

POEMs

Patient-Oriented Evidence That Matters

Overview of New ACC/AHA Lipid Guidelines

Clinical Question

What do cardiologists recommend for the management of hyperlipidemia?

Bottom Line

These updated guidelines, made without any input from primary care physicians who manage most patients with hyperlipidemia, are more complex than the 2013 guidelines and will likely lead to even more recommendations for statins, ezetimibe (Zetia), and PSK9 inhibitors. Rather than a “fire and forget” strategy involving a risk-based prescription of a moderate- or high-intensity statin, we are supposed to go back to monitoring low-density lipoprotein (LDL) levels and targeting a percentage reduction in LDL cholesterol—and in very high-risk patients targeting an LDL level of less than 70 mg per dL (1.81 mmol per L). (Level of Evidence = 1a–)

Synopsis

This is an update to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which were the first to base treatment decisions primarily on the 10-year risk of an atherosclerotic cardiovascular disease (ASCVD) event rather than on specific LDL targets. This guideline reemphasizes regularly measuring lipids and a return to an LDL target for assessing effectiveness and deciding when to prescribe one of the new and pricey PSK9 inhibitors (\$14,000 to \$15,000 per year at <http://www.goodrx.com>, December 1, 2018). Statins are divided into high intensity (atorvastatin [Lipitor], 40 to 80 mg; rosuvastatin [Crestor], 20 to 40 mg), moderate-intensity (atorvastatin,

10 to 20 mg; simvastatin [Zocor], 20 to 40 mg; rosuvastatin, 5 to 10 mg), and low-intensity (simvastatin, 10 mg) groups. For primary prevention in people 20 to 39 years of age, the guidelines recommend an assessment of the lifetime risk of ASCVD as a way to frighten patients into compliance with lifestyle changes. For people 20 to 39 years of age with LDL levels greater than 160 mg per dL (4.14 mmol per L) or a family history of premature ASCVD, a statin is recommended. For patients 40 years and older, a high-intensity statin is recommended for an LDL level greater than 190 mg per dL (4.92 mmol per L) and a moderate- or high-intensity statin (depending on other risk factors) for those with diabetes mellitus.

For all other patients, the Pooled Cohort Equations are used to place patients into one of four risk groups; the old guideline had only three. If the 10-year risk of an ASCVD event is less than 5%, no statin is recommended. If the 10-year risk is 5% to 7.5%, consider a moderate-intensity statin if there is also a “risk enhancer,” such as LDL level greater than 160 mg per dL, family history of premature ASCVD, chronic kidney disease, metabolic syndrome, South Asian ancestry, preeclampsia, HIV, rheumatoid arthritis, or psoriasis. For persons with a 7.5% to 20% risk, they recommend a moderate-intensity statin for most patients to target a 30% to 49% reduction in LDL cholesterol. Finally, if the risk is greater than 20%, a statin to target a 50% or more reduction in LDL cholesterol is recommended. For prevention in persons with known vascular disease, a new category of very high risk is described. It is defined as two or more of the following major events: acute coronary syndrome in the past 12 months, previous myocardial infarction, previous ischemic stroke, or symptomatic peripheral artery disease. A patient is also very high risk if he or she has one of those major ASCVD events and multiple high-risk conditions, such as familial hypercholesterolemia, age of at least 65 years, hypertension, diabetes, chronic kidney disease, tobacco use, heart failure, or LDL level greater than 100 mg per dL (2.59 mmol per L) despite maximal statin plus ezetimibe therapy. Patients in this category should be taking a high-intensity statin, adding ezetimibe if necessary, to target an LDL level of 70 mg per dL. If that is not achieved, a PSK9 inhibitor should be considered.

Regarding PSK9 inhibitors, it is notable that the guideline cautions that “the long-term safety (more than 3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.” Although the previous guideline was silent on the question of monitoring lipid levels, this one recommends regular monitoring (at least once per year) to verify

POEMs (patient-oriented evidence that matters) are provided by Essential Evidence Plus, a point-of-care clinical decision support system published by Wiley-Blackwell. For more information, see <http://www.essentialevidenceplus.com>. Copyright Wiley-Blackwell. Used with permission.

For definitions of levels of evidence used in POEMs, see http://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=oxford.

