

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

Frequently Asked Questions

#	Question/Answer	CPG Page with Additional Information
1	<p>Question (Q): Why use the VA/DoD clinical practice guideline (CPG) versus the American College of Cardiology and American Heart Association (ACC/AHA) or National Lipids Association (NLA) guidelines?</p> <p>Answer (A):</p> <ol style="list-style-type: none"> 1. No conflict of interest (COI) among the content experts 2. More recent assessment of the evidence 3. Allows for more tailored shared decision making in the intermediate risk populations where the evidence is less certain, and the risk-benefit trade-off less clear 	<p>Page 5: About This Clinical Practice Guideline</p> <p>Page 7: Conflict of Interest</p> <p>Page 41: Evidence Review Methodology</p>
2	<p>Q: Which risk calculator should I use?</p> <p>A: The risk calculators are for primary prevention only in patients without a history of atherosclerotic cardiovascular disease (ASCVD) or acute coronary syndrome (ACS). They are all valid for predicting risk, but they are all limited in their precision of risk prediction. Several are available:</p> <ol style="list-style-type: none"> a. Framingham: (http://cvdrisk.nhlbi.nih.gov/) b. Pooled Risk: (http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx) c. Mayo Statin Decision Aid: (http://statindecisionaid.mayoclinic.org/index.php/site/index, has the ability to print out a patient friendly “decision aid” document.) 	<p>Pages 19-21: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention Recommendation 4</p>
3	<p>Q: Existing VA lipid performance measures accept either a low density lipoprotein cholesterol (LDL-C) < 100mg/dL or “on a moderate dose statin” in patients with ASCVD:</p> <ol style="list-style-type: none"> a. The first criteria still focuses on labs, not risk. b. What about patients with CAD who have an LDL-C < 100mg/dL WITHOUT a statin? <p>A: New performance measures are being created that will be reconciled with this CPG. Also we do not identify any LDL-C threshold for statin treatment in patients with known ASCVD. Patients with known ASCVD should be offered treatment with a moderate dose statin, regardless of their lipid levels. In the Heart Protection Study (simvastatin 40 mg) patients with pretreatment LDL-C <100 mg/dL experienced similar proportional reductions in the risk of first major vascular event.</p>	<p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendation 14</p>

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4	<p>Q: Why a high dose statin when the patient is already on a moderate dose statin? (What is the incremental benefit of making that change?)</p> <p>A: In secondary prevention, the evidence supports a reduction in all-cause mortality, nonfatal myocardial infraction (MI), coronary heart disease (CHD) death, fatal and nonfatal stroke with moderate dose statins (reducing LDL-C by 30-<50%). In 5 studies comparing high versus moderate dose statins, improvement in the primary outcome of major cardiovascular events was observed in only two trials, and the differences were limited to a reduction in <u>nonfatal events</u>.</p> <p>Since adverse events such as muscle complaints (e.g., myalgias) occur more commonly with higher dose statins, we advise prescribers that since the majority of benefit of statins is obtained with a moderate dose, we do NOT advise high dose statins unless the patient has had an ACS, or multiple uncontrolled risk factors, or recurrent ASCVD events despite moderate doses.</p>	<p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendation 18</p> <p>Pages 88-95: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Recommendation 18</p>
5	<p>Q: In what situations should the use of a high-dose statin be considered?</p> <p>A: High dose statin dose may be considered in patients with ACS, or multiple uncontrolled risk factors, or recurrent ASCVD events. The recommendation is based upon a very low level of evidence from a meta-analysis by Mills et al. (2011), which included 10 trials (n=41,778) comparing high versus low-to-moderate dose statins for secondary prevention. There was no significant effect on overall mortality between high and lower statin doses (relative risk [RR] 0.92, 95% confidence interval [CI] 0.83-1.03, p=0.14) and no statistically significant difference in cardiovascular disease (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). A subgroup analysis of three trials with ACS patients found a significant reduction in all-cause mortality and CVD death associated with higher statin doses.</p>	<p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendations 14-19</p> <p>Pages 88-95: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Recommendations 14-19</p>

