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Editorial

The 2018 ACC/AHA Lipid Guidelines: A Little More or Less Canadian?

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In November 2018, the American College of Cardiology (ACC) and the American Heart Association (AHA), in conjunction with several other US organizations, released the long-awaited revision of the US lipid guidelines.[1] These guidelines have garnered widespread support from experts in the United States for providing more nuance to the recommendations to manage dyslipidemia, while at the same time being criticized by some as being increasingly complex. Indeed, these guidelines appear to epitomize John Lydgate's famous words that "you can't please all of the people all of the time." Nonetheless, there are many positive changes in these updated guidelines.

In recommendations for both primary and secondary prevention, there is greater emphasis on the value and importance of maintaining a heart-healthy lifestyle, which is an important message in these times of rampant obesity and inactivity. For primary prevention, several risk enhancers have been added, and coronary artery calcium testing has been given a greater role in making statin treatment decisions. In secondary prevention, treatment thresholds have been proposed for treatment intensification, and additional guidance has been provided for using proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). In this commentary, we provide a Canadian perspective on these new US guidelines: what we consider was well done, what could have been done better, and what we might see in future iterations of the Canadian guidelines.

Primary Prevention

Risk assessment

For primary prevention, the new US guidelines represent more of an evolution from previous guidelines, with only few major changes. The pooled cohorts equation (PCE) remains the risk algorithm recommended, despite some previous concerns regarding the reliability of this tool (Table 1).[2] These concerns appear to have been somewhat attenuated, with recent evidence suggesting that with proper capture of all cardiovascular (CV) events, the model provides adequate accuracy in estimation of risk.[3] This represents a departure from the 2016 Canadian guidelines, which have adhered to recommending the use the modified Framingham risk algorithm as well as use of vascular age.[4] A major advantage of the PCE is the availability of race-specific risk estimates, which could be of value in a multiracial and multicultural country such as Canada. Whether the PCE would be appropriate and adequately calibrated for Canada remains to be seen, but ethnic-specific data, preferably from one of several Canadian cohorts,[5] would be advantageous for the Canadian context and should be a research priority in Canada.

Another advantage of the PCE is that only so-called "hard" CV events are predicted (death, myocardial infarct [MI], or stroke). However, this has led to different risk thresholds for treatment decisions in the US and Canada. US guidelines consider a 10-year risk of 7.5% to 20% as intermediate risk, which is somewhat different than the equivalent Canadian range of 10% to 20% (for which the outcome also includes slightly different CV event definitions). More importantly, US guidelines continue to consider therapy in all patients in this intermediate-risk group, whereas Canada has always used an additional low-density lipoprotein cholesterol (LDL-C) threshold to determine if treatment is warranted. This remains an important distinction that may more appropriately select individuals recommended for therapy in Canada compared with the United States.

Nonetheless, the US guidelines, like recent Canadian guidelines,[4] remain focused on 10-year CV risk assessment despite the many limitations of this approach. Although longer-term horizons—including lifetime risk—are considered, they are not fully integrated into the algorithm. Furthermore, an important extension to risk assessment—that is, the concept of predicted treatment benefit for primary prevention—received limited emphasis. The benefit

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Table 1. Highlights of 2019 US lipid guidelines for primary prevention and comparison with 2016 Canadian guidelines

Primary prevention	2018 US recommendations	Comparison with 2016 Canadian recommendations	Considerations for future Canadian guidelines
1. Risk assessment	Pooled cohorts equation for risk estimation	Modified Framingham for risk estimation and vascular age assessment for patient counselling	Is the PCE appropriate for Canada? (eg, calibration, ethnicity) A Canadian multiethnic risk equation should be a research priority Possible integration of a predicted treatment benefit calculator
2. Earlier treatment	New recommendation for lifestyle change and statin therapy in young patients (20 to 39 years) with LDL-C > 4.1	No formal recommendation but early treatment with high LDL-C acceptable	Possible integration of formal recommendation using predicted benefit calculator
3. Risk enhancers	• LDL-C ≥ 4.1 mmol/L • family history of premature ASCVD • High lifetime risk • Abnormal coronary artery calcification (CAC) or ABI • hs-CRP ≥ 2 mg/L Newly added: • Chronic kidney disease • Metabolic syndrome • High-risk conditions in women (eg, pre-eclampsia) • Inflammatory diseases (eg, rheumatoid arthritis, psoriasis, and HIV) • High-risk ethnicity (eg, South Asian) • apoB ≥ 120 mg/dL • Lp(a) > 30 mg/dL	• Family history of premature ASCVD • apoB ≥ 120 mg/dL • Lp(a) > 30 mg/dL • Chronic kidney disease • Clinical ASCVD • HOPE-3 inclusion criteria (in men ≥ 50 years of age or women ≥ 60 years of age and older at intermediate risk, recommend preventive treatment, if 1 additional risk factor was present (eg, low HDL-C, impaired fasting glucose, increased waist circumference, cigarette smoking, and hypertension)	Further refinement to consider high-risk conditions in women, inflammatory diseases, and possibly other factors as risk enhancers
4. Coronary artery calcium	CAC = 0 is low risk; statin may be withheld	CAC = 0 should not be used to avoid statin therapy in patients who otherwise meet criteria	

