Lipid Lowering: What? When?

This Heartbeat will update one from June 2017 (www.sjhg.org) about lipid lowering, presenting new and important information for you and your patients, along with a summary of the just-released cholesterol guidelines. We are firm believers that lipids are the “smoking gun” when it comes to heart attacks and strokes. This Heartbeat will help us with a plan of attack for lipid-lowering treatment based on what we know in 2018. Let’s take away the gun!

Lowering Already Low LDL: Is There Additional Benefit?

Yes. A large meta-analysis suggests further lowering of LDL-C levels in patients with already low LDL-C proved beneficial in terms of reduced risk for major adverse cardiovascular events (MACE) with no serious adverse effects (AEs). The Cholesterol Treatment Trialists Collaboration (CTTC) showed that in patients with baseline LDL-C levels of approximately 131.5 mg/dL, each 38.7 mg/dL lowering of LDL-C was associated with a 22 percent reduction in MACE.¹

However, any additional clinical benefit of further LDL-C lowering in patients who already have very low LDL-C levels is still unclear. Non-statin drugs are now available to further lower LDL-C levels and cardiovascular (CV) risk when given together with statins.

The goal of this meta-analysis of 29 cholesterol-lowering outcome clinical trials with statin and non-statin drugs was to examine the efficacy and safety of further reducing LDL-C levels in patient populations with baseline median LDL-C levels of 70 mg/dL or less.²

Data was analyzed for a subgroup of patients with mean baseline LDL-C levels 65.7 mg/dL from the CTTC meta-analysis and showed that further lowering of already low LDL-C proved beneficial in terms of reduced MACE with no serious AEs.

In 26 trials with statin therapy, the relative risk (RR) for MACE (coronary heart disease [CHD] death, myocardial infarction [MI], ischemic stroke or coronary revascularization) was 22 percent lower for every 38.7 mg/dL decrease in LDL-C (RR=0.78 [95 percent CI: 0.65, 0.94]).

A similar benefit emerged when the researchers analyzed data on more than 50,000 patients from three randomized trials of non-statin LDL-C-lowering therapies added to statins: FOURIER, which used the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor evolocumab³; IMPROVE-IT, which used ezetimibe⁴; and REVEAL, which used the cholesteryl
ester transfer protein (CETP) inhibitor anacetrapib. In these three trials, baseline LDL-C ranged from 63 mg/dL to 70 mg/dL. Non-statin therapy added to a statin lowered LDL-C by 11 mg/dL to 45 mg/dL, with a 21 percent relative risk reduction (RRR) for MACE per 38.7 mg/dL reduction in LDL-C (RR = 0.79 [95 percent CI: 0.70, 0.88]); P < 0.001.

These three studies, along with ODYSSEY Outcomes, which used the PCSK9 inhibitor alirocumab—not included in the study and felt to have minimal effect on reported results—have shown that achieving lower levels of LDL-C results in greater event reduction, regardless of agent. This has resulted in the LDL-C hypothesis replacing the previously favored statin hypotheses. The clinical benefit (22 percent reduction of MACE) for every 38.7 mg/dL reduction in LDL-C was the same with statins or any of the non-statin medications.

The authors concluded that there was a consistent reduction in MACE in high-CV-risk patients with median LDL-C levels of 63 mg/dL, with further LDL-C reduction to a median of 21 mg/dL. Accordingly, some have recommended < 50 mg/dL, but > 20 mg/dL for secondary prevention, which this study would support. What the levels should be for primary prevention was not considered.

Importantly, they said, further lowering of LDL-C was not associated with any increased risk for serious AEs, myalgias and/or myositis, elevation in aminotransferases, new-onset diabetes, hemorrhagic stroke or cancer.

Discussion: This study is extremely well done and is encouraging, but unfortunately did not establish new targets for LDL-C. The findings support bringing back targets (lower) and updating the American Heart Association/American College of Cardiology 2013 guidelines.