To subscribe to a free podcast of these and other POEMs that appear in *AFP*, search in iTunes for “POEM of the Week” or go to <http://goo.gl/3niWXb>.

This series is coordinated by Sumi Sexton, MD, Editor-in-Chief.

A collection of POEMs published in *AFP* is available at <https://www.aafp.org/afp/poems>.

adherence to the medication and to estimate the percentage reduction in LDL level. It is also worth noting which organizations were not among the 12 that endorsed this guideline: the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP). This is reminiscent of the recent, aggressive hypertension guidelines from the ACC/AHA that the AAFP and ACP also did not participate in or endorse.

Study design: Practice guideline

Funding source: Government

Setting: Various (guideline)

Reference: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018;S0735-1097(18)39034-X.

Mark H. Ebell, MD, MS

Professor
University of Georgia, Athens, Ga.

Aspirin, Eicosapentaenoic Acid, and Placebo Equally Effective in Preventing Colorectal Adenomas in High-Risk Patients

Clinical Question

Is aspirin or eicosapentaenoic acid (EPA) effective in preventing colorectal adenomas in patients with previous high-risk colorectal neoplasia?

Bottom Line

After 12 months, neither aspirin nor EPA, alone or in combination, are any better than placebo at preventing colorectal adenomas in patients with high-risk neoplasia. (Level of Evidence = 1b)

Synopsis

The Systematic Evaluation of Aspirin and Fish Oil (seAFOod) Polyp Prevention Trial was a factorial trial that randomized patients with high-risk colorectal neoplasms detected on screening colonoscopy. The included patients had three or more adenomas, one of which had to be 1 cm in diameter, or they had five or more smaller adenomas. The researchers randomized patients to receive EPA (1,000 mg twice daily; n = 179) plus placebo, aspirin (300 mg daily; n = 177) plus placebo, EPA plus aspirin (n = 177); or placebo plus placebo (n = 176). The researchers performed a follow-up colonoscopy 12 months after enrollment. Sixty-six patients (9%) did not have a follow-up colonoscopy and were excluded from the analysis. The rate of subsequent adenomas at follow-up was high (61% to 63%) and not statistically significantly different for each group. The rate of adverse events was low in all groups.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: Hull MA, Sprange K, Hepburn T, et al.; seAFOod Collaborative Group. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 x 2 factorial trial. *Lancet.* 2018;392(10164):2583-2594.

Henry C. Barry, MD, MS

Professor
Michigan State University, East Lansing, Mich.

Probiotic Ineffective for Treatment of Acute Gastroenteritis in Young Children

Clinical Question

Is the probiotic *Lactobacillus rhamnosus* GG safe and effective for the treatment of acute gastroenteritis in young children?

Bottom Line

Treatment with the probiotic *L. rhamnosus* GG does not result in faster symptomatic improvement or less moderate or severe diarrhea in young children with acute gastroenteritis. (Level of Evidence = 1b)

Synopsis

Although some studies have shown a benefit to probiotics for the treatment of acute gastroenteritis in children, they have generally been small, funded by industry, or had methodologic flaws. This study was a large, well-designed randomized trial that attempted to more definitively answer this question. Children three months to four years of age with at least three watery stools per day for less than seven days were identified in 10 university pediatric emergency departments. Children were excluded if they or their caregivers were potentially immunocompromised, or if the children were taking long-term corticosteroids, had been premature, or had chronic gastrointestinal disease. Children were also excluded if they had any biliary tract disease, hematochezia, or allergies to the study medication or to any antibiotics used to treat invasive *L. rhamnosus* infection. They were then randomized to receive the probiotic or placebo once daily for five days, stratified by presentation within or later than 48 hours of the onset of illness, and with the first dose given in the emergency department. Of the 971 patients randomized, 943 completed the study, with a similar rate of loss to follow-up in both groups. The median age of participants was 1.4 years, 53% were male, and the median duration of diarrhea was 53 hours; groups were balanced at the start of the study. After 14 days, the

likelihood of moderate to severe symptoms based on the modified Vesikari scale score was similar between groups (11.8% in the probiotic group and 12.6% in the placebo group). There were also no differences between groups regarding secondary symptom outcomes such as the duration or frequency of diarrhea. There was more wheezing in the probiotic group (5 vs. 0; $P = .03$).