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; Lp(a), lipoprotein(a).

approach,[6-9] which considers both the risk of a CV event and the baseline LDL-C, provides a more efficient and mathematically superior approach to determining in whom statins will be beneficial and provides clinicians with a tool to better select patients for statins in primary prevention.[6,10-12] Such an approach should be considered for greater integration into future guidelines, both in the United States and in Canada. A major obstacle to broad uptake and recommendation of the benefit approach has been the lack of a widely available calculator to estimate treatment benefit conveniently at the point of care. However, a web-based calculator has been developed recently and is freely available (https://tgetgood.github.io/statin-benefit/resources/public/production/index.html), which should make this tool more amenable to widespread use.

Earlier treatment

Although the US guidelines did not fully integrate the benefit approach to statin therapy, which makes recommendations for earlier treatment in younger patients, they did consider the evidence that life-long elevations in LDL-C (and apolipoprotein B [apoB]) are associated with high lifetime risk of CV events. Data from several sources, including powerful data from Mendelian randomization,[13-16] strongly indicate that earlier treatment would likely lead to marked reductions in event rates. In this context, the US guidelines make a new bold recommendation to promote aggressive lifestyle management and consider statin therapy among young (ie, 20 to 39 years of age) low-risk patients with elevated LDL-C > 4.1 mmol/L, especially with risk-enhancing factors. This represents a major departure from previous guidelines, which strongly emphasized risk estimation and acknowledges both the high lifetime risk (which is poorly captured by 10-year risk estimates) and the potential for high benefit in these vulnerable young people. This recommendation is consistent with previous Canadian Cardiovascular Society (CCS) guidelines that allow for therapy to be considered in younger patients with moderate to high levels of LDL-C (although no specific threshold of LDL-C was noted). Further refinement and development of specific Canadian recommendations to select younger patients for therapy appropriately may be warranted in future guidelines.

Risk enhancers

Although both US and Canadian guidelines have previously recommended the inclusion of additional risk markers to aid in the decision to initiate statins, the new US guidelines have more formally recognized such "risk enhancers" and integrated these more directly in their recommendations. Here, the US guidelines took a decidedly more Canadian approach. Canadian guidelines have long considered family history of premature CV disease, elevated apoB (≥ 120 mg/dL) and elevated lipoprotein(a) [Lp(a)] (> 30 mg/dL), chronic kidney disease, clinical atherosclerotic cardiovascular disease (ASCVD), which includes abnormal ankle-brachial index (ABI) as well as abdominal aortic aneurysm (AAA), as risk

modifiers (or statin-indicated conditions).[4] The 2016 Canadian guidelines also integrated results from the **H**eart **O**utcomes **P**revention **E**valuation (HOPE-3) trial, and in men ≥ 50 years of age or women ≥ 60 years of age and older at intermediate risk, recommended preventive treatment if 1 additional risk factor was present (eg, low HDL-C, impaired fasting glucose, increased waist circumference, cigarette smoking, and hypertension). The 2013 US guidelines had previously recommended that persistent elevations in LDL-C ≥ 4.1 mmol/L, family history of premature ASCVD, high lifetime risk, abnormal coronary artery calcification (CAC), or ABI and hs-CRP ≥ 2 mg/L could be considered to recommend statin therapy in individuals with estimated risk between 5.0% and 7.5%.[17] In the most recent guidelines, this list of risk enhancers has been broadened to also include many conditions characterized by high cardiovascular risk: chronic kidney disease, metabolic syndrome, high-risk conditions in women (eg, pre-eclampsia), inflammatory diseases (rheumatoid arthritis, psoriasis, and HIV), as well as high-risk ethnicity (eg, South Asian). In addition, several biomarkers were also added including Lp(a) > 125 nmol/L (50 mg/dL) and apoB ≥ 130 mg/dL, further aligning with previous Canadian recommendations. The inclusion of several additional high-risk conditions as risk enhancers, especially those specific to women and high-risk ethnicities, is certainly warranted. Previous Canadian guidelines have acknowledged the higher risk among these groups and recommended earlier LDL-C screening but have not made formal recommendations regarding preventive treatment for these specific patients. This may be an area of potential refinement in subsequent Canadian guidelines.

