

McPherson R, Frohlich J, Fodor G, Genest J. Canadian Cardiovascular Society position statement – recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006;22:913-27.

To the Editor:

Recommendations for the diagnosis and treatment of dyslipidemia have become an important source of guidance for Canadian primary care practitioners. Because of the widespread implications of these recommendations, it is vitally important that the statements made are firmly based in the evidence.

The decision to use the Appraisal of Guidelines Research and Evaluation (AGREE) principles for guideline formulation should be applauded. The use of evidence grading for the recommendations and the inclusion of a conflict of interest statement are important improvements over the 2003 recommendations (1). However, the AGREE tool (2) contains 23 key items, and many of these do not appear to have been addressed in the 2006 position statement.

Item 5 – the patients' views and preferences have been sought. There appears to have been no process for assessing patient perspectives or acquiring patient input into the recommendations. If such a process was undertaken, it was not described within the content of the publication.

Item 7 – the guidelines have been piloted among target users. There is no indication that these recommendations were pretested by any end users before publication. The focus and practicality of the document have been previously questioned by users (3).

Item 10 – the methods used for formulating the recommendations are clearly described. The development of recommendations is seldom a black-and-white process. A method of how the final recommendations were agreed on, along with a description of how disagreement was resolved was not discussed.

Item 14 – a procedure for updating the guideline is provided. There was no explicit statement regarding the procedure or timelines for updating the recommendations.

Perhaps the most challenging feature of interpreting this position statement is the heterogeneity of approach taken with the AGREE tool, Item 12 – there is an explicit link between the recommendations and the supporting evidence. For many of the recommendations (laboratory measurements, lifestyle and noninvasive investigations), the link to literature and the grading of evidence-base is explicit. Some medication recommendations, such as the drop of the high-risk low-density lipoprotein cholesterol (LDL-C) target from 2.5 mmol/L to less than 2.0 mmol/L, have clear evidence base (TNT [4], IDEAL [5], PROVE-IT [6], REVERSAL [7], ASTEROID [8]) and appropriate grading. However, these recommendations are blended with other statements that have less of an evidence base and no evidence grading. Consider the recommendation that low- and moderate-risk patients lower their LDL-C by at least 40%. Examination of the primary prevention trials reveals that none of these trials

TABLE 1
Low-density lipoprotein cholesterol (LDL-C) reduction of primary prevention studies

Study (reference)	Agent, dose	LDL-C reduction in treatment group, %
WOSCOP (9)	Pravastatin, 40mg	26
AFCAPS/TexCAPS (10)	Lovastatin, 20 mg – 40mg	25
PROSPER* (11)	Pravastatin, 40mg	33
ALLHAT-LLT (12)	Pravastatin, 40mg	28
ASCOT-LLA (13)	Atrovastatin, 10mg	33
ALERT (14)	Fluvastatin, 40mg	32
CARDS† (15)	Atrovastatin, 10mg	40

*56% of patients in the PROSPER trial had no history of cardiovascular events. †CARDS contained only patients with diabetes

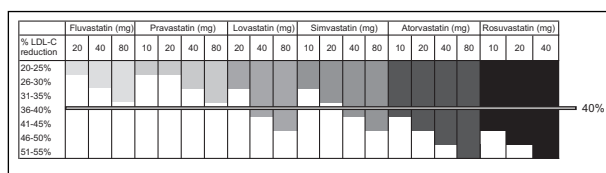


Figure 1 Average low-density lipoprotein cholesterol (LDL-C) reductions of HMG-CoA reductase inhibitors (16)

have exceeded the 40% minimum threshold recommended in the position paper (Table 1).

It is also reasonable to consider the practical implications of these recommendations (the AGREE tool, Items 5 and 7). By recommending agents that lower LDL-C by at least 40%, one-half of the agents studied for primary prevention would no longer be considered appropriate. The only agents with research data in primary prevention that, on average, meet the 40% LDL-C cut-off are atorvastatin 10 mg and lovastatin 40 mg (Figure 1) (16). Higher-potency agents not studied in primary prevention that lack outcome data would be chosen over agents with an established evidence base.

