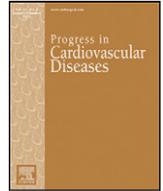




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# Progress in Cardiovascular Diseases

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## Lipid update 2020 - Introduction and foreword



Lipid management guidelines continue to evolve based on new clinical trial and epidemiologic data. Dr. Neil Stone chaired, and I was Vice-Chair, of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults which represented a paradigm change from earlier National Cholesterol Education Program ATP guidelines.<sup>1</sup> The 2013 ACC/AHA cholesterol guideline for the first time used the concept of net atherosclerotic cardiovascular disease (ASCVD) risk reduction benefit for guiding treatment, and identified 4 statin benefit groups supported by strong evidence from multiple CVD outcomes trials. In contrast, the previous Adult Treatment Program guidelines recommended treating patients to the same low-density lipoprotein cholesterol (LDL-C) goal regardless of the magnitude of potential benefit, or the harms or costs of additive non-statin therapies.<sup>2,3</sup> Although the 2013 ACC/AHA cholesterol guideline was initially controversial, subsequent analyses have supported the superiority of the 2013 guideline's benefit-based approach.<sup>4–6</sup>

Dr. Scott Grundy, chair for previous ATP guidelines and Dr. Stone, the chair of the 2013 ACC/AHA guideline, led the 2018 AHA/ACC cholesterol guideline. We are fortunate to have Drs. Stone and Grundy contribute an authoritative overview of prior guidelines and key aspects of the 2018 AHA/ACC/Multisociety guideline to lead-off this lipid update issue, The 2018 AHA/ACC/Multisociety Cholesterol Guideline: Looking at Past, Present, and Future". The 2018 AHA/ACC/Multisociety cholesterol guideline builds on the 2013 ACC/AHA guideline's benefit-based treatment approach to address the clinical use of non-statins and consideration of additional risk characteristics.<sup>7</sup> The 2018 guideline for the first time further considers cost in treatment decisions.

Contemporary guidelines are based on a systematic review of the evidence at the time of their convening. Therefore, by definition, the most recent evidence may make aspects of the guideline out of date. The rest of this issue is therefore devoted to authoritative commentaries on new data that may inform clinical practice beyond the 2018 AHA/ACC/Multisociety guideline, and will likely contribute to future guideline updates.

In my paper, "Lipid Management Beyond the Guidelines", I argue that following over 60% reductions in their acquisition price, the proprotein convertase subtilisin kexin type 9 monoclonal antibodies are now a reasonable or even good value in selected high to extremely high risk patient groups when guided by their LDL-C level on maximal

statin therapy, especially when LDL-C is  $\geq 100$  mg/dl. In primary prevention, the  $\geq 7.5\%$  10-year ASCVD risk treatment threshold is more effective than other guideline strategies for reducing the most ASCVD events in the population identified for treatment treated. Recent analyses have also shown primary prevention statin therapy is also cost-saving even in lower risk groups. Data from younger populations has become available for coronary artery calcium (CAC) scoring (mean age of 51 years) and found that statins could keep CAC = 0 in those with risk factors. Epidemiologic pooling studies now clearly show that LDL-C and non-high-density lipoprotein cholesterol (HDL-C) levels in young adulthood confer excess risk for ASCVD later in life. Accumulating data support earlier risk factor intervention trials as the next research priority.

My companion piece "New Insights into Managing Symptoms During Statin Therapy", reviews recent data from clinical trials that clearly demonstrates a statin "nocebo" effect, and that the large majority of patients can tolerate and adhere to long-term statin therapy. Potential brain pathways mediating the nocebo effect have been identified, and evidence-based strategies from the field of pain management are recommended for addressing patients reporting symptoms during statin therapy.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) study was published after the 2018 AHA/ACC/Multisociety guideline was released. In this trial, icosapent ethyl, a highly concentrated form of modified eicosapentaenoic acid (EPA) was shown to reduce the relative risk of major CVD events by 25% in high risk ASCVD and diabetic patients with moderate hypertriglyceridemia on statin therapy. Dr. Vera Bittner, an outstanding cardiologist and researcher reviews the benefits and harms of icosapent ethyl in her definitive article "Implications for REDUCE-IT in Clinical Practice". She then provides expert guidance on how icosapent ethyl might best be incorporated into the clinical care of high and very high risk patients.

The mechanisms contributing to the striking reduction in CVD risk in REDUCE-IT are unclear. The very modest reduction in LDL-C, non-HDL-C and triglycerides does not appear to account for the 25% reduction in the relative risk of CVD events in REDUCE-IT. Dr. William Harris is the key expert on omega-3 fatty acid metabolism and epidemiology. He has contributed an outstanding review of the potential mechanisms for icosapent ethyl's benefit in REDUCE-IT, "Understanding Why REDUCE-IT was Positive – Mechanistic Overview of EPA". This information should also prove helpful for interpreting the results of ongoing omega-3 fatty acid supplement trials.