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6	<p>Q: If I used a high-dose statin in ACS, is there evidence about how long high- doses should be continued? Should I lower the dose to a moderate dose statin after a given period of time?</p> <p>A: No. None of the studies were designed to assess the impact of reducing statin doses (or back titration) on CVD events. However, all of the studies allowed back titration if there was an adverse drug reaction (ADR). So, It is not clear how long high dose statins need to be maintained after ACS. Trials comparing a high to moderate dose statin were conducted over a period of up to 24 months. If your patient is experiencing adverse events related to their high dose statin, consider reducing to a moderate dose.</p> <p>We do not have high quality evidence to support high dose statins in any other patients or for any longer periods of time. The majority of benefit is derived from being on a moderate dose statin. Higher doses may increase the risk of adverse events without appreciably decreasing the risk of CVD.</p>	<p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendations 14-19</p> <p>Pages 88-95: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Recommendation 18</p>
7	<p>Q: What is the evidence for combination therapy with statins (e.g., niacin, fibrates, bile acid sequestrants or ezetimibe) for reducing CVD risk beyond what is achieved with statins?</p> <p>A: Niacin: Two studies (Athero-thrombosis Intervention in Metabolic Syndrome with Low HDL/High TG: Impact on Global Health Outcomes [AIM-HIGH] and Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]) showed no additional benefit and increased risk of harm by adding niacin to statin therapy.</p> <p>Fibrates: In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, over 5000 diabetic patients (36% with known ASCVD) were given fenofibrate or placebo in addition to simvastatin. There was no difference between groups in the primary outcome of first occurrence of nonfatal MI or stroke or death from CVD causes.</p> <p>Bile acid sequestrants: There is no evidence to support addition of these agents to statins.</p> <p>Ezetimibe: There is no evidence to support addition of these agents to statins. However, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study is ongoing and is expected to answer this question.</p> <p>Stated simply: If patients want to lower risk of CVD, they should be offered a moderate dose statin. Adding other medications is not proven to lower risk of CVD and will likely increase risk of ADRs.</p>	<p>Pages 25-26: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention</p> <p>Pages 32-33: Management of Pharmacotherapy for Secondary Prevention</p> <p>Pages 86-87, 96-98: Appendix D Pharmacologic Therapy: Additional Supporting Evidence</p>

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8	<p>Q: Should I treat low, high density lipoprotein cholesterol (HDL-C) with medications to reduce CVD risk?</p> <p>A: No. There is no evidence to support additional CVD risk reduction by initiation of drug treatment targeted at increasing low HDL-C in patients receiving statins. Clinical trials of fibrates or niacin added to statin based therapy have not shown an incremental benefit despite an effect on HDL-C.</p> <p>However, in male Veterans with CHD, low HDL-C and moderately elevated LDL-C, gemfibrozil reduced nonfatal MI and cardiac death versus placebo in the VA-HIT trial. These patients were not receiving statin therapy, and since first line therapy for reducing CVD risk is statins, this strategy should only be employed among patients who cannot take statins.</p>	<p>Pages 25-26: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention</p> <p>Pages 95-98: Appendix D Pharmacologic Therapy: Additional Supporting Evidence</p>
9	<p>Q: Should I treat high triglycerides (TGs) with medications to reduce CVD risk?</p> <p>A: No. There is no evidence to support reducing CVD risk by initiation of drug treatment targeted at reducing elevated TGs either as monotherapy or when added to statins. Clinical trials of fibrates or niacin added to statin based therapy have not shown an incremental benefit despite an effect on TGs. Secondary causes of hypertriglyceridemia should be investigated and managed accordingly. Positive lifestyle changes are recommended as first-line.</p>	<p>Pages 4-5: Background</p> <p>Page 38-39: Non-Pharmacologic Approaches Recommendations 23 and 24</p>
10	<p>Q: Is there any proven reduction to treating TGs with drugs to prevent pancreatitis?</p> <p>A: Evidence is lacking to support reducing TGs with drug treatment in patients with severely elevated TGs (i.e., >500 mg/dL) who are asymptomatic and have not experienced pancreatitis. In fact there is evidence to suggest that clinical manifestations of pancreatitis are not likely to appear in patients with a history of pancreatitis with TGs <2000 mg/dL. Attempts to reduce TGs with diet, attention to and intensified management of secondary causes (e.g., diabetes, hypothyroidism) and positive lifestyle changes are encouraged. It should be noted that fibrates may INCREASE the risk of pancreatitis (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] study, number needed to treat to harm [NNT_H] ~ 200, absolute risk increase [ARI] = ~ 0.5%)</p>	<p>Pages 4-5: Background</p>
11	<p>Q: How often (if ever) should I check lipids if patients are on effective treatment?</p> <p>A: In patients receiving moderate or high dose statins, lipids do not need to be checked during treatment. However, periodic monitoring can be considered at the discretion of the provider if that might indicate continued adherence to statin therapy. In general we recommend assessing adherence through patient-provider communication, but when there is doubt, lipid measurement is reasonable. In many patients, non-adherence is an indication that they are having medication side effects or simply have not understood an explanation of the benefits of statins.</p>	<p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention</p>

