Lipid screening to prevent coronary artery disease: a quantitative evaluation of evolving guidelines

Research

Recherche

Steven A. Grover,[*] Marc Dorais,[*] Gilles Paradis,[†] J. George Fodor,[‡] Jiri J. Frohlich,[§] Ruth McPherson,[¶] Louis Coupal,[*] Hanna Zowall[*]

From *the Centre for the Analysis of Cost-Effective Care and the Divisions of General Internal Medicine and Clinical Epidemiology, The Montreal General Hospital, and the Departments of Medicine and Epidemiology and Biostatistics, McGill University; †the Division of Preventive Medicine, McGill University Health Centre and the Department of Epidemiology and Biostatistics, McGill University, Montreal, Que.; ‡the Prevention and Rehabilitation Centre and ¶the Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ont.; and §the Healthy Heart Program, St. Paul's Hospital, Vancouver, BC.

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Abstract

Background: There is strong evidence to support the treatment of abnormal blood lipid levels among people with cardiovascular disease. Primary prevention is problematic because many individuals with lipid abnormalities may never actually develop cardiovascular disease. We evaluated the 1998 Canadian lipid guidelines to determine whether they accurately identify high-risk adults for primary prevention.

Methods: Using data from the Lipid Research Clinics and receiver operating characteristic (ROC) curves, we compared the diagnostic performance of the 1998 lipid guidelines when risk factors for coronary artery disease (CAD) were counted versus calculating risk using Framingham risk equations. We also compared the diagnostic accuracy of the 1998 guidelines with guidelines previously published by the National Cholesterol Education Program in the United States and the 1988 Canadian Consensus Conference on Cholesterol and then used Canadian Heart Health Survey data to forecast lipid screening and treatment rates for the Canadian population.

Results: The Framingham risk equations were more accurate than counting risk factors for predicting CAD risk (areas under the ROC curves, 0.83 [standard deviation (SD) 0.02] v. 0.77 [SD 0.03], $p < 0.05$). Risk counting was a particularly poor method for predicting risk for women. The 1998 Canadian guidelines identified high-risk individuals more accurately than the earlier guidelines, but the increased accuracy was largely due to a lower false-positive rate or a higher true-negative rate (i.e., increased test specificity). Using the 1998 lipid guidelines we estimate that 5.9 million Canadians currently free of cardiovascular disease would be eligible for lipid screening and 322 705 (5.5%) would require therapy.

Interpretation: Calculating risk using risk equations is a more accurate method to identify people at high risk for CAD than counting the number of risk factors present, especially for women, and the 1998 Canadian lipid screening guidelines are significantly better at identifying high-risk patients than the 1988 guidelines. Many of our findings were incorporated into the new 2000 guidelines.

Despite progress in prevention and treatment, cardiovascular disease remains a leading cause of death and disability among Canadians.[1] Epidemiologic studies have identified important cardiovascular risk factors including hypertension, diabetes mellitus, a sedentary lifestyle, obesity, cigarette smoking, elevated low-density lipoprotein (LDL) cholesterol and depressed high-density lipoprotein (HDL) cholesterol.[2–4] Many of these risk factors, including blood lipids, are modifiable and amenable to treatment.[5–11] This has resulted in increasing interest in the benefits of lipid therapy, as well as rising health care expenditures associated with lipid-lowering medication.[12–14]

A decision to treat abnormal blood lipid levels in those who have already

developed cardiovascular disease is a relatively simple one given the clinical trial results to date.[7,8,11] Primary prevention is more problematic, however, because many individuals with lipid abnormalities may never actually develop cardiovascular disease, or they may develop it only after many years.[5,6,9,10] Also, physicians may not be particularly accurate at estimating cardiovascular risk on the basis of an intuitive evaluation of an individual patient.[15] Treatment guidelines have therefore been developed to help physicians target high-risk patients for primary prevention therapy.

In 1988 the Canadian Consensus Conference on Cholesterol (CCCC) published national guidelines for screening and treating hyperlipidemia.[16] Similar guidelines have been published in the United States[17,18] and Europe.[19] Although there are substantial differences between these guidelines, their common purpose is to identify individuals who are most likely to benefit from the treatment of lipid abnormalities.

Health Canada recently completed an initiative to update lipid screening and treatment guidelines for Canada. In 1998 the Working Group on Hypercholesterolemia and Other Dyslipidemias published the preliminary results of these deliberations[20] emphasizing that the evolving guidelines were a working document open to amendments, revisions and adjustments based on new research and a careful evaluation of the guidelines themselves. We present a quantitative evaluation of the 1998 screening guidelines and compare them with guidelines published in the United States by the National Cholesterol Education Program (NCEP I and NCEP II)[17,18] and in Canada by the CCCC.[16] Our analyses of the accuracy of the guidelines identify potential areas for improvement, many of which have been incorporated into the new 2000 guidelines.[30]

Methods

We used data provided by the Lipid Research Clinics (LRC) Prevalence and Follow-up Studies[21–23] to evaluate the diagnostic performance of the 1998 screening guidelines. We also used the Canadian Heart Health Survey[24] (CHHS) data to estimate the prevalence of cardiovascular risk factors among the adult population in Canada and the number of individuals who would require lipid therapy.

