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ACC/AHA lipids & ASCVD guidelines: 2018 update☆

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The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Guidelines [1] represents the 4th iteration of cholesterol-based guidelines that originated 3 decades earlier. The first 3 versions were orchestrated by NIH-NHLBI comprising a nationally recognized expert panel that formulated the National Cholesterol Education Program Adult Treatment Panels I-III (ATP I, 1989; ATP II, 1993; and ATP III, 2001) [2–4]. The earliest guideline (ATP 1) was derived using early evidence-based trials that included the Lipid Research Clinics Primary Prevention Trial [5] and supported bile-acid sequestrants as first-line therapy. In ATP II, an LDL-C target of <100 mg/dL (or 2.6 mmol/L) was recommended based upon arteriographic studies that suggested reduced progression of coronary disease when LDL-C levels were below this level [3]. By ATP III, a number of statin based clinical outcome trials had been reported and an LDL-C target of <100 mg/dL (or 2.6 mmol/L) was recommended for either CHD or its risk equivalence (e.g., T2DM). An optional LDL-C target of <70 mg/dL (or 1.8 mmol/L) was recommended for the highest risk patients with established CHD (e.g., following an acute coronary syndrome) [6]. The most recent revision in 2013, a collaborative effort between ACC and AHA emphasized the intensity of LDL-C lowering rather than the target goals favored in prior guidelines. Depending upon the patient's level of CHD risk, the guidelines recommended statin-directed LDL-C reduction of high (~50%), moderate (30–50%) or low (<30%) intensity. While this rationale was evidence-based inasmuch as the higher percent reduction in LDL-C translated into greater clinical benefit, as evidenced in the PROVE-IT trial, [7], some clinicians viewed the removal of LDL-C targets as a setback. This was because 1) they were easy to monitor and 2) had been in place for two decades (dating back to ATP II). Moreover, they argued that to calculate percent LDL-C reduction, they would need to know their patient's baseline LDL-C. However, because many patients had already been on statin therapy for years, that would be a near impossible task except for new patients presenting for initial evaluation. The second shortcoming voiced by critics was insufficient evidence to recommend the use of the Pooled Cohorts equation in primary prevention, in part because it tended to overestimate CHD risk and failed to incorporate other valuable risk predictors (e.g. coronary calcium score, hs-CRP) [8].

The 2018 ACC/AHA guidelines assuage these concerns by building upon the strengths of the 2013 ACC/AHA and ATP III guidelines and incorporating new clinical trial evidence generated since 2013. Specifically, the 3 most noteworthy studies included are IMPROVE-IT [9], FOURIER [10] and ODYSSEY OUTCOMES [11], all of which demonstrated lower on-treatment LDL-C to confer greater benefit beyond statin monotherapy. In IMPROVE-IT, the combination of simvastatin and ezetimibe reduced LDL-C to ~50 mg/dL and was associated with ~6% RRR in MACE compared to on-treatment LDL-C of ~70 mg/L (or 1.8 mmol/L) with statin treatment. This represented the first lipid-based clinical trial designed to test the hypothesis that "lower (LDL-C) is better" compared to the PROVE-IT trial that was designed as a non-inferiority trial (i.e., atorvastatin would not be clinically superior to pravastatin) [12].

To further explore the "lower is better" hypothesis, the FOURIER study found that treatment with the PCSK9 inhibitor, evolocumab, resulted in improved outcomes (15% relative risk reduction) associated with low on-treatment LDL-C. In fact, a post-hoc analysis observed continued benefit (without increases in non-CHD events) even with on-treatment LDL-C <10 mg/dL [13]. Similarly, the ODYSSEY OUTCOMES trial, testing the PCSK9 inhibitor, alirocumab in ACS patients receiving maximal statin and/or ezetimibe demonstrated improved outcomes (15% relative risk reduction) with the greatest benefit attained in patients with baseline LDL-C levels of 100 mg/dL (2.6 mmol/L) or greater (24% relative risk reduction) [11].

The 2018 guidelines continue to focus on secondary prevention although considerably more guidance is now placed in primary

Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ATP, Adult Treatment Panel; CHD, coronary heart disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HTG, Hypertriglyceridemia; IMPROVE IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; IPE, Icosapent Ethyl; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; NHLBI, National Heart, Blood, Lung Institute; NIH, National Institutes of Health; ODYSSEY OUTCOMES, Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; PROMINENT, Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REDUCE IT, Reduction of Cardiovascular Events With EPA - Intervention Trial; RRR, relative risk reduction; STRENGTH, Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia; T2DM, Type 2 diabetes mellitus.

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Table 1
Very high risk of future CVD events.

Major ASCVD events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85, previous revascularization or amputation
High risk conditions
Age ≥ 65 y
Heterozygous familial hypercholesterolemia
History of prior CABG or PCI outside of major ASCVD event(s)
Diabetes Mellitus
Hypertension
CKD (eGFR 15–59 ml/min/1.73 m^2
Current smoking
Persistently elevated LDL-C (≥100 mg/dL or ≥ 2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

Table 2
ASCVD Risk Enhancers.

