### Question 1: 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?

**Answer:**
- No conflict of interest (COI) among the content experts.
- More efficient guidance by limiting recommendations to the best evidence.

**CPG Reference Pages:**
- Page 6: About This Clinical Practice Guideline
- Page 8: Reconciling 2014 CPG Recommendations
- Page 10: Conflict of Interest
- Page 59: Evidence Review Methodology

### Question 2: Which risk calculator should I use?

**Answer:**
Risk calculators stratify risk for primary prevention outside of certain high-risk conditions. Risk is high enough to warrant medication independent of risk calculation with diabetes or LDL cholesterol of 190 mg/dl or greater.

- **Pooled Cohort Risk calculator:** [http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx](http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx)
- **Framingham Risk Score Calculator:** [https://www.thecalculator.co/health/Framingham-Risk-Score-Calculator-for-Coronary-Heart-Disease-745.html](https://www.thecalculator.co/health/Framingham-Risk-Score-Calculator-for-Coronary-Heart-Disease-745.html)

**CPG Reference Pages:**
- Pages 21-22: Recommendation 3
- Page 78: Appendix B, Cardiovascular Disease Risk Calculators

### Question 3: In what situations should the use of a high-dose statin be considered?

**Answer:**
High-dose statins should be considered in secondary prevention patients at higher risk.

In secondary prevention, high-dose statins reduce non-fatal cardiac events over moderate-dose statin without reducing mortality. These studies primarily included patients with:

- MI or ACS in past 12 months.
- Recurrent ACS, MI, or CVA.
- Established CVD and with additional risk factors (e.g., currently smoking, DM, PAD, or CABG/PCI).

*High dose statins are not recommended, as they show no improvement over moderate dose statins.*

**CPG Reference Pages:**
- Page 17-18: Recommendations 11-13
- Pages 33-35: Recommendation 12
Question 4: What is the evidence for combination therapy with statins for reducing CVD risk beyond what is achieved with statins?

Answer:
In primary prevention, no treatments added to statins have been shown to reduce cardiovascular risk over moderate dose statins alone. In secondary prevention, several medications can reduce cardiovascular events when added to statins. These medications generally do not affect mortality.
- Ezetimibe: When added to both moderate and high-dose statins in secondary prevention, ezetimibe reduces non-fatal cardiovascular events.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce risk of non-fatal cardiovascular events when added to statins more than statins alone.
- Icosapent ethyl, a purified omega-3 fatty acid, was shown to reduce both cardiovascular mortality and events over statins alone in secondary prevention. The single trial of icosapent ethyl is controversial.

CPG Reference Pages:
Pages 17-18 & Pages 30-38
Recommendations 9, 12, 13, & 14
Page 36: Discussion
Page 41: Summary
Pages 56-57: Comparison of Medical Therapies in Primary and Secondary Prevention
Pages 60-61: Key Questions 4, 6, 7

Question 5: Should I treat high triglycerides (TGs) with medications to reduce CVD risk?

Answer:
Possibly for secondary prevention. Icosapent ethyl, a purified omega-3 fatty acid, appears to reduce cardiovascular events and cardiovascular mortality over placebo. The single trial of icosapent ethyl is controversial.

CPG Reference Pages:
Page 18 & Pages 43-44: Recommendations 18-19

Question 6: Is there any proven reduction to treating TGs with drugs to prevent pancreatitis?

Answer:
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, clinical manifestations of pancreatitis are not likely to appear in patients with a history of pancreatitis as long as 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. There is some evidence that fibrates may INCREASE the risk of pancreatitis (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] study, number needed to treat to harm [NNTH] ~ 200, absolute risk increase [ARI] = ~ 0.5%)
**Question 7: How often (if ever) should I check lipids if patients are on effective treatment?**

**Answer:**
In patients receiving statins, lipids do not need to be monitored during treatment. Management by target dose is recommended based on evidence, while cholesterol targets are unproven.

However, baseline LDL assessment would be reasonable in higher risk patients before considering stepped intensification by maximizing the statin dose, adding ezetimibe, or adding a PCSK9i.

