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 and epidemiologic evidence. Developed by a panel of multidisciplinary experts (all practicing clinicians), 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 recommendations.

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 health care 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 TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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Background

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the United States (US) and globally. In Western countries, most CVD is due to atherosclerosis. [1] Atherosclerosis is the buildup of plaque (cholesterol, proteins, calcium and inflammatory cells) in the walls of arteries that carry oxygenated blood to the heart and other parts of the body. This plaque narrows the opening of the 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 on the plaque and may obstruct the flow of oxygenated blood to the heart or brain, resulting in an acute coronary syndrome (ACS), myocardial infarction (heart attack; MI) or stroke with potentially irreversible damage to the tissue of the heart or brain.

Control and reduction of atherosclerotic cardiovascular disease (ASCVD) risk factors, including high cholesterol levels, elevated blood pressure (BP), insulin resistance, smoking and a sedentary lifestyle, can contribute to a reduction in ASCVD morbidity and mortality.

Dyslipidemia is defined as one or more of the following: low density lipoprotein cholesterol (LDL-C) >130 mg/dL, high density lipoprotein cholesterol (HDL-C) <40 milligram per deciliter (mg/dL), or triglyceride (TG) >200 mg/dL. [2] In patients with known CVD or high risk for CVD, even "normal" levels of lipids can be deemed amenable to intervention for the purpose of reducing CVD risk.

Dyslipidemia may remain clinically silent until the development of complications. This condition can be diagnosed with a blood test measuring plasma levels of total cholesterol (TC), HDL-C, TG, or individual lipoproteins. LDL-C is measured directly or determined by the following equation: TC-HDL-(TG/5). Sometimes, non-HDL cholesterol is also determined as TC minus HDL. A TC of less than 180 mg/dL is thought to be optimal. [3] Yet, the average TC for American adults is about 200 mg/dL. [4]

The etiology of dyslipidemia involves genetic, lifestyle and other factors. Genetic factors that result in either overproduction or slow clearance of TGs and LDL-C, or underproduction or fast clearance of HDL-C, can lead to dyslipidemia. A sedentary lifestyle with excessive dietary intake of saturated fat, trans fats, added sugars, and cholesterol can also lead to dyslipidemia. Other risk factors include insulin resistance, diabetes mellitus (DM or diabetes), central obesity, and chronic kidney disease (CKD).

About 71 million adults in the US (33.4%) have high LDL-C and only one out of every three adults with high LDL-C has the condition under control. [4]The percentage of American adults with high LDL-C has remained around 34 percent over the past decade, but treatment of high LDL-C has increased from 28.4 percent in 1999–2002 to 48.1 percent in 2005–2008. [4] Treatment usually involves dietary changes and lipid-lowering drugs. However, the management of dyslipidemia has shifted away from treating the dyslipidemia itself as a discrete entity, and moved toward managing dyslipidemia in the context of overall risk for CVD.

This guideline addresses the various treatment and management strategies for managing overall CVD risk among patients with dyslipidemia. As TG levels above 300mg/dl are above the 95th percentile, few patients in the US will have levels above 300mg/dl. Even fewer patients will have TGs >500mg/dl (99th

percentile). Due to the infrequency of clinically significant hypertriglyceridemia this guideline does not address hypertriglyceridemia other than to look for secondary causes and non-pharmacologic interventions. Interested readers can refer to Lederle and Bloomfield's 2012 article for additional information. [5]

About this Clinical Practice Guideline

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Clinical Practice Guideline (CPG) for the Management of Dyslipidemia is intended to assist health care providers in the most common aspects of patient care. The system-wide goal of evidence-based guidelines is to improve the patient's health and wellbeing. The overall expected outcome of successful implementation of this guideline is to:

- Formulate an efficient and effective assessment of the patient's condition
- Optimize the use of therapy to reduce symptoms and enhance functionality
- Minimize preventable complications and morbidity
- Emphasize the use of personalized, proactive, patient-driven care
- Translate the available yet incomplete body of evidence into recommendations that allow clinicians to participate in shared, informed decisions with patients

This VA/DoD guideline represents a significant step toward achieving these goals for patients covered by VA and DoD health care delivery systems. However, as with other CPGs, remaining challenges involve developing effective strategies for guideline implementation and evaluating the effect of guideline adherence on clinical outcomes.

This guideline is directed toward VA and DoD clinicians involved in the care of beneficiaries who are at risk for or have CVD. The purpose of this guideline is to:

- Enhance clinician awareness of risk factors that increase CVD risk
- Highlight evidence to manage dyslipidemia, a contributor to the development of CVD
- Identify pharmacologic and non-pharmacologic strategies that improve CVD outcomes

Scope of this CPG

This CPG is designed to assist primary care providers in managing lipids among patients at risk for CVD. An acronym list of abbreviations used throughout the CPG is provided in Appendix F.

Population

The patient population of interest for this CPG is adults (men and women) who are eligible for care in the VA and DoD health care delivery systems. This CPG does not provide recommendations for the management of dyslipidemia in children or adolescents.

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Methods

The methodology used in developing the 2014 CPG follows the *Guideline for Guidelines*, [6] an internal document of the VA and DoD Evidence-based Practice Working Group (EBPWG). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the submission of an updated Management of Dyslipidemia For CVD Risk Reduction CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA and DoD health care delivery systems. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management of patients with dyslipidemia. The Champions also assisted in:

- Conducting the evidence review, including providing direction on inclusion and exclusion criteria
- Assessing the level and quality of the evidence
- Identifying appropriate disciplines to be included as part of the Work Group
- Directing the Work Group and the guideline development and review process

The Work Group was responsible for providing their expertise throughout the guideline development process and participating in developing key questions, reviewing evidence, forming and grading recommendations, and drafting the updated CPG.

The VA Office of Quality, Safety and Value, in collaboration with the DoD, identified two clinical leaders, Dr. John R. Downs, MD from the VA and COL Patrick O'Malley, MD, MPH from the DoD, as the Champions for the 2014 CPG. The Lewin Team, including The Lewin Group, DutyFirst Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and the DoD to support the development of this CPG. The Lewin Team held the first conference call on September 30, 2013, with participation from the Contracting Officer's Representatives (CORs), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review on the management of dyslipidemia. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of dyslipidemia, from which the Work Group members were recruited. These specialties and clinical areas included: Internal Medicine, Health Information Technology, Electronic Health Record Documentation, Preventive Cardiology, Pharmacy, Dietetics, Primary Care, Nursing, and Family Practice.

The guideline development process for the 2014 CPG consisted of the following steps:
- Formulating evidence questions (key questions)
- Conducting the systematic review
- Convening a three and a half day face-to-face meeting with the CPG Champions and Work Group members
- Drafting and submitting a final CPG to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past two years, including verbal affirmations of no conflict of interest at regular meetings. The project team was also subject to random web-based surveillance (e.g., ProPublica). If there was a positive (yes) conflict of interest response (actual or potential), then action was taken by the co-chairs and evidence-based practice program office, based on level and extent of involvement, to mitigate the COI. Actions ranged from restricting participation and/or voting on sections related to a conflict, to removal from the Work Group. Recusal was determined by the individual, co-chairs, and evidence-based practice office. One DoD Work Group Member was removed for potential COI. No member of the final project team had any COI.

Patient-Centered Care

Guideline recommendations are patient-centered. Regardless of setting, or the availability of professional expertise, all patients in the VA and DoD health care systems should be provided with the interventions that are recommended in this guideline, if found to be appropriate to the patient's specific condition and needs.

Good communication between health care professionals and the patient is essential. Patient-centered decisions should be supported by evidence-based information tailored to the patient's needs. The information about treatment and care should be culturally appropriate and available to people who do not speak or read English, or with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities.
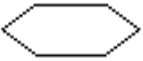
Algorithm

This CPG includes an algorithm, which is designed as a quick reference for clinicians at the point of care to maximally facilitate clinical decision-making for the management of CVD risk in the most common clinical situations involving dyslipidemia. The use of the algorithm format was chosen based on the understanding that such a format can allow for expeditious diagnostic and therapeutic decision-making and has the potential to improve patterns of resource use. The algorithmic format allows the provider to

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follow a linear approach to obtaining the critical information needed at major decision points in the clinical care process, and includes:

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

A clinical algorithm describes a guideline in a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed. [7]

	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.

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 advances. This CPG is based on information available at the date of publication, and is intended to provide a general guide to best practices. This guideline can assist providers in care of patients, but the recommendations must always be considered suggestions, within the context of a provider's clinical judgment, in the care of an individual patient.

Management of Dyslipidemia

1 Men >35 and women >45 and all patients with ASCVD [A]

↓

2 Does patient have CHF (EF<35% and NYHA Class >1), ESRD and on dialysis, or LE<5 years? [B] — Y → **3** Exit algorithm: Discussion with provider [B]

N ↓

4 History of ASCVD or ACS [C] — Y → **5** Recent ACS or recurrent ASCVD [C] — Y →

5 N ↓

7 Advise moderate dose statin, consider titrating to high dose as tolerated [E]

4 N ↓

6 Calculate 10-year CVD risk: Measure lipids, BP Assess RFs and medications [D]

↓

8 10-year risk >12% or LDL-C>=190 or DM with hypertension or smoking [F] — Y → **9** Advise moderate dose statin [E]

8 N ↓

10 10-year risk 6-12% [G] — Y → **11** Shared decision making results in statin initiation or continuation [E] — Y → (to 9)

11 N ↓

10 N ↓

12 Positive lifestyle changes; Optimize comorbid conditions [H]

↓

14 Repeat CVD risk evaluation: 6-12%, every 2yrs <6%, every 5yrs [G]

13 Mediterranean diet plus positive lifestyle changes [H]

↓

15 Routine monitoring and follow-up, including for adverse drug effects [I]

ASCVD and Equivalents

- All ACS/MI
- CABG/PCI
- Stable obstructive CAD (stable symptoms of angina or equivalent)
- CVA/TIA
- Atherosclerotic PVD (claudication or AAA)

Does **not** include asymptomatic atherosclerosis (CAC, exercise test, IMT, ABI, brachial reactivity**)**

Statin Dose (by10-yr CVD Risk)

10-yr risk	Statin Dose
ASCVD (2nd prevention)	Mod-Hi
>12%	Mod
6-12% (with SDM)	Mod
<6%	None

Drug Doses

	Moderate	High
Generic:		
Atorvastatin	10-20mg	40-80mg
Simvastatin	20-40mg	
Pravastatin	40mg	
Lovastatin	40-80 mg	
Fluvastatin	80 mg (80 mg XL QD or 40 mg BID)	
Brand:		
Rosuvastatin	5-10mg	20-40mg

In patients unable to tolerate appropriate mod-hi dose statin according to their risk, then the highest tolerable statin dose is an option

AAA – abdominal aortic aneurysm; ABI – ankle brachial index; ACS – acute coronary syndrome; ASCVD – atherosclerotic cardiovascular disease; BID – twice a day; BP – blood pressure; CABG – coronary artery bypass graft; CAC – coronary artery calcium; CAD – coronary artery disease; CHF – chronic heart failure; CVA – cerebral vascular accident; DM – diabetes mellitus; EF – ejection fraction; ESRD – end stage renal disease; IMT – intimal medial thickness; LE – life expectancy; LDL-C – low density lipoprotein cholesterol; MI – myocardial infarction; Mod – Hi - moderate to high; NYHA – New York Heart Association; PCI – percutaneous coronary intervention; PVD – peripheral vascular disease; QD – once a day; RF – risk factors; SDM – shared decision making; TIA – transient ischemic attack

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Populations Excluded from this Guideline

Patients with Severe Systolic Chronic Heart Failure (CHF), End Stage Renal Disease (ESRD) and on Dialysis, or a Limited Life Expectancy

Patients with moderate-to-severe systolic chronic heart failure (CHF), a limited life expectancy (LE) (<5 years), or end stage renal disease (ESRD) and on maintenance dialysis were excluded from most clinical outcome trials; therefore, available data are not applicable to such patients. Thus, the guideline panel was unable to provide evidence-based recommendations for these populations, and suggests that providers consider basing treatment decisions on comorbidities, quality of life considerations, and patient's preferences, values, and culture.

Discussion

All but five trials excluded patients with systolic CHF (Ejection fraction [EF] <35%) or those on hemodialysis (HD). [8-12] In the Controlled rosuvastatin multinational study in heart failure (CORONA) (2007), 5011 patients with New York Heart Association (NYHA) functional class II, III or IV symptoms and ischemic systolic heart failure (HF) (EF <35%) were randomized to rosuvastatin 10mg or placebo. [10] There was no reduction in the primary endpoint of cardiovascular death, nonfatal MI or nonfatal stroke. There was a 9% absolute risk reduction in the secondary endpoints of cardiovascular and CHF hospitalizations; however the study was powered only for the primary endpoints. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Heart Failure (GISSI-HF) trial (2008) enrolled and randomized 4574 patients with CHF (EF<35%) from any etiology and NYHA functional class II, III or IV symptoms to rosuvastatin 10mg or placebo. [11] There was no difference in primary outcomes (i.e., time to death or admission to hospital for cardiovascular evaluation). No safety concerns or increased adverse events were noted in the treatment groups of either trial.

Three trials examined patients on maintenance hemodialysis treated with either statin monotherapy (Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis [4D], A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA]) or a statin-ezetimibe combination (Study of Heart and Renal Protection [SHARP]). The 4D trial (2005) included diabetic patients, AURORA (2009) looked at patients with renal failure from any cause and SHARP (2011) included patients with CKD on HD or peritoneal dialysis and patients not receiving dialysis. [8,9,12,13] In 4D and AURORA, CVD events were not reduced in any patients undergoing dialysis. [9,12] In SHARP, the primary outcome of any major atherosclerotic event was reduced in favor of simvastatin/ezetimibe versus (vs.) placebo (11.3% vs. 13.4%, absolute risk reduction [ARR] 2.1%, risk ratio 0.83, 95% CI 0.74-0.94, p=0.0021, respectively) but nearly 70% of patients were not receiving dialysis at baseline. [8,13] The authors noted that the trial was not powered to determine whether there were differences in outcomes between those receiving dialysis and those who were not. The adverse event rates were high in both statin users and placebo groups; study investigators identified no subgroups (among patients on dialysis) that experienced benefit from treatment. [8] Hou et al. (2013) assessed the efficacy of statin therapy vs. placebo or lower dose statin in patients with CKD with or without dialysis and with or without a history

of CKD. [14] Statistically significant benefits were generally restricted to patients not on dialysis for all-cause mortality, cardiovascular death and coronary events. There were non-significant effects on stroke, kidney failure and adverse events regardless of dialysis status.

The American College of Cardiology and American Heart Association (ACC/AHA) Guideline (2013) concluded there is no evidence that statins confer a benefit in patients with heart failure or ESRD and on dialysis and suggest clinicians engage in patient-centered discussions acknowledging the limited available evidence on harms and benefits for individual patients. [15] Given the lack of data demonstrating benefit, and the possibility of increased adverse events in the dialysis population, the committee concurred with this approach. [16] As the rest of the guideline does not apply to patients with moderate-to-severe systolic HF or ESRD and on dialysis, these patient populations exit the algorithm for patient-centered discussions of harms and benefits with their treating providers. As patients with CKD not yet on dialysis appeared to have improved outcomes, they continue on in the algorithm.

Reconciling 2006 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence or as scheduled subject to time-based expirations. For example, the US Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services. [17] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed or revised within the past five years.

The Dyslipidemia Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the key questions. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous version of this CPG, Management of Dyslipidemia, published in 2006 [2], subject to evolving practice in today's environment for CVD risk. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. For these "modified" recommendations, the Guideline Work Group referred to the available evidence as summarized in the body of the 2006 CPG, though not to the evidence review that was conducted for the 2006 CPG. These modified recommendations are denoted in the list shown on pages 14-17.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2006 CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system), the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2006 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2006 CPG, as well as harms and benefits, values and

preferences, and other implications, where possible. In some instances, peer-reviewed literature published since the 2006 CPG was considered along with the evidence base used for that CPG. Consideration of such newer literature when converting the strength of the recommendation from the USPSTF to GRADE system is noted in the discussion that follows the corresponding recommendation.

The Guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations [18] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review.

Implementation

This CPG and algorithm are designed to be adapted by individual facilities in consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine best interventions and timing of care for their patients in order to optimize quality of care and clinical outcomes.

Although this CPG represents clinical practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. This CPG can assist in identifying priority areas for research and optimal allocation of resources.

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Recommendations

#	Algorithm Reference	Recommendations	Strength
Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention (patients without a history of atherosclerotic cardiovascular disease [ASCVD] or acute coronary syndrome [ACS])			
1	A	We recommend cardiovascular disease (CVD) risk screening for men > age 35 and women > age 45, including a lipid profile and a risk calculation.	Strong For
2	A	We recommend against <u>routine</u> screening for dyslipidemia outside of the context of a cardiovascular risk assessment.	Strong Against
3	D	For risk calculation, we suggest a 10-year risk calculator.	Weak For
4	C	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	Weak For

#	Algorithm Reference	Recommendations	Strength
		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.**	
5	C	We suggest against the <u>routine</u> use of high-sensitivity C-reactive protein (hsCRP) testing.	Weak Against
6	C	We suggest against the <u>routine</u> use of coronary artery calcium (CAC) testing.	Weak Against
7	E, F	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
8	E, F	We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater.	Weak For
9	E, F	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
10	E, F	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
11	E	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
12	E	We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy.	Weak For
13	I	We recommend against <u>routinely</u> measuring LFTs or CK after a moderate dose statin is initiated.	Strong Against
Management of Pharmacotherapy for Secondary Prevention (patients with a history of ASCVD or ACS)			
14	E	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

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#	Algorithm Reference	Recommendations	Strength
15	E	In patients with ASCVD who are able to tolerate statins, we recommend against the <u>routine</u> 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
16	E	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
17	E	We strongly recommend against the routine monitoring of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD.	Strong Against
18	E	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
19	I	We suggest measuring LFTs 4-12 weeks after the initiation of high-dose statin.	Weak For
Non-pharmacologic Approaches			

20	H	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

21	H	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

#	Algorithm Reference	Recommendations	Strength
22	H	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
23	H	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
24	H	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
Monitoring and Follow-up			
25	G	We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy.	Weak For
26	G	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

* These "modified" recommendations from the previous CPG published in 2006 were considered still relevant to health care providers and were carried forward into this CPG. For additional information please refer to the section on Reconciling 2006 CPG Recommendations.

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Future Research Needs

Despite the progress that has been made in assessing and treating dyslipidemia and CVD risk since the publication of the previous CPG in 2006, many important gaps remain, including the value of a risk prediction score in the VA and DoD population.

Research distinguishing the value of CVD risk prediction for type 1 and type 2 diabetic patients is also needed. The current guidelines do not differentiate between type 1 and type 2 diabetics.

There is also a need for research that evaluates the cost effectiveness of pharmacologic therapy among low-to intermediate-risk adults (adults without CVD) and considers the balance between harms and benefits of drug treatment in these lower risk patients.

Since clinical trials typically do not extend beyond six years, there is no data on the optimal duration of statin therapy. Therefore, further research is needed to determine if statin therapy could be safely withdrawn after 10-15 years of treatment, in order to avoid the risk of adverse events associated with continued drug exposure. In addition, clinical outcome studies of back titration from high-dose statin to low- or moderate-dose statin are needed to assess the duration of high-dose statin therapy.

For patients with intolerance to daily statins trials evaluating intermittent statin strategies (e.g., weekly, every other day) on clinical outcomes would be valuable to clinicians.

To date there is no proven additional advantage of using high-dose statins rather than low or moderate statin doses in primary prevention. Comparative research studies are needed to clarify the role of statin dose in primary prevention.

Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention
(Patients without a history of ASCVD or ACS)

Recommendations

1. We recommend CVD risk screening for men > age 35 and women > age 45, including a lipid profile and a risk calculation. **Strong For**
2. We recommend against routine screening for dyslipidemia outside of the context of a cardiovascular risk assessment. **Strong Against**

Discussion

For young, low-risk patients frequent or routine cholesterol screening is unlikely to reclassify 10-year risk or influence clinical management. If the lipid profile is not interpreted in the context of overall cardiovascular risks, routine screening may lead to inappropriate pharmacologic treatment (i.e., no known benefits but known side effects and substantial costs). We therefore recommend that for patients potentially at risk for cardiovascular events (e.g., men >35 years old and women >45 years old),

a lipid profile should be evaluated as part of a complete risk assessment. The rationale for the age cut-offs is consistent with the USPSTF and the American College of Physicians guidelines based on observational evidence that populations above this age threshold are most likely to benefit from screening. [15,19]The USPSTF gives the recommendation for dyslipidemia screening in men >35 years old and women >45 years old a "strong for" (i.e., grade A) recommendation. Since the purpose of dyslipidemia screening is to identify patients at risk for CVD we have extrapolated this to apply to CVD risk assessment. [20] For patients at low-risk and with unremarkable lipid profiles, repeat screening could generally be considered after about five years. For patients with lipid profile abnormalities, additional testing and/or treatment may be indicated depending upon the result of a shared decision making process, and after a comprehensive cardiovascular risk assessment with the patient's clinician.

A non-fasting lipid profile provides measures of total cholesterol and HDL that differ little from measures after a 9 to 12 hour fast. [21] Compared with fasting measures, non-fasting LDL may be 10% lower and TGs as much as 20% higher. [21] Lipid measures are necessary to enable risk calculation. The most commonly used cardiovascular risk calculators, such as the ACC/AHA pooled risk calculator and the Framingham score are based only on measures of total cholesterol and HDL-C. Thus, a non-fasting lipid profile provides accurate measures for risk calculation, and the small variance in LDL-C is unlikely to affect classification of risk or therapeutic decisions. [22] If TGs are greater than 400 mg/dL, the Friedewald equation commonly used to calculate LDL-C may not be accurate. In this uncommon case, the non-fasting lipid profile may need to be repeated after fasting. Fasting lipid measures are also indicated if the purpose is to measure or monitor TG levels.

