1. **Is there a specific HDL guideline for women vs. men?**
   a. Our review did not find enough evidence to support a “treat to target” strategy for any lipid moiety. The failure of niacin and cholesteryl ester transfer protein (CETP) inhibitors to improve outcomes despite raising HDL cholesterol levels suggests that HDL targets are not effective. Hence, we do not recommend treating to a target HDL level, regardless of sex.

2. **Is there a specific LDL recommendation for the general population?**
   a. Although there is an association between lower LDL and diminished cardiovascular risk, our review did not find properly designed and conducted prospective evidence substantiating a “treat to target LDL” strategy. A “treat to target dose strategy according to risk level” is validated by the available evidence and recommended in this clinical practice guideline.

3. **For risk assessment, is the ratio of HDL and TG being used?**
   a. The ratio of HDL to triglyceride is not a risk variate utilized in the Pooled Cohort Equation, Framingham risk calculator, or any of the other validated risk prediction models captured in our evidence review. Although there might be a credible association between the HDL to triglyceride ratio and cardiovascular risk, clinical prediction models remain the most valid tools for risk assessment to inform treatment decision-making.

4. **Is there a point at which LDL is too low to treat, despite risk factors or indications for statin therapy?**
   a. Cholesterol plays various critical biological roles, such as constituting cellular membranes and myelin sheath. Hence, a “harm threshold” at excessively low LDL levels is biologically plausible. Although we found no evidence supporting harm arising from very low LDL levels, irrespective of threshold, this area is under researched. Epidemiological data from Hmong tribes in Southeast Asia and China do quite well with very low LDL levels, however the levels are a function of Hmong tribe diet and genetics rather than drug therapy. All PCSK9 trials had back titration steps in their protocols if LDL was <40. Similarly, statin intensification trials had similar back titration steps. At present, the lower limit for a ‘safe’ LDL is simply unknown.

5. **Are patients counseled on avoidance of seed oils to improve ratio of Omega3?**
   a. The ratio of omega 3 fatty acids is not a patient important outcome and therefore was not included in our evidence search algorithm. The composition of our work group included registered dieticians. According to their expert opinion, the answer is no. Avoiding seeds and seed oils would not improve the ratio of omega 3 fat in the diet. Fatty fish are the best source of omega 3 fats in the diet but are difficult to obtain in adequate amounts. Seeds and seed oils contain monounsaturated,
polyunsaturated and small amounts of omega 3 fats. Flax seed and chia seeds are the best plant sources of omega 3 fats. Walnuts, soy foods, oil, pumpkin seeds, and canola (rapeseed) oil are additional sources of Omega-3 fats.

6. Is statin treatment independent of age if LDL greater than 190 mg/dl?
   a. A paucity of data is available to inform the treatment of dyslipidemia in younger and older populations across all indications. Those below 40 and older than 75 are significantly underrepresented in available prospective trials. Furthermore, observational studies of patients with genetic hypercholesterolemia suggest CV risk is low in patients below the age of 40. Hence, treatment in these age groups regardless of indication should be directed by shared decision-making with the patient.

7. Is there a point at which LDL is so low that we need to decrease statin intensity?
   a. See #4. As noted in response #4, the lower limit for a ‘safe LDL’ is unknown. Since PCSK9 trials used a back-titration step for LDL < 40 many clinicians will decrease intensity of therapy using shared decision making if LDL is persistently <40

8. Will there be a change to checking lipids less frequently at the VA? We were always told to check lipids once a year.
   a. Which Healthcare Effectiveness Data and Information Set (HEDIS) measures to follow and clinical reminders (CRs) are determined at the national level in the Veterans Healthcare Administration (VHA), however CRs are currently subject to local modification. This clinical practice guideline does depart from the annual lipid monitoring orthodoxy. Based on the available evidence, we suggest against checking lipids more frequently than every 10 years for screening. Furthermore, lipid testing is not recommended in patients treated with a statin for primary prevention.