The long-term and potentially deleterious effects of very low LDL levels are unknown. Additionally, periodic monitoring can be considered to monitor 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.

**CPG Reference Pages:**
Pages 47-49: Monitoring and Adherence. Recommendation 22

**Question 8: What change or percent reduction in LDL-C is needed to ensure my patient is receiving the appropriate dose of statin or other lipid-lowering medication to reduce their CVD risk?**

**Answer:**
Based on the available evidence, we do not recommend a target or specific change in LDL. A graded association between lower LDL and improved CV risk exists. However, there is no prospective evidence from randomized controlled trials that treatment to a target LDL improves critical CV outcomes. We recommend a treat to target medication intensity based on individualized CV risk assessments.

**CPG Reference Pages:**
Pages 47-49: Monitoring and Adherence

**Question 9: 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?**

**Answer:**
Since relative risk reductions are relatively constant at 20-25%, absolute risk reductions (ARR) and the number needed to treat (NNT) primarily depend on risk. Based on available trial data, the pooled absolute risk reduction and number needed to treat are as follows:

- All-cause mortality ARR 0.40%, NNT 250 over 1 to 6 years
- Cardiovascular mortality ARR 0.43%, NNT 233 over 2 to 6 years
- Fatal or non-fatal MI ARR 0.81%, NNT 123 over 2 to 6 years.

**CPG Reference Pages:**
**Question 10: What is the risk of myopathy (in addition to actual rhabdomyolysis) in taking a statin?**

**Answer:**
This is not easy to determine for the general population 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. Increase in risk of myalgia with moderate or high dose statins has not been shown in pooled data from randomized controlled trials. Data showing elevated risk of rhabdomyolysis is limited to simvastatin at 80mg daily, which is no longer recommended by the FDA. However, observational data of the general population shows cessation of statins due to myalgias occurs in approximately 10-20% of patients prescribed the medications.

**CPG Reference Pages:**

**Question 11: How do I respond to patients who are leery of side effects from statin medications?**

**Answer:**
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.

While statins are generally safe for most patients, there is concern regarding use of high-dose statin regimens due to the potential for adverse events when compared to moderate intensity statin regimens. High-dose statins are 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 statins.

**CPG Reference Pages:**
Pages 29-31: Pharmacotherapy, Supplements, Nutraceuticals for Primary Prevention. Recommendations 6-8

**Question 12: Is there any evidence to support coronary artery calcium (CAC), and high-sensitivity C-reactive protein (hsCRP) testing?**

**Answer:**
No study has shown that a practice of incorporating such testing into practice improves outcomes. There is limited usefulness of these tests in scenarios where a patient is classified as intermediate-risk and there is uncertainty about the benefit of treatment.

**CPG Reference Pages:**
Pages 24-26: Screening and Assessment of Cardiovascular Risk. Recommendations 4-5
Question 13: How should I think about intensifying treatment in secondary prevention?

Answer:

In secondary prevention of cardiovascular disease, we recommend moderate-dose statins as the baseline therapy due to unmatched reduction of cardiovascular mortality.

Therapy should be intensified in a willing patient who is at higher cardiovascular risk due to:

- MI or ACS in past 12 months
- Recurrent ACS, MI, or CVA
- Established CVD with additional risk factors - currently smoking, DM, PAD, or CABG/PCI

In these patients, three intensification methods lead to similar reduction in non-fatal cardiovascular events. We recommend two initially due to low cost and established safety profiles:

1. Increase statin to high dose
2. Add ezetimibe to either a moderate-dose or high-dose statin

After these actions, consider adding a PCSK9 inhibitor to the high-dose statin and ezetimibe because of evidence of increased benefit.

In secondary prevention patients with elevated triglycerides, icosapent ethyl, a purified omega-3 fatty acid, can reduce both cardiovascular mortality and events over statins alone in secondary prevention based on a single trial. Our recommendation for this medication is less certain since this study’s findings are controversial.

CPG Reference Pages: