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Viewpoint

Are the ACC/AHA Guidelines on the Treatment of Blood Cholesterol a Game Changer? A Perspective From the Canadian Cardiovascular Society Dyslipidemia Panel

Todd J. Anderson, MD,[a] Jean Grégoire, MD,[b] Robert A. Hegele, MD,[c] Patrick Couture, MD, PhD,[d] G.B. John Mancini, MD,[e] Ruth McPherson, MD, PhD,[f] Gordon A. Francis, MD,[g] Paul Poirier, MD, PhD,[h] David C. Lau, MD, PhD,[a] Steven Grover, MD,[i] Jacques Genest, Jr., MD,[i] André C. Carpentier, MD,[j] Robert Dufour, MD,[k] Milan Gupta, MD,[l] Richard Ward, MD,[m] Lawrence A. Leiter, MD,[n] Eva Lonn, MD,[o] Dominic S. Ng, MD, PhD,[p] Glen J. Pearson, PharmD,[q] Gillian M. Yates, MN, NP,[r] James A. Stone, MD, PhD,[a] and Ehud Ur, MB[s]

[a] *Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada*

[b] *Institut de Cardiologie de Montréal, Université de Montréal, Montréal, Québec, Canada*

[c] *Robarts Research Institute, London, Ontario, Canada*

[d] *Centre hospitalier universitaire de Québec, Québec City, Québec, Canada*

[e] *Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada*

[f] *University of Ottawa Heart Institute, Ottawa, Ontario, Canada*

[g] *St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada*

[h] *Institut universitaire de cardiologie et de pneumologie de Québec, Faculté de pharmacie, Université Laval, Quebec City, Québec, Canada*

[i] *McGill University Health Center, Montreal, Québec, Canada*

[j] *Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Québec, Canada*

[k] *Institut de recherches cliniques de Montréal, Montréal, Québec, Canada*

[l] *Department of Medicine, McMaster University, Hamilton, Ontario, Canada*

[m] *Department of Family Medicine, University of Calgary, Calgary, Alberta, Canada*

[n] *Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*

[o] *Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada*

[p] *Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Ontario*

[q] *Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada*

[r] *QE II Health Sciences Centre, Halifax, Nova Scotia, Canada*

[s] *Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada*

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Corresponding author: Dr Todd J. Anderson, Libin Cardiovascular Institute of Alberta, University of Calgary, 1403-29th St NW, Calgary, Alberta T2N 2T9, Canada. Tel.: +1-403-944-1033; fax: +1-403-944-1592.

E-mail: todd.anderson@albertahealthservices.ca

The disclosure information of the authors and reviewers is available from the CCS on the following websites: www.ccs.ca and/or www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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The recent publication of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[1] on the treatment of blood cholesterol has resulted in some controversy, creating opportunity to reinforce the importance of the management of this important cardiovascular risk factor. Some confusion has been expressed as to how to interpret these new guidelines in light of the 2012 Canadian Cardiovascular Society (CCS) Dyslipidemia guidelines published in 2013.[2]

The present article reiterates the position of the CCS guidelines primary panel with respect to the risk stratification and treatment of subjects at risk of atherosclerotic events (Table 1); after careful review, our main recommendations to Canadian physicians are essentially unchanged in light of the new ACC/AHA guidelines. We will confine our discussion to what we believe to be the most important key messages.

What Is in the New ACC/AHA Guidelines

In 2008, the National Heart Lung and Blood Institute initiated these guidelines by commissioning a rigourous literature review with a focus on the highest quality of evidence. Partnering with the ACC and the AHA in 2013, the guidelines were written using an evidence-based approach. There was focus on 4 groups believed most likely to benefit from statin therapy based on randomized clinical trials. This included subjects with: (1) clinical evidence of atherosclerotic vascular disease; (2) diabetes between the age of 40 and 75 years with a low-density lipoprotein cholesterol (LDL-C) < 5 mmol/L; (3) primary levels of LDL-C > 5 mmol/L; and (4) subjects with an LDL-C level between 1.8 and 5 mmol/L and estimated 10-year risk $> 7.5\%$. There were also comments within the document about treatment goals, safety, global risk assessment, use of secondary testing, and future updates.

