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

Department of Veterans Affairs
Department of Defense

Clinician Summary

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 epidemiological 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**.**

Version 3.0 – 2014

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]

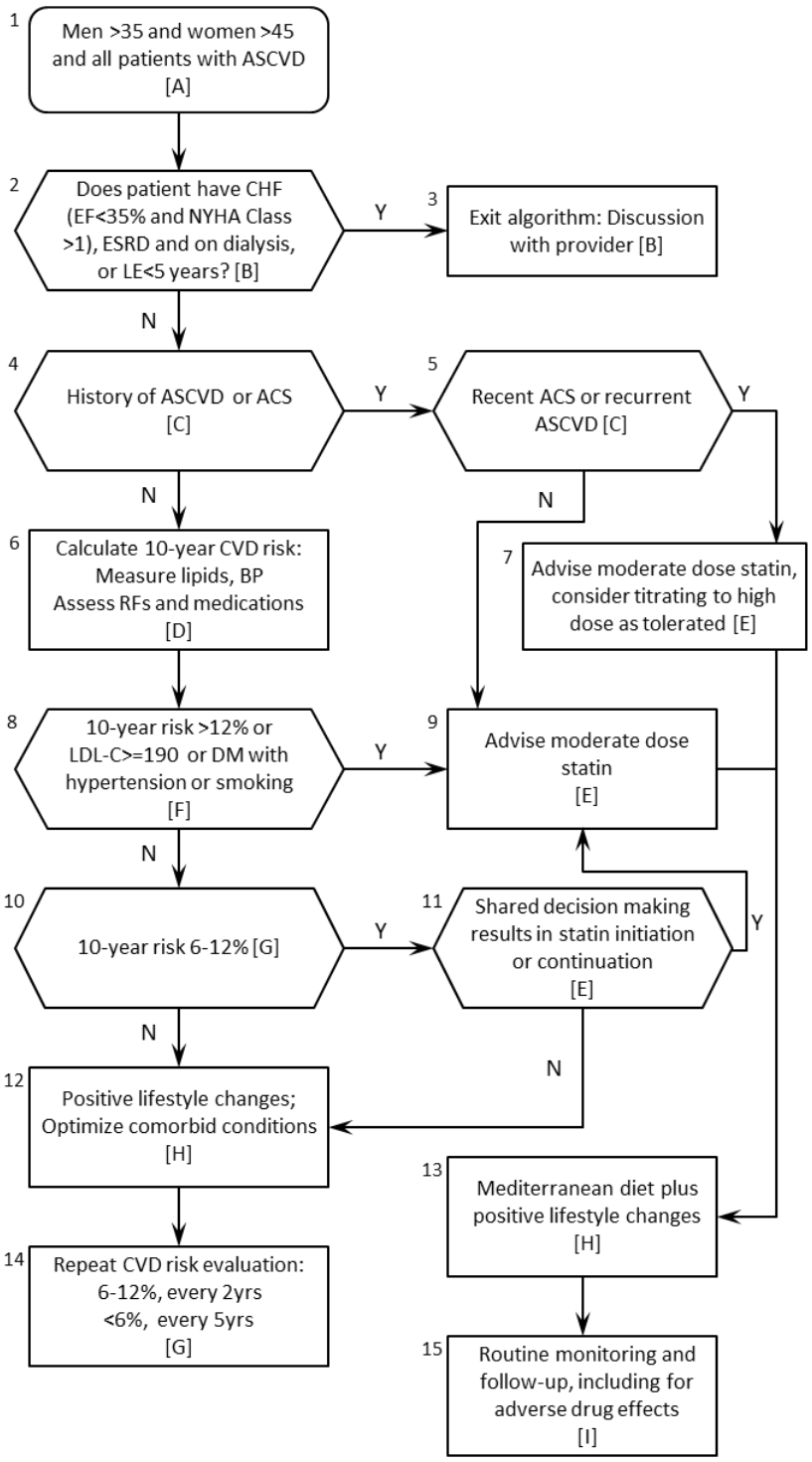
The etiology of dyslipidemia involves genetic, lifestyle and other factors. Genetic factors that result in either overproduction or slow clearance of TGs and LDL-C, or underproduction or fast clearance of HDL-C, can lead to dyslipidemia. A sedentary lifestyle with excessive dietary intake of saturated 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]

Algorithm

Management of Dyslipidemia



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

Recommendations

#	Place in Algorithm	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 routine 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 test. f. Level of high density lipoprotein cholesterol (HDL-C) (Less than 40 mg/dL confirmed on more than one occasion) *Modified from the 2006 CPG without an updated systematic review of the evidence.**	Weak For
5	C	We suggest against the routine use of high-sensitivity C-reactive protein (hsCRP) testing.	Weak Against
6	C	We suggest against the routine use of coronary artery calcium (CAC) testing.	Weak Against

#	Place in Algorithm	Recommendations	Strength
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 routinely 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
15	E	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
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

#	Place in Algorithm	Recommendations	Strength
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
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 Reconciling 2006 CPG Recommendations in the full CPG.

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	Adverse Drug Events	Notes
Statins			
Atorvastatin	10-80 mg once daily (high dose = 40-80 mg) (moderate dose = 10-20 mg)	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)		
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)		

Drug Category	Dose	Adverse Drug Events	Notes
Fibrates			
Fenofibrate	Nanocrystal 145 mg/day Micronized 43-200 mg/day Micronized taken with meals. Dose varies depending upon micronized product used.	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*). [6] Avoid in patients with CrCl < 30 ml/min, active liver disease including primary biliary cirrhosis, and preexisting gallbladder disease.
Fenofibric Acid	35-105 mg once daily Taken without regard to meals.	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.	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. [7] 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.	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.
Colestipol	5-30 g/day		
Colesevelam	3.75 g/day Take with meals daily or divided twice daily.		Colesevelam has less drug interactions than do the older BAS; will not decrease vitamin A, D, E, K absorption as much.

Drug Category	Dose	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	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. [8,9] An increased risk for serious adverse events was observed in HPS2-THRIVE in the niacin/laropiprant group. [8] 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		Unknown benefit for reducing cardiovascular risk in primary or secondary prevention.
Fish Oil			
Fish Oil	1-4 g/day, as single dose or divided twice daily	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. [10]

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; LDL-C= low density lipoprotein cholesterol; 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; INR= international normalized ratio; IR= immediate release; mg= milligram(s); ULN= upper limit of normal; VA-HIT= Veterans Affairs High-Density Lipoprotein Intervention Trial

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