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor*)).ti. or "HMG CoA".ti. or (statin* or lovastatin or meglutol or pravastatin or atorvastatin or simvastatin).ti.
	#4	Pharmacologic treatments: non-statins	Gemfibrozil/ or fenofibrate/ or niacin/ or exp Fatty Acids, Omega-3/ or exp Ezetimibe/ or exp Proprotein Convertase 9/tu or exp "Bile Acids and Salts"/tu OR (fibrate* or gemfibrozil or fenofibrate or bezafibrate or (nicotinic adj acid*) or niacin or (bile ADJ acid ADJ sequestrant*) or (bile ADJ acid ADJ resin*) or ezetimibe or (omega* ADJ3 fatty adj acid*) or "fish oil" or pcsk9 or pcsk-9 or "pcsk 9" or ((eicosapentaenoic or docosahexaenoic) ADJ acid*)).ti,ab.

Question	Set #	Concept	Strategy
Questions 4, 6, 8, 9 – Pertaining to pharmacologic treatment including cost (cont.)	#5	Outcomes of interest	Exp secondary prevention/ OR exp primary prevention/ OR exp mortality/ OR exp morbidity/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR stroke/ OR exp Angina, Unstable/ OR (stroke* OR (cerebrovascular ADJ accident*) OR morbidity OR mortality OR death OR (heart ADJ attack*) OR (myocardial ADJ infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) ADJ2 event*) OR (heart ADJ infarct*)).ti,ab. OR (morbidity OR mortality OR prevent* OR outcome*).ti,ab. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab. OR angina.ti,ab. OR ae.fs.OR to.fs. OR safety/ or exp patient harm/ OR ((side ADJ effect*) OR (adverse ADJ event*) OR safe OR safety).ti,ab.
		Additional outcome of interest for KQ 8 [change in lipid levels]	((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C") AND (level OR levels OR lower OR low OR reduce OR reduction OR profile* OR target*)).ti,ab.
	#6	Combine sets – including outcomes of interest	(#1 OR #2) AND (#3 OR #4) AND #5
	#7	Combine sets – without outcomes of interest	(#1 OR #2) AND (#3 OR #4)
	#8	Limit to RCTs	Randomized controlled trials hedge [see Search Limits at the end of this table]
	#9	Limit to SRs/Meta-analyses	Systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#10	Limit to cost studies	'health care cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR (cost OR costs OR costly OR costing OR price OR prices OR saving OR savings OR economi* OR financial OR finance* OR pharmacoeconomic* OR QALY or QALYs OR (quality NEXT/1 adjusted NEXT/1 life NEXT/1 year*) or (quality NEXT/1 adjusted life NEXT/1 expectanc*)):ti,ab
	#11	Combine sets	#6 AND (#8 OR #9)
	#12	Combine sets	#7 AND (#9 OR #10)
	#13	Combine sets	#11 OR #12
	#14	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 5 – Pharmacologic treatment to reach specific LDL-C or non-HDL-C goals	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR ((high OR elevated OR low) ADJ5 (cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C"))).ti,ab.
	#2	CVD	exp *Cardiovascular Diseases/pc OR cardiovascular diseases/ or heart diseases/ or vascular diseases/ or exp arterial occlusive diseases/ or cerebrovascular disorders/ OR exp brain ischemia/ or exp stroke/ or exp myocardial ischemia/ OR exp myocardial Infarction/ OR exp heart arrest/ OR exp hypertension/ OR exp peripheral vascular diseases/ OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) ADJ5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)).ti,ab. OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart ADJ attack*) OR (myocardial ADJ infarct*) OR stroke* OR (cerebrovascular ADJ accident*)).ti,ab.
	#3	LDL-C or non-HDL-C goals	(exp Cholesterol, HDL/bl OR exp Cholesterol, LDL/bl OR exp lipids/bl OR exp cholesterol/bl) AND (goal OR goals OR target* OR level OR levels).ti. OR ((exp Cholesterol, HDL/ OR exp Cholesterol, LDL/ OR exp lipids/ OR exp cholesterol/) AND exp goals/) OR ((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C" OR "non HDL C" OR "non-HDL C" OR "non-HDL-C") ADJ5 (goal OR goals OR target* OR level OR levels)).ti,ab.
	#4	Statins	exp Hypolipidemic Agents/ or exp Ezetimibe, Simvastatin Drug Combination/ or exp Anticholesteremic Agents/ or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or ((hydroxymethylglutaryl or hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor*)).ti. or "HMG CoA".ti. or (statin* or lovastatin or meglutol or pravastatin or atorvastatin or simvastatin).ti.
	#5	Non-statins	Gemfibrozil/ or fenofibrate/ or niacin/ or exp Fatty Acids, Omega-3/ or exp Ezetimibe/ or exp Proprotein Convertase 9/tu or exp "Bile Acids and Salts"/tu OR (fibrate* or gemfibrozil or fenofibrate or bezafibrate or (nicotinic ADJ acid*) or niacin or (bile ADJ acid ADJ sequestrant*) or (bile ADJ acid ADJ resin*) or ezetimibe or (omega* ADJ3 fatty adj acid*) or "fish oil" or pcsk9 or pcsk-9 or "pcsk 9" or ((eicosapentaenoic or docosahexaenoic) ADJ acid*)).ti,ab.
	#6	Outcomes of interest	Exp secondary prevention/ OR exp primary prevention/ OR exp mortality/ OR exp morbidity/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR stroke/ OR exp Angina, Unstable/ OR (stroke* OR (cerebrovascular ADJ accident*) OR morbidity OR mortality OR death OR (heart ADJ attack*) OR (myocardial ADJ infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) ADJ2 event*) OR (heart ADJ infarct*)).ti,ab. OR (morbidity OR mortality OR prevent* OR outcome*).ti,ab. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab. OR angina.ti,ab. OR ae.fs.OR to.fs. OR safety/ or exp patient harm/ OR ((side ADJ effect*) OR (adverse ADJ event*) OR safe OR safety).ti,ab.
	#7	Combine sets	(#1 OR #2) AND #3 AND (#4 OR #5 OR #6)
	#8	RCTs/SRs/meta-analyses	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#9	Combine sets	#7 AND #8
	#10	Apply limits	See Search Limits at the end of the table

Question	Set #	Concept	Strategy
Question 7 – Strategies to improve patient tolerance to statins	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR exp lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	CVD	exp *Cardiovascular Diseases/pc OR cardiovascular diseases/ or heart diseases/ or vascular diseases/ or exp arterial occlusive diseases/ or cerebrovascular disorders/ OR exp brain ischemia/ or exp stroke/ or exp myocardial ischemia/ OR exp myocardial Infarction/ OR exp heart arrest/ OR exp hypertension/ OR exp peripheral vascular diseases/ OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) ADJ5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)).ti,ab. OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart ADJ attack*) OR (myocardial ADJ infarct*) OR stroke* OR (cerebrovascular ADJ accident*)).ti,ab.
	#3	Statin tolerance/adherence/ substitution (controlled terms)	(exp Hypolipidemic Agents/ or exp Ezetimibe, Simvastatin Drug Combination/ or exp Anticholesteremic Agents/ or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/) AND (exp Medication Adherence/ or exp "Treatment Adherence and Compliance"/ OR exp Drug Substitution/ OR exp Drug Administration Schedule/)
	#4	Statin tolerance/adherence/ substitution (keywords)	(((hydroxymethylglutaryl or hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor*)) OR "HMG CoA" or statin* or lovastatin or meglutol or pravastatin or atorvastatin or simvastatin).ti,ab. AND (tolerate* or tolerance or adher* or nonadherence* or non-adherence or ((alternat* or low or lower or high or higher or increase or decrease) ADJ3 dose or dosing or dosag*)).ti,ab.
	#5	Combine sets	(#1 OR #2) AND (#3 OR #4)
	#6	RCTs/SRs/meta-analyses	Randomized controlled trials/systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#7	Combine sets	#5 AND #6
	#8	Apply limits	See Search Limits at the end of this table