CAC

Among the current changes in the recent US guidelines, the greater emphasis on CAC is among the most prominent and perhaps where the guidelines differ most from recent Canadian guidelines. Indeed, CAC has now been formally integrated into the decision-making process for all patients in the intermediate-risk category. More importantly, the way in which CAC is recommended has also changed and represents a major departure from previous guidelines. Rather than use high CAC as a risk enhancer, as recommended previously in both Canada and the United States, the recent US guidelines now allow for "de-risking" patients based on a CAC = 0. Indeed, US guidelines no statin therapy for persons with a CAC = 0, except in special circumstances associated with high lifetime risk (diabetes, family history of premature ASCVD, or cigarette smoking). Although the evidence for high CAC as a risk modifier is robust, and CAC is among the best markers for risk reclassification,[18-21] it remains unclear whether the evidence in favour of de-risking individuals based on CAC = 0 warrants the emphasis given. In fact, previous Canadian guidelines have specifically recommended against using CAC = 0 as rationale to avoid statin therapy in patients who otherwise meet criteria for statin therapy.[4] At the very least, it would appear that additional exceptions are necessary to avoid de-risking other high-risk groups (eg, younger people, in whom considerable coronary plaque may still be non-calcified,[22] as well as those with very high atherogenic particle burdens: for example, high apoB and/or Lp(a). Furthermore, the finding that certain groups generally considered to be healthy and fit have high CAC but have a low risk for CV events[23] further complicates the utility of CAC in making treatment decisions. Whether CAC will take on such a prominent role in future guidelines in Canada is unlikely, given these considerations, as well as the costs and limited access in many parts of the country. Nonetheless, CAC will remain a useful ancillary test to consider in very select patients for whom treatment remains uncertain.

Secondary Prevention

Treatment intensification and targets

In the secondary prevention setting, the US guidelines have re-emphasized the importance of monitoring LDL-C after high intensity statin therapy (eg, > 50% LDL-C reduction) is initiated and recommend intensification with ezetimibe and, in select patients, with PCSK9 inhibitors if LDL-C is ≥ 1.8 mmol/L[1,24] (Table 2). This approach parallels the approach taken by the 2016 Canadian guidelines, in which ezetimibe can be considered if LDL-C ≥ 2.0 mmol/L (or ≥ 1.8 mmol/L after recent ACS).[4] However, an important nuance should be noted in the recent US guidelines. Rather than recommend a treat-to-target approach, the guidelines recommend a primary *threshold* of LDL-C to consider intensification of therapy. This is an important change from previous guidelines and is in keeping with the evidence-based data from randomized controlled trials (RCTs), in which the baseline LDL-C at randomization in recent trials has been selected as the threshold for considering intensification. Rather than focusing on achieved LDL-C as in previous guidelines (ie, an LDL-C "target"), this approach likely better reflects the evidence and represents a more appropriate approach to identify patients for intensification of therapy.

A major omission is the lack of a secondary treatment threshold for apoB. ApoB is clearly emerging as the most effective marker for assessing both the benefit and the adequacy of lipid lowering,[25] with mounting evidence that it is the reduction in particle number, not the reduction in the lipid content (cholesterol or triglyceride) that drives the mechanism of reduced ASCVD from lipid-lowering therapy.[26,27] Although US guidelines accept non-HDL-C as a secondary threshold, they make no recommendation for apoB, despite the fact that baseline apoB levels were available in recent PCSK9i trials to inform such a threshold. Inadequate control of atherogenic particles, as measured by apoB, likely contributes to the residual risk in the post-MI setting and non−HDL-C only partially captures individuals with persistently elevated atherogenic particles. In Canada, both non−HDL-C (< 2.6 mmol/L) and apoB (< 0.8 g/L) are recommended as secondary treatment targets, which is more in keeping with the strong evidence in favour of apoB as a key determinant of benefit from therapy.