Treat Those for Whom There Is the Strongest Evidence

There is strong concordance between the ACC/AHA and CCS Guidelines to use statin-based therapy in subjects most likely to derive cardiovascular benefit, that is: (1) those with established atherosclerosis (so called secondary prevention); (2) most subjects with diabetes mellitus; and (3) those with LDL-C > 5 mmol/L. These are not new recommendations and are well recognized. Considering the greater risk of these subjects and the fact that up to a third of eligible patients in this category are not currently receiving statin therapy, both guidelines strongly support the need for therapy in this population and the large opportunity to improve cardiovascular health by advocating around this message. In addition, based on evidence from randomized controlled trials, the CCS guidelines also endorse statin-based therapy in subjects with significant chronic kidney disease and high-risk hypertension.[3]

The ACC/AHA guidelines also extended the range of people to be treated by recommending statin therapy for most "intermediate" risk subjects (using a new pooled cohort equations risk $> 7.5\%$).[4]

We did not advocate treating all subjects within an intermediate Framingham risk score[5] but instead included those with an LDL-C ≥ 3.5 mmol/L, or exceeding threshold values of non–high-density lipoprotein cholesterol (non–high-density lipoprotein cholesterol = total cholesterol minus high-density lipoprotein cholesterol) or apolipoprotein B. The 2 approaches would treat different numbers of at-risk subjects, with the ideal approach not clear. The CCS primary panel continues to believe that our evidence-derived approach, based on a level of atherogenic lipoprotein particles, provides a conservative number needed to treat. Decisions about treating additional subjects in the intermediate risk category in a primary prevention setting should be undertaken after risk-benefit discussions with individual patients including the use of the Cardiovascular Age. Cardiovascular Age was added to the CCS guidelines as a tool to improve adherence to lipid-lowering therapy. After this discussion, the primary panel outlines further secondary tests that might assist in making a final treatment decision. Although there is much promise for atherosclerosis imaging in risk assessment, randomized trials of these approaches will need to be completed.

Risk Assessment Is Important

Much of the controversy of the new American guidelines relates to the development of the new pooled cohort equations

Table 1. Comparison of ACC/AHA and CCS Dyslipidemia Guidelines

Criteria	2013 ACC/AHA	2012 CCS
Established atherosclerosis	Treat with statins	Treat with statins
Diabetes mellitus	40-75 years of age and LDL-C ≥ 1.8 mmol/L: treat with statins	Age ≥ 40 years or 15 years duration and ≥ 30 years: treat with Statins
LDL-C > 5 mmol/L	Treat with statins	Treat with statins
Intermediate to high risk	Pooled cohort equations $\geq 7.5\%$: treat with statins	Framingham risk score $\geq 20\%$: treat with statins; Framingham risk score 10%-19%: treat with statins if LDL-C ≥ 3.5*
CKD or high-risk hypertension	No specific treatment	Treat with statins
Target levels when treatment is started	No	Yes
Risk assessment tool	Pooled cohort equations	Modified Framingham risk score
Other factors to consider	Lifetime risk	Cardiovascular age
Safety issues	Discussed	Discussed
Secondary testing	In selected cases	In selected cases
Lifestyle modification	Separate and important guideline	Important aspect of guideline

ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease with eGFR $\leq$ 45 mL/min/1.73 m^2, or eGFR < 60 mL/min/1.73 m^2 and albumin/creatinine ratio ≥ 3.0 mg/mmol; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol.

*Or non–high-density lipoprotein cholesterol (non–high-density lipoprotein cholesterol = total cholesterol minus high-density lipoprotein cholesterol) ≥ 4.3 mmol/L or apolipoprotein B ≥ 1.2 mg/L.

for risk assessment. Although it is derived from several cohorts, including people of various ages, ethnicities, and geographic distribution and appropriately measures risk of hard cardiovascular end points including myocardial infarction and stroke, concern has been raised that it has not been well validated and might overestimate risk.[6]

The ACC/AHA guideline writers correctly recognize that early validation of the new risk engine is important for general uptake of the guidelines with a goal of increasing the number of Americans receiving evidence-based therapy. The CCS guidelines advocated the use of a modified Framingham risk score that evaluated total cardiovascular risk and recognized that this engine had many limitations including limited implementation by primary care clinicians. Instead of focusing on which approach is better, we encourage clinicians to use a risk assessment approach in subjects who do not fit into the previously mentioned treatment categories. Most clinicians caring for patients at risk do not systematically use any approach for risk factor stratification and by not doing so might not appropriately recognize those in whom statin therapy would be most helpful. Although it is appropriate to point out that randomized trials of lipid lowering therapy have not used risk assessment categories as eligibility criteria, it has nonetheless been a very useful framework for clinicians and patients over the years, ensuring evaluation of the risk imparted by lipid levels within the context of overall cardiovascular risk. Until further validation of the pooled cohort equations risk assessment is done, we believe that the modified Framingham risk score, familiar to most clinicians and widely validated, should be the primary risk assessment tool. In addition, individual decisions will need to be made in subjects who do not fit nicely into a risk engine including those with inflammatory conditions, high-risk ethnic backgrounds, and extremes of cardiovascular risk factors.