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12	<p>Q: What change or percent reduction in LDL-C is needed to ensure my patient is receiving the appropriate statin dose (e.g., moderate dose) to reduce their CVD risk?</p> <p>A: No specific percent reduction is needed. Moderate dose statins are recommended first-line in patients in whom treatment is deemed necessary for primary and secondary prevention. In these trials it has been noticed that moderate dose statins usually reduce LDL-C approximately 30 to <50% from baseline. Evidence supports a reduction in all-cause mortality, nonfatal MI, CHD death, fatal and nonfatal stroke with moderate dose statins.</p> <p>It should be noted that there are no trials that prove that targeting percent of LDL-C reduction is beneficial. Indeed, this fact is the most important change in the paradigm of pharmacologic treatment. We advise avoiding any discussion of “potency” or “percent of LDL-C reduction” until studies prove efficacy using that approach. We advise following what large trials have shown: a fixed dose (we refer to “moderate dose statin”) of a statin reduces CVD outcomes by about 25-30% over 5 years of treatment.</p>	<p>Pages 22-23: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention</p> <p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention</p> <p>Pages 88-95: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins</p>
13	<p>Q: What is the absolute risk reduction (ARR) and the number of patients needed to treat (NNT) with a moderate dose statin in primary prevention versus placebo?</p> <p>A: The best study that informs us about primary prevention is Air Force Coronary Primary Prevention Study/Texas Coronary Primary Prevention Study (AFCAPS/TexCAPS) which shows about a 2% ARR for acute major coronary events over 5 years of treatment and a NNT of 50. For Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), the ARR was 1.2% for major cardiovascular events and NNT was 82 over 2 years, however the population tested was restricted which limits generalizability of the results. Optimally, each patient contemplating statin treatment should use a risk calculator to assess 10-year risk of CVD. Then a discussion of harms and benefits can help decide if they wish to engage in statin therapy.</p>	<p>Pages 88-89: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins Table D-2</p>
14	<p>Q: What is the risk of myopathy (in addition to actual rhabdomyolysis) in taking a statin?</p> <p>A: This is not easy to determine for community dwelling patients because existing randomized controlled trials (RCTs) generally have a placebo “run in” period that selects patients who will comply with taking pills. These patients may not always be representative of community dwelling patients. The risk of rhabdomyolysis is very low in this selected group of patients (1/10,000 for moderate dose and 4/10,000 for high dose). However, in the general unselected population (our patients) cessation of statins due to myalgias is approximately 10-20%.</p>	<p>Pages 22-23: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention Statins</p> <p>Page 87: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins</p> <p>Page 93: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins Table D-4</p>