PCSK9i and other nonstatin lipid-lowering agents

The US lipid guideline panel had the benefit of the availability of the results of 2 large randomized trials of lipid lowering with PCSK9i before making their recommendations.[28,29] Based on these results, they recommended PCSK9i

Table 2. Highlights of 2019 US lipid guidelines for secondary prevention and comparison with 2016 Canadian guidelines

Secondary prevention	2018 US recommendations	Comparison with 2016 Canadian recommendations	Considerations for future Canadian guidelines
1. Treatment intensification and targets	Re-emphasized monitoring LDL-C on treatment LDL-C $\geq$ 1.8 mmol/L is threshold for treatment intensification (with ezetimibe followed by PCSK9i) in high-risk ASCVD No formal secondary apoB threshold for intensification	Monitoring on-treatment LDL-C is recommended Recommend treatment intensification (with ezetimibe followed by PCSK9i) to reach LDL-C $\leq$ 2.0 mmol/L ($\leq$ 1.8 mmol/L if recent ACS) Secondary treatment target: apoB $\leq$ 0.8 mg/L	Possible change from LDL-C target to intensification threshold as in US (supported by RCTs)
2. PCSK9i	Only for high-risk ASCVD, defined as recurrent ASCVD events OR first ASCVD event with $\geq$ 2 of the following: • $\geq$ 65 years • Familial hypercholesterolemia • Persistently elevated LDL-C > 2.6 mmol/L • Chronic kidney disease • History of heart failure • Presence of cardiovascular risk factors (eg, hypertension, diabetes, cigarette smoking)	Any ASCVD with LDL-C not at target	Further refinement of patient populations most-likely to benefit

ACS, acute coronary syndrome; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; RCTs, randomized controlled trials.

(after the addition of ezetimibe) among patients with maximally tolerated statins with an LDL-C $\geq$ 1.8 mmol/L with very high-risk features only. PCSK9i intensification is recommended among those with recurrent ASCVD events (ie, defined as recent ACS (< 1 year), MI, previous stroke, peripheral vascular disease, revascularization), or a first ASCVD event and at least 2 of the following: $\geq$ 65 years of age, familial hypercholesterolemia or persistently elevated LDL-C > 2.6 mmol/L, chronic kidney disease, history of heart failure, or presence of cardiovascular risk factors (eg, hypertension, diabetes, cigarette smoking). Given the costs of therapy, there is substantial merit in focusing PCSK9i therapy to those for whom benefit may be greatest; however, these criteria may ultimately be overly restrictive. Secondary analyses of the PCSK9i trials have been reported and identified several groups in which benefit may be highest, including recent ACS, recurrent MI, multivessel coronary disease, peripheral vascular disease, diabetes, and/or persistently elevated LDL-C. Indeed, the European Society of Cardiology, in their statement on PCSK9i, recommended intensification with PCSK9i based almost entirely on these high-benefit subgroups (they also used a LDL-C threshold of 2.6 mmol/L for intensification to PCSK9i, which is much higher than recommended by US guidelines).[30] The 2016 guidelines in Canada, published before many of these subgroup analyses, recommended that PCSK9i could be considered for all patients with atherosclerotic CV disease with LDL-C $\geq$ 1.8 mmol/L. Additional consideration to include criteria to better guide clinicians in selecting patients most likely to benefit—based on the available trial evidence—may be valuable in future guidelines.

Conclusions

Overall, the recent AHA/ACC guidelines have made several positive changes. In both primary and secondary prevention, the recommendations between Canada and the United States have become more closely aligned, notwithstanding a few important exceptions (eg, LDL-C thresholds in intermediate risk, prominence of CAC). In primary prevention, the addition of several risk enhancers provides the opportunity to broaden the treatment of select patients who are at higher risk and who are more likely to benefit from lipid lowering, and we may see greater use of this approach in future Canadian guidelines. In secondary prevention, the US guideline approach for treatment intensification thresholds is based on the enrollment of major randomized trials. This appears to be a fair approach to determine which patients are eligible for these therapies and further refinement to select those most likely to benefit from these more costly therapies and may require further consideration in Canada.

The recent publication of the PCSK9i outcome trials heralds a new poststatin era in prevention of CV disease, with greater focus on lipid-lowering therapy. Indeed, several novel lipid-lowering therapies are actively being developed to lower LDL (via new approaches):[31] triglyceride-rich lipoproteins[32,33] and Lp(a).[34] A recent trial with a highly purified omega-3 fatty acid formulation was also recently completed, showing marked reductions in CV events.[35] These developments, in parallel with a greater emphasis on lifestyle measures, including diet and physical activity, have the potential to greatly reduce cardiovascular disease in Canada and worldwide. The future for prevention of CV events is bright, and we expect to see new exciting evidence in the following years that could have a profound impact for prevention of CV disease in our patients.

Disclosures

Jean Gregoire: Speaker's Bureau: Amgen, AstraZeneca, Bayer, Boehinger-Ingelheim, Bristol-Myers Squibb, Merck. Novartis, Pfizer, Servier, Sanofi, Sunovion; Consulting Fees:

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