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL or (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asia ancestry)

Lipid/biomarkers:

- Persistently elevated triglycerides
- (≥175 mg/dL, [≥2.0 mmol/L])

In selected individuals if measured:

- hs-CRP ≥ 2.0 mg/L
- Lp(a) levels > 50 mg/dL or > 125 nmol/L
- apoB ≥ 130 mg/dL
- Ankle-branchial index (ABI) < 0.9

prevention. For secondary prevention, patients at very high risk of future CVD events, defined by either 2 major CVD events (i.e., ACS within the past year or history of MI, CVA or PAD) or 1 major CVD event and 2 or more high-risk conditions (Table 1), the recommendation is for a high-intensity statin to drive LDL-C levels down by at least 50% (e.g., atorvastatin 40–80 mg or rosuvastatin 20–40 mg per day) AND if LDL-C remains 70 mg/dL (1.8 mmol/L) or greater then to add a second agent beginning with ezetimibe, followed by a PCSK9 inhibitor to lower LDL < 70 mg/dL (or 1.8 mmol/L). In other words, the new guidelines incorporate both LDL-C measures in high-risk patients, the intensity of LDL-C lowering AND an LDL-C target goal.

With respect to primary prevention, the new guidelines include a Class I indication for treatment with a high-intensity statin at LDL-C levels equal to or exceeding 190 mg/dL or a moderate-intensity statin (e.g., atorvastatin 10–20 mg, rosuvastatin 5–10 mg, pitavastatin 2–4 mg, simvastatin 20–40 mg) in diabetics aged 40–75 years. The Pool Cohort Equation is also used to distinguish between "Low Risk" subjects (<5% likelihood of a CVD event over 10 years) who are not deemed candidates for statin therapy and "High Risk" subjects (≥20% likelihood of a CVD event over 10 years) for whom high-intensity statin therapy continues to be recommended (Class I indication). In addition to aiming for at least a 50% reduction in LDL-C, an LDL-C target of <100 mg/dL (or 2.6 mmol/L) is now recommended for these high-risk primary prevention cases.

While patients in "Intermediate Risk" (7.5%–19.9%) are recommended for moderate-intensity statin therapy, a new feature of the 2018 Guidelines is the incorporation of "ASCVD Risk Enhancers" (Table 2) to help identify potential patients in the "Borderline" risk range (5–7.5%, 10-year risk) who may benefit from moderate-intensity statin therapy. The presence of at least 1 risk enhancer and/or abnormal lipid biomarker would raise discussion for such treatment consideration. Another highlight of the updated guidelines is advocating coronary artery calcium (CAC) measurements in the "Intermediate-Risk" group when a treatment consensus is not reached. In these cases, CAC levels at or exceeding 100 Agatston Units or the 75% percentile based on age and gender would favor treatment.

Arguably, a major shortcoming of the 2018 Guidelines were recommendations for treating HTG. While recommendations for lifestyle therapy in patients with moderate HTG (175–499 mg/dL) was not altered [14] new recommendations were made for treatment with severe HTG (>500 mg/dL) and an ASCVD risk of 7.5% or greater. Specifically, it included the initiation or intensification of statin therapy, rather than primary HTG lowering agents (e.g., fibrate, niacin) as had been the case in prior guidelines. Ironically, the results of the REDUCE-IT clinical outcomes trial [15], that tested IPE (4 g daily) in patients with moderate HTG and elevated CVD risk were presented 2-hours after the ACC/AHA guidelines were released, leading some to conclude that the 2018 cholesterol guidelines were already out-of-date! That was because compared to placebo, IPE treated subjects experienced a 25% RRR in the primary endpoint (composite of cardiovascular death, nonfatal MI, nonfatal CVA, coronary revascularization, or unstable angina) and a 20% reduction in cardiovascular death, the first lipid-based study to demonstrate such benefit beyond statin monotherapy.

In summary, the 2018 ACC/AHA new guidelines expand the evidence base by re-incorporating LDL-C targets in high risk secondary (i.e., <70 mg/dL or 1.8 mmol/L) and primary (i.e., <100 mg/dL or 2.6 mmol/L) prevention patients receiving statin therapy. Cholesterol absorption inhibitors (i.e., ezetimibe) and PCSK9 inhibitors (evolocumab and alirocumab) are endorsed if patients are statin-intolerant or have not attained their LDL-C target goal. ASCVD risk enhancers are a new feature to aid in deciding whether statin therapy should be considered in borderline -intermediate risk patients without established CVD. The recommendations for moderate HTG are outdated based on the REDUCE-IT Trial results. However, completion of 2 additional clinical outcome trials in patients with moderate HTG (i.e., STRENGTH and PROMINENT) is likely to influence recommendations for treating HTG in future guidelines.

Disclosures

Dr. Miller served on the Steering Committee for the REDUCE-IT trial and is an advisor to Amarin.

References

[1] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. Circulation 2018;10. https://doi.org/10.1161/CIR.0000000000000625 [CIR0000000000000625. Epub ahead of print].
[2] Report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults The expert panel, Arch Intern Med 1988;148:36–69.
[3] Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II), JAMA 1993;269:3015–23.
[4] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[5] The Lipid Research Clinics Coronary Primary Prevention Trial results I Reduction in incidence of coronary heart disease, JAMA 1984;251:351–64.
[6] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
[7] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934. https://doi.org/10.1016/j.jacc.2013.11.002.
[8] Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. Ann Intern Med 2016;165:786–94. https://doi.org/10.7326/M16-1739.
[9] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–97. https://doi.org/10.1056/NEJMoa1410489.
[10] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22. https://doi.org/10.1056/NEJMoa1615664.
[11] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.
[12] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
[13] Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet 2017;390:1962–71. https://doi.org/10.1016/S0140-6736(17)32290-0.
[14] Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011;123:2292–333. https://doi.org/10.1161/CIR.0b013e3182160726.
[15] Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22. https://doi.org/10.1056/NEJMoa1812792.