There are major drawbacks to the routine use of fasting lipid measures. Most patients do not come to clinic visits fasting, and are thus required to take time away from work or family, and bear the expense and bother of a second visit after fasting. Some patients are not willing to make this effort and avoid lipid testing altogether. Laboratories are burdened by the large number of patients who present early in the morning after an overnight fast.

Thus, the small gain in accuracy of a fasting lipid profile over random measurement is outweighed by the burden on patients and laboratories. [23] Given this, we recommend non-fasting lipid profiles for cardiovascular risk calculation.

Recommendations

3. For risk calculation, we suggest a 10-year risk calculator. **Weak For**
4. We suggest that patients being considered for statin therapy be assessed for other CVD risk factors, including, but not be 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 (See 2010 VA/DoD Diabetes Mellitus 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 HDL-C (Less than 40 mg/dL confirmed on more than one occasion)

   Weak For
   Modified from the 2006 CPG without an updated systematic review of the evidence.

Discussion

Population-based observational studies provide the basis to calculate the estimated 10-year risk for CVD, using demographic (age, sex, race) and clinical (TC, HDL-C, BP) variables. Several calculators exist and are based on different (though sometimes overlapping) populations and a different combination of variables. Below are some examples of calculators that clinicians may want to consider using to calculate the 10-year risk, depending on the characteristics of their patient population:

- Framingham: http://cvdrisk.nhlbi.nih.gov/
- ASCVD Pooled Risk Calculator from the 2013 ACC/AHA Lipid Guideline: http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
- Cardiovascular Risk/Benefit Calculator: http://bestsciencemedicine.com/chd/calc2.html
- Mayo Statin Decision Aid: http://statindecisionaid.mayoclinic.org/index.php/site/index

Refer to Table C-1 in Appendix C for a breakdown of the population demographics of the risk calculator cohorts. While the Framingham risk calculator was developed based on a primarily white population, some observational studies have shown that it performs fairly well in other populations. [24,25]The more recently developed ACC/AHA calculator is based on a more diverse population that include a large enough number of African American subjects to calculate separately risk for white and for African American patients. Additionally, the ACC/AHA calculator includes ischemic stroke as an outcome. [15] The Cardiovascular Risk/Benefit Calculator uses the same prediction models as the previous two calculators, but displays the results in an interactive visual format that facilitates shared decision making with patients and can illustrate the potential effect of medications. The Mayo Statin Decision Aid also provides a patient-friendly illustration of risk.

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All of these risk calculators have limitations and their use has not been rigorously shown to improve outcomes. However, their wide acceptance may render such study difficult to perform. Risk calculators have been criticized for overestimating the risk. One of the reasons may be that they are based on data that were collected before the recent significant improvement in clinical care and prevention for CVD, when the overall population was at higher risk of events or death from CVD causes.

Another limitation of risk calculators is that they provide an average risk or probability and cannot precisely predict whether an individual patient will develop a CVD event or benefit from medications. They can, however, be useful to discuss CVD risks and potentials for harm or benefit from medications in the process of shared decision making. Based on these calculations, patients at low 10-year risk for CVD events are unlikely to benefit from medications in the near future, but could experience some of the side effects. On the other hand, patients at high risk may benefit from a significantly decreased risk of an acute event in the following 10 years. Therefore, the use of risk calculators to aid in medication decision making is currently recommended by most medical societies. Clinicians should choose the risk calculator with which they have the most experience and understanding as there is insufficient evidence to recommend a specific type.

Recommendations

5. We suggest against the <u>routine</u> use of high-sensitivity C-reactive protein (hsCRP) testing. **Weak Against**
6. We suggest against the <u>routine</u> use of coronary artery calcium (CAC) testing. **Weak Against**

Discussion

Although there has been strong interest in new risk markers (genetic, serologic, physiologic, anatomic, and psychosocial) that would improve risk prediction in populations where there is relative indifference to treatment (such as the "intermediate, 6-12% 10-yr risk" cohort), only two have demonstrated minimal additive predictive risk beyond conventional risk factors: C-reactive protein and coronary artery calcium testing. However, there is insufficient evidence to recommend for or against high-sensitivity hsCRP testing for patients at any level of risk for CVD. There is also insufficient evidence to recommend for or against coronary artery calcium testing. High-sensitivity CRP adds marginal additive strength to prediction models (area under the curve [AUC] increase of 0.004 and improved net reclassification of 1.5%). [26] CAC adds more to risk prediction (AUC increase of 0.05, and improved net reclassification of 5% to 16% [27-29]), but this is generally considered to be a small effect. Both factors tend to add more predictive power among men, smokers, and those at "intermediate-risk." No study has shown that a practice of incorporating such testing into practice improves outcomes. [30,31]

The only theoretical utility of these tests would be for intermediate-risk situations where there is uncertainty about the benefit of treatment. A "negative" test would lower the probability across a threshold of "no treatment," and a "positive" test would raise the probability across a "treat" threshold. This should be done in the context of a shared decision with the patient, and the rationale for the test should be clear prior to performance of the test. Routine use of these tests is not recommended in the absence of evidence that this practice improves patient outcomes; there are significant costs, and CAC testing exposes patients to potentially harmful radiation.

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Recommendations

7. 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**

8. We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater. **Weak For**

9. 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**

Discussion

Once the 10-year risk has been calculated, shared decision making is recommended to decide whether the potential benefits of medications outweigh the potential harms. For high-risk patients with a 10-year risk of 12% or more, it is estimated that risk can be decreased by 20-30% with use of medication for five years. The rationale for a threshold of 12% may appear arbitrary, but it reflects a threshold that most closely resembles the populations in the clinical trials for which the benefits clearly outweighed the risks. A similar rationale is used for the threshold of 6%. There are no clinical trials that specifically address this <6% ten-year risk category. The mean 10-year risk of the few primary preventions trials that included patients in what is considered an intermediate risk group (6-12%) was approximately 8%. However, these trials are few in number and had idiosyncratic inclusion criteria (e.g., Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin [JUPITER], Members of The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]). [32-34] Also, 6% has been used by the ACC/AHA as a conventional threshold for defining the transition from low to intermediate risk. Admittedly, these are arbitrary thresholds, but they also represent thresholds that rationally define inflection points of increasing risk and increasing congruency with the populations included in clinical trials that showed benefit from statin therapy.

Risk reduction may be challenging to communicate to patients. The use of tools such as the Cardiovascular Risk/Benefit Calculator or the Mayo Statin Decision Aid can facilitate the discussion.

For example, a patient with a 10% 10-year risk who experiences a 20% relative risk reduction will have a 2% absolute risk reduction. The medication can prevent 2% of the events or two events out of 100 patients with a similar 10-year risk.

The absolute risk reduction, rather than the relative risk reduction, is the figure that should be used to balance the potential benefits with the potential harms associated with a medication. It is important to understand that while the absolute benefit is dependent on the patient risk for CVD, the potential for harm is the same regardless of CVD 10-year risk. This is the reason why the balance between harm and benefit is more likely to result in an absolute benefit for higher risk than for lower risk patients.

Statins

While the absolute benefit of medication may appear low, even for relatively high-risk patients, the rate of harm is also relatively low and medications, such as statins, are relatively safe. The most frequent side

effect of statins is muscle-related symptoms. The incidence is estimated to be about 10-20% [35-38] and is thought to be higher in community cohorts based on observational data. This side effect is usually benign and disappears with interruption of treatment, but it may result in reluctance to restart statin treatment. Rhabdomyolysis is a more severe statin-related side effect, but is relatively rare and generally limited to higher doses of statins (such as simvastatin 80 mg) or in patients with factors that may predispose them to statin muscle toxicity (e.g., drug-drug interactions, impaired hepatic or renal function, hypothyroidism, advanced age, rheumatologic disorders, vitamin D deficiency, alcoholism). [8,39,40] Discontinuation of statin drug therapy is greater among patients on high-dose statin therapy (10.9%) compared to patients on placebo or moderate-dose statin therapy (7%). [41] In addition to the muscular side effects, a recent systematic review noted that high-dose statins increase the risk of asymptomatic liver enzyme elevation by 0.4% (number needed to harm [NNH]: 250) and increase the risk of type 2 diabetes by 0.5% (NNH: 200). [42] This means that out of 250 patients on high-dose statins, one will have an asymptomatic liver enzyme elevation, while 249 will not have this side effect. And out of 200 patients on high-dose statins, one will develop diabetes as an adverse event of the medication, while 199 patients will not have this adverse event. The Cholesterol Treatment Trialists' (CTT) meta-analyses of statin therapy for primary or secondary prevention did not show an increased incidence of cancer or cancer deaths, hemorrhagic stroke or nonvascular death in patients receiving moderate statins vs. placebo or between moderate and higher dose statins. [8]

Though all decisions should involve a degree of shared decision making, we feel that for patients with a risk of 12% or greater, the benefits of CVD risk reduction so substantially outweigh the risks that we strongly advocate for treatment with statins in order to maximize the reduction in CVD burden in the population.

There continues to be uncertainty about this value judgment among populations at intermediate risk (6-12% 10-year risk) due to the limited number of trials in this risk cohort, and the more tenuous balance between lower absolute risk reduction and stable adverse event risk. Thus, even though statins appear to be cost-effective in the 6% to 12% 10-year risk category, the decision to initiate therapy should be based on an individual patient assessment, incorporating the relative harms balanced against the uncertainty and relative small effect size of the effect. [43]

One of the ways to formally balance harm and benefit is to conduct cost-effectiveness analyses. For patients with 10-year CVD risk of 5% or more requiring moderate or high intensity drug therapy, statin therapy is cost-effective if costs are <$50/month. For patients with 10-year CVD risk of 10% or more requiring moderate or high intensity drug therapy, statin therapy is cost-effective if <$70/month. There is no evidence of cost-effectiveness at risk levels <5%. Therefore, one should not extrapolate this conclusion to very low-risk populations due to the uncertain benefits and known adverse effects associated with statins.

Table D-1 in Appendix D provides dose and adverse drug reactions for common statins.

Recommendation

10. 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**

Discussion

The use of statins led to a reduction in all-cause mortality, nonfatal MI, coronary death and nonfatal stroke when compared to placebo control in a meta-analysis involving more than 130,000 primary and secondary prevention patients. [8,39,40] See Table D-2 in Appendix D for more study details. Most statin studies, however, have been conducted for secondary prevention or among patients without a history of ASCVD but a relatively higher risk of developing an event in the following 10 years. Therefore, existing data may not be generalizable to patients at lower risk. Among the limited number of true primary prevention studies (West of Scotland Coronary Prevention Study [WOSCOPS], Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS], MEGA, JUPITER), WOSCOPS and AFCAPS involved a population with a mean 10-year risk >12%; and only showed benefit in nonfatal MI, ACS, and stroke. [32,34,44,45] MEGA was a trial in which 7832 low risk (mean 10 year risk of 8%) Japanese patients (mean age 58 years) with hypercholesterolemia (mean baseline LDL 157 mg/dL) and no history of coronary heart disease or stroke were randomized to diet or pravastatin 10-20 mg daily in addition to diet, and followed for a mean of 5.3 years. [34] In MEGA, the primary endpoint of first occurrence of coronary heart disease was reported in 61 patients in the pravastatin plus diet group vs. 101 patients in the diet alone group (HR 0.67, 95% CI 0/49-0.91, p=0.01). Improvement in Individual components of the primary endpoint was significant for nonfatal MI and coronary revascularization but not for stroke, coronary death or all-cause mortality. JUPITER was a large trial of 17, 802 healthy patients (median age 66 years) with high hsCRP, normal LDL (<130 mg/dL; median baseline LDL 108 mg/dL), and a mean 10-year risk of 8% who were randomized to rosuvastatin 20 mg or placebo once daily. JUPITER was discontinued early, after a median follow up of nearly two years. [32,45]There were 142 reports of first occurrence of first major cardiovascular events in the rosuvastatin group compared to 251 events in the placebo group (HR 0.56, 95% CI 0.46-0.69). Improvement in CVD risk was noted for fatal and nonfatal MI, stroke, revascularization and in overall mortality. In all, these trials represent a limited body of evidence for statins in primary prevention among a heterogeneous population of patients that may not be generalizable to the broader beneficiary population in the VA and DoD health systems.

By "moderate-dose statin," we mean the dose of a statin that has been proven in randomized controlled trials (RCTs) to be effective in reducing CVD risk. We do not refer to "potency" of a statin, as this pharmacologic term is based on LDL lowering rather than on CVD risk reduction. It should be noted that the VA and the ACC/AHA guidelines concur on the doses of statins that are considered to be the minimally effective proven dose. The VA has advocated for this definition of moderate-dose statin since November 2011 and incorporated this into performance measures. Based upon the existing evidence, there is no direct proven advantage of using high-dose statins over moderate doses in primary prevention. Any use of high-dose statins in primary prevention would reflect the intention of treating LDL levels rather than CV risk. [46] Future research is needed to determine whether there is an additional benefit in reducing CV risk with high vs. moderate-dose statins in primary prevention.

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As part of shared decision making, it is important to explain the possible harms of therapy, [37,47,48] including cost of treatment and potential adverse drug events, as well as the relative probability of benefits, if known. If there is no direct evidence of benefit (i.e., the patient's profile does not correspond with that of clinical trials), this should be explained clearly.

It is also important to explain that monitoring lipid levels is no longer recommended since results will not alter the course of treatment. [49]

Recommendation

11. 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 LDL-C >190 mg/dL. **Weak For**

Discussion

In patients who cannot tolerate a statin or decline treatment with a statin, the following information can guide the use of alternative medications for CVD risk reduction in this relatively small group of patients. Drug dose and adverse drug reactions for common non-statins are listed in Table D-1 in Appendix D. Additional scientific evidence to support Recommendation 11 is also provided in Appendix D.

Positive lifestyle changes include heart healthy strategies for controlling CVD risk factors, including dietary changes and physical activity. Addressing lifestyle factors contributing to CVD, through the avoidance of smoking and adoption of healthy dietary and physical activity habits, is recommended for all patients, regardless of their CVD risk. Refer to the Non-pharmacologic Approaches section of this CPG for additional detail.

Fibrates (gemfibrozil, fenofibrate)

As monotherapy, there is no proven efficacy of fibrates in improving overall mortality. In a meta-analysis that combined primary and secondary prevention trials, there was a small reduction in overall CVD events among patients on fibrates as compared to those on placebo. This benefit was primarily seen in patients with low HDL and measured at about a 1% ARR from 4.3% absolute risk in the control group or a 16% relative risk reduction (95% CI: 9% to 23%, P < 0.001) of cardiovascular events. [50]

In evaluating the evidence for reducing cardiovascular events with individual fibrates in a primary prevention population, the Helsinki Heart Study (HHS) did show a benefit of gemfibrozil vs. placebo on reducing cardiovascular events in asymptomatic men with primary dyslipidemia (LDL-C >190 mg/dL). In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of more than 9,000 diabetic patients with (n=2131) or without (n=7664) CVD, fenofibrate did not significantly reduce CVD events vs. placebo. Available evidence does not support a benefit of fenofibrate in primary prevention vs. placebo while gemfibrozil reduced CVD events in a population limited to men with primary dyslipidemia. [51]

While it is difficult to find absolute percentages on adverse drug events, discontinuation rates in the fibrates groups of trials were higher than for placebo. Potential adverse effects of fibrates include

myalgia, skin rash, and gastrointestinal symptoms. [52] Finally, there was a signal suggesting increased risk of pancreatitis (absolute risk increase of 0.5%, NNH = 200) found with the use of fenofibrate. [51] Given the small benefit of fibrates, any adverse drug event should prompt reassessment of continuation of therapy.

No study has supported an incremental benefit of these agents over statins alone. Therefore, we recommend against routinely using combination therapy, such as a statin with a fibrate. [51,53]

Bile acid sequestrants

As monotherapy there is no proven efficacy of bile acid sequestrants (BAS) in improving overall mortality. In patients who cannot or will not consider a statin or gemfibrozil or niacin, there is evidence of a slight reduction in cardiovascular events with BAS. Over a 7.4 year period, a 1.7% ARR from 9.8 % absolute risk in the control group or a 19% relative risk reduction (95% CI: 3% to 32%) in definite cardiovascular events was seen with cholestyramine in men with very high LDL (>200 mg/dL). [54,55] The only harm noted was an increase in gastrointestinal side effects. BAS remains an option for patients who cannot or will not use more effective therapy (i.e., statins) for reducing cardiovascular events.

While it is difficult to find absolute percentages on adverse drug events, discontinuation rates in the BAS groups of trials were higher than for placebo. Given the small benefit of BAS, any adverse drug event should prompt reassessment of continuation of therapy.

No study has supported an incremental benefit of these agents over statins alone. Therefore, we recommend against routinely using combination therapy with a BAS.

Niacin

There is no primary prevention data about use of niacin.

Ezetimibe

While ezetimibe is shown to reduce LDL-C, there is no evidence that it lowers the risk of CVD in primary prevention. However, in patients intolerant to or unable to take statins, ezetimibe monotherapy can be considered for reducing LDL-C.

Long Chain Omega-3 Fatty Acids (Fish oils)

We identified one fair quality meta-analysis, which included both primary and secondary prevention studies and showed no benefit of long chain omega-3 fatty acids in all-cause mortality, stroke, or coronary heart disease (CHD). Adverse effects were more common in patients taking fish oil and were primarily mild gastrointestinal disturbances. [56] Another systematic review and meta-analysis by Rizos et al. (2012), was conducted to examine the effect of omega-3 polyunsaturated fatty acids (PUFAs) on major cardiovascular outcomes and included 60 studies enrolling 68,680 primary and secondary prevention patients. Use of omega-3 fatty acids was not associated with a reduction in all-cause mortality, cardiac death, MI, stroke or sudden death. [57]

Fish oils that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be helpful in decreasing severe hypertriglyceridemia (e.g., >500 mg/dL). While reducing TGs might mitigate acute pancreatitis, the benefit on CVD events is unclear. It should be noted that many over-the-counter fish oil

supplements vary in quantities of EPA-DHA. If using over-the-counter fish oil supplements, patients should be instructed to consult the label of the supplement and use the combined total of EPA and DHA, rather than the dose of fish oil to calculate the daily dose. There are, however, several FDA-approved prescription omega-3 products that contain close to 1 gram (g) of EPA-DHA per capsule. The recommended dose is usually 4g per day of EPA-DHA (not grams of fish oil or grams of omega-3), i.e., 4 pills per day of the prescription form or the number of OTC pills corresponding to this amount of EPA-DHA (number of pills depends on the amount of EPA-DHA available in each pill, but can vary from 5 to 40 pills per day). Refer to Table 10 in the AHA Scientific Statement on Triglycerides and Cardiovascular Disease for additional information on food sources for EPA and DHA. [58]

Recommendations

12. We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy. **Weak For**
13. We recommend against <u>routinely</u> measuring LFTs or CK after a moderate-dose statin is initiated. **Strong Against**

Discussion

Establishing a baseline CK level and LFTs is clinically prudent to interpret potential future laboratory results or symptoms. Since all clinical trials which studied the efficacy of statins excluded patients with elevated liver transaminases, and there is a concern that statins may exacerbate hepatotoxicity, we suggest assessing for evidence of liver damage prior to initiation, and recommend against statin use in patients with evidence of worsening liver damage or fluctuating LFTs. However, statins can be used in patients with stable 1-2x elevation of LFTs with periodic LFT monitoring.

Once low- or moderate-dose statins have been initiated, it has been traditionally recommended to measure LFTs on a regular basis to detect asymptomatic liver damage and to measure CK levels if muscular symptoms occur. However, the ACC/AHA and other associations' recommendation for frequent laboratory monitoring is based on the indirect evidence that such monitoring was used in most large RCTs. It is not based on studies specifically designed to test the effectiveness of frequent monitoring. Despite an extensive review of the literature, no direct evidence was uncovered by our group that frequent laboratory monitoring improves detection of myopathy (rhabdomyolysis or lesser degrees of myopathy) or liver dysfunction (except at higher doses of statins). Additionally in 2012, the US Food and Drug Administration (FDA) announced their revisions in periodic liver monitoring while on statin therapy and concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing this rare side effect.

Less than 1% of patients taking low- to intermediate-dose statins and up to 2-3% of patients on high-dose statins experience abnormal liver tests (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). This lab abnormality alone does not diagnose liver injury, and whether it is harmful is not known. Most often this resolves, even if continuing statin therapy with no change. The risk of serious liver injury while on statin therapy is extremely rare and was not different from placebo in clinical trials. Patients with mild AST or ALT elevations (less than 3x normal) do not warrant immediate

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dose change but should continue to follow-up and consider repeat testing with their treating provider. For patients with AST and ALT elevation greater than 3x the lab normal, evaluation of the risks/benefits of continuing statin therapy with repeat lab testing vs. adjusting or discontinuation the medication should be addressed with the patient's treating provider. [42,59]

Frequent laboratory testing also has negative consequences. From a patient perspective, potential harms include infections, such as septic phlebitis or cellulitis, pain at site of blood draw, inconvenience of appointments to get labs done and follow up of results by phone or with a visit to the provider. From a provider perspective, potential negative consequences of frequent testing include not following up on an abnormal result due to the large number of tests. If there is no benefit in terms of outcomes, patients and providers seem to prefer fewer laboratory tests. There is also an opportunity cost associated with retrieving results and documenting that the results were reviewed with the patient. This use of time takes away from time with patients and reduces patient access to care.

Additional scientific evidence to support recommendations 12 and 13 is provided in Appendix D.