New 2018 AHA/ACC Cholesterol Treatment Guidelines

The numbers are back in the guidelines (LDL-C goals), and the emphasis is on “lower is better” with proven therapies. High cholesterol treatment is not one size fits all, and this guideline strongly establishes the importance of personalized care. The guidelines document advocates a “heart-healthy lifestyle across the life course” and provide new guidance on the use of PCSK9 inhibitors, namely evolocumab (Repatha, Amgen) and alirocumab (Praluent, Sanofi/Regeneron). The new document carries over much from the 2013 guidelines, especially the four major categories of patients with different management needs for whom statins may be considered:

1. Primary Prevention: No clinical atherosclerotic cardiovascular disease (ASCVD) or diabetes: There is a revamped approach to risk assessment in primary prevention, but it still starts with the same calculation of 10-year CAD risk estimate (Qx Calculate app on your phone). There’s much greater guidance now about how the patient and the clinician should approach the risk discussion that didn’t get as much attention in 2013.

The 10-year CAD risk score is an “educated guess” that for most patients in the broad, intermediate-risk range of 7.5 percent to less than 20 percent should be an opportunity for a more detailed discussion and shared decision-making. To help in the shared decision-making process, the guideline specifies a number of “risk-enhancing factors” that are not considered in the risk calculator and, if present, might push us to go ahead and prescribe a statin, if the patient is agreeable.
The risk enhancers include the following:

- LDL-C of >160 mg/dL, a C-reactive protein (high-sensitivity assay) > 2.0 mg/L, apolipoprotein B > 130 mg/dL, or elevated lipoprotein(a)
- Ankle-brachial index less than 0.9
- Comorbid conditions, such as metabolic syndrome; chronic kidney disease (CKD); chronic inflammatory disorders, such as rheumatoid arthritis, lupus or HIV; or premature menopause
- Family history of premature ASCVD
- Southern Asian ancestry
- Elevated lifetime ASCVD risk.

The guideline says for patients at borderline ASCVD risk, that is a 10-year risk of 5 percent to less than 7.5 percent, the presence of risk enhancers would favor moderate-intensity statin therapy with class IIb recommendation. The enhancers would favor statins with a class I recommendation for those at intermediate risk of 7.5 percent to less than 20 percent. For patients at high risk (score of >20 percent), high-intensity statins are favored (class 1).

If after that discussion, the doctor and patient are still uncertain, or if the patient really wants a little bit more confirmation, there are recommendations about using coronary artery calcium (CAC) screening “Tiebreaker.” CAC imaging would be an option primarily for patients at intermediate risk.

If the CAC score is 0 (about 50 percent of these people), a statin isn’t indicated.

Patients with a CAC score of at least 100 Agatston units (the 75th percentile adjusted for age and sex) will benefit from statin therapy. Not only do we think they’re at higher risk, but their calcium scores indicate that they’ve got a significant burden of atherosclerosis.

If the CAC score is in the indeterminate range of 1 to 99 Agatston units, the decision might be to initiate a statin or repeat the coronary calcium scan at least two years later checking for progression.

2. Diabetes without clinical ASCVD: The guideline recommends that all patients with diabetes aged 40 to 75 years with an LDL-C >70 mg/dL be taking a moderate-intensity statin and do not need a calculated 10-year ASCVD risk assessment. A high-intensity statin should be considered for such patients with multiple risk factors.
3. Secondary Prevention with ASCVD: The guideline recommends maximally tolerated statin therapy, and consideration of added ezetimibe for those who do not reduce LDL-C by at least 50 percent, or <70 mg/dL. On average, ezetimibe should result in an additional 20 percent drop in LDL-C. If LDL-C remains >70 mg/dL, then it would be reasonable to try a PCSK9 inhibitor.

4. Severe primary hypercholesterolemia, or familial hypercholesterolemia (FH): For patients who have an LDL-C >190 mg/dL, you don’t have to calculate their 10-year risk. Start maximally tolerated statin therapy for everybody. If they do not then show a 50 percent reduction in LDL-C and it remains >100 mg/dL, start ezetimibe first, and then consider PCSK9 inhibitors if their LDL-C is still >100 mg/dL.

Comments: Obviously, the greatest absolute magnitude of LDL-C reduction will be for those with higher baseline LDL-C levels. We feel that the best statin that gives the most reduction in LDL-C is rosuvastatin. It also increases HDL-C a little and lowers triglycerides. Many people are on atorvastatin because it was generic long before rosuvastatin and is on all hospital formularies.

The addition of PCSK9 inhibitors, proven in terms of efficacy but underused because of high prices and burdensome preauthorization requirements, should be considered on a case-by-case basis, via a two-way clinician-patient discussion of cost, CVD risk-reduction benefit and patient preferences. The most benefit of PCSK9 inhibition for secondary prevention would be seen in those who cannot tolerate statins, and we strongly recommend PCSK9 inhibitor treatment for those patients. We would also recommend for our high-risk primary prevention patients who can’t tolerate statins (FH).