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15	<p>Q: In which, if any, patients must I monitor for hepatotoxicity (e.g., liver function tests [LFTs])?</p> <p>A: Because risk of liver harm while taking a statin is extremely rare, In February 2012 the U.S. Food and Drug Administration (FDA) removed the recommendation for periodic monitoring of LFTs in patients receiving statins. Instead, baseline LFT testing is recommended and as clinically indicated thereafter. However, the incidence of elevated LFTs was significantly increased in several studies of high dose statins (e.g., atorvastatin) and therefore it is recommended that patients receiving high dose statins have their LFTs monitored 4-12 weeks after initiation of high statin doses and as clinically indicated thereafter.</p> <p>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 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 versus adjusting or discontinuing the medication should be addressed with the patient’s treating provider. Potential signs of serious liver injury that should be discussed with a treating physician include: jaundice (yellow skin or eyes), fatigue, pain in the right upper abdomen, swelling of the abdomen with fluid, increased bleeding or bruising.</p> <p>While there is concern about the safety of statins in prevalent or incident liver disease, there is no evidence for or against the use of statins in this population. RCTs generally excluded patients with liver disease but retrospective observation suggests that patients with existing transaminase elevation can take statins with reasonable safety if properly monitored. In fact, for some conditions with elevated liver enzymes (e.g., fatty liver) statins may be recommended as standard therapy. Clinicians and patients should engage in a discussion about whether or not to take a statin based on a clear appreciation of our lack of knowledge in this area.</p>	<p>Pages 22-23: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention Statins</p> <p>Page 27: Management of Pharmacotherapy for Secondary Prevention Recommendations 12 and 13</p> <p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendation 19</p> <p>Page 87: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins Recommendations 12 and 13</p> <p>Page 94: Appendix D Pharmacologic Therapy: Additional Supporting Evidence Statins Recommendation 19 Table D-5</p>

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16	<p>Q: How do I respond to patients who are leery of side effects from statin medications?</p> <p>A: Using shared decision making, explain to patients that using a statin (as with ALL medications) is a personal choice. We can help them decide by using a risk calculator that shows their estimated risk and estimated benefit and then allow them to decide about treatment.</p> <p>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 Cholesterol Treatment Trialists' [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. There is also a higher risk for new onset diabetes in patients receiving high dose versus moderate dose statins as demonstrated in the meta-analysis by Preiss et al. (2011).</p>	<p>Pages 24-25: Management of Pharmacotherapy for Secondary Prevention Recommendation 10</p> <p>Pages 29-32: Management of Pharmacotherapy for Secondary Prevention Recommendations 14- 19</p> <p>Pages 93-94: Appendix D Additional Supporting Evidence Recommendations 14-19 Tables D-4 and D-5</p>
17	<p>Q: Can I recommend non-fasting lipids?</p> <p>A: Yes. In most patients, fasting will NOT impact therapeutic recommendations. In those with very high TGs (>500 mg/dL) fasting testing can be arranged before recommending lifestyle or pharmacologic options.</p> <p>In the event that the patient is unable to present for fasting lab work, a non-fasting lipid profile will provide measures of total cholesterol and HDL-C that can be used for risk calculation. A non-fasting lipid profile provides measures of total cholesterol and HDL-C that differ little from measures after a 9 to 12 hour fast. Compared with fasting measures, non-fasting LDL-C may be 10% lower and TGs as much as 20% higher. Risk calculators, such as the pooled risk and Framingham calculators are based only on measures of total cholesterol and HDL-C.</p>	<p>Pages 18-19: Assessment of Cardiovascular Risk and Pharmacotherapy for Primary Prevention Recommendation 1</p>
18	<p>Q: Is there any evidence to support coronary artery calcium (CAC), and high-sensitivity C-reactive protein (hsCRP) testing?</p> <p>A: No study has shown that a practice of incorporating such testing into practice improves outcomes. There may be limited usefulness of these tests in scenarios where a patient is classified as intermediate-risk and there is uncertainty about the benefit of treatment.</p>	<p>Page 21: Assessment for Cardiovascular Risk and Pharmacotherapy for Primary Prevention Recommendations 5-6</p>