Management of Pharmacotherapy for Secondary Prevention
(Patients with a history of ASCVD or ACS)

Recommendations

14. 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**

15. In patients with ASCVD who are able to tolerate statins, we recommend against the <u>routine</u> 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**

16. 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**

17. We strongly recommend against the routine use of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD. **Strong Against**

18. 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**

19. We suggest measuring LFTs 4-12 weeks after the initiation of high-dose statin. **Weak For**

Discussion

Secondary prevention is intended to prevent subsequent CVD events in patients with a clinical diagnosis of ASCVD. These include acute coronary syndrome (ACS), MI, coronary arteries bypass graft (CABG), percutaneous coronary interventions (PCI), stable obstructive CAD including angina and equivalent, cerebrovascular accident (CVA), transient ischemic attack (TIA), atherosclerotic peripheral vascular disease (PVD) including claudication or abdominal aortic aneurysm (AAA), but NOT asymptomatic arteriosclerosis, as detected by measurement of coronary artery calcium (CAC), exercise test, intima media thickness (IMT) ultrasound measurement, ankle brachial index (ABI), or brachial reactivity. The VA/DoD lipid guideline working group considered the following outcomes for its evidence review: overall or all-cause mortality, nonfatal MI, CHD death, fatal and nonfatal stroke. These represent the outcomes of treatment most relevant to patients and providers, and least susceptible to bias. The group conceded that revascularizations were not as clear an outcome since the indications for these interventions are less well-defined, may have regional variation, and their impact on mortality or other important outcomes (e.g., CHF) is less certain.

Additional scientific evidence to support recommendations 14-19 is provided in Appendix D.

Statins

The recommendation to initiate moderate-dose statin and titrate to high dose as tolerated for secondary prevention is based upon a high level of evidence from three published meta-analyses from the CTT collaborators *(involving 14 [CTT 2005], 21 [CTT 2010-focus on comparison of higher vs. lower or*

moderate-dose statin therapy] and 22 [CTT 2012-focus on examining benefit of statins at varying degrees of risk] trials consisting of primary and secondary prevention populations treated with statins). The use of statins led to a reduction in all-cause mortality, nonfatal MI, coronary death and nonfatal stroke when compared to placebo control in these meta-analyses of secondary prevention studies. Statin doses used in these trials, involving more than 130,000 patients, were primarily fixed moderate doses (e.g., mean or median reduction in LDL-C of 30-40% from baseline [e.g., simvastatin 20-40 mg, pravastatin 40 mg, lovastatin 20-80 mg, atorvastatin 10 mg, etc.]). See Table D-2 in Appendix D for outcome data. [8,39,40]

The recommendation that a higher statin dose may be considered in patients with acute ACS and in patients with multiple uncontrolled risk factors or recurrent ASCVD events is based upon a very low level of evidence from a meta-analysis by Mills et al. (2010). [60] This meta-analysis included 10 trials (n=41,778) comparing high- vs. low- to moderate-dose statins for secondary prevention. There was no significant effect on overall mortality between high and lower statin doses (RR 0.92, 95% CI 0.83-1.03, p=0.14) and no statistically significant difference in CVD deaths (RR 0.89, 95% CI 0.78-1.01, p=0.07). There was a significant difference in favor of higher statin doses in nonfatal MI (RR 0.82, 95% CI 0.76-0.89, p≤0.0001), and combined nonfatal and fatal stroke (RR 0.0.86, 95% CI 0.77-0.96, p=0.006). The authors performed a subgroup analysis of three trials in patients with ACS and found a statistically significant reduction in all-cause mortality and CVD death with higher statin doses. Interestingly, conflicting statistical differences were noted between the ACS subgroup and the overall pooled findings in other outcomes as well (e.g., nonfatal MI, no difference in ACS, etc.). Limitations of this meta-analysis were that 5 of the 10 trials randomized less than 1000 patients who were followed for less than two years and some included intermediate endpoints (e.g., arteriosclerotic progression) as their primary endpoint. Additionally, endpoints were not consistently available or reported in the individual trials, thereby lessening the strength of the findings. [60]

Results from a second good quality meta-analysis by Preiss et al. (2011) [61] which included five studies of low- or moderate- vs. high-dose statins, showed that new onset diabetes occurred more frequently in the higher statin dose vs. low-to-moderate dose groups (OR 1.12, 95% CI 1.04-1.22, NNH 498). Authors reported an additional two cases per 1000 patients treated over a weighted mean follow up of 4.9 years. Cardiovascular events (composite: all-cause mortality, cardiovascular death, nonfatal MI, nonfatal stroke and coronary revascularization) occurred less often in the high-dose statin group (OR 0.84, 95% CI 0.75-0.94, NNT 155) translating into 6.5 fewer CVD events per 1000 patient-years treated in the high-dose group over a weighted mean follow up period of 4.9 years. [61]

Another good quality meta-analysis examined data from four of the trials comparing moderate- to high-dose statins and found that treatment with high-dose atorvastatin or simvastatin was associated with a higher risk for any adverse event (OR 1.44, 95% CI 1.33-1.55, p<0.001) and events leading to withdrawal of the statin (OR 1.28, 95% CI 1.18-1.39). There were also statistically greater abnormalities in liver function tests (LFTs) and creatinine kinase with the high-dose regimens. The authors do note the benefits of higher dose statins in terms of CVD risk reduction, as is detailed in this section, but caution that because of the risk for adverse events and potential for more frequent cessation of treatment with statins, use of moderate-dose statins may be preferred in a majority of patients. [62]

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While statins are generally safe for most patients, there is concern regarding use of high-dose statin regimens in increasingly larger numbers of patients due to the potential for adverse events when compared to moderate intensity statin regimens (See Table D-4 for CTT meta-analysis findings and Table D-5 for individual trials in Appendix D). In a meta-analysis by Silva et al. (2007), high-dose statins were associated with a greater risk for any adverse event and a higher frequency of discontinuation due to adverse events. Higher doses were also associated with a higher frequency of abnormalities in LFTs and creatinine kinase. [62] There is also a higher risk for new onset diabetes in patients receiving high-dose vs. moderate-dose statins as demonstrated in the meta-analysis by Preiss et al. (2011) [61] Alternatively, authors of this meta-analysis did report a reduction in a composite of CVD events with high-dose compared to moderate-dose statins. [61] Therefore, if high-dose statins are being contemplated, providers should carefully consider the known added harms and additional benefits of such therapy, and limit prescribing of high-dose statins to those patients at greatest CVD risk. None of the individual studies or meta-analyses that looked at high doses of statin vs. lower doses addressed back titration from a high to lower dose of statin after a period of time. This is an area of research priority. In the meantime providers will have to use individualized clinical judgment.

In summary, improvement in the primary outcome of major cardiovascular events was not consistently observed with a higher vs. moderate statin dose, as only two of the five original trials showed a greater efficacy advantage of the higher dose and differences were limited to a reduction in nonfatal events. Although the risk for serious adverse events related to statins is low, other less severe adverse events, such as muscle complaints (e.g., myalgias), occur more commonly with higher dose statins and may lead to decreased adherence and reluctance to continue any dose of statin therapy.

Beneficiaries should be provided an opportunity for a shared, informed decision regarding the benefits and harms of statin therapy. Use of high intensity statins is associated with a small reduction in nonfatal CVD events, a small but greater risk for adverse events, and a higher rate of study withdrawal due to adverse events vs. moderate doses in the populations studied. Thus, providers should consider this in their approach to patients already on and/or those being considered for initiation of statin therapy.

The recommendation against routine use of LDL-C and non-HDL-C treatment targets for the secondary prevention of ASCVD was derived after a systematic review of the literature on this question. We did not find any properly conducted RCTs that demonstrated the benefit of using LDL or non-HDL targets. There were several studies that deserve specific comment. The Cholesterol Treatment Trialists' Collaboration (CTTC) of 2010 was a meta-analysis of various statin trials that were not designed as treat-to-target studies. [8] Any conclusions regarding treatment goals are post hoc analyses, which can only be regarded as hypothesis generating and not proof of benefit. Also, utilization of the soft end point of revascularization in the composite primary endpoint fundamentally changed the results of the individual trials in patients with ACS and stable CAD, and was a different primary endpoint from the original CTTC analyses in 2005 [39] of 90,056 patients and 18,686 diabetic patients in 2008. [63] As noted by some authors, the use of revascularization in the primary endpoint is a post hoc analysis that severely limits the validity of the results. [64] As such, the CTTC 2010 analyses provide no evidence of a benefit for treating to LDL-C targets with statins. [8] There was, however, clear evidence that moderate fixed-dose statin monotherapy improved total mortality and resulted in fewer CVD events.

Our panel found and reviewed one study which was inconclusive in establishing the utility of LDL-C and non-HDL-C targets. This was a RCT published by Kohro et al. (2011) [65], which was under-powered and utilized a strictly Japanese population with ≥75% stenosis in at least one major coronary artery.

Treatment directed at LDL or non-HDL targets can result in escalating doses of statins and combinations of drugs with higher rates of adverse effects and no proven improvement in clinical outcomes. The Work Group did consider follow-up lipid monitoring as a way to measure adherence. Although there is no evidence to support routine lipids testing for adherence, providers may want to consider lipid testing in select patients to address adherence.

The panel's review of the evidence does not support the use of LDL-C nor non HDL-C treatment goals.

Fibrates (gemfibrozil, fenofibrate)

As monotherapy there is no proven efficacy of fibrates in improving overall mortality. In a meta-analysis that combined primary and secondary prevention trials, there was a small reduction in overall CVD events among patients on fibrates as compared to those on placebo. This benefit was primarily seen in patients with low HDL and measured at about a 1% ARR from 4.3% absolute risk in the control group or a 16% relative risk reduction (95% CI: 9% to 23%, P < 0.001) of cardiovascular events. [50]

In evaluating the evidence for reducing cardiovascular events with individual fibrates in a secondary prevention population, the evidence did not show a reduction in CV events with fenofibrate vs. placebo in the FIELD study of more than 9000 diabetic patients with (n=2131) or without (n=7664) CVD [51]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) trial, gemfibrozil reduced nonfatal MI and death of cardiac origin compared to placebo in men with CHD, low HDL-C and moderately elevated LDL-C. [66] Available evidence does not support a benefit of fenofibrate in reducing CV outcomes compared to placebo in the populations studied while gemfibrozil reduced nonfatal MI and cardiac death in males with CHD and low HDL-C.

While it is difficult to find absolute percentages on adverse drug events, discontinuation rates in the fibrates groups of trials were higher than for placebo. Potential adverse effects of fibrates include myalgia, skin rash, and gastrointestinal symptoms. [52] Finally, there was a signal suggesting increased risk of pancreatitis (absolute risk increase of 0.5%, NNH = 200) found with the use of fenofibrate. [51] Given the small benefit of fibrates, any adverse drug event should prompt reassessment of continuation of therapy.

No study has supported an incremental benefit of these agents over statins alone. Therefore, we recommend against routinely using combination therapy, such as a statin with a fibrate. [51,53]

Bile acid sequestrants

No trials were identified that addressed the effect of BAS (e.g., colestipol, cholestyramine, etc.) either alone or in combination with statins for reducing CVD events in patients treated for secondary prevention of ASCVD.

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Niacin

The available evidence is insufficient for using niacin as monotherapy since 3g of immediate-release niacin daily in the Coronary Drug Project (CDP) did not reduce the primary outcome of total mortality; but there was a significantly lower risk for nonfatal MI in favor of niacin vs. placebo. Existing evidence does not support an incremental reduction in CVD outcomes when niacin is added to statins. [67,68] However, there was an increase in serious adverse events observed in patients receiving niacin/laropiprant vs. those on placebo in a study of more than 25,000 patients well controlled on statin-based therapy (Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]). The contribution of the anti-flushing drug laropiprant to the increase in adverse events, separate from niacin, is unknown. (See Appendix D for more details on relevant studies supporting recommendations 14-19).

Ezetimibe

The available evidence is insufficient for using ezetimibe as monotherapy to reduce cardiovascular events, and existing evidence does not support an incremental reduction in CVD outcomes when ezetimibe is added to statins.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) has recently completed and will address if there is any incremental benefit of adding ezetimibe to simvastatin on CVD outcomes in patients with ACS. IMPROVE-IT preliminary results were reported at the American Heart Association meeting in November 2014 at the time of completion of this guideline. There is currently no peer-reviewed publication available for review. As this guideline relies on published peer-reviewed data for inclusion, the guideline committee will evaluate the peer-reviewed publication when available and update this guideline accordingly.

Long Chain Omega-3 Fatty Acids (Fish oils)

We identified one fair quality meta-analysis, which included both primary and secondary prevention studies and showed no difference in all-cause mortality, stroke, or CHD. Adverse effects were more common in patients taking fish oil and were primarily mild gastrointestinal disturbances. [56] Another systematic review and meta-analysis by Rizos et al. (2012) was conducted to examine the effect of omega-3 polyunsaturated fatty acids (PUFAs) on major cardiovascular outcomes and included 60 studies enrolling 68,680 primary and secondary prevention patients. Use of omega-3 fatty acids was not associated with a reduction in all-cause mortality, cardiac death, MI, stroke or sudden death. [57]

EPA and DHA, individually reduce TGs. Fish oils that contain EPA and/or DHA can be helpful in decreasing severe hypertriglyceridemia (e.g., >500 mg/dL). While reducing TGs might mitigate acute pancreatitis, the benefit on CVD events is unclear. It should be noted that many over-the-counter fish oil supplements vary in quantities of EPA-DHA. If using over-the-counter fish oil supplements, patients should be instructed to consult the label of the supplement and use the combined total of EPA and DHA, rather than the dose of fish oil to calculate the daily dose. There are, however, several FDA-approved prescription omega-3 products that contain close to 1g of EPA-DHA per capsule. The recommended dose is usually 4g per day of EPA-DHA (not gram of fish oil or gram of omega-3), i.e., 4 pills per day of the prescription form or the number of OTC pills corresponding to this amount of EPA-DHA (number of pills

depends on the amount of EPA-DHA available in each pill, but can vary from 5 to 40 pills per day). Refer to Table 10 in the AHA Scientific Statement on Triglycerides and Cardiovascular Disease for additional information on food sources for EPA and DHA. [58]

Non-Pharmacologic Approaches

Recommendation

20. We recommend all adults adopt healthy lifestyles to reduce CVD risk, including:
    a. Tobacco cessation for all smokers (See 2008Tobacco Use CPG,
       http://www.healthquality.va.gov/guidelines/CD/mtu/)
    b. Therapeutic Lifestyle Changes (TLC) diet to optimize nutrition (For overweight and/or
       obese patients, see 2014Obesity CPG,
       (http://www.healthquality.va.gov/guidelines/CD/obesity/VADoDCPGManagementOfOv
       erweightAndObesityFINAL070714.pdf)
    c. Optimal physical activity (See 2008 Physical Activity Guidelines for Americans,
       http://www.health.gov/paguidelines/pdf/paguide.pdf)

Strong For
Modified from the 2006 CPG without an updated systematic review of the evidence.

Discussion

A healthy lifestyle is the foundation of primary CVD prevention. Positive lifestyle changes include heart healthy strategies for controlling CVD risk factors, including dietary changes and physical activity. Addressing lifestyle factors contributing to CVD, through the avoidance of smoking and adoption of healthy dietary and physical activity habits, is recommended for all patients, regardless of their CVD risk. Due to the many challenges in developing an approach to maximize the likelihood of compliance with positive lifestyle changes, behavior modification and individualizing specific interventions need to be considered. [69]

Therapeutic Lifestyle Changes Diet

The TLC diet includes limiting saturated and trans fat, limiting cholesterol, consuming more polyunsaturated and monounsaturated fatty acids, and consuming adequate fiber. [70] Minimum dietary modifications included in the TLC Diet are illustrated in Table E-3 in Appendix E. The TLC Diet is to reduce saturated fat intake (animal, dairy fat, coconut, and palm kernel oils) in conjunction with an overall reduction in total dietary fat. Trans fatty acids also raise serum LDL-C levels similar to saturated fats and dietary intake should be kept as low as possible. [71] Major sources of trans fatty acids include partially hydrogenated oils such as those in many commercially-prepared baked products and desserts, snack foods, fried foods and non-dairy creamers.

Patients should be encouraged to maintain healthy diets that include the intake of a variety of fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, and sources of protein low in saturated fat (e.g., poultry, lean meats, plant sources), while reducing intake of red meat products, refined sugars (including sweetened beverages, candies, syrups and table sugar) [72], processed food with high sodium content, and high-fat cheeses.

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Patient-friendly tools to plan food choices and menus, accessible without the assistance of a RD, are available at MyPlate.gov and the AHA websites.

Weight Loss

> Refer to VA/DoD CPG Management of Obesity and Overweight (OBE) (2014);
> http://www.healthquality.va.gov/guidelines/CD/obesity/VADoDCPGManagementOfOverweightAndObesityFINAL070714.pdf

Achieving and maintaining a healthy weight is essential in the prevention and reduction of CVD risk. Clinicians should encourage maintenance of a healthy weight through referral to a weight management program that will implement an appropriate balance of caloric intake, physical activity, and behavioral modification, to maintain and achieve a healthy weight.

Physical Activity

The results of observational studies support an inverse relationship between physical activity and CVD risk. [73] Clinicians should advise patients of all ages to follow a well-balanced exercise plan consisting of 30 minutes or more of moderate intensity, such as brisk walking, on most (and preferably all) days of the week. [69] Physical activity guidelines are illustrated in Table E-1 of Appendix E.

Exercise, when performed at the aforementioned recommended levels, has been shown to reduce LDL-C and non-HDL-C. More research on the effect of exercise on CVD outcomes is needed. Additionally, the effects of exercise on HDL-C and TGs in persons with known CVD has been inconsistent and additional research is needed to determine the optimal quantity and type of exercise that will achieve the desired changes in these outcomes. [74]

The 2008 Physical Activity Levels for Americans (http://www.health.gov/paguidelines/pdf/paguide.pdf) [75] and ACC/AHA vs. Guideline on Lifestyle Management to Reduce Cardiovascular Risk [69] document physical activity as an integral component in the reduction of CVD risk and the key guidelines from the former are illustrated in Table E-2 of Appendix E.

Patient-friendly tools to assess fitness level and track physical activity are available on the health.gov website, http://www.health.gov/paguidelines/resources/.

Smoking Cessation

> Refer to the Department of Health and Human Services (DHHS) Public Health Service (PHS) guideline, Treating Tobacco Use and Dependence: 2008 Update;
> http://www.healthquality.va.gov/guidelines/CD/mtu/.

Smoking cessation is effective in reducing the risk for CVD disease and other atherosclerotic diseases. Providers' direct advice to discontinue smoking increases quit rates compared with the absence of such advice. There is further evidence of the effectiveness of even brief smoking cessation treatments lasting less than 10 minutes in the office or during a single visit. [76] All medical providers should strongly advise smokers to discontinue this habit. [77]

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Clinicians should screen all adults for tobacco use and provide tobacco cessation interventions for those who use tobacco products. Interventions, including screening, brief counseling (three minutes or less), and or pharmacotherapy have proven to increase tobacco abstinence rates. However, there is a dose-response relationship between quit rates and the intensity of counseling. Effective interventions may be delivered by a variety of primary care clinicians. [76]

Recommendations

21. 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 30g 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**

22. We suggest that each patient's diet be individualized based on a nutrition assessment (preferably by a RD), other CVD risk factors, other disease conditions, and patient's lifestyle. **Weak For**

Modified from the 2006 CPG without an updated systematic review of the evidence.

Discussion

Nutrition Counseling

RDs should provide Medical Nutrition Therapy (MNT) for high-risk patients to lower CVD risk and treat dyslipidemia through diet and lifestyle interventions in conjunction with pharmacologic therapy. MNT should include the provision of monitored dietary education, specifically the common elements that constitute a Mediterranean diet. Effective MNT is time intensive and the first visit will usually take approximately one hour. Following the initial visit, the RD should schedule regular follow-up appointments to assess the patient's progress and determine if changes in nutritional goals and relevant treatment plans are necessary.

Mediterranean Diet

While a dietitian-directed Mediterranean diet is recommended for patients at high-risk, patients at lower risk may also benefit from developing healthy eating habits that lower CVD risk. Traditionally, the Mediterranean diet is one that focuses on a high intake of fruits, vegetables, olive oil, nuts, legumes, seeds, herbs, and whole grains. The diet also includes a moderate amount of wine, fish/seafood, and poultry along with a reduced intake of red meat, processed meats, and sweets. The Mediterranean diet encourages mono- and poly-unsaturated fatty acids while discouraging saturated and trans fats. Those who consume alcohol on a regular basis should include wine as their main source of alcohol. Although alcohol is recommended in moderate amounts, it is important to consider personal history, including history of habitual drinking, as well as religious beliefs, personal preferences, and a family history of alcoholism, before encouraging alcohol consumption. [78]

Estruch et al. (2013) demonstrated that a Mediterranean diet resulted in a decrease in cardiovascular risk in those considered high-risk. [78] High risk was defined in this study as type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a

family history of premature coronary heart disease. The control group received a low-fat diet and two intervention groups followed a Mediterranean diet supplemented with either extra-virgin olive oil (roughly one liter per week) or 30g of mixed nuts per day (15g of walnuts, 7.5g of hazelnuts, and 7.5g of almonds). Dietitians conducted both individual and group sessions at the baseline visit and quarterly sessions thereafter in the two Mediterranean diet groups. Additionally, the Mediterranean diet groups increased their weekly servings of fish, legumes, and extra-virgin olive oil when compared to the control group. No relevant adverse effects related to dietary patterns were reported. A total of 7447 patients participated with the median follow-up being 4.8 years. Overall, 288 primary-outcome events were reported with 96 (3.8%) and 83 (3.4%), respectively, for the two Mediterranean diet groups supplemented with olive oil and nuts, while the control diet group events were 109 (4.4%). This resulted in a clinically and statistically significant ARR of about three major cardiovascular events per 1000 persons and a relative-risk reduction of about 30% among high-risk persons. [78]

In order for VA and DoD patients to benefit from these findings, health care providers should refer a high-risk patient to a RD to educate and assess compliance with a Mediterranean diet. The recommended inclusion of tree nuts and peanuts should be an isocaloric substitution rather than an addition to the diet plan. Patients should also be aware of the caloric density of mixed nuts and olive oil when formulating a dietary plan. Therefore, patients should focus on an isocaloric substitution rather than an addition to the diet plan. Dietary modifications included in the Mediterranean diet are illustrated in Table E-4 in Appendix E.

Dietitians should provide dietary guidance that includes recommendations focused on using an abundant amount of olive oil, consumption of ≥2 servings of vegetables daily (with at least one portion raw vegetables), ≥3 daily servings of fresh fruit, ≥3 servings of legumes weekly, ≥3 servings of fish/shellfish weekly, ≥1 serving of nuts or seeds weekly, selecting white meats in place of red and processed meats, and cooking regularly with tomato, garlic, onion, with or without the addition of aromatic herbs simmered in olive oil. [78] Consumption of nuts (raw, unsalted), eggs, fish/seafood, low-fat cheese, whole-grain cereals, and chocolate with ≥ 50 percent cocoa is acceptable. Patients should be advised to limit and/or eliminate butter, cream, margarine, cold meat, duck, sugar-sweetened and/or carbonated beverages, pastries, industrial (commercial) baked goods, industrial desserts, French fries and potato chips, and cakes/sweets that are not homemade. Additionally, cured ham, red meat with all visible fat removed, and cured and/or high-fat cheeses limited to ≤1 serving per week is desirable. [78]

To assess compliance with the dietary recommendations, dietitians may use the 14-item questionnaire illustrated in Table E-5 in Appendix E. Following completion of the questionnaire, the dietitian should direct dietary counseling with a goal of increasing the patient's quantitative score.

Recommendations

23. We recommend treating the common secondary causes of elevated TGs: dietary indiscretion (e.g., refined sugars), alcohol use, hypothyroidism, and hyperglycemia. **Strong For**

Modified from the 2006 CPG without an updated systematic review of the evidence.

24. 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**

Discussion

Hypertriglyceridemia can be caused by or exacerbated by an underlying medical disorder. When secondary disorders of hyperlipidemia are appropriately treated, TG levels can greatly improve or, in some cases, even return to the normal range. Hypertriglyceridemia has been associated with obesity and alcohol use/abuse. Diabetes (especially sub-optimally controlled) and hypothyroidism have also been documented as potential causes for hypertriglyceridemia. See Table 11 in the AHA Scientific Statement on Triglycerides and Cardiovascular Disease for additional information on lowering TGs. [58] Dietary fat should be restricted to < 15% of total calories. [79] Referral to RD or other qualified nutritional professional is encouraged.

Monitoring and Follow-up

Recommendations

25. We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy. **Weak For**

26. 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 DM or hypertension) and not on statin therapy. **Weak For**

Discussion

Repeat risk assessments should be done at a periodicity appropriate to the patient's previously identified level of risk. For patients with calculated risk levels of under 6%, in the absence of additional risk factors (e.g., DM, HTN, starting smoking), risk assessment should be undertaken at five-year intervals. All persons with average or below average risk for atherosclerotic events should be screened for CVD risk every five years. For patients with intermediate levels of risk, calculated between 6% and 12%, more frequent re-assessment at two-year intervals may be appropriate. This may be a particularly useful strategy as the patient approaches the point where age begins to dominate the result of the risk calculator (about 53 for men, 58 for women). For patients known to be at high-risk (recent ACS, established ASCVD, diabetes with additional risk factors, or previous risk calculation greater than 12%) and already on a statin (or alternative lipid lowering therapy), there is no utility to repeat risk assessments. For patients in these high-risk groups not utilizing optimal risk reduction strategies (including medication), reassessment may be appropriate if it has the potential to alter patient or provider values and preferences about medication or other risk reduction strategies (i.e., smoking cessation). For patients that develop a condition with limited life expectancy while on lipid therapy, providers and patients may have a shared decision making (SDM) discussion on discontinuation of treatment, as harms (e.g., polypharmacy, adverse drug reactions [ADRs]) may outweigh any individual patient benefit. [80]

There is no evidence regarding the optimal interval and frequency of CVD risk assessment. Using the basic decision thresholds of 6% and 12% and the known factor of age as the strongest factor in risk prediction, it is reasonable to reassess risk every five years among those at <6% 10-year risk, and every two years among those between 6-12% 10-year risk. We recommend the recalculation of risk upon the development of any new risk factor.

Appendix A: Evidence Review Methodology

The CPG Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on 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 key questions 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 [81]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, comorbidities and other patient characteristics or demographics.
I	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.
C	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.
O	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.
(T)	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).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 contains the final set of key questions used to guide the systematic review for this CPG.

Population(s)

The key questions are specific to adults 18 years or older who are considered candidates for lipid-lowering therapies for primary or secondary prevention of CHD or ASCVD. Patients without a CHD or ASCVD diagnosis but with risk factors (e.g., diabetes) or various levels of 10-year risk are candidates for primary prevention, while patients with a CHD or CVD diagnosis are candidates for secondary prevention.

Interventions

The diagnostic technologies assessed include the following:

- Pharmacologic treatments, including statins, gemfibrozil, fenofibrate, nicotinic acid or niacin, BAS (including bile acid resins), ezetimibe, and omega-3 fatty acids

- Management strategies related to specific cholesterol targets (various target levels for LDL-C and non-HDL-C)

- Management strategies related to frequency of lipid monitoring in new patients treated with statins

- Use of additional risk-stratifying tests (hsCRP and CAC) to improve risk prediction in patients with intermediate-risk (5-15% risk of developing CVD over 10 years)

Outcomes

For Key Questions (KQ) 1, 2 and 4 the outcomes of interest are major CHD or CVD events (including cardiovascular mortality, all-cause mortality, fatal and non-fatal MI, fatal and non-fatal stroke, and need for revascularization) and treatment-related adverse events (including muscle myopathy and liver dysfunction). For KQ 3, the outcomes of interest include all of the above in addition to lipid levels and attrition. For KQ 5 the outcomes of interest are death, MI, stroke, muscle myopathy and liver dysfunction. KQ 6 includes all clinical outcomes relevant to KQ 1, 2, and 4 plus intermediate measures such as increased AUC or net reclassification.

Conducting the Systematic Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by the Agency for Healthcare Research and Quality (AHRQ) in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* [82] The methods also follow the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document. [6]

Extensive literature searches identified 5,925 citations potentially addressing the key questions of interest to this evidence review. Of those, 1,741 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, 4,183 abstracts were reviewed with 2,843 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll a population of interest, or published prior to January 2010. A total of 1,340 full-length articles were reviewed. Of those, 947 were excluded at a first pass review for the following: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, not meeting inclusion criteria for any key question, or being a duplicate. A total of 393 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 295 were ultimately

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excluded. Reasons for their exclusion are presented in Figure A-1 below. A table listing all studies excluded at the full-article level is included as a separate file to this report.

Overall, 90 studies (in 98 publications) addressed one or more of the Key Questions 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. PRISMA diagram of literature search results

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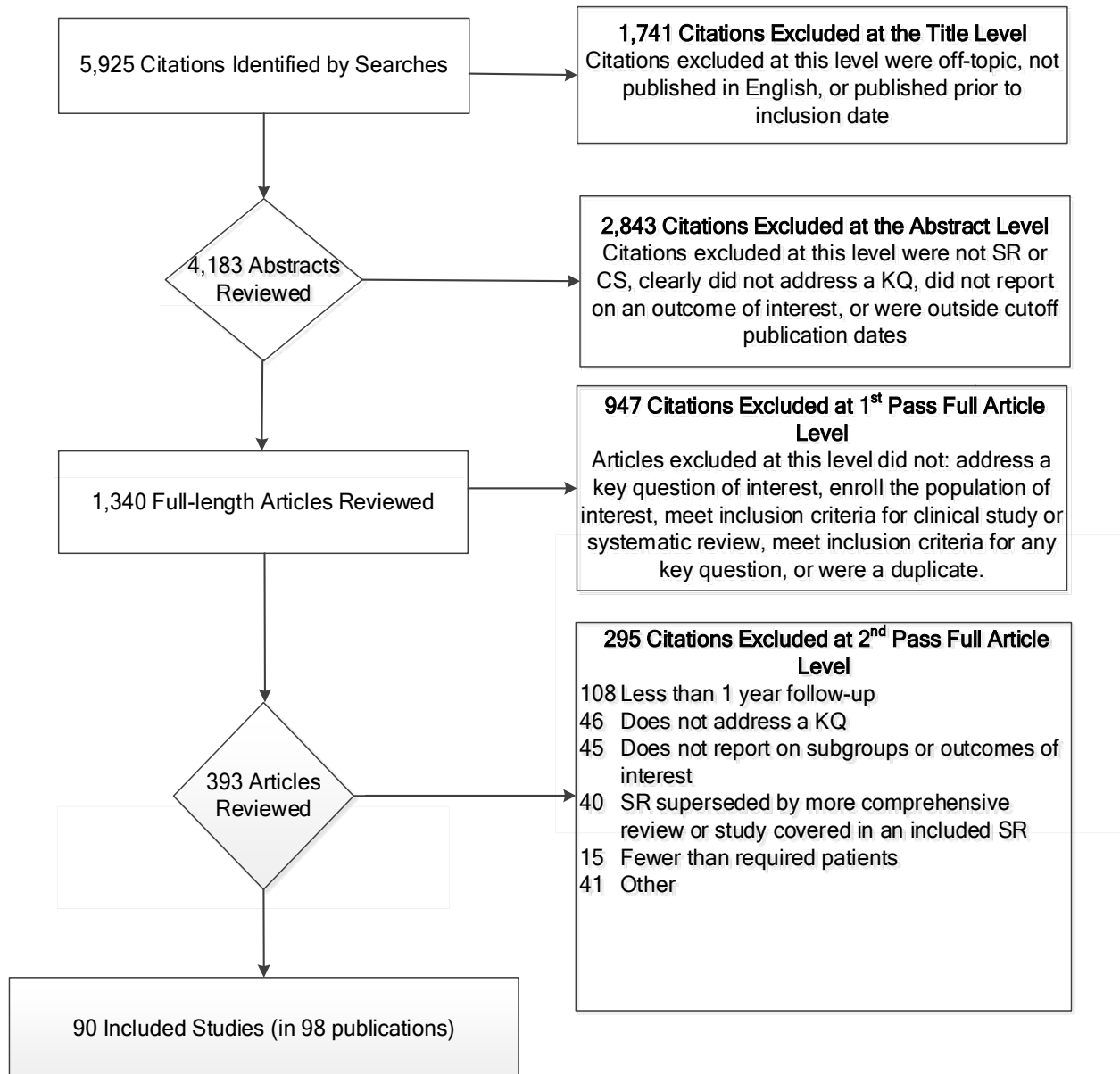
Table A-2. Evidence Base for Key Questions

Number of Question	Question	Number of Studies and Type of Studies
1	What is the evidence for low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) goals for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD)?	1 systematic review and 3 RCTs
2	What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD?	1 RCT and 2 simulation studies
3 statins	For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?	24 systematic reviews, 28 RCTs
3 fibrates		4 systematic reviews and 1 RCT
3 niacin		1 systematic review and 4 RCTs
3 bile acid sequestrants		No studies that met inclusion criteria
3 ezetimibe		1 systematic review and 1 RCT
3 omega-3 fatty acids		2 systematic reviews and 2 RCTs
4	Among low to intermediate risk adults (adults without a CHD or CVD diagnosis) what is the cost-effectiveness of pharmacologic therapy?	1 systematic review and 4 cost-effectiveness studies
5	Among new patients being treated with statins what is the effect of frequent lipid monitoring (e.g., every 3 months or 4 months) versus (vs.) less frequent lipid monitoring (e.g., every 12 months) on clinical outcomes and adverse events?	No studies identified
6	Among patients at intermediate risk where there is equipoise about treatment with statins (i.e., 5-15%), are there additional risk stratifying tests (e.g., hsCRP, CAC) which improve risk prediction (e.g., increased area under the curve [AUC] or net reclassification, compared with Framingham Risk Index [FRI]/pooled cohort risk calculators) or clinical outcomes?	1 systematic review and 9 prognostic studies
7	What is the effect of any comprehensive dietary intervention on CVD outcomes (as an a priori primary outcome)?	1 systematic review and 1 RCT
Total Evidence Base		**92 studies**

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Criteria for Study Inclusion/Exclusion

General Criteria

- Clinical studies or systematic reviews published on or after January 1, 2010.
- Studies must be published in English.
- Publication must be a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies were not accepted as evidence.
- Studies enrolled adults 18 years or older. In studies that mixed adults and children, at least 85 percent of the enrolled patients had to be 18 years or older.
- Studies must have followed patients for at least one year.

Treatment Goals (LDL-C and non-LDL-C Target Levels) (KQ 1-2)

- Study must have been a RCT or systematic review of RCTs.
- Crossover trials were considered only if data from the first treatment period were reported separately.
- Study must have enrolled ≥ 10 patients per treatment arm.
- Study must have compared clinical outcomes (major CHD or CVD events) for patients who achieved one lipid target level and patients who achieved a different lipid target level through dose titration of lipid-lowering drugs.

Effectiveness and Safety of Cholesterol-modifying Drugs (KQ 3)

- Study must have been a RCT or systematic review of RCTs.
- Crossover trials were considered only if data from the first treatment period were reported separately.
- For statins, study must have enrolled ≥ 1000 patients; for other drugs, study must have enrolled ≥ 10 patients per treatment arm.

Cost-effectiveness of Cholesterol-modifying Drugs (KQ 4)

- Study must have been a cost-effectiveness study based on clinical outcome data (major CHD or CVD events) from RCTs or a systematic review of cost-effectiveness studies that meet this criterion.
- Patients must be at low-to-intermediate 10-year risk for a CHD or CVD event (adults without a CHD or CVD diagnosis).
- Study must have been based on clinical trials undertaken in the US.
- Study must have enrolled ≥10 patients per treatment arm.
- Study must have compared frequent lipid monitoring (e.g., every three or four months) to less frequent lipid monitoring (e.g., every 12 months) on specific clinical outcomes and adverse events (MI, stroke, death, myopathy, and liver dysfunction) among new patients being treated with statins.

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Additional Risk Stratifying Tests (KQ 6)

- Study must have enrolled ≥1000 patients.
- Study must have compared the accuracy of risk prediction using hsCRP or CAC plus standard risk factors to the accuracy of risk prediction using only standard risk factors among patients at intermediate-risk (i.e., 5–15%) where there is equipoise about treatment with statins.

Supplementary Key Question (KQ7)

This was a new key question requested by the Work Group at the face-to-face meeting, following review of the completed evidence report. The Work Group decided that this was an important question and wished to develop evidence-based recommendations to address it. A literature review was performed using the same methods and general inclusion/exclusion criteria used for KQs 1-6; the evidence base was small enough to allow a rapid evidence synthesis. The search identified one relevant RCT that directly addressed the question and one systematic review that marginally addressed the question.

Literature Search Strategy

Electronic Database Searches

The following databases were searched for relevant information:

Name	Date Limits	Platform/Provider
Bibliographic Databases		
The Cochrane Central Register of Controlled Trials (CENTRAL)	2010 through: December 2013 (KQ1-3); January 2014 (KQ 4 and 5) February 2014 (KQ6)	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	2010 through: December 2013 (KQ1-3); January 2014 (KQ 4 and 5); February 2014 (KQ6)	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	2010 through: December 2013 (KQ1-3); January 2014 (KQ 4 and 5); February 2014 (KQ6)	Wiley
Database of Abstracts of Reviews of Effects (DARE)	2010 through: December 2013 (KQ1-3); January 2014 (KQ 4 and 5); February 2014 (KQ6)	Wiley
EMBASE (Excerpta Medica)	2010 through: December 2013 (KQ1 and 2); January 2014 (KQ 4 and 5); February 2014 (KQ6) 2011 through December 2013 (KQ3)	OVIDSP
Health Technology Assessment Database (HTA)	2010 through December 2013 (KQ1-3); January 2014 (KQ 4 and 5); February 2014 (KQ6)	Wiley

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Name	Date Limits	Platform/Provider
MEDLINE/PreMEDLINE	2010 through: December 2013 (KQ1 and 2); January 2014 (KQ 4 and 5); February 2014 (KQ6) 2011 through December 2013 (KQ3)	OVIDSP
PubMed (In-process and Publisher records)	2010 through: December 2013 (KQ 1and 2); January 2014 (KQ 4 and 5); February 2014 (KQ6) 2011 through December 2013 (KQ3)	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED)	2010 through: December 2013 (KQ1-3); January 2014 (KQ 4 and 5); February 2014 (KQ6)	Wiley
Tufts Cost-effectiveness Analysis (CEA) database	2010 through January 17, 2014 (KQ4)	Tufts University
Gray Literature Resources		
Agency for Healthcare Research and Quality (AHRQ)	2010 through December 17, 2013	AHRQ
Healthcare Standards database	2010 through January 20, 2014	ECRI Institute
National Guideline Clearinghouse™ (NGC)	2010 through January 20, 2014	AHRQ
National Institute of Health and Clinical Excellence	2010 through January 16, 2014	NHS
TRIP database	2010 through January 20, 2014	TRIP

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-specific Search Terms

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Medical Subject Headings (MeSH), EMTREE, and Keywords

Concept	Controlled Vocabulary	Keywords
C-Reactive Protein	**MEDLINE (MESH)** c-reactive protein/ **EMBASE (EMTREE)** c reactive protein/	CRP" "c-reactive protein" "hsCRP" "hs-CRP"
Cardiovascular Disease	**MEDLINE (MeSH)** exp*cardiovascular diseases/ *plaque, atherosclerotic/ *stroke/ **EMBASE (EMTREE)** exp *cardiovascular disease/ [note: stroke and atherosclerotic plaque are narrower terms under this term]	Acute coronary syndrome ACS angina (artery OR arteries) AND (disease$ OR event$ OR syndrome$) ASCVD Atherosclerosis Atherosclerotic (cardiac$ OR cardio$)AND (disease$ OR event$ OR syndrome$) Cerebrovascular AND (disease$ OR syndrome$ OR event$) Cerebrovascular accident$ CHD Coronary AND (disease$ OR event$ OR syndrome$) CVD heart attack$ heart$ AND (disease$ OR event$ OR syndrome$) Hypertens$ ischem* ischaem* myocardial infarct$ plaque$ stroke vascular AND disease$ vascular AND event$ vascular AND syndrome$
Cholesterol **HDL-C/ LDL-C**	**MEDLINE (MeSH)** exp *cholesterol, LDL/ exp *cholesterol, HDL/ exp *cholesterol/ **EMBASE (EMTREE)**	alpha ADJ lipoprotein beta$ ADJ1 lipoprotein$ cholesterol$ cholesteryl$ "HDL-C"

Concept	Controlled Vocabulary	Keywords
	*low density lipoprotein/ exp *high density lipoprotein/	"HDL C" HDL$ O (high ADJ1 density) (low ADJ1 density) "ldl" "LDL-C" "LDL C". non ADJ1 HDL$
Coronary artery calcium	**MEDLINE (MESH)** Vascular calcification **EMBASE (EMTREE)** exp coronary artery calcium score/	"CAC" coronary adj2 calcium
Cost-effectiveness	**MEDLINE (MeSH)** exp "Costs and Cost analysis"/ exp economics, pharmaceutical/ quality-adjusted life years/ value of life/ health care costs/ **EMBASE (EMTREE)** exp economic evaluation/ exp pharmacoeconomics quality adjusted life year/ exp health economics/ health care cost/	Cost costs costly costing price prices expense$ expenditure$ saving savings economi$ financial finance$ pharmacoeconomic$ QALY QALYs quality-adjusted life year$ quality adjusted life year$ quality-adjusted life expectanc$ quality adjusted life expectanc$
Dyslipidemia	**MEDLINE (MeSH)** exp *dyslipidemias/ exp *cholesterol/ exp *lipids/ **EMBASE (EMTREE)** exp *dyslipidemia/ exp *cholesterol/ exp *lipid/	cholesteryl$ cholesterol$ dyslipidemia$ dyslipidaemia$ dyslipidproteinemia$ dyslipidproteinaemia$ "HDL-C" "HDL C" hyperlipidemia$ hyperlipidaemia$ hypercholesterolemia$ hypercholesterolaemia$

Concept	Controlled Vocabulary	Keywords
		hyperlipoproteinemia$ hyperlipoproteinaemia$ hypertriglyceridemia$ hypertriglyceridaemia$ hyperlipemia hyperlipaemia "LDL-C" "LDL C" lipid$ lipoprotein$ tryglycer$ triaclyglycer$
Lipid Monitoring	**MEDLINE (MeSH)** exp monitoring, physiologic/ lipid metabolism/de [drug effects] exp mass screening/ diagnostic tests, routine/ exp hematologic tests/ **EMBASE (EMTREE)** exp mass screening/ drug monitoring/ physiologic monitoring/ blood examination/ exp diagnostic test/ exp monitoring/ exp lipid analysis/ exp lipid metabolism/	monitor$ measure$ surveillance test tests testing
Non-statin cholesterol modifying agents of interest	*Gemfibrozil/ *fenofibrate/ *niacin/ exp *Fatty Acids, Omega-3/ **EMBASE (EMTREE)** *gemfibrozil/ *nicotinic acid/ *bile acid sequestrant/ *ezetimibe/ *omega 3 fatty acid/	"BAS" bezafibrate bile acid sequestrant$ bile acid resin$ ezetimibe fenofibrate fibrate$ "fish oil" gemfibrozil niacin nicotinic acid$ omega 3 fatty acid$ omega-3 fatty acid$ resin$
Outcomes for lipid monitoring	**MEDLINE (MeSH)** Stroke/ exp muscular diseases/ exp liver diseases/ exp mortality/	cerebrovascular accident$ cirrhosis death (heart ADJ attack$) (heart ADJ infarct$)

Concept	Controlled Vocabulary	Keywords
	exp death/ exp myocardial infarction/ **EMBASE (EMTREE)** cerebrovascular accident/ exp muscle disease/ exp liver disease/ heart infarction/ Exp mortality/ Exp death/	(liver OR hepati$ OR hepato$) AND (disease$ OR disorder$ OR dysfunction$ OR damag$) morbidity mortality (muscle OR muscular) AND (disease$ OR pain$ OR weakness OR atrophy$) myalgia$ myocardial ADJ infarct$ myofibros$ myopathat$ stroke
Primary and Secondary prevention/risk/adverse effects	**MEDLINE (MeSH)** secondary prevention/ exp primary prevention/ risk assessment/ risk factors/ exp morbidity/ exp mortality/ exp treatment outcome/ **EMBASE (EMTREE)** exp treatment outcome/ secondary prevention/ primary prevention/ exp morbidity/ exp mortality/ risk assessment/ **Floating Subheadings** Adverse events (ae.fs.) Toxicity (to.fs.) Contraindication (it.fs.)	morbidity mortality prevent$ outcome$ goal$ secondary prevention primary prevention
Risk Stratification	**MEDLINE (MESH)** risk assessment/ risk factors/ exp risk/ "predictive value of tests"/ **EMBASE (EMTREE)** Risk assessment/ Exp *risk/ predictive value/ "prediction and forecasting"/ Exp cardiovascular risk/ Risk benefit analysis/ Risk factor/	risk ADJ2 benefit (risk or risks) and (stratify or stratifying or stratification or define or defining or predict or prediction or assessment)

Concept	Controlled Vocabulary	Keywords
Statins	**MEDLINE (MeSH)** Exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ **EMBASE (EMTREE)** exp *hydroxymethylglutaryl coenzyme A reductase inhibitor/	atorvastatin ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor$)) HMG CoA lovastatin meglutol pravastatin simvastatin statin$

Search Strategies

EMBASE/Medline for Key Questions 1 and 2 (ldl-c and Non-HDL-C goals) (presented in OVID syntax)

Set #	Concept	Search Statement
1	LDL-C (focused search – major concepts, keywords in title)	exp *cholesterol, LDL/ OR exp *low density lipoprotein/ OR (((cholesterol$ OR cholesteryl$) AND ((low ADJ1 density) OR "ldl" OR (beta$ ADJ1 lipoprotein$))) OR LDL-C OR "LDL C").ti.
2	HDL-C (focused search – major concepts, keywords in title)	exp *cholesterol, HDL/ OR exp *high density lipoprotein/ OR ("HDL-C" OR "HDL C" OR ((cholesterol$ OR cholesteryl$) AND ((high ADJ1 density) OR HDL$ OR (non ADJ1 HDL$) OR (alpha ADJ lipoprotein)))).ti.
3	Cholesterol (focused)	Exp *cholesterol/
4	Combine sets - Cholesterol	1 OR 2 OR 3
5	Cardiovascular disease (focused search – major concepts, keywords in title)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti.
6	Combine sets (focused search)	4 AND 5
7	LDL-C (broader search – mesh terms not focused to major headings, keywords in title and abstract)	exp cholesterol, LDL/ OR exp low density lipoprotein/ OR (((cholesterol$ OR cholesteryl$) AND ((low ADJ1 density) OR "ldl" OR (beta$ ADJ1 lipoprotein$))) OR LDL-C OR "LDL C").ti,ab.
8	HDL-C (broader search – mesh terms not focused to major headings, keywords in title and abstract)	exp cholesterol, HDL/ OR exp high density lipoprotein/ OR ("HDL-C" OR "HDL C" OR ((cholesterol$ OR cholesteryl$) AND ((high ADJ1 density) OR HDL$ OR (non ADJ1 HDL$) OR (alpha ADJ lipoprotein)))).ti,ab.
9	Cardiovascular disease	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp

Set #	Concept	Search Statement
	(broader search – mesh terms focused to major headings, keywords in title and abstract)	*cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti,ab.
10	Primary/secondary prevention; risk reduction	secondary prevention/ OR exp primary prevention/ OR risk assessment/ OR risk factors/ OR exp treatment outcome/ OR exp morbidity/ OR exp mortality/ OR (morbidity OR mortality OR prevent$ OR outcome$ OR goal$).ti. OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab.
11	Combine sets(LDL-C; non–HDL-C – broader search with prevention terms)	(7 OR 8) AND 9 AND 10
12	Combine sets	6 OR 11
13	Remove unwanted publication types	12 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
14	Limit to Systematic reviews/meta-analyses	13 AND (systematic review/ or meta analysis/ or meta-analysis/ or meta-analysis.pt. or "systematic review".mp. or search$.ab.)
15	Limit to RCT's	13 AND (Randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or sham$)).mp. or latin square.mp. or ISRTCN or ACTRN$ or (NCT$ not NCT))
16	Combine sets	14 OR 15
17	Apply limits	Limit to humans, English language, yr="2010-Current"
18	Eliminate overlap	Remove duplicates from 17

EMBASE/Medline for Key Question 3 (presented in OVID syntax)

Set #	Concept	Search Statement
1	Dyslipidemia– focused search (major concept headings, keywords in the title)	exp *dyslipidemias/ OR exp *dyslipidemia/ OR exp *cholesterol/ OR exp *lipids/ OR exp *lipid/ 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.
2	Dyslipidemia - broader	exp *dyslipidemias/ OR exp *dyslipidemia/ OR exp *cholesterol/ OR

Set #	Concept	Search Statement
	search (major concepts headings, keywords in the title AND Abstracts)	exp *lipids/ OR exp *lipid/ 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.
3	Cardiovascular Diseases – focused search (major concept headings, keywords in the title)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti.
4	Cardiovascular disease - broader search (major concepts headings, keywords in the title AND Abstracts)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti,ab.
5	Prevention/outcomes/ adverse events	secondary prevention/ OR exp primary prevention/ OR exp treatment outcome/ OR exp morbidity/ OR exp mortality/ OR ae.fs. OR to.fs. OR it.fs. OR (morbidity OR mortality OR prevent$ OR outcome$).ti OR (secondary ADJ prevention).ti,ab. OR (primary ADJ prevention).ti,ab.
6	Statins – focused search (major concept headings, keywords in the title)	Exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR exp *hydroxymethylglutaryl coenzyme A reductase inhibitor/ OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor$)).ti. OR (HMG CoA).ti. OR (statin$ OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin).ti.
7	statins– - broader search (major concepts headings, keywords in the title AND Abstracts)	Exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR exp *hydroxymethylglutaryl coenzyme A reductase inhibitor/ OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor$)).ti,ab. OR (HMG CoA).ti,ab. OR (statin$ OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin).ti.ab.
8	Combine sets- focused search	(1 OR 3) AND 6
9	Combine sets – broader search w/ prevention terms	(2 OR 4) AND 5 AND 7
10	Combine sets	8 OR 9
11	Remove unwanted publication types	10 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR

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Set #	Concept	Search Statement
		conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
12	Limit to Systematic Reviews	11 AND (Systematic review/ or meta analysis/ or meta-analysis/ or pooled or meta-analysis.pt. or "systematic review" or search$.ab.)
13	Apply limits	Limit 12 to humans, english language, yr="2011-Current"
14	Remove duplicates	Remove duplicates from 13
15	Other drugs of interest - – focused search (major concept headings, keywords in the title)	*Gemfibrozil/ OR *fenofibrate/ OR *niacin/ OR exp *Fatty Acids, Omega-3/ OR *gemfibrozil/ OR *nicotinic acid/ OR *bile acid sequestrant/ OR *ezetimibe/ OR *omega 3 fatty acid/ OR (fibrate$ OR gemfibrozil OR fenofibrate OR bezafibrate).ti. OR (nicotinic ADJ acid$).ti,ab. OR niacin.ti. OR (bile ADJ acid ADJ sequestrant$).ti. OR "BAS".ti. OR (bile ADJ acid ADJ resin$).ti. OR resin$.ti. OR ezetimibe.ti,ab. OR (omega$ ADJ3 fatty ADJ acid$ OR "fish oil").ti.
16	Other drugs of interest - broader search (major concepts headings, keywords in the title AND Abstracts)	*Gemfibrozil/ OR *fenofibrate/ OR *niacin/ OR exp *Fatty Acids, Omega-3/ OR *gemfibrozil/ OR *nicotinic acid/ OR *bile acid sequestrant/ OR *ezetimibe/ OR *omega 3 fatty acid/ OR (fibrate$ OR gemfibrozil OR fenofibrate OR bezafibrate).ti,ab. OR (nicotinic ADJ acid$).ti,ab. OR niacin.ti,ab. OR (bile ADJ acid ADJ sequestrant$).ti,ab. OR "BAS".ti,ab. OR (bile ADJ acid ADJ resin$).ti,ab. OR resin$.ti,ab. OR ezetimibe.ti,ab. OR (omega$ ADJ3 fatty ADJ acid$ OR "fish oil").ti,ab.
17	Other drugs of interest (focused search)	(1 OR 3) AND 15
18	Other drugs of interest (broader search with prevention terms)	(2 OR 4) AND 5 AND 16
19	Combine sets	17 OR 18
20	Remove unwanted publication types	19 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
21	Limit to meta-analysis/systematic reviews	20 AND (Systematic review/ or meta analysis/ or meta-analysis/ or pooled or meta-analysis.pt. or "systematic review" or search$.ab.)
22	Limit to RCTs	20 AND (Randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or sham$)).mp. or latin square.mp. or ISRTCN or ACTRN$ or (NCT$ not NCT))
23	Combine sets	21 OR 22
24	Apply limits	Limit 23 to humans, English language, yr="2011-Current"
25	Remove duplicates	Remove duplicates from 24

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EMBASE/Medline for Key Question 4 (presented in OVID syntax)

Set #	Concept	Search Statement
1	Dyslipidemia (major concepts headings, keywords in the title AND Abstracts)	exp *dyslipidemias/ OR exp *dyslipidemia/ OR exp *cholesterol/ OR exp *lipids/ OR exp *lipid/ 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	Cardiovascular disease - broader search (major concepts headings, keywords in the title AND Abstracts)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti,ab.
3	Statins	Exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR exp *hydroxymethylglutaryl coenzyme A reductase inhibitor/ OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor$)).ti,ab. OR (HMG CoA).ti,ab. OR (statin$ OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin).ti,ab.
4	Other lipid lowering drugs	*Gemfibrozil/ OR *fenofibrate/ OR *niacin/ OR exp *Fatty Acids, Omega-3/ OR *gemfibrozil/ OR *nicotinic acid/ OR *bile acid sequestrant/ OR *ezetimibe/ OR *omega 3 fatty acid/ OR (fibrate$ OR gemfibrozil OR fenofibrate OR bezafibrate).ti,ab. OR (nicotinic ADJ acid$).ti,ab. OR niacin.ti,ab. OR (bile ADJ acid ADJ sequestrant$).ti,ab. OR "BAS".ti,ab. OR (bile ADJ acid ADJ resin$).ti,ab. OR resin$.ti,ab. OR ezetimibe.ti,ab. OR (omega$ ADJ3 fatty ADJ acid$) OR "fish oil").ti,ab.
5	Cost-effectiveness	exp "Costs and Cost analysis"/ OR exp economics, pharmaceutical/ OR exp economic evaluation/ OR exp pharmacoeconomics OR quality-adjusted life years/ or Value of Life/ or exp health economics/ or health care cost/ or quality adjusted life year/ OR (cost OR costs OR costly OR costing OR price OR prices OR expense$ OR expenditure$ OR saving OR savings OR economi$ OR financial OR finance$ OR pharmacoeconomic$ OR QALY or QALYs OR (quality ADJ1 adjusted ADJ life ADJ year$) or (quality ADJ1 adjusted life ADJ expectanc$)).ti,ab.
6	Combine sets	(1 OR 2) AND (3 OR 4) AND 5
7	Remove unwanted publication types	6 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note

Set #	Concept	Search Statement
		OR proceeding).pt.)
8	Apply limits	Limit 7 to humans, english language, yr="2010-Current"
9	Remove results from previous searches	8 NOT (results from KQ3)
10	Remove duplicates	Remove duplicates from 9

EMBASE/Medline for Key Question 5 (presented in OVID syntax)

Set #	Concept	Search Statement
1	Dyslipidemia (major concepts headings, keywords in the title AND Abstracts)	exp *dyslipidemias/ OR exp *dyslipidemia/ OR exp *cholesterol/ OR exp *lipids/ OR exp *lipid/ 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	Cardiovascular disease - (major concepts headings, keywords in the title AND Abstracts)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti,ab.
3	Statins (major concepts headings, keywords in the title AND Abstracts)	Exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ OR exp *hydroxymethylglutaryl coenzyme A reductase inhibitor/ OR ((hydroxymethylglutaryl OR hydroxy-methylglutaryl) ADJ5 (reductase ADJ inhibitor$)).ti,ab. OR (HMG CoA).ti,ab. OR (statin$ OR lovastatin OR meglutol OR pravastatin OR atorvastatin OR simvastatin).ti,ab.
4	Lipid monitoring	Exp Monitoring, physiologic/ OR lipid metabolism/de OR exp mass screening/ OR diagnostic tests, routine/ OR exp hematologic tests/ OR drug monitoring/ OR physiologic monitoring/ OR blood examination/ OR exp diagnostic test/ OR exp monitoring/ OR exp lipid analysis/ OR exp lipid metabolism/ OR (monitor$ OR measure$ OR test OR tests OR testing OR surveillance).ti,ab.
5	Outcomes	Stroke/ OR exp muscular diseases/ OR exp liver diseases/ OR exp mortality/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR exp muscle disease/ OR exp liver disease/ OR heart infarction/ OR (stroke$ OR (cerebrovascular ADJ accident$) OR myopath$ OR myalgia$ OR myofibros$ OR ((muscle OR muscular) AND (disease$ OR pain$ OR weakness OR atrophy$)) OR morbidity OR mortality OR ((liver OR hepati$ OR hepato$) AND (disease$ OR disorder$ OR dysfunction$ OR damag$)) OR cirrhosis OR death OR (heart ADJ attack$) OR (myocardial ADJ infarct$) OR (heart

Set #	Concept	Search Statement
		ADJ infarct$)).ti,ab.
6	Combine sets	(1 OR 2) AND 3 AND 4
7	Remove unwanted publication types	6 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
8	Limit to systematic reviews	7 AND (Systematic review/ or meta analysis/ or meta-analysis/ or pooled or meta-analysis.pt. or "systematic review" or search$.ab.)
9	Limit to Randomized controlled trials	7 AND (Randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or sham$)).mp. or latin square.mp. or ISRTCN or ACTRN$ or (NCT$ not NCT))
10	Combine sets	8 OR 9
11	Apply limits	Limit 10 to humans, English language, yr="2010-Current"
12	Remove duplicates	Remove duplicates from 11

EMBASE/Medline for Key Question 6 (presented in OVID syntax)

Set #	Concept	Search Statement
1	Dyslipidemia	exp dyslipidemias/ OR exp dyslipidemia/ OR exp cholesterol/ OR exp diabetes mellitus/ OR exp lipids/ OR exp lipid/ 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" OR diabetes OR diabetic$).ti,ab.
2	Cardiovascular disease - broader search	exp *cardiovascular diseases/ or *plaque, atherosclerotic/ or exp *cardiovascular disease/ or *stroke/ or ("ASCVD" or "ACS" or "CVD" or "CHD" or (heart$ adj disease$) or (cardiac adj disease$) or (cardiac adj event$) or (cardiovascular adj disease$) or (cardiovascular adj event$) or (coronary adj3 disease$) or (artery adj3 disease$) or hyperten$ or atherosclero$ or arteriosclero$ or angina or (Heart adj attack$) or (myocardial adj infarct$) or ischem$ or ischaem$ or plaque$ or stroke$ or (cerebrovascular adj accident$)).ti,ab.
3	Risk prediction	*risk assessment/ OR *risk factors/ OR exp *risk/ OR *predictive value/ OR *"predictive value of tests"/ OR *"prediction and forecasting"/ OR *exp cardiovascular risk/ or *risk benefit analysis/ or *risk factor/ OR (risk ADJ2 benefit).ti. OR ((risk or risks) and (stratify or stratifying or stratification or define or defining or predict or prediction or assessment)).ti,ab.

Set #	Concept	Search Statement
4	Tests (high sensitivity c-reactive protein; coronary artery calcium; calcium score	*c-reactive protein/ or *c reactive protein/ or *vascular calcification/ or exp *coronary artery calcium score/ or ("hsCRP" or "hs-CRP" or "CAC" or (coronary adj2 calcium) or "CRP" or "c-reactive protein").ti,ab.
5	Combine sets	1 AND 2 AND 3 AND 4
6	Publication types	letter/ or editorial/ or news/ or comment/ or case report.mp. or case reports/ or review/ or note/ or conference paper/ or (letter or editorial or news or comment or case reports or review or conference abstract$).pt.
7	Publication types	book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt.
8	Remove unwanted publication types	5 NOT (6 OR 7)
9	Systematic reviews/meta-analyses	Systematic review/ or meta analysis/ or meta-analysis/ or pooled.mp. or meta-analysis.pt. or "systematic review".mp. or search$.ab.
10	Clinical trials	Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis.mp. or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)).mp. or latin square.mp. or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not NCT).mp.
11	Limit to clinical studies and systematic reviews/meta-analyses	8 AND (9 OR 10)
12	Apply limits	Limit 11 to humans, English language, yr="2010-Current"
13	Remove duplicates (Medline and Embase)	Remove duplicates from 12

EMBASE/Medline for Key Question 7 (presented in OVID syntax)

Set#	Concept	Search Statement
1	Dyslipidemia (major concepts headings, keywords in the title AND Abstracts)	exp *dyslipidemias/ OR exp *dyslipidemia/ OR exp *cholesterol/ OR exp *lipids/ OR exp *lipid/ 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	Cardiovascular disease - (major concepts headings, keywords in the title AND Abstracts)	exp *cardiovascular diseases/ OR *plaque, atherosclerotic/ OR exp *cardiovascular disease/ exp OR *stroke/ OR ("ASCVD" OR "ACS" OR "CVD" OR "CHD" OR ((heart$ OR cardio$ OR cardiac$ OR coronary OR vascular OR cerebrovascular OR artery OR arteries) AND (disease$ OR syndrome$ OR event$)) OR hyperten$ OR atherosclero$ OR arteriosclero$ OR angina OR (Heart ADJ attack$) OR (myocardial ADJ infarct$) OR ischem$ OR ischaem$ OR plaque$ OR stroke$ OR (cerebrovascular ADJ accident$)).ti,ab.
3	Diet	Exp*diet/ OR *diet therapy/ OR exp *ketogenic diet/ or exp *elemental diet/ or exp *raw food diet/ or *carbohydrate diet/ or exp *protein diet/ or exp *fruitarian diet/ or *atherogenic diet/ or exp *vegan diet/ or exp *low calory diet/ or exp *Mediterranean diet/ or exp *lactoovovegetarian diet/ or exp *renal diet/ or exp *pescovegetarian diet/ or exp *diet restriction/ or exp *lactovegetarian diet/ or *cholesterol diet/ or exp *gluten free diet/ or exp *lipid diet/ or exp *low carbohydrate diet/ or exp *low fat diet/ or *diet therapy/ or *diabetic diet/ or exp *macrobiotic diet/ or exp *high fiber diet/ or exp *vegetarian diet/ OR *caloric restriction/ or *diet, carbohydrate-restricted/ or *diet, fat-restricted/ or *diet, gluten-free/ or diet, mediterranean/ or *diet, protein-restricted/ or *diet, reducing/ or *diet, sodium-restricted/ or exp *diet, vegetarian/ or *diet, macrobiotic/ 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)).ti,ab. OR ("Mediterranean diet" OR "diabetic diet" OR "DASH diet" OR (dietary ADJ approaches ADJ1 stop ADJ hypertension)).ti,ab. |

Set#	Concept	Search Statement
4	Outcomes	exp mortality/ OR exp death/ OR exp myocardial infarction/ OR cerebrovascular accident/ OR heart infarction/ OR (stroke$ OR (cerebrovascular ADJ accident$) OR morbidity OR mortality OR death OR (heart ADJ attack$) OR (myocardial ADJ infarct$) OR (heart ADJ infarct$)).ti,ab. OR (((clinical adj (validity or utility)) or (treatment adj2 (response or respond$ or monitor$)) or exp prognosis/ or exp treatment outcome/ or exp disease progression/ or exp disease course/ or treatment response/ or time factors/ or outcome assessment health care/ or outcome assessment/ or follow-up studies/ or prognosis/ or prognos$.tw.))
5	Combine sets	(1 OR 2) AND 3
6	Remove unwanted publication types	5 NOT (book/ OR edited book/ OR case report/ OR case reports/ OR comment/ OR conference abstract/ OR conference paper/ OR conference review/ OR editorial/ OR letter/ OR news/ OR note/ OR proceeding/ OR (book OR edited book OR case report OR case reports OR comment OR conference OR editorial OR letter OR news OR note OR proceeding).pt.)
7	Limit to systematic reviews	6 AND (Systematic review/ or meta analysis/ or meta-analysis/ or pooled or meta-analysis.pt. or "systematic review" or search$.ab.)
8	Limit to Randomized controlled trials	6 AND (Randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or sham$)).mp. or latin square.mp. or ISRTCN or ACTRN$ or (NCT$ not NCT))
9	Combine sets – RCT's reporting outcomes	8 AND 4
10	Combine sets – SR's and RCT's reporting outcomes	7 OR 9
11	Apply limits	Limit to humans, English language, yr="2010-Current"; All adult [Medline only – not valid in EMBASE]
12	Remove duplicates	Remove duplicates from

OVID syntax:

$ or * = truncation character (wildcard)

ADJ*n* = search terms within a specified number (*n*) of words from each other in any order

/ = search as a subject heading (note that terms preceded by an asterisk are searched as a major subject headings)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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.mp.   =   combined search fields (default if no fields are specified)