Question	Set #	Concept	Strategy
Questions 9, 10, 11, 12 – Pertaining to non-pharmacologic treatment including cost	#1	Dyslipidemia	exp dyslipidemias/ OR exp cholesterol/ OR lipids/ OR (dyslipidemia* OR dyslipidaemia* OR dyslipidproteinemia* OR dyslipidproteinaemia* OR hyperlipidemia* OR hyperlipidaemia* OR hypercholesterolemia* OR hypercholesterolaemia* OR hyperlipoproteinemia* OR hyperlipoproteinaemia* OR hypertriglyceridemia* OR hypertriglyceridaemia* OR hyperlipemia OR hyperlipaemia OR cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C").ti,ab.
	#2	CV risk	(exp *Cardiovascular Diseases/ OR *heart diseases/ or *vascular diseases/ or exp *arterial occlusive diseases/ or *cerebrovascular disorders/ OR exp *brain ischemia/ or exp *stroke/ or exp *myocardial ischemia/ OR exp *myocardial Infarction/ OR exp *heart arrest/ OR exp *hypertension/ OR exp *peripheral vascular diseases/ OR ((heart* OR cardio* OR cardiac* OR coronary OR vascular OR cerebrovascular OR artery OR arteries) ADJ5 (disease* OR syndrome* OR event* OR ischem* OR ischaem* OR plaque*)).ti. OR (hyperten* OR atherosclero* OR arteriosclero* OR angina OR (Heart ADJ attack*) OR (myocardial ADJ infarct*) OR stroke* OR (cerebrovascular ADJ accident*)).ti.) AND (prevent* OR risk*).ti.
	#3	Dietary supplements/ neutraceuticals	exp dietary supplements/ OR exp herbal medicine/ OR exp plants, Medicinal/ OR vitamins/ OR exp plant extracts/ OR exp Fatty Acids, Omega-3/ or exp garlic/tu OR exp Dietary Fiber/tu OR exp psyllium/tu OR exp ginger/tu OR exp phytosterols/ OR exp tea/ or exp teas, herbal/ OR exp niacin/tu OR (((diet OR dietary) ADJ5 supplement*) OR neutraceutical* OR (omega* ADJ3 fatty ADJ acid*) or "fish oil" or ((eicosapentaenoic or docosahexaenoic) ADJ acid*) OR ((diet* OR soluable) ADJ5 fiber) OR garlic OR ginger OR phytosterol* OR (plant ADJ2 sterol*) OR (green ADJ tea*) OR niacin* OR psyllium).ti.
	#4	Diet therapy	exp Diet Therapy/ or ((Diet or diets or dietary or nutrition) and ("low sodium" or "low fat" or (gluten ADJ2 free) or "low gluten" or "low carb" or "low carbohydrate" or "low calorie" or vegetarian or vegan or macrobiotic or Mediterranean or DASH)).ti. or "diabetic diet".mp. or (dietary ADJ approaches ADJ1 stop ADJ hypertension).ti. or diet*.ti.
	#5	Exercise	exp Exercise/ OR exp Resistance Training/ OR (aerobics OR dance OR dancing OR exercise* OR fitness OR kinesiotherapy OR muscle strengthening OR physical activity OR physical conditioning OR plyometric training OR resistance training OR strength training OR tai chi OR walk* OR weight lifting OR yoga OR swim OR swimming OR run OR running OR weight training).ti.
	#6	Outcomes of interest	exp *Cardiovascular Diseases/pc OR Exp secondary prevention/ OR exp primary prevention/ OR exp mortality/ OR exp morbidity/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR stroke/ OR exp Angina, Unstable/ OR (stroke* OR (cerebrovascular ADJ accident*) OR morbidity OR mortality OR death OR (heart ADJ attack*) OR (myocardial ADJ infarct*) OR ((vascular OR cardiac OR coronary OR cerebrovascular) ADJ2 event*) OR (heart ADJ infarct*)).ti,ab. OR (morbidity OR mortality OR prevent* OR outcome*).ti,ab. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab.OR ((cholesteryl* OR cholesterol* OR lipid* OR lipoprotein* OR tryglycer* OR triaclyglycer* OR "HDL-C" OR "LDL-C" OR "HDL C" OR "LDL C") AND (level OR levels OR lower OR low OR reduce OR reduction OR profile* OR target*)).ti,ab. OR angina.ti,ab. OR ae.fs.OR to.fs. OR safety/ or exp patient harm/ OR ((side ADJ effect*) OR (adverse ADJ event*) OR safe OR safety).ti,ab.
	#7	Combine sets – including outcomes of interest	(#1 OR #2) AND (#3 OR #4 OR #5) AND #6