9. Is there a point where HDL elevation is considered negative?
   a. The scope of our evidence review did not include this question. That said, we found no circumstantial evidence suggesting an association between elevated HDL and harm.

10. What if a patient is on moderate statin dose for primary prevention (adherence confirmed) and the LDL remains "suboptimal", should we intensify?
    a. No. The patient is on the correct target dose. See #2.

11. Are the EPRP measures/clinical reminders going to reflect the new testing and guidelines?
    a. See #8. EPRP measures are generally drawn from HEDIS measures. The HEDIS measures for lipids are 1) Men or women with DM or CAD on at least a moderate dose statin 2) Medication possession ratio (MPR) of 80% for prescribed statin. Our CPG recommendations comport with these measures. Updates to the CRs would be determined by the National Clinical Reminders work group and any local modifications.

12. If a patient is statin intolerant, would ezetimibe be at least tried in these patients?
    a. Our evidence review found no randomized control trials assessing the efficacy of ezetimibe as monotherapy in patients without a history of cardiovascular disease.
Studies of ezetimibe added to statin therapy or as a combination treatment for primary prevention exist, however surrogates such as LDL were used instead of vascular mortality or other patient centered outcomes (e.g. MI, Stroke). Consequently, insufficient evidence exists to support ezetimibe monotherapy for primary prevention and its consideration in patients intolerant to statins should be based on shared decision-making with the patient. Robust evidence exists supporting use of ezetimibe added to statins for secondary prevention to improve patient centered outcomes, however evidence evaluating ezetimibe monotherapy in this population is lacking. Consequently, using ezetimibe alone in patients with a history of CVD but who are intolerant to statins should be considered in the treatment armamentarium, but predicated on shared decision-making considering the evidence gap.

13. if the LDL is 50 do you still recommend a statin?
   a. Almost any dose of statin would make the LDL <40 in this circumstance and long-term safety of very low LDLS is unknown. See #4. That said, the Heart Protection Study (HPS), which looked at moderate dose simvastatin 40mg vs placebo in secondary prevention (N=40,000 pts; 8,000 with DM), noted the same improvements in CV events and mortality for the decile of patients with a LDL <100 and those patients with higher baseline LDLS. This data reinforces the concept of treating to a target dose, no LDL level.

14. Is there ever a role for high intensity statin therapy? If so, when?
   a. Yes, high intensity statins should be considered in some risk groups. Evidence shows incremental benefit with high-dose statin compared to moderate dose statin in patients with a history of CVD at “higher risk” as determined by the presence of certain risk factors (i.e. recurrent or recent event, diabetes, smoking, peripheral arterial disease, CABG/PCI). However, benefit is balanced by an increase in the risk of statin associated adverse effects. Additionally, benefit in critical outcomes such as all-cause and vascular mortality was not seen in trials of high-dose statin therapy. Rather, efficacy was relegated to outcomes frequently seen as important but not critical such as nonfatal events. Clinical equipoise stemming from incremental harm and important but not critical benefit punctuates the importance of shared decision-making when considering intensification.