.pt.   =   publication type

.ti.   =   limit to title

.tw.   =   limit to title and abstract fields

PUBMED (PreMEDLINE) For Key Questions 1 And 2

Set #	Concept	Search Statement
1	LDL-C/HDL-C (broader search – keywords in title and abstract field)	"LDL-C"[tiab] OR "LDL C"[tiab] OR "HDL-C"[tiab] OR "HDL C"[tiab] OR ((lipoprotein*[tiab] OR cholesterol[tiab])AND ("high density"[tiab] OR "low density"[tiab]))
2	LDL-C/HDL-C (narrow search – keywords in title field)	"LDL-C"[ti] OR "LDL C"[ti] OR "HDL-C"[ti] OR "HDL C"[ti] OR ((lipoprotein*[ti] OR cholesterol[ti])AND ("high density"[ti] OR "low density"[ti]))
3	Cardiovascular disease (broader search – keywords in title and abstract field)	"ASCVD"[tiab] OR "ACS"[tiab] OR "CVD"[tiab] OR "CHD"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "cardiovascular event"[tiab] OR "cardiovascular events"[tiab] OR hyperten*[tiab] OR atherosclero*[tiab] OR arteriosclero*[tiab] OR angina[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR plaque*[tiab] OR stroke*[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "heart failure"[tiab]
4	Cardiovascular disease (narrow search – keywords in title field)	"ASCVD"[ti] OR "ACS"[ti] OR "CVD"[ti] OR "CHD"[ti] OR ((heart*[ti] OR cardiovasc*[ti] OR cardiac[ti] OR coronary[ti] OR vascular[ti] OR cerebrovascular[ti] OR artery[ti] OR arteries[ti]) AND (disease*[ti] OR syndrome*[ti] OR event*[ti])) OR hyperten*[ti] OR atherosclero*[ti] OR arteriosclero*[ti] OR angina OR (Heart[ti] AND attack*[ti]) OR (myocardial AND infarct[ti]) OR ischem*[ti] OR ischaem*[ti] OR plaque*[ti] OR stroke[ti] OR (cerebrovascular[ti] AND accident*[ti])
5	Prevention/risk/outcomes	((secondary[tiab] OR primary[tiab]) AND prevent*[tiab]) OR risk*[tiab] OR morbidity[tiab] OR mortality[tiab] OR prevent*[tiab] OR outcome*[tiab] OR goal*[tiab]
6	Combine sets (broader search with prevention terms)	1 AND 3 AND 5
7	Combine sets (narrower title word search)	2 AND 4
8	Combine sets	6 OR 7
9	Remove unwanted publications	8 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
10	Limit to RCTs	9 AND (Random*[tiab] OR randomized[tiab] OR RCT*[tiab])
11	Limit to meta-analysis/systematic reviews	9 AND (meta-analysis[tiab] OR meta-analysis[pt] OR systematic*[tiab] OR "systematic review"[tiab])
12	Combine sets	10 OR 11
13	Limit to In Process citations	12 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

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PUBMED (PreMEDLINE) For Key Question 3

Set #	Concept	Search Statement
1	Dyslipidemia	Dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR dyslipidproteinemia*[tiab] OR dyslipidproteinaemia*[tiab] OR hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR hyperlipemia OR hyperlipaemia OR cholesteryl*[tiab] OR cholesterol*[tiab] OR lipid*[tiab] OR lipoprotein*[tiab] OR tryglycer*[tiab] OR triaclyglycer*[tiab] OR "HDL-C"[tiab] OR "LDL-C"[tiab] OR "HDL C"[tiab] OR "LDL C"[tiab]
2	Cardiovascular disease	"ASCVD"[tiab] OR "ACS"[tiab] OR "CVD"[tiab] OR "CHD"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "cardiovascular event"[tiab] OR "cardiovascular events"[tiab] OR hyperten*[tiab] OR atherosclero*[tiab] OR arteriosclero*[tiab] OR angina[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR plaque*[tiab] OR stroke*[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "heart failure"[tiab] OR ((heart*[ti] OR cardiovasc*[ti] OR cardiac[ti] OR coronary[ti] OR vascular[ti] OR cerebrovascular[ti] OR artery[ti] OR arteries[ti]) AND (disease*[ti] OR syndrome*[ti] OR event*[ti]))
3	Statins	((hydroxymethylglutaryl[tiab] OR "hydroxy-methylglutaryl"[tiab]) AND (reductase[tiab] AND inhibitor*[tiab])) OR "HMG CoA".tiab. OR statin*[tiab] OR lovastatin[tiab] OR meglutol[tiab] OR pravastatin[tiab] OR atorvastatin[tiab] OR simvastatin[tiab]
4	Combine sets-	(1 OR 2) AND 3
5	Remove unwanted publication types	4 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
6	Limit to Systematic Reviews	5 AND (meta-analysis[tiab] OR meta-analysis[pt] OR systematic*[tiab] OR "systematic review"[tiab])
7	Limit to RCTs	5 AND (random[tiab] OR randomized[tiab] OR placebo*[tiab] OR "control group"[tiab] OR "clinical trial"[tiab] OR "clinical trials"[tiab])
8	Combine sets	6 OR 7
9	Limit to "in process" citaitons	8 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
10	Apply publication date filter:	Publication date from 2011/01/01 to 2013/12/31
11	Other drugs of interest - – focused search (keywords in the title and abstract)	fibrate*[tiab] OR gemfibrozil[tiab] OR fenofibrate*[tiab] OR bezafibrate*[tiab] OR "nicotinic acid"[tiab] OR niacin[tiab] OR ("bile acid"[tiab] AND (sequestrant*[tiab] OR resin*[tiab])) OR "BAS"[tiab] OR resin*[tiab] OR ezetimibe[tiab] (omega*[tiab] AND fatty[tiab] AND acid*[tiab]) OR "fish oil"[tiab]
12	Combine sets	(1 OR 2) AND 11
13	Remove unwanted publication types	12 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])

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Set #	Concept	Search Statement
14	Limit to meta-analysis/systematic reviews	13 AND (meta-analysis[tiab] OR meta-analysis[pt] OR systematic*[tiab] OR "systematic review"[tiab])
15	Limit to RCTs	13 AND (random OR randomized OR placebo* OR "control group" OR "clinical trial"[tw] OR "clinical trials"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
16	Combine sets	14 OR 15
17	Limit to "in process" citaitons	16 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
18	Apply publication date filter:	Publication date from 2011/01/01 to 2013/12/31

PUBMED (PreMEDLINE) For Key Question 4

Set #	Concept	Search Statement
1	Dyslipidemia	Dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR dyslipidproteinemia*[tiab] OR dyslipidproteinaemia*[tiab] OR hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR hyperlipemia OR hyperlipaemia OR cholesteryl*[tiab] OR cholesterol*[tiab] OR lipid*[tiab] OR lipoprotein*[tiab] OR tryglycer*[tiab] OR triaclyglycer*[tiab] OR "HDL-C"[tiab] OR "LDL-C"[tiab] OR "HDL C"[tiab] OR "LDL C"[tiab]
2	Cardiovascular disease	"ASCVD"[tiab] OR "ACS"[tiab] OR "CVD"[tiab] OR "CHD"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "cardiovascular event"[tiab] OR "cardiovascular events"[tiab] OR hyperten*[tiab] OR atherosclero*[tiab] OR arteriosclero*[tiab] OR angina[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR plaque*[tiab] OR stroke*[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "heart failure"[tiab] OR ((heart*[ti] OR cardiovasc*[ti] OR cardiac[ti] OR coronary[ti] OR vascular[ti] OR cerebrovascular[ti] OR artery[ti] OR arteries[ti]) AND (disease*[ti] OR syndrome*[ti] OR event*[ti]))
3	Statins	((hydroxymethylglutaryl[tiab] OR "hydroxy-methylglutaryl"[tiab]) AND (reductase[tiab] AND inhibitor*[tiab])) OR "HMG CoA".tiab. OR statin*[tiab] OR lovastatin[tiab] OR meglutol[tiab] OR pravastatin[tiab] OR atorvastatin[tiab] OR simvastatin[tiab]
4	Other drugs of interest - – focused search (keywords in the title and abstract)	fibrate*[tiab] OR gemfibrozil[tiab] OR fenofibrate*[tiab] OR bezafibrate*[tiab] OR "nicotinic acid"[tiab] OR niacin[tiab] OR ("bile acid"[tiab] AND (sequestrant*[tiab] OR resin*[tiab])) OR "BAS"[tiab] OR resin*[tiab] OR ezetimibe[tiab] (omega*[tiab] AND "fatty acid"[tiab]) OR "fish oil"[tiab]

Set #	Concept	Search Statement
5	Cost	Cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR expense*[tiab] OR expenditure*[tiab] OR saving[tiab] OR savings[tiab] OR economi*[tiab] OR financial[tiab] OR finance*[tiab] OR pharmacoeconomic*[tiab] OR QALY[tiab] or QALYs[tiab] OR "quality adjusted life year"[tiab] or "quality adjusted life expectancy"[tiab]
6	Combine sets	(1 OR 2) AND (3 OR 4) AND 5
7	Remove unwanted publication types	6 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
8	Limit to "in process" citations	7 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
9	Apply publication date filter:	Publication date from 2010/01/01 to 2014/01/10

PUBMED (PreMEDLINE) For Key Question 5

Set #	Concept	Search Statement
1	Dyslipidemia	Dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR dyslipidproteinemia*[tiab] OR dyslipidproteinaemia*[tiab] OR hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR hyperlipemia OR hyperlipaemia OR cholesteryl*[tiab] OR cholesterol*[tiab] OR lipid*[tiab] OR lipoprotein*[tiab] OR tryglycer*[tiab] OR triaclyglycer*[tiab] OR "HDL-C"[tiab] OR "LDL-C"[tiab] OR "HDL C"[tiab] OR "LDL C"[tiab]
2	Cardiovascular disease	"ASCVD"[tiab] OR "ACS"[tiab] OR "CVD"[tiab] OR "CHD"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "cardiovascular event"[tiab] OR "cardiovascular events"[tiab] OR hyperten*[tiab] OR atherosclero*[tiab] OR arteriosclero*[tiab] OR angina[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR plaque*[tiab] OR stroke*[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "heart failure"[tiab] OR ((heart*[ti] OR cardiovasc*[ti] OR cardiac[ti] OR coronary[ti] OR vascular[ti] OR cerebrovascular[ti] OR artery[ti] OR arteries[ti]) AND (disease*[ti] OR syndrome*[ti] OR event*[ti]))
3	Statins	((hydroxymethylglutaryl[tiab] OR "hydroxy-methylglutaryl"[tiab]) AND (reductase[tiab] AND inhibitor*[tiab])) OR "HMG CoA".tiab. OR statin*[tiab] OR lovastatin[tiab] OR meglutol[tiab] OR pravastatin[tiab] OR atorvastatin[tiab] OR simvastatin[tiab]
4	Lipid monitoring	monitor*[tiab] OR measure*[tiab] OR test[tiab] OR tests[tiab] OR testing[tiab] OR surveillance[tiab]
5	Outcomes	stroke*[tiab] OR "cerebrovascular accident*"[tiab] OR myopathy*[tiab] OR myalgia*[tiab] OR myofibros*[tiab] OR ((muscle[tiab] OR muscular[tiab]) AND (disease*[tiab] OR pain*[tiab]

Set #	Concept	Search Statement
		OR weakness[tiab] OR atrophy*[tiab])) OR morbidity[tiab] OR mortality[tiab] OR ((liver[tiab] OR hepatic*[tiab] OR hepato*[tiab]) AND (disease*[tiab] OR disorder*[tiab] OR dysfunction*[tiab] OR damage*[tiab])) OR cirrhosis[tiab] OR death[tiab] OR "heart attack"[tiab] OR "myocardial infarction"[tiab] OR "heart infarction"[tiab] OR "myocardial infarct"[tiab] OR "heart infarct"[tiab]
6	Combine sets	(1 OR 2) AND 3 AND 4 AND 5
7	Remove unwanted publication types	6 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
8	Limit to systematic reviews	7 AND (meta-analysis[tiab] OR meta-analysis[pt] OR systematic*[tiab] OR "systematic review"[tiab])
9	Limit to Randomized controlled trials	7 AND (random[tiab] OR randomized[tiab] OR placebo*[tiab] OR "control group"[tiab] OR "clinical trial"[tiab] OR "clinical trials"[tiab])
10	Combine sets	8 OR 9
11	Apply limits	10 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
12	Apply date limits	Publication date from 2010/01/01 to 2013/12/31

PUBMED (PreMEDLINE) For Key Question 6

Set #	Concept	Search Statement
1	Dyslipidemia	Dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR dyslipidproteinemia*[tiab] OR dyslipidproteinaemia*[tiab] OR hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR hyperlipemia OR hyperlipaemia OR cholesteryl*[tiab] OR cholesterol*[tiab] OR lipid*[tiab] OR lipoprotein*[tiab] OR tryglycer*[tiab] OR triaclyglycer*[tiab] OR "HDL-C"[tiab] OR "LDL-C"[tiab] OR "HDL C"[tiab] OR "LDL C"[tiab]
2	Cardiovascular disease - broader search	"ASCVD"[tiab] OR "ACS"[tiab] OR "CVD"[tiab] OR "CHD"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "cardiovascular event"[tiab] OR "cardiovascular events"[tiab] OR hyperten*[tiab] OR atherosclero*[tiab] OR arteriosclero*[tiab] OR angina[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR plaque*[tiab] OR stroke*[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "heart failure"[tiab] OR ((heart*[ti] OR cardiovasc*[ti] OR cardiac[ti] OR coronary[ti] OR vascular[ti] OR cerebrovascular[ti] OR artery[ti] OR arteries[ti]) AND (disease*[ti] OR syndrome*[ti] OR event*[ti]))
3	Risk prediction	(Risk[tiab] or risks[tiab]) and (stratify[tiab] or stratifying[tiab] or stratification[tiab] or define[tiab] or defining[tiab] or predict[tiab] or prediction[tiab] or assessment[tiab])
4	Tests (high sensitivity c-reactive protein; coronary artery calcium; calcium score	"hsCRP"[tiab] or "hs-CRP"[tiab] or "CAC"[tiab] or (coronary[tiab] AND artery[tiab] AND calcium[tiab]) or "CRP"[tiab] or "c-reactive protein"[tiab]

Set #	Concept	Search Statement
5	Combine sets	1 AND 2 AND 3 AND 4
6	Remove unwanted Publication types	5 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
7	Limit to in process citations	6 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
8	Apply limits	Limit 7 to publication year 2010-2014

PubMed syntax:

  *   =   truncation character (wildcard)

[ti]   =   limit to title field

[tiab]   =   limit to title and abstract fields

[tw]   =   text word

Convening the Face-to-Face Meeting

In consultation with the Contracting Officer's Representative (COR), the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on May 6-9, 2014. These experts were gathered to develop and draft clinical recommendations based on the evidence review for an update to the 2006 CPG. Lewin presented detailed information on the process used to grade. ECRI presented findings from the evidence review for each of the key questions. The presentations helped prepare the Champions and Work Group members for their work in reviewing and synthesizing the evidence and forming new recommendations.

Additionally, under the direction of the Champions, the Work Group members had the opportunity to discuss the existing recommendations from the 2006 CPG. They made a decision on whether to retain, revise, or reject each recommendation using an explicit process.

As they drafted each recommendation, the Work Group assigned a grade based on modified GRADE and USPSTF methodologies. Each recommendation was graded 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. The methodology used for grading the recommendations is further described below.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [83]

- 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 (QoL), 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, conducted by ECRI, used to develop recommendations for the Lipids CPG assessed the confidence in the quality of the evidence base and assigned a rate of "High", "Moderate", "Low" or "Very Low".

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

- Is there high or moderate quality evidence that answers this question?

- What is the overall certainty of this evidence?

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 resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple comorbidities 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 practically of the recommendation.

Discussion questions for other implications can include:

- 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?

The framework below was used by the Work Group to guide discussions on each domain.

Table A-4: Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	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	High Moderate Low Very low
Values and preferences	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations):	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. [83] 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. [84] 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 of 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.

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 …")
- Weak Against (or "We suggest not 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.

In addition to the GRADE strength of recommendation and USPSTF grade of recommendation, in the case of recommendations modified from the previous version of this CPG published in 2006, the Evidence Table in Appendix B shows the specific references supporting each recommendation provided in this CPG.

Appendix B: Evidence Table

Recommendation	2006 USPSTF Grade[1]	2014 Evidence[2]	2014 GRADE Strength[3]
Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention (patients without a history of atherosclerotic cardiovascular disease [ASCVD] or acute coronary syndrome [ACS])			
1. We recommend cardiovascular disease (CVD) risk screening for men > age 35 and women > age 45, including a lipid profile and a risk calculation.	--	Additional evidence: [20]	Strong For
2. We recommend against <u>routine</u> screening for dyslipidemia outside of the context of a cardiovascular risk assessment.	--	Additional evidence: [15] [19] [21-23]	Strong Against
3. For risk calculation, we suggest a 10-year risk calculator.	--	Additional evidence: [15] [24,25]	Weak For

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[1] The 2006 VA/DoD Dyslipidemia CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system.
http://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

[2] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2014 guideline Work Group, the literature cited corresponds directly to the 2014 evidence review. For these new recommendations, the phrase "additional evidence" in the evidence column refers to studies that support the recommendation, but were not systematically identified through a literature review. For recommendations that have been carried over from the 2006 VA/DoD Lipids CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the phrase "additional evidence" refers to studies that support the recommendation, but were not systematically identified through a literature review.

[3] Refer to the Grading Recommendations description for more information on how the strength of the recommendation was determined using GRADE methodology.

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Recommendation	2006 USPSTF Grade[1]	2014 Evidence[2]	GRADE Strength[3]
4. 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 2010 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.*	Not Graded	Additional evidence: [15] [24,25]	Weak For
5. We suggest against the <u>routine</u> use of high-sensitivity C-reactive protein (hsCRP) testing.	--	[26] Additional evidence: [30,31]	Weak Against
6. We suggest against the <u>routine</u> use of coronary artery calcium (CAC) testing.	--	[27-29]	Weak Against

		2006	2014	
	Recommendation	**USPSTF Grade[1]**	**Evidence[2]**	**GRADE Strength[3]**
7.	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.	--	[37] [41] Additional evidence: [8] [35,36] [38-40] [42]	Weak For
8.	We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater.	--	--	Weak For
9.	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.	--	Additional evidence: [32-34] [43]	Weak For
10.	For primary prevention, we recommend a moderate-dose statin as the agent of choice to reduce CVD risk if the patient chooses pharmacologic therapy.	--	[8] [37] [47] Additional evidence: [32-34] [39,40] [44-46] [48,49]	Strong For
11.	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.	--	[50] [52] [85-87] Additional evidence: [51] [53-58]	Weak For

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Recommendation	2006 USPSTF Grade[1]	2014 Evidence[2]	GRADE Strength[3]
12. We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy.	--	Additional evidence: [42] [59] [44,88-90]	Weak For
13. We recommend against routinely measuring LFTs or CK after a moderate-dose statin is initiated.	--	[42] [59]	Strong Against
Management of Pharmacotherapy for Secondary Prevention (patients with a history of ASCVD or ACS)			
14. 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.	--	[8] Additional evidence: [39,40] [64] [91-93] [94,95]	Strong For
15. 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.	--	[50] [52] [56] [68] [85,86] Additional evidence: [51] [53] [57,58] [66] [67] [96-98]	Strong Against

Recommendation	2006 USPSTF Grade[1]	2014 Evidence[2]	GRADE Strength[3]
16. 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).	--	[50] [52] [68] [86] Additional evidence: [51] [53] [66] [67] [96-98]	Weak for
17. We strongly recommend against the routine monitoring of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD.	--	[65]	Strong Against
18. 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.	--	[8] [60,61] Additional evidence: [39,40] [62-64]	Weak for
19. We suggest measuring LFTs 4-12 weeks after the initiation of high- dose statin.	--	Additional evidence: [62]	Weak for

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	2006	2014	
Recommendation	**USPSTF Grade[1]**	**Evidence[2]**	**GRADE Strength[3]**
Non-pharmacologic Approaches			
20. 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.*	a. [A] b. [B] c. [B]	Additional evidence: [69-77] →	Strong for
21. 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 30g of mixed nuts per day (15g of walnuts, 7.5g of hazelnuts, and 7.5g of almonds) for the reduction of CVD events.	--	[78]	Weak For
22. 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.*	I	[78] Additional evidence: [75] [99] →	Weak For
23. 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.*	[B]	Additional evidence: [58] [79] →	Strong For

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	2006	2014	
Recommendation	USPSTF Grade[1]	Evidence[2]	GRADE Strength[3]
24. 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.	--	Additional evidence: [58] [79]	Weak For
Monitoring and Follow-up			
25. We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy.	--	--	Weak For
26. 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

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Drafting and Submitting the Final CPG

During the face-to-face meeting, the Champions and Work Group members were given writing assignments for the recommendations created during the face-to-face meeting and recommendations carried forward from the 2006 CPG that would form portions of the narrative text for the 2014 CPG. During this time, the Champions and Work Group members also revised the 2006 algorithms. Following the face-to-face meeting, the Champions and Work Group identified the content for the guideline summary and pocket card, as part of the provider toolkits developed by the Evidence-Based Practice Working Group (EBPWG) following the publication of the 2014 CPG.

The algorithm is included as part of this CPG to provide a clear description of the flow of patient care. The final 2014 CPG was submitted in December 2014.

Appendix C: CVD Risk Calculators

Table C-1. Risk Calculators: Characteristics of Patient Population* [15,24,25,100-102]

	ACC/AHA pooled cohort[1]	ARIC[2]	CARDIA[3]	CHS[4]	Framingham[5,6]
Sample size	24,626	13,701	408	4,052	6,465
Sex					
Women	56.4%	55.8%	59.1%	62.3%	53.7%
Men	43.6%	44.2%	40.9%	37.7%	46.3%
Race					
White	82.6%	74.4%	57.4%	84.9%	100.0%
Black / African American	17.4%	25.6%	42.6%	15.1%	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%	0.0%	0.0%
Age					
Mean**	56.3	54.0	40.2	71.0	53.2
range	40 to 79	44 to 66	40 to 45	65 to 79	40 to 74

* Adapted from the following sources:

1. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Nov 12. [Epub ahead of print] PubMed PMID: 24222018.
2. Investigators TA. The Atherosclerosis risk in communities (ARIC) study: design and objectives. Am J Epidemiol. 1989;129:687-702.
3. Fried LP, Borhani NO, Enright P et al. The Cardiovascular Health Study: design and rationale. Annals of Epidemiology. 1991;1:263-76.
4. Friedman GD, Cutter GR, Donahue RP et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41:1105-16.
5. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham study. Ann NY Acad Sci 1963;107:539-556.
6. Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol 1979;110:281-290.