Question	Set #	Concept	Strategy
Questions 9, 10, 11, 12 – Pertaining to non-pharmacologic treatment including cost (cont.)	#8	Combine sets – without outcomes of interest	(#1 OR #2) AND (#3 OR #4 OR #5)
	#9	Limit to RCTs	Randomized controlled trials hedge [see Search Limits at the end of this table]
	#10	Limit to SRs/Meta-analysis	Systematic review/meta-analysis hedge [see Search Limits at the end of this table]
	#11	Limit to cost studies (KQ 9)	'health care cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR (cost OR costs OR costly OR costing OR price OR prices OR saving OR savings OR economi* OR financial OR finance* OR pharmacoeconomic* OR QALY or QALYs OR (quality NEXT/1 adjusted NEXT/1 life NEXT/1 year*) or (quality NEXT/1 adjusted life NEXT/1 expectanc*)):ti,ab
	#12	Combine sets	#7 AND (#9 OR #10)
	#13	Combine sets	#8 AND (#10 OR #11)
	#14	Combine sets	#12 OR #13
	#15	Apply limits	See Search Limits at the end of this table
Search Limits Applied to Each Search		Limit to humans and items published since searches were conducted for 2014 CPG [December 9, 2013]	AND (english language and humans); limit 18 to ed=20131209-2019
		Exclude conference publications, books, letters, editorials, case studies, etc.	NOT ("column/opinion" OR "comment/reply" OR dissertation OR editorial OR letter OR book).dt. OR book.pt. OR letter/ or editorial/ or news/ or comment/ or case report or case reports/ or note/ or conference paper/ or (letter or editorial or news or comment or case reports or conference abstract*).pt. OR (child* or teen* or adolescen* or school* or baby or babies or infant* or neonat* or pediatric* or kid or kids or preschool*).ti.
		Limit to meta-analyses and SRs	AND ('systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis')
		Limit to RCTs	AND (Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies).de. or placebo*.mp. or random*.ti. or randomized controlled trial.pt. OR crossover*.mp. or cross over.mp. or ((singl* or doubl* or tripl* or trebl*) ADJ3 (blind* or mask* or sham*)).mp. or latin square.mp. or ISRTCN or ACTRN* or (NCT* not NCT) or (clinical trials/ and random*.ti.)

Appendix K: Alternative Text Description of Algorithm

The following outline narratively describes the Algorithm: Management of Dyslipidemia for Cardiovascular Risk Reduction. An explanation of the purpose of the algorithms and description of the various shapes used within the algorithms can be found in the Algorithm background section. The sidebars referenced within this outline can also be found in the Algorithm background section.

Algorithm: Management of Dyslipidemia for Cardiovascular Risk Reduction

1. Module A begins with Box 1, in the shape of a rounded rectangle: "Patient ≥40 years old (There are no evidence-based recommendations for patients under age 40 because there is no evidence for the benefit of lipid screening and treatment within this age group. In patients younger than 40 years old interested in pursuing lipid testing and management, shared decision making is recommended to discuss the risks and unknown benefit of pharmacotherapy, with therapeutic lifestyle changes being the primary focus of CVD primary prevention.)"
2. Box 1 connects to Box 2, in the shape of a hexagon, asks the question: "Does patient have HF with EF <35%, ESRD, or life expectancy <5 years?"
    a. If the answer is "Yes" to Box 2, then Box 3, in the shape of an oval: "Discuss lack of evidence demonstrating benefit and continue ongoing care"
    b. If the answer is "No" to Box 2, then Box 4, in the shape of a hexagon, asks the question: "Does patient have higher risk CVD? (see **Sidebar 2**)"
        i. If the answer is "Yes" to Box 4, then Box 5, in the shape of a rectangle: "Recommend stepped intensification: 1. Maximize statin or add ezetimibe 2. Consider PCSK9 inhibitor only after maximizing statin and adding ezetimibe"
            1) Box 5 connects to Box 10, in the shape of a rectangle: "If MI, ACS, or CABG/PCI in past 6 weeks, refer for cardiac rehab"
            2) Box 10 connects to Box 11, in the shape of a rectangle: "Recommend dietitian-led Mediterranean diet for risk >12%"
            3) Box 11 connects to Box 12, in the shape of a rectangle: "Recommend regular aerobic exercise (Suggest regular aerobic activity of any intensity or duration. Although incremental benefit is associated with increased doses of physical activity, lower doses including leisure time activity [i.e., walking, landscaping, washing dishes] are associated with benefit when compared to mostly sedentary behavior. A provider's considerations when recommending physical activity might include a patient's motivation, functional capacity, and physical activity preferences.) and smoking cessation (if applicable)"
            4) Box 12 connects to Box 13, in the shape of a rectangle: "Follow up evaluation: 1. Primary prevention, no statin: Lipids every 10 years, recommend non-fasting; Repeat risk evaluation at Box 1: Every 2 years if 6 – 12%, Every 5 years if <6%, If risk factors change. 2. Secondary prevention: lipids as needed only if higher risk and willing to intensify; 3. Once on optimal therapy, no need to recheck lipids routinely"