15. When would you consider PCSK9 for secondary prevention? Event after patient on high intensity statin + ezetimibe?
   a. Patients with a history of CVD at “higher risk” as determined by the presence of certain risk factors (i.e. recurrent or recent event, diabetes, smoking, peripheral arterial disease, CABG/PCI) already on maximally tolerated therapy with a statin and ezetimibe can be considered for treatment with a PCSK9i. The trigger for this treatment doesn’t have to be a recurrent event despite high-dose statin and ezetimibe. Instead, we recommend shared decision-making based on perceived risk and patient interest in a weekly injection therapy. Clinical Pearl: Physiologically statins upregulate LDL receptors which means there will be more PCSK9 receptors around for PSCK9 inhibitors to work on. So, any tolerated dose of statin will make PCSK9s work better. Note all studies of PCSK9s were in combination with a maximally tolerated dose of statin and not as PCSK9 monotherapy.
16. Why not fibrates with Statins?
   a. The quality of the available evidence assessing the potential benefits of adding fibrates to statin therapy is low. Despite reductions in surrogate outcomes such as triglyceride levels, fibrates do not reduce patient centered outcomes such as all-cause mortality, CHD mortality, or cardiovascular events in either primary or secondary prevention. Furthermore, some evidence suggests the potential for harm associated with fibrate therapy including transaminase elevation, renal injury and increased CV events in women on the combination formulation for secondary prevention (ACCORD study). In 2016 the FDA removed the approval of statins in combination with fibrates (reference 93 of the CPG). Given the lack of benefit in both primary and secondary prevention, the Work Group determined the potential for harm outweighed potential benefits and does not recommend fibrates with statins.

17. Is the lipid panel a reliable/useful tool to assess adherence?
   a. Our review did not address this question. While determining compliance might be aided by lipid testing in some circumstances, other strategies such as refill history queries or asking the patient directly do not require additional resource utilization or cost and therefore might be equally reliable or even superior means of assessing compliance. Furthermore, substantial test-to-test variation in lipid levels is viewed by some as a reason to discourage lipid testing for determining adherence.

18. Any evidence for TLC diet vs. Mediterranean?
   a. Our evidence search found no comparative effectiveness evidence for the Mediterranean and TLC diets.

19. Do you ever check Lp(a) levels?
   a. Our review found very low-quality evidence assessing the effect of nontraditional biomarkers on predictive risk. Furthermore, biomarkers such as Lp(a) have not been shown to improve calibration or patient outcomes when added to established clinical prediction models such as the Pooled Cohort Equation or Framingham Risk Score. As a result, we suggest against the routine use of Lp(a) to refine CV risk assessments.

20. Is there any role for statins in Palliative or Hospice setting? Providers are hesitant to discontinue statins in these settings, particularly if used for secondary prevention.
   a. Patients with limited life expectancy have been routinely excluded from dyslipidemia clinical trials and our review found no evidence addressing the role of continuing statin therapy in this population of patients. Given the gap in evidence, the decision to continue or stop statin therapy in patients with limited life expectancy should be based on shared decision-making, balancing the harms of drug-drug interactions and pill burden vs living long enough to achieve tangible benefit.

21. When would you consider adding icosapent ethyl/re-checking lipids if we aren't to routinely recheck lipids?
22. Is there any consideration given to Trig/HDL ratio?
   a. See #3.

23. If we have a patient indicated for moderate-intensity statin per the info in this presentation, but currently tolerating high-intensity statin well, would you recommend de-escalating therapy to moderate-intensity or continuing high-intensity? Any difference in your recommendation for primary vs. secondary prevention?
   a. In primary and secondary prevention patients tolerating high-dose statin therapy for whom a moderate dose is indicated, both de-escalation and maintenance at the current dose are reasonable and should be determined by shared decision-making. It is noteworthy that statin tolerance at any given point in the treatment course is not necessarily fixed and subject to variations in drug metabolism directed by changes in age, drug-drug interactions, and co-morbidities.

24. Is there a recommendation for baseline screening? If no other health issues, should a person have lipids done before age 40?
   a. We suggest screening starting at age 40 or when the patient develops a new cardiovascular risk factor. Based on the limited observational evidence that cardiovascular events are rare prior to age 40 even in familial hypercholesterolemia, we do not see a need for universal screening in young people. For a patient who is very concerned and is willing to start a life-long medication, early screening would be reasonable.

25. Are there statin discontinuation recommendations for secondary prevention in geriatric patients 75 years + to reduce pill burden/polypharmacy?
   a. See #6. There are ongoing studies in patients 75+.

26. Cardiologists in the community have recommended/prescribed PCSK9i’s based on LDL level.
   a. See #2.