ne



Overview of 2013 American College of Cardiology/American Heart Association cholesterol guideline for reducing cardiovascular risk

"The updated guidelines are intended to provide focused recommendations for reducing the risk of atherosclerotic cardiovascular disease events based on evidence from randomized controlled trials."

Keywords: cardiovascular disease • cholesterol • evidence based • guideline • prevention • statins • systematic review

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults represents a paradigm shift in how cardiovascular prevention guidelines are developed and how cholesterol is treated [1]. The National Heart, Lung and Blood Institute convened the Adult Treatment Panel IV in 2008 to update the ATP III guidelines. The updated guidelines were never intended to provide comprehensive recommendations for the identification, detection and treatment of lipid disorders. The updated guidelines are intended to provide focused recommendations for reducing the risk of atherosclerotic cardiovascular disease (ASCVD) events based on evidence from randomized controlled trials (RCTs). Therefore, the Guideline Pane undertook a rigorous systematic review of RCTs of cholesterol-lowering drug therapy that had ASCVD outcomes, and meta-analyses of these RCTs to address three critical questions important for clinical practice. The guideline development process adhered to most of the principles that were subsequently advocated by the Institute of Medicine for developing trustworthy guidelines [2].

The 2013 ACC/AHA cholesterol recommendations focus on using the appropriate intensity of statin therapy in those most likely to experience a net ASCVD risk-reduction benefit. By contrast, the previous ATP III guideline recommended treatment to specific low density lipoprotein cholesterol (LDL-C) and nonhigh density lipoprotein cholesterol (non-HDL-C) treatment goals. The major 2013 cholesterol recommendations highlighted below.

A healthy lifestyle for all adults

The 2013 ACC/AHA cholesterol guideline endorses the recommendations of the 2013 ACC/AHA Lifestyle Management Guideline [3]. Adherence to a healthy diet, regular physical activity, maintaining a healthy weight and avoidance of smoking are essential for reducing ASCVD risk over the lifespan. Unfortunately, with advancing age many adults will need drug therapy to significantly reduce ASCVD risk. Notably, the RCTs reviewed for the 2013 cholesterol guideline were performed in the setting of healthy lifestyle advice.

Initiate statin therapy in those most likely to experience a net benefit

Strong evidence supports the use of the appropriate intensity of statin therapy for ASCVD risk reduction in four groups of patients (Box 1).

Moderate evidence supports the use of a statin for primary prevention in those with 5 to <7.5% 10-year ASCVD risk and LDL-C 70–189 mg/dl. Statin therapy may also be considered in those who do not meet these criteria if other indications of increased ASCVD risk are present (see below). Statins have not been shown to reduce ASCVD events in individuals with New York Heart Association



Departments of Epidemiology & Medicine University of Iowa, 145 N Riverside Dr S455 CPBH, Iowa City, IA 52242, USA Tel.: +1 319 384 1563 jennifer-g-robinson@uiowa.edu



Commentary Robinson

Box 1. Major treatment groups.

Secondary prevention

• Clinical ASCVD:

- High-intensity statin age ≤75 years and no safety concerns
- Moderate intensity statin age >75 years or safety concerns
- Primary prevention
- Age \geq 21 years with LDL-C \geq 190 mg/dl:
 - High-intensity statin
 - Nonstatin may be added for additional LDL-C lowering
- Diabetes, aged 40–75 years and LDL-C 70–189 mg/dl:
 Moderate intensity statin
 - High-intensity statin if ≥7.5% 10-year ASCVD risk
- No diabetes with ≥7.5% 10-year ASCVD risk aged 40-75 years and LDL-C 70–189 mg/dl:
 - Moderate or high-intensity statin

ASCVD: Atherosclerotic cardiovascular disease; LDL-C: Low density lipoprotein cholesterol.

Class II to IV heart failure, or in those receiving maintenance hemodialysis and so statin therapy should not be routinely initiated in these patients.

High-intensity statins lower LDL-C by \geq 50% (atorvastatin 40–80 mg or rosuvastatin 20–40 mg). Moderate intensity statins lower LDL-C by 30 to <50% (atorvastatin 10–20 mg, fluvastatin 80 mg, lovastatin 40 mg, pitvastatin 2–4 mg, pravastatin 40 mg, rosuvastatin 5–10 mg and simvastatin 20–40 mg). Statins and doses in bold reduced ASCVD in the RCTs reviewed for the 2013 cholesterol guideline.

Statins have an excellent margin of safety in properly selected patients who are appropriately monitored

Statins have an excellent safety record in RCTs, where the inclusion and exclusion criteria enhanced safety. Individuals with an increased risk of statin adverse effects (age >75 years, a history of statin intolerance, or other characteristics or drug therapy that may influence statin safety) should receive moderate intensity statin therapy, or a lower intensity if recommended in manufacturer's prescribing information.

Hepatic transaminases should only be measured if symptoms of hepatotoxicity develop. Muscle symptoms are common, and often not related to statin therapy. A causal relationship for muscle, or other symptoms, can be established by discontinuing the statin until symptoms resolve, then restarting the same or lower dose of the same or a different statin. Severe myopathy (muscle symptoms with marked creatine kinase elevations), rhabdomyolysis, and possible hemorrhagic stroke are rare complications of statin therapy. A modest excess of diabetes has been observed in statin-treated subjects in RCTs. However, for moderate intentisty statins, the ASCVD event reduction benefits exceed the potential for adverse effects, including diabetes, in all but the lowest risk primary prevention patients. For high-intensity statins, the risk for adverse events approaches or exceeds the ASCVD risk-reduction benefit when 10-year ASCVD risk is <7.5%.