Emerging evidence has demonstrated that most subjects could obtain a relative risk reduction of 25%-35% with statin therapy.[7]

A risk assessment approach can engage the patient in the decision-making process and improve the management of dyslipidemia and hypertension. Letting patients know what might be expected for them with therapy or how treatment will change their cardiovascular age might improve adherence. The evidence for incorporating a discussion on cardiovascular age is reviewed in the previous CCS guideline document.

Statins Have the Most Compelling Evidence

The introduction of statins has created a paradigm shift for cardiovascular risk reduction, but there remains misunderstanding and fear of their use. The CCS guidelines are very much aligned with the ACC/AHA and European recommendations that statins are the cornerstone of pharmacotherapy in addition to lifestyle intervention. The evidence supporting their use in appropriate populations is undeniable and this remains an essential message to convey to prescribing clinicians and patients alike. The CCS guidelines also address safety concerns for statin use and provide practical information on dealing with possible side effects.

Targets of Therapy Should Not Be Abandoned

We continue to recommend LDL-C (or alternative) targets as a useful concept for physicians and patients, as is used, for example, for blood pressure management. The ACC/AHA guidelines had a self-imposed mandate to use the highest level of evidence, which was based on randomized trials. The treatment trials to date have enrolled patients with defined phenotypic criteria and randomized them to fixed-dose medication regimes. Trials have not aimed to achieve specific levels of LDL-C, but some studies have essentially achieved this based on different doses of the same drug or different drugs. In addition, several recently published trials have failed to show decreased event rates in subjects who were prescribed combination therapy compared with statins alone. For these reasons, the ACC/AHA guidelines advocated a novel yet controversial approach of treatment based on risk phenotype with different potency statins but not recommending LDL-C targets. In many ways this simplifies the approach for primary care providers and patients. The CCS guidelines primary panel had certainly considered this option but in the end elected to continue to support the concept of lipid targets for several reasons: (1) direct epidemiology and indirect evidence from clinical trials metaregression analyses suggest that lower LDL-C levels result in fewer cardiovascular events; (2) coronary plaque regression based on intravascular ultrasound and angiography can be achieved at LDL-C levels or a percentage LDL-C reduction as recommended in the guidelines; (3) measuring levels does provide some metrics around patient adherence, and the individual response to a given dose of statin; (4) it is a paradigm that people have been comfortable with; and (5) this leaves the door open for combination therapy which might still prove to be useful in subjects with aggressive atherosclerosis, or statin intolerance. In addition, this approach is similar to that put forward by the European community.[8]

It is important to remember that guidelines are simply a framework to guide clinical decision-making in at-risk patients. Restricting such guidance to a priori trial designs without any consideration for other sources of knowledge might leave primary care physicians without guidance in some uncomfortable situations (ie, a patient with unexpectedly poor or great response to statin therapy). We would do much better as a preventative community if we were able to identify risk, and treat and maintain statin therapy in patients who were appropriate, rather than simply debate whether targets should or should not be uncompromisingly pursued.

Ongoing Assessment of the Guidelines Is Required

Evaluation of the new ACC/AHA guidelines and their associated risk engine will need to be undertaken to determine their validity and relevance for the Canadian environment. Risk assessment tools have been available for many decades and it is clear that no single model is ideal. It is not even clear if the new ACC/AHA guidelines will result in classification of more subjects to risk groups that are eligible for statin therapy, although this is likely to be the case. We believe that a broader use of statins on the background of aggressive lifestyle modification will result in beneficial reductions in cardiovascular event rates, but this will need prospective evaluation. In addition, ongoing randomized trials of new lipid-modifying agents will soon provide exciting evidence about the value of lowering LDL-C to levels that cannot be achieved with

statins alone. As such, although we acknowledge the many novel recommendations in the new ACC/AHA cholesterol treatment guidelines, we see no reason to alter our own recommendations at this time. We wish to reinforce the importance of appropriate screening coupled with risk assessment and challenge our colleagues to work to develop novel local solutions to transmit this message to our patients. Treatment and adherence rates can be improved with an assertive advocacy approach such as those that have been successfully achieved for blood pressure control. Harmonization with guidelines by other societies as part of the **C**anadian **C**ardiovascular **Ha**rmonization of **N**ational **G**uidelines **E**ndeavour (C-CHANGE) is an important concept to simplify the overall approach to our patients.[9] The adoption of the C-CHANGE recommendations by the provincial ministries emphasizes the importance of this harmonized approach and the general concept of cardiovascular risk reduction. This is not the time to debate the theoretical merits of one guideline vs another, but rather to use this opportunity to raise awareness of the importance of lipid management in reducing the clinical and socioeconomic effects of cardiovascular disease and advocating for improved heart health for our patients.

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