ii. If the answer is "No" to Box 4, then Box 6, in the shape of a hexagon, asks the question: "Does patient have CVD per **Sidebar 1**, DM, or LDL ≥190 mg/dL?"

1) If the answer is "Yes" to Box 6, then Box 7, in the shape of a rectangle: "Recommend moderate-dose statin (see **Sidebar 3**)"

2) If the answer is "No" to Box 6, then Box 8, in the shape of a hexagon, asks the question: "Is patient's 10-year CVD risk >12%?"

a) If the answer is "Yes" to Box 8, then Box 7, in the shape of a rectangle: "Recommend moderate-dose statin (see **Sidebar 3**)"

b) If the answer is "No" to Box 8, then Box 9, in the shape of a hexagon, asks the question: "Is patient's 10-year risk 6 – 12% and does patient prefer statin treatment?"

i) If the answer is "Yes" to Box 9, then Box 7, in the shape of a rectangle: "Recommend moderate-dose statin (see **Sidebar 3**)"

ii) If the answer is "No" to Box 9, then Box 12, in the shape of a rectangle: "Recommend regular aerobic exercise (Suggest regular aerobic activity of any intensity or duration. Although incremental benefit is associated with increased doses of physical activity, lower doses including leisure time activity [i.e., walking, landscaping, washing dishes] are associated with benefit when compared to mostly sedentary behavior. A provider's considerations when recommending physical activity might include a patient's motivation, functional capacity, and physical activity preferences.) and smoking cessation (if applicable)"

(1) Box 12 connects to Box 13, in the shape of a rectangle: "Follow up evaluation: 1. Primary prevention, no statin: Lipids every 10 years, recommend non-fasting; Repeat risk evaluation at Box 1: Every 2 years if 6 – 12%, Every 5 years if <6%, If risk factors change. 2. Secondary prevention: lipids as needed only if higher risk and willing to intensify; 3. Once on optimal therapy, no need to recheck lipids routinely"

3. Box 7 connects to Box 11, in the shape of a rectangle: "Recommend dietitian-led Mediterranean diet for risk >12%"

4. Box 11 connects to Box 12, in the shape of a rectangle: "Recommend regular aerobic exercise (Suggest regular aerobic activity of any intensity or duration. Although incremental benefit is associated with increased doses of physical activity, lower doses including leisure time activity [i.e., walking, landscaping, washing dishes] are associated with benefit when compared to mostly

sedentary behavior. A provider's considerations when recommending physical activity might include a patient's motivation, functional capacity, and physical activity preferences.) and smoking cessation (if applicable)"

5. Box 12 connects to Box 13, in the shape of a rectangle: "Follow up evaluation: 1. Primary prevention, no statin: Lipids every 10 years, recommend non-fasting; Repeat risk evaluation at Box 1: Every 2 years if 6 – 12%, Every 5 years if <6%, If risk factors change. 2. Secondary prevention: lipids as needed only if higher risk and willing to intensify; 3. Once on optimal therapy, no need to recheck lipids routinely"

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