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Emergency department

Reference: Schnadower D, Tarr PI, Casper TC, et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. *N Engl J Med.* 2018;379(21):2002-2014.

Mark H. Ebell, MD, MS

Professor

University of Georgia, Athens, Ga.

Benefits and Harms for Low-Dose Aspirin in Patients with Diabetes Mellitus

Clinical Question

What are the benefits and harms of low-dose aspirin in adults with diabetes mellitus?

Bottom Line

The 7,740 patients who took low-dose aspirin experienced 51 fewer vascular deaths, nonfatal myocardial infarctions (MIs), or nonfatal ischemic strokes; 29 fewer transient ischemic attacks (TIAs); and 44 fewer revascularizations than patients who took placebo over a mean of 7.4 years. This is balanced by an additional 69 major bleeding episodes during that period, with no effect on vascular or all-cause deaths, and no difference in the incidence of cancer. (Level of Evidence = 1b)

Synopsis

This British study recruited adults 40 years and older with diabetes, no known cardiovascular disease, no contraindications to aspirin, and no major comorbidity that would keep them from participating in the study for at least five years. After a placebo run-in period to assure adherence, 15,480 participants were randomized to receive aspirin 100 mg once daily or matching placebo. They were also randomized to receive an omega-3 fatty acid capsule or placebo; those results are reported separately. The groups were balanced at the start of the study: the patients had a mean age of 63 years, 63% were men, and 96% were white. Almost all (94%) had type 2 diabetes. A validated risk score determined that approximately 40% of participants were at low risk of vascular events (less than 5% at five years), 40% had a five-year risk of 5% to 10%, and the remainder were at

high risk. Because the trial was ongoing, the authors added TIA to the original primary composite efficacy outcome of vascular death, nonfatal MI, or nonfatal stroke (excluding intracranial hemorrhage). The primary safety outcome was a composite of intracranial hemorrhage, intraocular hemorrhage that threatens sight, gastrointestinal bleeding, or any other serious bleeding event. After a mean follow-up of 7.4 years, 99% of patients had complete follow-up data, with outcomes adjudicated for more than 90% by a committee masked to treatment assignment. The authors also looked at the effect of adding revascularization to the composite efficacy outcome. There was no difference between groups in the original efficacy outcome of vascular death, nonfatal MI, and nonfatal ischemic stroke (7.0% with aspirin vs. 7.6% with placebo; hazard ratio [HR] = 0.92; 95% CI, 0.82 to 1.03). When you add TIA to the composite outcome, the difference between groups is statistically significant (8.5% vs. 9.6%; HR = 0.88; CI, 0.79 to 0.97; number needed to treat [NNT] = 90 for 7.4 years). Adding revascularization to the original efficacy outcome had a similar result (10.8% vs. 12.1%; HR = 0.88; CI, 0.80 to 0.97; NNT = 77 for 7 years). When examining results stratified by vascular risk, those at moderate and higher vascular risk also experienced more major bleeding events (8.9 to 9.6 vs. 2.8 per 5,000 person-years in the low-risk group). The number of serious vascular events avoided per 5,000 person years was 5.7 in the low-risk group, 11.2 in the moderate-risk group, and only 4.9 in the high-risk group. For the composite harm outcome, there was a significantly increased risk of major bleeding, primarily due to more serious gastrointestinal and other bleeds (4.1% vs. 3.2%; HR = 1.29; CI, 1.09 to 1.52; number needed to treat to harm = 111 over 7 years). There was no difference in fatal bleeding events or hemorrhagic strokes. There was no difference in the incidence of cancer (11.6% for aspirin vs. 11.5% for placebo), including for gastrointestinal cancers (2.0% vs. 2.0%). There were no significant differences between groups in all-cause mortality or in vascular deaths.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry and foundation

Allocation: Concealed

Setting: Outpatient (any)

Reference: Bowman L, Mafham M, Wallendszus K, et al.; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379(16):1529-1539.

Mark H. Ebell, MD, MS

Professor

University of Georgia, Athens, Ga.

Editor's Note: Dr. Ebell is Deputy Editor for Evidence-Based Medicine for *AFP* and cofounder and Editor-in-Chief of *Essential Evidence Plus*. ■