Two leaders in the area of cost-effectiveness, Dr. Druv Kazi and Dr. Salim Virani, have contributed important insights into the role of drug cost in patient care. In their article, "Implications of Cost-Effectiveness Analyses of Lipid-Lowering Therapies: From the Policy-maker's Desk to the Patient's Bedside", they explain the basic principles of cost-

*Abbreviations:* AHA, American Heart Association; ACC, American College of Cardiology; ASCVD, Atherosclerotic cardiovascular disease; ATP, Adult Treatment Panel; CAC, Coronary artery calcium scoring; CV, Cardiovascular; CVD, Cardiovascular disease; EPA, Eicosapentaenoic acid; FH, Familial hypercholesterolemia; LDL-C, Low density lipoprotein cholesterol; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

effectiveness analyses, the concept of cost-effectiveness versus affordability, other considerations relevant to resource allocation in healthcare, and the limitations of cost-effectiveness research. They echo my argument for greater use of potential for net benefit in cost-effectiveness analyses.

Dr. Raul Santos from Brazil is a global leader in the field of familial hypercholesterolemia (FH) epidemiology, imaging, and lipid management. Dr. Marcio Mineme and Dr. Santos have provided an absolutely state-of-the-art review, "Reducing Cardiovascular Risk in Patients with Familial Hypercholesterolemia: Risk Prediction and Lipid Management" that extends well beyond what was available for the 2018 AHA/ACC/Multisociety guideline. Recent studies show that ASCVD risk in FH patients is heterogeneous. Drs. Mineme and Santos clearly discuss the genetic, lipid, risk factor and imaging factors contributing to this heterogeneity of risk. While high intensity statin therapy is recommended for all adult patients with LDL-C  $\geq$  190 mg/dl, a more accurate estimation of ASCVD risk may better guide the use of nonstatin therapies.

Dr. Michael Blaha is a leader in cardiovascular imaging, with many seminal publications on the epidemiology of coronary artery calcification (CAC) and CVD risk. In a paper led by Dr. Omar Dayze, Dr. Blaha and colleagues have contributed an important and necessary review of CAC that was not addressed in the 2018 AHA/ACC guideline entitled, "Coronary Artery Calcium Scoring for Individualized Cardiovascular Risk Estimation in Important Patient Subpopulations After the 2019 AHA/ACC Primary Prevention Guidelines". The 2018 AHA/ACC/Multispecialty cholesterol guidelines recommends consideration of CAC scoring when the statin treatment decision is uncertain in intermediate risk patients. The CAC data available for the guideline largely came from middle or older aged, predominantly male, European ancestry populations. Dr. Dayze, Blaha and colleagues review an extensive amount of data to provide important insights into issues surrounding risk assessment and CAC utilization in a wide range of patient groups: women, younger adults, older adults, non-European ancestry patients, patients with a family history of premature ASCVD, or a personal history of diabetes mellitus, chronic renal disease, metabolic syndrome, inflammatory disorders, or human immunodeficiency virus infection. They also discuss issues surrounding the use of coronary computed tomographic angiography for risk stratification.

To round out the issue, we have included 2 papers providing insight into the lipid effects of two lifestyle-related changes. The esteemed editor of *Progress in Cardiovascular Diseases* and world renowned expert on physical fitness, Dr. Carl Lavie, reviews the epidemiologic evidence showing an association between aerobic exercise and cardiorespiratory fitness and maintenance of healthy CV lipid and risk factor levels and longevity in his paper, "Impact of Fitness and Changes in Fitness on Lipids and Survival". Recent evidence also supports similar positive associations for resistance exercise training and muscle strength. Interesting data also suggests that cardiorespiratory fitness protects against the modest excess risk of diabetes in statin-treated patients.

Coconut oil consumption has dramatically risen due to the public perception of health benefits, weight loss, and the popularity of diets such as the "Paleo" diet. Dr. Heitor Santos and colleagues in their paper, "Coconut Oil Intake and Its Effects on the Cardiometabolic Profile" found no support for this perception in their structured literature review of randomized trials. They found coconut oil, and its main constituent lauric acid, increases LDL-C and total cholesterol when compared with other vegetable oils. Although coconut oil also increases HDL-C levels, pharmaceutically increasing HDL-C levels has not proven to be cardioprotective in randomized CVD outcomes trials. They recommend continuing to limit saturated fat intake to 10% of total calories, as is recommended in the 2018 AHA/ACC/Multisociety cholesterol and other major dietary guidelines.

## Disclosures

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Jennifer G. Robinson

Departments of Epidemiology and Internal Medicine, Division of Cardiology, University of Iowa, United States of America  
E-mail address: jennifer-g-robinson@uiowa.edu.