Initiate statins for primary prevention based on estimation of 10-year ASCVD risk & a clinician-patient discussion

The first step in primary prevention patients without diabetes is to estimate 10-year ASCVD risk with the newly developed Pooled Cohort Equations recommended by the 2013 ACC/AHA Guideline for the Assessment of Cardiovascular Risk [4]. Risk calculators can be found at [5]. Based on age, sex, race, smoking, diabetes, total cholesterol, HDL-C, systolic blood pressure and antihypertensive drug treatment, these equations estimate the risk of nonfatal myocardial infarction, coronary heart disease death, and nonfatal and fatal stroke in white and African–American women and men who are not receiving statin therapy and who have an untreated LDL-C <190 mg/dl.

The Pooled Cohort Equations have been criticized for overestimating 10-year ASCVD risk in cohorts of health professionals and clinical trial participants [6]. However, these low-risk white populations are not representative of the US population of white and African–American adults [7]. Moreover, the Pooled Cohort Equations estimate risk quite accurately in lower risk individuals. Overestimation only occured in higher risk individuals for whom a treatment decision is already clear.

The clinician and patient should discuss whether statin therapy should be initiated based on the potential for an ASCVD risk-reduction benefit, adverse effects, drug–drug interactions and patient preferences. Other factors may be considered when a risk-based decision is unclear: LDL-C \geq 160 mg/dl, family history of premature ASCVD, lifetime ASCVD risk, high sensitivity C-reactive protein \geq 2.0 mg/l, coronary artery calcification score \geq 300 Agatston units or ankle–brachial index <0.9.

Regularly monitor adherence & safety

All RCTs regularly monitored drug adherence and safety. The patient should be evaluated with a fasting lipid panel at baseline, with another fasting lipid panel within 4–12 weeks of statin initiation or changes in therapy. Further follow-up should occur at 3–12 month intervals.

Percent reduction in LDL-C consistent with statin intensity may provide an guide to the anticipated thera-

peutic response: approximately \geq 50% for a high-intensity statin, or approximately 30–50% for a moderate intensity statin. If the baseline LDL-C is not known, it is noted that an LDL-C <100 mg/dl was achieved by most participants receiving a high-intensity statin. Do not use percent LDL-C reduction or achieved level as performance measures.

If an less than anticipated response occurs, encourage improved adherence to lifestyle and drug therapy, and/ or statin intensity can be increased. Secondary causes of hypercholesterolemia should be ruled out if indicated (most common causes are weight gain or obesity, high saturated or *trans*-fat intake, hypothyroidism, biliary obstruction or pregnancy).

If further LDL-C lowering is needed once the maximally tolerated or recommended intensity of statin has been reached, non-statin therapy can be added in high-risk individuals if the ASCVD risk-reduction benefits are considered to outweigh the increased risk of adverse effects. High-risk individuals include those with clinical ASCVD, untreated LDL-C \geq 190 mg/dl suggesting gentic hypercholesterolemia, or diabetes aged 40–75 years.

Conclusion & future perspective

Despite substantial advances in prevention, ASCVD still kills one out of three Americans [8]. The 2013

References

- Stone N, Robinson J, Lichtenstein A et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation* doi:10.1016/j.jacc.2013.11.002. (2013) (Epub ahead of print).
- 2 Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust, 2011.* The National Academies Press, DC, USA (2011).
- 3 Eckel RH, Jakicic JM, Ard JD *et al.* 2013 AHA/ ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* doi:01.cir.0000437740.48606.d1 (2013) (Epub ahead of print).
- Goff DC, Lloyd-Jones DM, Bennett G et al.
 2013 ACC/AHA Guideline on the Assessment of

ACC/AHA cholesterol guideline provides a comprehensive, evidence-based approach to reducing ASCVD risk. This patient-centered approach to drug treatment should be based on the potential for a net ASCVD risk-reduction benefit and the unique characteristics and preferences of each patient.

More research will be needed to determine the optimal strategies for refining risk estimation for individual patients, and whether new nonstatin therapies will further reduce ASCVD events in statin-treated patients. On the basis of this new evidence, future evidence-based updates to the 2013 will be developed.

Financial & competing interests disclosure

Most of the guideline development was funded by the NIH. Research grants from Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Genentech/Hoffmann-La Roche, GlaxoSmithKline, Merck, Pfizer, Regeneron/Sanofi and Zinfandel/Takeda were given to the University of Iowa. JG Robinson is a consultant for Amgen, Hoffmann-La Roche, Merck, Pfizer and Sanofi. JG Robinson has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* doi:01. cir.0000437741.48606.98 (2013) (Epub ahead of print).

- 5 American Heart Association. 2013 Prevention Guidelines. http://my.americanheart.org/professional/ StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
- 6 Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet* 382(9907), 1762–1765 (2013).
- ⁷ Lloyd-Jones D, Goff D, Stone N. Letter to the editor: statins, risk assessment, and the new American prevention guidelines. *Lancet* 383, 600–602 (2014).
- 8 Go AS, Mozaffarian D, Roger VL *et al.* Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation* 9(3), e28–e292 (2012).