LRC Program Prevalence Study

The LRC Prevalence Study was conducted from 1972 to 1976 in 10 North American clinics to determine the prevalence of lipid abnormalities.[21–23] The focus of our analysis is a 15% random sample of participants who were selected to provide a representative cross-section of the population. We excluded individuals with cardiovascular disease, subjects not eligible for screening (i.e., men younger than 40 or older than 70 years of age and women younger than 50 or older than 70), those suspected of having coronary artery disease (CAD) because they were taking digitalis or antiarrhythmics, individuals who were pregnant or were taking lipid medications and those for whom we did not have all laboratory test results. After these exclusions, data for 2218 (52%) of the randomly selected participants were analysed.

Participants were followed for an average of 12.2 years, and specific causes of death were verified using death certificates. Because nonfatal coronary events were not documented in the LRC study, we used death due to CAD as a proxy for coronary risk. Framingham Study data[25] demonstrated that these 2 outcomes share the same risk factors. For our analyses "coronary deaths" included those classified as definite or suspected CAD-related deaths according to the LRC protocol.[21–23]

The 1998 guidelines recommend that target values for blood lipid levels be based on an assessment of the overall risk of a cardiovascular event using 1 of 2 strategies.[20] The first requires a 10-year risk calculation based on multivariate equations published by the Framingham Heart Study,[3,25] also known as the multivariate risk approach. The second strategy, referred to as the risk-counting approach, estimates CAD risk on the basis of the number of risk factors present.[20] For example, using the 1998 screening guidelines, patients with 4 or more risk factors or with a calculated 10-year risk of 40% or more are considered at very high risk for a cardiac event (Table 1); among such very high-risk individuals treatment should be initiated if their LDL-cholesterol level is greater than or equal to 3.5 mmol/L or the total cholesterol:HDL-cholesterol ratio is greater than 5 (Table 2).

Table 1: The 1998 Canadian guideline definitions for level of risk*

Level of risk	No. of risk factors†	10-year risk of CAD, %
Very high	≥ 4 or coronary artery disease present	≥ 40
High	3	20–39
Moderate	2	10–19
Low	0 or 1	< 10

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*Valid for men 40–70 years of age and women 50–70 years of age. See 2000 guidelines[30] for updated definitions.
†Risk factors include: age (≥ 45 years for men, ≥ 55 for women or postmenopausal and not on hormone replacement therapy); history of premature coronary artery disease in a first-degree relative (men ≤ 55 years of age and women ≤ 65); smoking (1 or more cigarettes per day); hypertension (systolic blood pressure at least 140 mm Hg or diastolic at least 90 mm Hg [at least twice] or taking antihypertensive medication); diabetes mellitus (the following criteria met on 2 occasions: casual venous plasma glucose ≥ 11.1 mmol/L and classic signs of diabetes; fasting venous plasma glucose ≥ 7.0 mmol/L on 2 occasions or a positive 75-g glucose tolerance test [2-h post-test glucose ≥ 11.1 mmol/L] on 2 occasions]; left ventricular hypertrophy.

Table 2: The 1998 Canadian guideline lipid values indicating therapy for each level of risk*

Level or risk	LDL-C level, mmol/L	TC:HDL-C ratio
Very high†	≥ 3.5	> 5
High	≥ 4.5	> 6
Moderate	≥ 5.0	> 7
Low	≥ 6.0	> 8

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Note: LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol.
*Therapy is indicated if the LDL-C level or TC:HDL-C ratio is greater than either of the values given for each level of risk. The 2000 guidelines[30] define lipid targets rather than treatment thresholds.
†For example, for patients considered at very high risk (see Table 1) treatment is initiated if their LDL-C level is ≥ 3.5 mmol/L or TC:HDL ratio is > 5.