The derivation and choice of the LDL-C reduction by more than 40% is unclear. A number of hypothesis-generating ideas from two meta-analyses are presented as indirect support of this recommendation. The Cholesterol Treatment Trialists' Collaboration meta-analysis of 14 randomized controlled statin trials reported relative reductions of 25% in major coronary events, 19% in coronary mortality and 12% in all-cause mortality associated with every 1 mmol/L reduction in LDL-C (17). Based on these results, the authors predict a proportionally greater efficacy with larger LDL-C reductions of 2.0 mmol/L to 2.5 mmol/L and therefore indirectly justify the appropriateness of higher-potency treatments. It is important to remember that the average LDL-C reduction in all 14 trials in this analysis was 1.01 mmol/L, with a range of 0.35 mmol/L to 1.77 mmol/L, and the average reduction in a subset of the seven primary prevention trials was 0.95 mmol/L (range 0.54 mmol/L to 1.14 mmol/L). Extrapolation beyond the range of trial results should be considered hypothesis-generating, and not as conclusive evidence of benefit. It is also important to consider that, despite the consistency of relative risk reduction

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across various groups, the absolute benefits are lower in lower-risk groups and at lower cholesterol levels (18,19).

The second supporting meta-analysis included 58 cholesterol-lowering trials of both primary and secondary prevention with a variety of cholesterol-lowering agents (20). Once again, the majority of trials (45) showed modest average cholesterol reductions of 0.5 mmol/L to 1.0 mmol/L and associated relative reductions in ischemic heart disease events of 21% to 30% after five years. Five of the remaining trials that showed larger reductions in LDL-C (1.6 mmol/L) showed 50% relative reductions in ischemic heart disease events. The information included in the 2006 recommendations comes from an age-based analysis of 10 cohort studies, suggesting that a 60-year-old patient with a 1.8 mmol/L reduction would have a 61% relative reduction in ischemic heart disease events. The same analysis estimates that at the age of 50 years, a 3.0 mmol/L reduction in LDL-C would lead to a 91% reduction in the same end point. Cohort analysis is considered a lower level of evidence and even the study's authors acknowledge the need to consider dose-related side effects, the lack of outcome data with some high-potency agents and the prudence of selecting commonly used older drugs for general use (20).

We are encouraged by the improvements in the rigour of the 2006 document, but suggest that more uniform and complete application of the AGREE tool may enhance the practicality of the document and provide greater transparency to the evidence base supporting all recommendations.

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On behalf of the Canadian Academic Detailing
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NOTE: The above letter was forwarded to the authors of the mentioned manuscript for comment, but no response has been received.

SOURCES OF SUPPORT: This commentary was based on work done by the Canadian Academic Detailing Collaboration, made possible by a financial contribution (5590027) from the Health Care Strategies, Policy Contribution Program, Health Canada. The views expressed herein do not necessarily represent the official policies of Health Canada.

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LETTER TO THE EDITOR

From the Authors:

We would like to thank Mr MacNair and Mr Bugden for their kind comments regarding the new Canadian Cardiovascular Society position statement on the recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. We have previously changed some aspects of the guidelines in response to constructive criticism by members of the medical community, and these changes are reflected in the 2006 position statement. We were particularly fortunate to follow this advice and use the Appraisal of Guidelines Research and Evaluation (AGREE) formula. As noted by Mr MacNair and Mr Bugden, the AGREE tool contains many items that some of our reviewers have found either not applicable or too cumbersome to complete.

The process of evaluating the evidence and compiling recommendations has been ongoing by our group since 1994, first under Health Canada and lately under the guidance of the Canadian Cardiovascular Society. The level of evidence, the

grading of the evidence and the evaluation of novel clinical studies is a continuously ongoing process. This entire process, therefore, was not a de novo experience, but rather the continuation of ongoing work for the past decade or so. We agree with Mr MacNair and Mr Bugden that some of the evidence in primary prevention is necessarily extrapolated from large-scale clinical studies in high-risk patients. We believe that the cumulative sum of evidence derived from meta-analysis data, especially by the Cholesterol Treatment Trialists' Collaboration published in *Lancet* in 2005, is particularly compelling.

We certainly appreciate Mr MacNair's and Mr Bugden's endorsement of the AGREE tool as a way to better evaluate guidelines and recommendations, and it is our intent to continue to improve on the process and the level of evidence-based recommendations.

Sincerely,
Jacques Genest MD FRCPC FACC
Ruth McPherson MD