We believe many at-risk patients are missed with the 10-year risk score. The lifetime risk is more accurate, but burdensome to calculate. We also believe statins are extremely beneficial with minimum long-term downside risk. We therefore use enhancers, and especially CAC scoring, as a tiebreaker in those with > 5 percent risk for primary prevention to convince patients to take statins. CAC scoring costs around $100 and should be covered by insurances soon.

**Take home for the clinician:** In our practice, among our secondary prevention high-risk patients, we will continue to prioritize high-intensity statins (rosuvastatin 40 mg) with ezetimibe 10 mg being the first add-on for further lowering of LDL-C because of much lower cost, along with lifestyle changes (diet and exercise). We consider PCSK9 inhibition in the minority, who still have LDL-C >70 mg/dL, but push hard if > 100 mg/dL (more value for the cost).

---

**Is there any benefit to anyone taking prescription omega-3 pills?**

*The answer is yes. Omega-3 pills prevent CV events in high-risk patients.* We know that despite statins, triglyceride (TG)-related risk is substantial. In a recent analysis to determine whether high TG, in the presence of statin-controlled LDL-C, influence the risk of CVD among patients with diabetes in real-world clinical practice, the authors concluded that despite statin controlled LDL-C levels, CV events were greater among patients with diabetes and high TG levels. They thought that treatments to optimize high TG levels could provide these very high-risk patients more protection from CV complications.

The omega-3 acid EPA (an omega-3 fatty acid contained in fish oil, in ethyl-ester form)—Vascepa (icosapent ethyl)—approved to treat very high triglyceride levels (>500 mg/dL) significantly lowered the risk for MACE on top of the risk reduction brought about...
by cholesterol lowering statins in patients at high CV risk. Findings from the REDUCE-IT trial were presented at the American Heart Association’s annual meeting earlier this month.11

Over 8,000 adults with LDL-C levels controlled on statins to between 41 and 100 mg/dL (median LDL-C: 75 mg/dL), triglyceride levels of 135–499 mg/dL (median baseline TG: 216 mg/dL), and either CVD or diabetes, plus an additional CV risk factor, were randomized to take Vascepa (4 g daily) or placebo. During roughly five years of follow-up, incidence of the primary endpoint—MACE or hospitalization for unstable angina—was 25 percent lower with Vascepa, to a high degree of statistical significance (p<0.001)—including a 31 percent lowered risk of MI, a 28 percent reduced risk of stroke and a 20 percent reduction in CV death. These findings are exciting, unexpected and provocative, especially in light of negative findings for over-the-counter (OTC) omega-3 supplements. The number needed to treat is 28 to prevent a key secondary endpoint of CV death, heart attack or CVA. This is in contrast to PCSK9 inhibitors or ezetimibe.

Comment: The debate about fish oil has generated a lot of flip-flopping in the scientific community, causing a lot of “superfishal” comments—not all fish oils are created equal. As a supplement, fish oils come in many forms and concentrations, with varying portions of EPA and DHA. This study evaluated the efficacy of highly purified ethyl ester of EPA. Prior studies used combinations of EPA and DHA at varying dosages, with mostly no or controversial outcomes benefits. It is reassuring that these results agree with the Japan EPA Lipid Intervention Study (JELIS), an open-label trial which reported that the risk of MACE was 19 percent lower with statin therapy plus 1.8 g of EPA daily than with statin therapy alone.12 The mechanism of benefit is not yet known, but Bhatt et al. postulate possible anti-inflammatory, anti-thrombotic and membrane stabilization (pleiotropic) effects.

Remember, prescription omega-3s or fenofibrates are the initial treatment of choice for very high TGs > 500mg/dL, but statins are the initial treatment for high TGs 200-499mg/dL because of their association with high-risk and statin’s proven benefit. Omega-3s are an add-on.

Take home for the clinician: Consider adding prescription omega-3s (Vascepa) to maximal statin therapy in patients with CVD or diabetes and one other risk factor with high TG (200-499 mg/dL).
References


2. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. [published online August 1, 2018]. JAMA Cardiol September 1 2018; 3: 823-828.