**Simple weighted average, no statistical weight applied.

Appendix D: Pharmacologic Therapy

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

Note: 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.

Drug Category	Dose	Major Drug Interactions	Adverse Drug Events	Notes
Statins				
Atorvastatin	10-80 mg once daily (high dose = 40-80 mg) (moderate dose = 10-20 mg)	There are many statin-drug interactions that need to be considered. Concomitant use of statins should be avoided with certain medications or the dose of the statin should be restricted to a lesser dose. Since statins vary in their metabolic pathway, refer to product labeling for the most up to date information regarding drug-drug interactions with the selected statin and which drugs to avoid and/or statin dose limits.	Statins are generally well tolerated. Myalgia, myopathy and rarely, rhabdomyolysis may occur. Risk of rhabdo is increased in the presence of interacting drugs, higher statin doses, renal or liver impairment, hypothyroidism, frailty, advanced age, etc. Other adverse events include diabetes, LFT elevation and possible non-serious, reversible cognitive effects including memory loss and confusion. However, an association between statins and an effect on cognition has not been confirmed.	First line therapy for primary or secondary prevention of ASCVD. Monotherapy with statins represents the best evidence for cardiovascular risk reduction.
Rosuvastatin	5-40 mg once daily (high dose = 20-40 mg) (moderate dose = 5-10mg)			
Simvastatin	5-40 mg once daily (moderate dose = 20-40 mg)			

Drug Category	Dose	Major Drug Interactions	Adverse Drug Events	Notes
Lovastatin	20-80 mg once daily (moderate dose = 40 mg)			
Pravastatin	10-80 mg once daily (moderate dose = 40-80 mg)			
Fluvastatin	20-80 mg/day (moderate dose = 40 mg twice daily or 80 mg XR/day)			
Pitavastatin	1-4 mg once daily (moderate dose **=** 2-4 mg)			
Fibrates				
Fenofibrate	Nanocrystal 145 mg/day Micronized 43-200 mg/day Micronized taken with meals. Dose varies depending upon micronized product used.	Potentially nephrotoxic in cyclosporine or tacrolimus treated patients. The levels/effects of Fenofibrate and derivatives may be decreased by BAS. May potentiate warfarin's effect on INR. Concomitant use of colchicine may increase the risk of myopathy and rhabdomyolysis.	Skin rash, gastrointestinal (Nausea, bloating, dyspepsia, cramping), headache myalgia, myopathy, increased serum transaminases, elevation in serum creatinine, cholelithiasis, etc.	Combination with a statin in the ACCORD trial showed no evidence of improved patient outcomes beyond statin based therapy (*Subgroup analysis showed potential harm in women and a potential benefit in those with high TG and low HDL-C*). [53] Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.

Drug Category	Dose	Major Drug Interactions	Adverse Drug Events	Notes
Fenofibric Acid	35-105 mg once daily Taken without regard to meals.	See fenofibrate.	See fenofibrate.	Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.
Gemfibrozil	600 mg twice daily Take 30-60 min before meals.	Avoid use with statins. Absorption of gemfibrozil is diminished by BAS. May potentiates effect of warfarin.	See fenofibrate.	VA-HIT (secondary prevention) gemfibrozil BID for 5 years vs. placebo in men with low HDL-C and moderately elevated LDL-C resulted in a significant reduction in nonfatal MI and death or cardiac origin. [66] Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.
Bile Acid Sequestrants (BAS)				
Cholestyramine	4-24 g/day Take within 30 min of a meal.	This class of medications may decrease the effect of a number of medications by interfering with drug absorption. In general, it is recommended to administer BASs 2 to 4 hours before or after other medications to avoid interactions.	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase and increases in triglycerides.	Separate BAS from other medications by taking them at least 1 hour before BAS or at least 4-6 hours after BAS to avoid a reduced effect of other medications. Colesevelam has less drug interactions than do the older BAS; will not decrease vitamin A, D, E, K absorption as much.
Colestipol	5-30 g/day			
Colesevelam	3.75 g/day Take with meals daily or divided twice daily.			

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Drug Category	Dose	Major Drug Interactions	Adverse Drug Events	Notes
Niacin Products				
Niaspan (ER Niacin)	500-2000 mg/day Initial: 500 mg at bedtime x 4 weeks, then 1 g at bedtime x 4 weeks; adjust dose to response and tolerance.	May increase the adverse effects of statins. Take BAS at least 4-6 hours before niacin.	Flushing, edema, glucose intolerance, GI distress (abdominal pain, diarrhea, dyspepsia, nausea, vomiting), pruritus, GI bleeding, elevation of liver transaminases and hepatic toxicity.	Combination with a statin in AIM-HIGH and HPS2-THRIVE showed no evidence of improved patient outcomes beyond statin based therapy in patients with ASCVD with well controlled LDL-C. [86,98] An increased risk for serious adverse events was observed in HPS2-THRIVE in the niacin/laropiprant group. [86] The contribution of laropiprant to the increased risk for adverse events is unknown. Avoid in patients with active liver disease, active peptic ulcer disease, and arterial bleeding.
Niacor (IR Niacin)	250-6000 mg/day Initial: 250 mg daily with evening meal; increase frequency and/or dose every 4-7 days.			
Cholesterol absorption inhibitors				
Ezetimibe	10 mg/day	Increased incidence of transaminase elevation >3x ULN when combined with statins versus (vs.) statins alone (1.3% vs. 0.4%, respectively).		Unknown benefit for reducing cardiovascular risk in primary or secondary prevention.

Drug Category	Dose	Major Drug Interactions	Adverse Drug Events	Notes
Fish Oil				
Fish Oil	1-4 g/day, as single dose or divided twice daily	May increase the risk of bleeding in patients receiving warfarin or other drugs affecting coagulation.	Taste perversion, dyspepsia, pruritus, and rash; hepatic ALT and AST increased. May increase LDL-C.	Meta-Analysis by Rizos et al. (2012) included 60 studies enrolling 68,680 patients. Use of omega-3 fatty acids was not associated with a reduction in all-cause mortality, cardiac death, MI, stroke or sudden death. [57]

Abbreviations: ALT= alanine transaminase; ASCVD= atherosclerotic cardiovascular disease; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes; AST= aspartate aminotransferase; BAS= bile acid sequestrants; BID= twice daily; CrCl= creatinine clearance; g= gram(s); HDL –C= high density lipoprotein cholesterol; HPS2-THRIVE= Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events; hrs= hours; INR= international normalized ratio; IR= immediate release; LDL-C= low density lipoprotein cholesterol; mg= milligram(s); ULN= upper limit of normal; VA-HIT= Veterans Affairs High-Density Lipoprotein Intervention Trial

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Additional Supporting Evidence
Recommendation 11

> **Recommendation 11:** 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**

Fibrates (gemfibrozil, fenofibrate)

There is one fair meta-analysis focusing on stroke risk with fibrates and included five studies in patients on gemfibrozil (n=12,326) or fenofibrate (n=5,661) in primary and secondary prevention populations. There was a reduction in nonfatal stroke in patients receiving gemfibrozil vs. placebo (RR 0.72, 95% CI 0.53-0.98, p=0.04) but no reduction in stroke in patients receiving fenofibrate. No differences were observed in risk of fatal stroke for either fibrate. [87]

In the FIELD study, 9795 patients with diabetes and with (n=2131) or without (n=7664) CVD were randomized to receive fenofibrate or placebo for a mean of five years. The primary endpoint of total cardiovascular events (cardiovascular death, MI, stroke and coronary and carotid revascularization) occurred in 5.2% of patients on fenofibrate and 5.9% of those on placebo (HR 0.89, 95% CI 0.75-1.05, p=0.16). [51]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD), 5518 patients with diabetes who were receiving open-label simvastatin were randomized to receive fenofibrate or placebo for a mean of 4.7 years. Approximately 36% of patients in each group had experienced a prior CVD event. The primary outcome of first occurrence of nonfatal MI or stroke or death from cardiovascular causes was not different between groups and occurred in 2.2% of patients receiving fenofibrate vs. 2.4 % of those on placebo (HR 0.92, 95% CI 0.79-1.08, p=0.32). Pre-specified subgroups showed some benefit in men and in patients with high triglycerides (TG) and low HDL-C at baseline and possible harm in women. [53]

Data from a fair quality meta-analysis did not find an increased risk of cancer or cancer incidence in patients taking either gemfibrozil or fenofibrate. [85]

Available evidence does not support a benefit of fenofibrate monotherapy in reducing CVD outcomes compared to placebo in the populations studied. Results from ACCORD do not support a statistically significant reduction in CVD events when fenofibrate was added to statins in diabetic patients. In pre-specified subgroup analyses of ACCORD, a benefit of fenofibrate was observed in the primary endpoint of reduced CVD events in men and in patients with elevated TG and low HDL at baseline, but possible harm in women.

Niacin

One systematic review of primary and secondary prevention, involving use of niacin alone or in combination with other lipid-lowering therapies, was identified. Of the 11 studies in the systematic

review, the effects of niacin alone were discernable in only four of them (n=8437). Data from these four studies showed that major CVD events (coronary death, MI, stroke, revascularization, etc.) were not statistically reduced between groups, but reduction in the combined endpoint of nonfatal MI and cardiac death did statistically favor niacin (OR 0.86, 95% CI 0.75-0.98, p=0.03). [86]

Recommendations 12 – 13

Statins

Recommendations 12: We suggest establishing baseline liver function tests (LFTs) and creatinine kinase (CK) before initiation of drug therapy. **Weak For**

Recommendation 13: We recommend against routinely measuring LFTs or CK after a moderate-dose statin is initiated. **Strong Against**

Some representative studies include The MRC-BHF Heart Protection Study (HPS) [88] and the Air Force/Texas Coronary Primary Prevention Study (AFCAPS/TexCAPS) [89] for moderate-dose statins. HPS examined 20,536 secondary prevention patients (including 8,000 with diabetes) over five years who were randomly assigned to simvastatin 40mg vs. placebo and concluded routine monitoring of LFTs was not useful for detecting liver-related adverse events. Similarly, for CK monitoring, clinical symptoms of myopathy were the trigger to identify patients with muscle-related adverse events not protocol-driven CK testing. [88] In a primary prevention population, AFCAPS/TexCAPS examined 6605 patients randomly assigned to lovastatin 40mg vs. placebo and followed over 5.2 years. [44] Despite >100,000 LFTs, clinically meaningful elevations of LFTs were infrequent (18 participants on lovastatin with 17 /18 recovering on continued treatment or rechallenge and 1/18 associated with cholelithiasis). Despite a similar number of CK tests (>100,000) rhabdomyolysis (or lesser degrees of myopathy) were not detected by routine testing of asymptomatic patients. There were no treatment group differences in the frequency of CK elevation of 10X> ULN (21 participants, 0.6%) in each treatment group and all recovered on treatment (20/21) or resumed treatment without subsequent elevation (1/21). Again symptoms were most effective in detecting myopathic symptoms. For higher dose statins, five studies compared high- vs. moderate- dose statins in different secondary prevention populations, two studies in patients with acute coronary syndrome (ACS) (PROVE-IT, and A to Z) and three in stable patients with CAD (TNT, IDEAL and SEARCH). The 2010 CTTC meta-analysis notes a risk of rhabdomyolysis of 1/10,000 for moderate-dose statins and 4/10,000 for high-dose statins. [89] Given the frequency of rhabdomyolysis, routine CK testing is not likely to be beneficial. However for LFTs, individual trial data for high-dose statins notes an absolute risk increase (ARI) of LFTS >3x upper limit of normal (ULN) ranging from 0.5% in A to Z (80mg simvastatin) to 2.2% in PROVE-IT (80mg atorvastatin) with NNH of 45 (PROVE-IT) to 200 (A to Z). [90] These LFT abnormalities were detected via protocol-driven lab testing. While package inserts for higher dose statins recommend establishing baseline LFTs, periodic checking after initiation is not routinely recommended, except "as clinically indicated." For high-dose statins, there is indirect evidence that checking LFTS in 4-12 weeks after initiation of a high-dose statin may detect clinically important 3x ULN LFT elevations. Given NNH of 45 to 200, checking LFTs 4-12 weeks after a high-dose statin is initiated and, if stable, according to clinical judgment thereafter, seems clinically reasonable.

Recommendation 14: 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**

Recommendation 15: 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**

Recommendation 16: 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**

Recommendation 17: We strongly recommend against the routine monitoring of LDL–C and non-HDL–C goals for the secondary prevention of ASCVD. **Strong Against**

Recommendation 18: 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**

Recommendation 19: We suggest measuring LFTs 4-12 weeks after the initiation of high- dose statin. **Weak For**

Table D-2. Outcomes Reported in the CTT 2005 and 2010 Meta-Analyses [8,39]

Outcome	CTT 2005 (n=14 trials; 90,056 pts)	CTT 2010 (n=21 trials; 129,526 pts)*
All-Cause Mortality	8.5% vs. 9.7%, ARR 1.2%, NNT 83 RR 0.88 (0.84-0.91)	*21 trials+5 trials of high vs. lower dose statins:* 2.1% vs. 2.3%, ARR 0.2, NNT 500 RR 0.90 (0.87-0.93)
Coronary Death	3.4% vs. 4.4%, ARR 1%, NNT 100 RR 0.81 (0.76-0.85)	0.5% vs. 0.6%, ARR 0.1%, NNT 1000 RR 0.8 (0.0.73-0.86)
Nonfatal MI	4.4% vs. 6.2%, ARR 1.8%, NNT 55 RR 0.74 (0.70-0.79)	0.9% vs. 1.2%, ARR 0.3%, NNT 333 RR 0.74 (0.69-0.78)
Fatal Stroke	0.6% vs., 0.6% NS RR 0.91 (0.74-1.11)	*21 trials+5 trials of high vs. lower dose statins:* 0.1% vs. 0.1% NS RR 0.96 (0.84-1.09)
Nonfatal Stroke	*Any stroke*: 3% vs. 3.7%, ARR 0.7%, NNT 143 RR 0.83 (0.78-0.88)	*Any stroke*: 0.7% vs. 0.8%, ARR 0.1%, NNT 1000 RR 0.85 (0.8-0.9)
Revascularizations	*Coronary revascularize* 5.8% vs. 7.6%, ARR 1.8%, NNT 55 RR 0.76 (0.73-0.80)	*Coronary revascularize* 1.2% vs. 1.6% ARR 0.4%, NNT 250 RR 0.76 (0.73-0.80)

*CTT 2010 included patient level data from 5 trials that compared a higher dose to a lower or moderate statin dose. Data from those five trials is not included in the table, when reported separately from the other 21 trials, but is included in a subsequent section. If data from 21 trials is not provided separately from the five statin comparison trials, a notation is made and data represent findings from 26 trials (21+5 trials). The CTT 2012 categorized reductions in outcomes by baseline quintiles of risk and is not included in the table. Relative risks (RR) are weighted to represent reduction in rate per 1.0 mmol/L reduction in LDL-C at one year of treatment. ARR=absolute risk reduction, CTT=Cholesterol Treatment Trialists', NNT=number needed to treat

Table D-3. ASCVD Outcomes: CTT Meta-Analysis 2010 [Pooled results of the five studies comparing statin doses] and the Five Individual Studies Comparing Moderate to High Dose Statins

	CTT 2010	PROVE-IT TIMI -22	A to Z	IDEAL	TNT	SEARCH
Intervention	(See Table D-2 in appendix D)	A80 vs. P40, respectively	S40 x 1 mo, ⇒S80 x 20 mo vs. Placebo x 4 mo, ⇒S20 x 20 mo, respectively	A80 vs. S20, respectively	A80 vs. A10, respectively	S80 vs. S20, respectively
Population		ACS		Prior MI	Stable CHD and LDL < 130 mg/dl	Prior MI
N		4162	ACS	8,888	10,001	12,064
Duration		24 months	24 months	4.8 years	4.9 years	6.7 years
Run-in phase		No run-in phase	No run-in phase	No run-in phase	A10 run-in phase	S20 run-in phase
Primary Outcomes	Any major coronary event [fatal or nonfatal MI], coronary revascularization or stroke	Composite: All-cause mortality, MI, unstable angina (USA) requiring hosp., revascularization and stroke	Composite: cardiovascular (CV) death, nonfatal MI, readmit for ACS and stroke.	Major coronary event: Coronary death, nonfatal MI, or cardiac arrest with resuscitation	Major CV event: death from CHD, nonfatal, non-procedure related MI, cardiac arrest with resuscitation and stroke	Major vascular events: coronary death, MI, stroke or arterial revascularization
Primary Outcome Results	4.5% vs. 5.3%. ARR 0.8%, NNT 125, RR 0.72 (0.66-0.78) p<0.0001	22.4% vs. 26.3%, ARR 3.9% NNT 26, p=0.005 *Individual outcomes significantly different: revascularization and hospitalization for USA*	14.4% vs. 16.7%, ARR 2.5%, HR 0.89, 95% CI 0.76-1.04, p=0.14	9.3% vs. 10.4%, ARR 1.1%, HR 0.89, 95% CI 0.78-1.01, p=0.07	8.7% vs. 10.9%, ARR 2.2%, NNT 45, HR 0.78, 95% CI 0.69-0.89, p<0.001	24.5% vs. 25.7%, ARR 1.2%, RR 0.94, 95% CI 0.88-1.01, p=0.10

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	CTT 2010	PROVE-IT TIMI -22	A to Z	IDEAL	TNT	SEARCH
All-cause Mortality	*21 trials+5 trials of high vs. lower dose statins:* 2.1% vs. 2.3%, ARR 0.2, NNT 500 RR 0.90 (0.87-0.93)	2.2% vs. 3.2%, ARR 1%, p=0.07	5.5% vs. 6.7%, ARR 1.2%, HR 0.79, 95% CI 0.61-1.02, p=0.08	8.2% vs. 8.4%, ARR 0.2%, HR 0.98, 95% CI 0.85-1.13, p=0.81	5.7% vs. 5.6%, HR 1.01, 95% CI 0.85-1.19, p=0.92	16% vs. 16.1%, ARR 0.01%, RR 0.99, 95% CI 0.91-1.09, p=0.9
CAD Death (MI)	0.7% vs. 0.7%, RR 0.85 (0.0.63-1.15) NS	1.1% vs. 1.4%, ARR 0.3% NS	4.1% vs. 5.4%, ARR 1.3%, HR 0.75, 95% CI 0.57-1, p=0.05	5% vs. 4.9%, HR 1.03, 95% CI 0.85-1.24, p=0.78	2% vs. 2.5%, ARR, 0.5%, HR 0.8, 95% CI 0.61-1.03, p=0.09	2.7% vs. 3.2%, ARR 0.5%, NS (MI) 4.7% vs. 4.1%, NS (other CHD deaths) 9.4% vs. 9.5%, ARR 0.1%, RR 0.99, 95% CI 0.87-1.15, p=0.96 (Any vascular death)
Nonfatal MI	1.3% vs. 1.5%, ARR 0.2%, NNT 500 RR 0.71 (0.58-0.87)	6.6% vs. 7.4%, ARR 0.8% NS	7.1% vs. 7.4%, ARR 0.3%, HR 0.96, 95% CI 0.77-1.21), p=0.74	6% vs. 7.2%, ARR 1.2%, NNT 83, HR 0.83, 95% CI 0.71-0.98, p=0.02	4.9% vs. 6.2%, ARR 1.3%, NNT 77, HR 0.78, 95% CI 0.66-0.93, p=0.004	6.6% vs. 7.7%, ARR 1.1%, RR 0.85, 95% CI 0.75-0.99
Fatal Stroke	*21 trials+5 trials of high vs. lower dose statins:* 0.1% vs. 0.1% NS RR 0.96 (0.84-1.09)	Not provided	Not provided	Not provided	Not provided	0.9% vs. 1.1%, ARR 0.2%, RR 0.85, 95% CI 0.6-1.21 (NS)

	CTT 2010	PROVE-IT TIMI -22	A to Z	IDEAL	TNT	SEARCH
Nonfatal Stroke	*Any stroke*: 0.6% vs. 0.7%, RR 0.74 (0.59-0.92) ARR 0.1%, NNT 1000	*Any stroke:* 1% vs. 1%, NS	*Any stroke* 1.3% vs. 1.8%, ARR 0.5%, HR 0.79, 95% CI 0.48-1.3, p=0.36	*Any stroke* 3.4% vs. 3.9%, ARR 0.5%, HR 0.87, 95% CI 0.7-1.08, p=0.2	*Any stroke* 2.3% vs. 3.1%, ARR 0.8%, NNT 125, HR 0.75, 95% CI 0.59-0.96, p=0.02	3.5% vs. 3.8%, ARR 0.3%, RR 0.91, 95% CI 0.75-1.10, (NS) *Any stroke* 4.2% vs. 4.6%, ARR 0.4%, RR 0.91, 95% CI 0.77-1.08, p=0.3
Revascularization	*Coronary revascularize* 2.6% vs. 3.2% ARR 0.6%, NNT 166 RR 0.66 (0.60-0.73)	*Coronary revascularize* 16.3% vs. 18.8% ARR 2.5%, NNT 40 P=0.04	*Coronary revascularize* 5.9% vs. 6.2%, ARR 0.3%, HR 0.93, 95% CI 0.73-1.2, p=0.6	*Coronary revascularize* 13% vs. 16.7%, ARR 3.7%, NNT 27, HR 0.77, 95% CI 0.69-0.86, p<0.001	*Coronary revascularize* Not provided	*Coronary revascularize* 9.5% vs. 10.1%, ARR 0.6%, RR 0.94, 95% CI 0.66-1.34 (NS)
Comments	**Nonfatal events responsible for differences.** -Results in Table D-2 from five studies comparing low-moderate statin dose to high dose	**Nonfatal events responsible for differences.** -Pts with baseline LDL >125 ml/dl had a 34% reduction in hazard ratio vs. 7% in those less than 125 mg/dl at baseline. -No statistical benefit in patients on statins at baseline	**No differences in fatal or nonfatal events.** -Early withdrawal: S80 34% vs. S20 32% -S20 group received placebo for first 4 months	**Primary endpoint not met but any difference was in nonfatal events, MI and revascularization.** -End of study, 23% of patients increased to simva 40 mg and 13% reduced their atorva dose to 40 mg -Open-label, blinded endpoint	**Nonfatal events responsible for differences.**	**No differences in fatal or nonfatal events with exception of nonfatal MI just reaching statistical significance.**

A10, A20=atorvastatin-dose, ACS=acute coronary syndrome, ARR=absolute risk reduction, CAD=coronary artery disease, CTT=Cholesterol Treatment Trialists', CHD=coronary heart disease, CV=cardiovascular, HR=hazard ration, MI=myocardial infarction, NNT=number needed to treat, NS=not significant, RR=risk ratio, S20, S40, S80=simvastatin-dose, USA=unstable angina

Table D-4. CTT Collaboration Meta-Analysis of Twenty-Six Clinical Trials (Safety and Efficacy) and ACC/AHA Evidence Summary (Moderate vs. High Intensity Statin)

Outcome	Moderate Intensity (Events/N)	High Intensity (Events/N)	NNT or NNH
Rhabdomyolysis*	1/10,000	4/10,000	--
Diabetes	1/1000 treated for 1 yr	3/1000 treated for 1 yr	NNH 498
First Major Cardiovascular Event	5.3%/year	4.5%/year	ARR 0.8%, NNT 125
Major CVD Events	--	6.5 fewer events/1000 pts treated for one year vs. moderate-dose statins	NNT 155

*Rhabdomyolysis was increased in the simvastatin 80 mg groups compared to moderate intensity statins (A to Z and SEARCH).