Diagnostic performance of the 1988 guidelines

We used receiver operating characteristic (ROC) curves[26] to compare the true-positive rate (sensitivity) and false-positive rate (1 – test specificity) of the various guidelines when only LRC subjects classified above a specific decision threshold (low, moderate, high or very high risk) were considered to be at increased risk for CAD-related death. For example, a fixed number of CAD-related deaths occurred over 12.2 years, a proportion of which occurred among very high-risk individuals. The higher this proportion, the better the true-positive rate of the guidelines if only very high-risk individuals are eligible for treatment. However, some of those classified as very high-risk who died of noncardiac-related causes would be needlessly concerned about their blood lipid levels (i.e., the false-positive rate). This exercise can be repeated at different thresholds (e.g., where only those at high or very high risk are treated). An ROC curve plots the true-positive rate on the *y* axis and the corresponding false-positive rate on the *x* axis for each treatment threshold. The area under the resulting fitted curve represents the diagnostic performance or discriminating ability of the guidelines. We compared the diagnostic performance of the 4 different guidelines by comparing the areas under their ROC curves.[26]

Canadian Heart Health Surveys data

The Canadian Heart Health Surveys (CHHS) represent the main findings of 9 provincial surveys conducted between 1986 and 1990.[24] We analyzed the data for men between 40 and 70 years of age and women between 50 and 70 years of age with no symptomatic CAD or stroke (n = 4174). The risk factors menopause, family history of premature CAD and left ventricular hypertrophy were not included in our analyses because the data were not collected in the CHHS. Glucose levels were also absent from the CHHS data; for our purposes this variable was replaced with diabetic status.

Each adult sampled in the CHHS was assigned a weight for the number of Canadians he or she represented.[24] These weights, based on the 1992 Canadian census, were used when forecasting the results of implementing the 1998 screening guidelines nationwide.

Results

Risk profiles of the LRC follow-up cohort and the CHHS participants

The 1998 Canadian lipid screening guidelines focus primary prevention screening efforts on 40- to 70-year-old men and 50- to 70-year-old women. A comparison of the cardiovascular disease risk profiles of the LRC and CHHS participants is presented in Table 3. Although the mean ages of the men and women were slightly lower in the LRC population, the distribution of risk factors in the 2 samples was remarkably consistent.

Diagnostic accuracy of counting risks versus calculating multivariate risk

The accuracy of the 2 proposed risk assessment strategies was compared using ROC curve analyses on 40- to 70-year-old men and 50- to 70-year-old women in the LRC cohort. The risk-counting strategy demonstrated an overall discriminating ability of 0.77 (standard deviation [SD] 0.03), which was significantly lower ($p < 0.05$)

Table 3: Cardiovascular disease risk profile of participants in the Lipid Research Clinics (LRC) Follow-up Study and the Canadian Heart Health Surveys (CHHS)

	Men		Women	
Risk factor*	LRC *n = 1484*	CHHS *n = 2506*	LRC *n = 734*	CHHS *n = 1668*
Age, yr	50.8 (7.8)	55.7 (9.8)	57.8 (5.7)	61.4 (6.2)
Systolic blood pressure, mm Hg	127.0 (17.8)	132.5 (16.5)	131.3 (20.4)	133.9 (18.2)
Diastolic blood pressure, mm Hg	82.2 (10.6)	82.0 (9.1)	80.0 (10.3)	79.5 (8.9)
Total cholesterol, mmol/L	5.5 (0.9)	5.5 (0.9)	5.8 (1.1)	5.9 (1.0)
LDL-C, mmol/L	3.7 (0.8)	3.5 (0.8)	3.8 (1.1)	3.7 (0.9)
HDL-C, mmol/L	1.2 (0.3)	1.2 (0.3)	1.6 (0.4)	1.4 (0.4)
Triglycerides, mmol/L	1.6 (1.1)	1.7 (0.8)	1.4 (0.8)	1.7 (0.8)
TC:HDL-C ratio	4.9 (2.0)	4.8 (1.4)	3.9 (1.5)	4.4 (1.3)
LDL-C:HDL-C ratio	3.3 (1.4)	3.1 (1.1)	2.6 (1.3)	2.8 (1.1)
TG:HDL-C ratio	1.5 (2.2)	1.6 (1.0)	1.0 (0.9)	1.3 (0.9)
Body mass index	26.4 (3.4)	27.0 (4.0)	25.1 (4.9)	27.2 (5.6)
No. (and %) who smoke	526 (35.4)	580 (23.1)	200 (27.2)	284 (17.0)
No. (and %) with diabetes	70 (4.7)	178 (7.1)	31 (4.2)	137 (8.2)
No. (and %) with left ventricular hypertrophy	5 (0.3)		5 (0.7)	

Note: TG = triglycerides.
*Values are expressed as means (and SD) unless otherwise indicated.

than the 0.83 (SD 0.02) obtained using the multivariate risk-assessment approach. Further analyses demonstrated that this was largely because of the poor performance of the risk-counting strategy for predicting CAD among women compared with men (discriminating ability 0.59 [SD 0.12] for women v. 0.81 [SD 0.03] for men). Results of the multivariate risk-assessment approach were similar for men and women (discriminating ability 0.83 and 0.82, respectively).