ACC/AHA=American College of Cardiology/American Heart Association, ASCVD=atherosclerotic cardiovascular disease, CTT=Cholesterol Treatment Trialists', N=number, NNH=number need to harm during a given time for one adverse event to occur, NNT=number needed to treat during a given time for one less event to occur.

Table D-5. Individual Clinical Trials Comparing High Intensity to Moderate or Low Intensity Statins

Trial	Statin	Medication Adherence/ Compliance	LFTs 3x ULN*	CK 10xULN	Rhabdo	Non-Vascular Death	Discontinue Statin Due to ADE
PROVE-IT N=4162	A80/P40	Not reported	69 (3.3%)/23 (1.1%) p<0.001 NNH 45	2 (0.1%)/ 3 (0.15%) NS	None	17 (0.8%)/ 27 (1.3%) (?NS)	Not provided-only overall W/D
A to Z N=4497	S80/S20	Not reported	19 (0.9%)/8 (0.4%) p=0.05	9 (0.4%)/ 1 (0.04%) p=0.02 NNH 278	3 (0.1%)/ None	21 (0.9%)/ 21 (0.9%) NS	1.5%/1.8% p=0.49 Myopathy statistically greater in S80 vs. S20
TNT N=10,001	A80/A10	Not reported	60 (1.2%)/9 (0.2%) p<0.001 NNH 100	None	2 (0.04%)/ 3 (0.06%) NS	158 (3.2%)/ 127 (2.5%) (?NS)	7.2%/ 5.3% p<0.001 NNH 52.6
IDEAL N=8888	A80/S20	89% vs. 95%	43 (0.97%)/5 (0.11%) p<0.001 NNH 116	6 (0.14%)/ 11 (0.25%) NS	2 (0.05%)/ 3 (0.07%) NS	143 (3.2%)/ 156 (3.5%) NS	426 (9.6%)/ 186 (4.2%) p<0.001 NNH 18.5 Myalgia, diarrhea, abdominal pain and nausea all statistically greater in A
SEARCH N=12,064	S80/S20	77% vs. 69% More pts on S20 were placed on non-study statin due to perceived need for higher intensity.	14 (0.2%)/10 (0.2%) NS	53 (0.9%)/ 2 (0.03%) p<0.0001 NNH 115	7 (0.12%)/ None	399 (6.6%)/ 398 (6.6%) NS	259 (4.3%/ 164 (2.7%) (?NS)

*In February 2012, the FDA removed the recommendation for periodic monitoring of LFTs in patients receiving statins. Instead, baseline LFTs testing is recommended and thereafter, as clinical indicated. The FDA has concluded that serious hepatic injury is rare and unpredictable in patients receiving statins and routine monitoring does not appear to be useful in detection or prevention of liver injury. So in the case of LFT elevation, the NNH would account for the number of patients needed to treat to identify one case of asymptomatic LFT elevation (>3x ULN) with unclear clinical significance, however most providers would interrupt or stop therapy while evaluating. p-values are provided when available. A=atorvastatin, ACS=acute coronary syndrome, ADE=adverse drug event, CAD=coronary artery disease, CK=creatine kinase, LFTs=liver function tests, N=number, NNH=number need to harm during a given time for one adverse event to occur, NNT=number needed to treat during a given time for one less event to occur, NS=non-significant, P=pravastatin, S=simvastatin, Rhabdo=Rhabdomyolysis, W/D=withdrawal, ?NS=unknown if the difference is significant.

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Why does the VA/DoD Guideline Differ From the ACC/AHA Guideline with Regard to Statin Dose?

High- vs. Moderate- Dose Statins: Efficacy

The ACC/AHA recommendation for using high intensity statins for secondary prevention relies heavily on a meta-analysis published in 2010 by the Cholesterol Treatment Trialists' (CTT) Collaboration. [8] In this meta-analysis, which included the five trials comparing moderate or low intensity statins to high intensity statins, there were significant reductions in first major vascular events (ARR 0.8%, 5.3 vs. 4.5%, respectively), first major coronary events (ARR 0.3%, 2.2 vs. 1.9%, respectively [driven by a significant reduction in non-fatal MI but no difference in coronary death]), coronary revascularization (ARR 0.6%, 3.2% vs. 2.6%, respectively) and stroke (ARR 0.1%, 0.7 vs. 0.6% [significant reduction in ischemic stroke and non-significant excess in hemorrhagic stroke]) in favor of high-dose statins. The absolute difference in the incidence of any major vascular event was 0.8% (NNT 125) in favor of the higher intensity group. Of note, revascularizations were included in the primary composite outcome measure in the CTT meta-analysis and patient-level data from different patient populations (ACS and stable ASCVD) were combined in order to conduct the meta-analysis and have been cited as severe limitations affecting the validity of the meta-analysis. [64]

The five major clinical trials comparing moderate or low intensity statins to high intensity statin therapy consist of two trials comparing simvastatin 80 mg to simvastatin 20 mg (Phase Z of the A to Z trial [92] and SEARCH [91]) and one trial comparing atorvastatin 80 mg to simvastatin 20 mg. [93] None of these three trials showed a statistically significant difference in the primary endpoint of major cardiovascular events between high-dose and moderate-dose statins. Alternatively, there have been two trials showing a benefit of higher dose statins on cardiovascular outcomes. One compared atorvastatin 80 mg to lower doses of atorvastatin (10 mg, TNT [95]) and another compared atorvastatin 80 mg to lower doses of a less potent statin (pravastatin 40 mg, PROVE-IT-TIMI 22 [94]). The A to Z and PROVE-IT trials were conducted in patients with ACS while SEARCH, TNT and IDEAL in patients with stable CAD. In these studies, differences in CVD outcomes between high- and moderate- dose statins were restricted to nonfatal events (nonfatal MI and coronary revascularization). Refer to Table D-3 in Appendix D for detailed results from the CTT 2010 meta-analysis and the five individual clinical trials comparing a moderate-to high- dose statin.

None of these trials addressed back titration of high-dose statins to low or moderate dose after a period of time.

It is important to keep in mind that these studies did not include more moderate doses of atorvastatin or simvastatin (e.g., 40 mg) in the vast majority of patients so the direct incremental benefit of using those doses in comparison to the maximum statin doses is unknown. Of note, there are no published trials examining cardiovascular outcomes that compared a moderate or high intensity dose of rosuvastatin vs. a lower intensity dose of another statin/intensity. Therefore, it is unknown whether use of higher doses of rosuvastatin vs. moderate or high doses of other statins will lead to improved outcomes.

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Fibrates (gemfibrozil, fenofibrate)

There is one fair meta-analysis focusing on stroke risk with fibrates and included five studies in patients on gemfibrozil (n=12,326) or fenofibrate (n=5,661) in primary and secondary prevention populations. There was a reduction in nonfatal stroke in patients receiving gemfibrozil vs. placebo (RR 0.72, 95% CI 0.53-0.98, p=0.04) but no reduction in stroke in patients receiving fenofibrate. No differences were observed in risk of fatal stroke for either fibrate. [87]

A sub study of the Helsinki Heart Study (HHS) was conducted in males excluded from the primary prevention cohort of HHS if they had a history of MI, angina or prior electrocardiogram (ECG) changes. There were 628 subjects enrolled in the secondary prevention component of the study who received either gemfibrozil or placebo for five years. The primary outcome in this study was cardiac events (combined fatal and non-fatal MI and sudden cardiac death). There was no difference in the primary endpoint between gemfibrozil and placebo (p=0.14, 95% CI 0.88-2.48). [96]

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), 2531 men with CHD, low HDL-C (<40 mg/dL) and moderately elevated LDL-C (<140 mg/dL), were randomized to receive gemfibrozil 600 mg twice daily or placebo for five years. Participants were included if their triglyceride level was <300 mg/dL or 3.38 mmol/L. The primary outcome was nonfatal MI or death of cardiac origin. A primary event occurred in 21.7% of those receiving placebo vs. 17.3% receiving gemfibrozil for a relative risk reduction of 22% (95% CI 7-35, p=0.006). The relative risk reduction for combined cardiac events (nonfatal MI, death from coronary causes or stroke) with gemfibrozil was 24% compared to placebo (95% CI 11-36, p<0.001). There was no difference between groups in the rates of coronary revascularization, hospitalization for unstable angina, overall death or cancer. [66]

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9795 patients with diabetes and with (n=2131) or without (n=7664) CVD were randomized to receive fenofibrate or placebo for a mean of five years. The primary endpoint of total cardiovascular events (cardiovascular death, MI, stroke and coronary and carotid revascularization) occurred in 5.2% of patients on fenofibrate and 5.9% of those on placebo (HR 0.89, 95% CI 0.75-1.05, p=0.16). [51]

In ACCORD, 5518 patients with diabetes who were receiving open-label simvastatin were randomized to receive fenofibrate or placebo for a mean of 4.7 years. Approximately 36% of patients in each group had experienced a prior CVD event. The primary outcome of first occurrence of nonfatal MI or stroke or death from cardiovascular causes was not different between groups and occurred in 2.2% of patients receiving fenofibrate vs. 2.4% of those on placebo (HR 0.92, 95% CI 0.79-1.08, p=0.32). Pre-specified subgroups showed some benefit in men and in patients with high TGs and low HDL-C at baseline and possible harm in women. [53]

Data from a fair quality meta-analysis did not find an increased risk of cancer or cancer incidence in patients taking either gemfibrozil or fenofibrate. [85]

In summary, gemfibrozil significantly reduced nonfatal MI or cardiac death compared to placebo in male Veterans with CHD, low HDL and moderately high LDL. Available evidence does not support a benefit of fenofibrate monotherapy in reducing CVD outcomes compared to placebo in the populations studied.

Results from ACCORD do not support a statistically significant reduction in CVD events when fenofibrate was added to statins in diabetic patients. In pre-specified subgroup analyses of ACCORD, a benefit of fenofibrate was observed in the primary endpoint of reduced CVD events in men and in patients with elevated TG and low HDL at baseline, but possible harm in women.

Niacin

Two large, long-term clinical trials (Athero-thrombosis Intervention in Metabolic Syndrome with Low HDL/High TG: Impact on Global Health Outcomes [AIM-HIGH study] and Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]) and one systematic review, involving use of niacin alone or in combination with other lipid-lowering therapies, were identified. Of the 11 primary and secondary prevention studies in the systematic review, the effects of niacin alone were discernable in only four of them (n=8437). Data from these four studies showed that major CVD events (coronary death, MI, stroke, revascularization, etc.) were not statistically reduced between groups but reduction in the combined endpoint of nonfatal MI and cardiac death did statistically favor niacin (OR 0.86, 95% CI 0.75-0.98, p=0.03). [86]

In the AIM-HIGH study, 3414 patients with established CVD and receiving moderate-to-high dose simvastatin were randomized to receive extended-release niacin (Niaspan) 1.5-2g daily or placebo. In this trial, LDL-C was maintained between 40 and 80 mg/dl. After a mean follow up of three years, the trial was stopped due to a lack of efficacy in the primary endpoint, which was a first event of death from CHD, MI ischemic stroke, ACS, or revascularization. By three years, the primary endpoint had occurred in 16.4% of niacin recipients and 16.2% of those on placebo (HR 1.02, 95% CI 0.87-1.21, p=0.79). [67]

In the HPS2-THRIVE study, 25,673 eligible patients with occlusive arterial disease who were able to tolerate extended-release niacin 2 gm plus laropiprant 40 mg daily, (ERN/LRPT) daily, for one month were randomized to receive the ERN/LRPT combination or placebo in addition to simvastatin 40 mg with or without ezetimibe daily and were followed for median of 3.9 years. After a mean follow up of 3.9 years, safety outcomes have been published. Although improvements were noted in LDL-C, HDL-C and triglycerides in the combination group, there was no incremental benefit on cardiovascular outcomes when niacin/laropiprant was added to statins. Pre-specified subgroup analyses, including patients with low HDL/high TGs, likewise showed no benefit, although the authors reported a nominally statistically significant difference observed in the primary endpoint in a subgroup of patients with higher baseline LDL-C (p=0.02). The combination of niacin/laropiprant plus statins was associated with a statistically significant increase in serious adverse events (skin, gastrointestinal, musculoskeletal, bleeding, infection, etc.) compared to statins with or without ezetimibe. [103]

In the Coronary Drug Project (CDP), 8,341 men having one or more MIs were randomized to one of six treatment groups. Three of those treatment groups were stopped early due to increased events (e.g., nonfatal MI, death, thromboembolism and cancer) compared to placebo. These included both estrogen groups and the dextrothyroxine group. The remaining three groups included clofibrate 1.8g daily, niacin 3g daily and placebo. The primary endpoint was total mortality. Secondary endpoints included cardiac and noncardiac mortality and nonfatal events (e.g., MI, angina, CHF, stroke, pulmonary embolism and arrhythmias). The trial had a planned follow up of five years but actual follow up ranged from 5-8.5

years. Although there was no difference in total mortality in the niacin vs. placebo group, there was a significantly lower risk for nonfatal MI in favor of niacin vs. placebo. [97]

Appendix E: Exercise and Mediterranean Diet

Table E-1. Physical Activity Guidelines for Americans: Health Benefits of Physical Activity [75]

Physical Activity Health Benefits
Regular physical activity reduces the risk of many adverse health outcomes.
Some physical activity is better than none.
For most health outcomes, additional benefits occur as the amount of physical activity increases through higher intensity, greater frequency, and/or longer duration.
Most health benefits occur with at least 150 minutes (2 hours and 30 minutes) a week of moderate intensity physical activity, such as brisk walking. Additional benefits occur with more physical activity.
Both aerobic (endurance) and muscle-strengthening (resistance) physical activity are beneficial.
Health benefits occur for children and adolescents, young and middle-aged adults, older adults, and those in every studied racial and ethnic group.
The health benefits of physical activity occur for people with disabilities.

Table E-2. Key Guidelines for Adults & Older Adults [75]

All Adults	Older Adults
Avoid inactivity. Some physical activity is better than none and adults who participate in any amount of physical activity gain some health benefits.	Be as physically active as abilities and conditions allow when unable to do 150 minutes of moderate-intensity aerobic* activity a week.
For substantial health benefits, do at least 150 minutes (2 hours and 30 minutes) a week of moderate intensity or 75 minutes (1 hour and 15 minutes) of vigorous aerobic* physical activity, or an equivalent combination of moderate and vigorous intensity aerobic* activity.	Do exercises that maintain or improve balance if at risk of falling.
Do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.	Consider level of fitness before determining level of activity.
For additional and more extensive health benefits, increase aerobic physical activity to 300 minutes (5 hours) a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic* physical activity, or an equivalent combination of moderate and vigorous intensity activity as additional health benefits are gained by engaging in physical activity beyond this amount.	Understand how chronic conditions affect ability to do regular physical activity safely.
*Aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week. [75]	

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Table E-3. Nutrient Composition of the Therapeutic Lifestyle Changes (TLC) Diet* [104]

Nutrient	Recommended Intake
Saturated fat[1]	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25 – 35% of total calories
Carbohydrate[2]	50 – 60% of total calories
Fiber	20 – 30 grams/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)[3]	Balance dietary energy intake and expenditure to maintain desirable body weight/prevent weight gain

*Adapted from VA/DoD Overweight/Obesity CPG (2014)

[1]Trans fatty acids are another low-density lipoprotein cholesterol-raising fat that should be kept as a low intake.

[2]Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.

[3]Daily calorie expenditure should include at least moderate physical activity (contributing approximately 200 kcal per day).

Table E-4. Summary of Dietary Recommendations in the Mediterranean Diet* [78]

Food	Goal
Recommended	
Olive oil	≥ 4 tbsp. per day
Tree nuts and peanuts	≥ 3 servings per week
Fresh fruits including natural fruit juices	≥ 3 servings per day
Vegetables	≥ 2 servings per day
Seafood (primarily fatty fish)	≥ 3 servings per week
Legumes	≥ 3 servings per week
Sofrito†	≥ 2 servings per week
White meat	In place of red meat
Wine with meals (optional)	≥ 7 glasses per week
Discouraged	
Soda drinks	< 1 drink per day
Commercial baked goods, sweets, pastries‡	< 3 servings per week
Spread fats	< 1 serving per day
Red and processed meats	< 1 serving per day

*Adapted from Estruch, et al. (2013)

† Sofrito is a sauce made with tomato and onion, and often includes garlic, herbs, and olive oil.

‡ Commercial bakery goods, sweets, and pastries included cakes, cookies, biscuits, and custard, and did not include those that are homemade.

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Table E-5. Quantitative Score of Compliance with the Mediterranean Diet* [78]

#	Food and Frequency of Consumption	Criteria for 1 point
1	Do you use olive oil as your main culinary fat (in hot and/or cold food preparation)?	Yes
2	How much olive oil do you consume in a typical day?	≥ 4 tbsp. per day
3	How many vegetable servings do you consume each day?	≥ 2 servings per day (with at least 1 portion raw or as salad)
4	How many fruit servings do you consume in a typical day?	≥ 3 servings per day
5	How many servings of red meat or meat products do you consume in a typical day?	< 1 serving per day
6	How many servings of butter, margarine, or cream do you consume in a typical day?	< 1 serving per day
7	How many sweet/carbonated beverages do you consume in a typical day?	< 1 serving per day
8	How much wine do you drink in a typical week?	≥ 7 glasses per week
9	How many servings of legumes do you consume in a typical week?	≥ 3 servings per week
10	How many servings of fish and/or shellfish do you consume in a typical week?	≥ 3 servings per week
11	How many servings of commercial sweets or pastries (not homemade) do you consume in a typical week?	< 3 servings per week
12	How many servings of nuts do you consume in a typical week?	≥ 3 servings per week
13	Do you typically consume chicken, turkey, or rabbit meat in place of veal, pork, hamburger, or sausage?	Yes
14	How many times in a typical week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito†?	≥ 2 servings per week

*Adapted from Estruch, et al. (2013)

† Sofrito is a sauce made with tomato and onion, and often includes garlic, herbs, and olive oil.

Appendix F: Acronym List

4D	Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis
AAA	abdominal aortic aneurysm
ABI	ankle brachial index
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	acute coronary syndrome
ADR	adverse drug reaction
AFCAPS/TEXCAPS	Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
AIM-HIGH	Athero-thrombosis Intervention in Metabolic Syndrome with Low HDL/High TG: Impact on Global Health Outcomes
ALT	alanine aminotransferase
ARR	absolute risk reduction
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ATP	Adult Treatment Panel
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events
BAS	bile acid sequestrants
BID	twice a day
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass
CAC	coronary artery calcium
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CDP	Coronary Drug Project
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
COI	conflict of interest
CORs	Contracting Officer's Representatives
CORONA	Controlled rosuvastatin multinational study in heart failure
CPG	clinical practice guideline
CRP	C-reactive protein
CV	cardiovascular
CVA	cerebral vascular accident
CVD	cardiovascular disease

DHA	docosahexaenoic acid
DM	diabetes mellitus or diabetes
DoD	Department of Defense
EBPWG	Evidence-based Practice Working Group
EF	ejection fraction
EPA	eicosapentaenoic acid
ESRD	end stage renal disease
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FRS	Framingham Risk Score
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Heart Failure
gm	gram(s)
HDL-C	high density lipoprotein cholesterol
HbA1c	hemoglobin A1c
HHS	Helsinki Heart Study
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events
HsCRP	high sensitivity C- reactive protein
HF	heart failure
IHD	ischemic heart disease
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
IMT	intimal medial thickness
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL-C	low density lipoprotein cholesterol
LE	life expectancy
LFT	liver function tests
MI	myocardial infarction
mg	milligram(s)
mg/dL	milligram(s) per deciliter(s)
MNT	Medical Nutrition Therapy
Mod-Hi	moderate to high
NHLBI	National Heart, Lung, and Blood Institute
NNH	number needed to harm
NNT	number needed to treat
NSGP	net splanchnic glucose production
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PUFAs	polyunsaturated fatty acids
PVD	peripheral vascular disease
RCT	randomized controlled trial
RD	Registered Dietitian
RF	risk factors

QD	once a day
SDM	shared decision making
SHARP	Study of Heart and Renal Protection
TC	total cholesterol
TG	triglycerides
TIA	transient ischemic attack
TLC diet	Therapeutic Lifestyle Changes diet
US	United States
VA	Department of Veterans Affairs
VA-HIT	Veterans Affairs High-Density Lipoprotein Intervention Trial

Appendix G: Participant List

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