Comparing guidelines

We compared the diagnostic accuracy of the 1998 lipid screening guidelines with the CCCC[16] guidelines and the American NCEP I and NCEP II recommendations for predicting CAD in the LRC cohort.[17,18] Although these earlier guidelines also targeted adults 30 years of age and older, we restricted our analyses to the age groups in the 1998 guidelines (i.e., 40- to 70-year-old men and 50- to 70-year-old women).

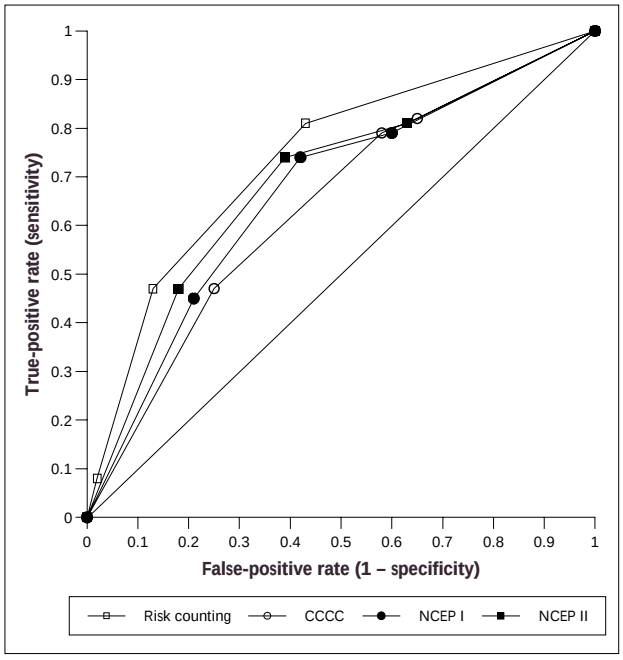

Fig. 1: Receiver operating characteristic curves comparing the discriminating ability of the 1998 lipid guidelines, the Canadian Consensus Conference on Cholesterol (CCCC) Guidelines and the original National Cholesterol Education Program (NCEP) I and the later revised NCEP II guidelines.

Overall, the discriminating ability of the 1998 screening guidelines risk-counting strategy was significantly better than that of the CCCC (0.77 [SD 0.03] v. 0.66 [SD 0.04], $p < 0.05$) (Fig. 1). The 1998 guidelines were also marginally better than the NCEP I (0.69 [SD 0.04], $p = 0.06$) and the NCEP II (0.70 [SD 0.04], $p = 0.15$).

However, on closer inspection the better discrimination of the 1998 guidelines was related to a higher true-negative rate (or improved test specificity) at the expense of a lower true-positive rate (or reduced test sensitivity). For example, earlier guidelines classified approximately 19%–26% of LRC adults as high risk and suitable for treatment, whereas the 1998 guidelines would target only 10.5% of adults for treatment (Table 4). Raising the requirements for being classified as suitable for treatment increases the true-negative rate of the 1998 screening guidelines to 90% compared with 75%–82% for older guidelines.

Projected results of screening Canadians

Using the 1998 guidelines and the CHHS data, we projected that approximately 5.9 million Canadians free of known cardiovascular disease would be eligible for lipid screening (Table 5). This number represents approximately 3.7 million men between 40 and 70 years of age and 2.2 million women between 50 and 70. Given that risk counting is more likely to be adopted by busy physicians than multivariate risk assessment, we projected our results using the risk-counting approach. Less than 1%, or 18 646 men, would be identified as very high risk for CAD with 4 or more risk factors, whereas 61% (2 237 684 men) would be classified as low risk with either 1 or no risk factors. The results for Canadian women were similar.

Table 4: Predicted level of risk for coronary artery disease (CAD) for the LRC cohort using each of the lipid screening guidelines and diagnostic accuracy based on disease outcome

Screening guidelines	Predicted level of risk, no. (and %) of LRC subjects *n = 2218*		CAD-related death *n = 62* (true-positive rate, %)	No CAD-related death *n = 2156* (true-negative rate, %)
	Low risk	High risk		
NCEP I	1745 (78.7)	473 (21.3)	45	79
NCEP II	1802 (81.2)	416 (18.8)	47	82
CCCC	1649 (74.3)	569 (25.7)	47	75
1998 guidelines*	1985 (89.5)	233 (10.5)	42	90

Note: NCEP I and NCEP II = first and second National Cholesterol Education Program Guidelines, respectively, CCCC = Canadian Consensus Conference on Cholesterol.
*Subjects identified for treatment are considered high risk; untreated subjects are considered low risk.

The number of Canadians who would require treatment was also forecasted using the threshold lipid values (Table 2) for initiating treatment (see Table 6). Overall, 322 705 adults or 5.5% of the Canadian screened would require therapy. Among the 26 237 Canadians with 4 or more risk factors 11 904 (45.4%) would undergo treatment; 16 246 (0.5%) of the the 3.6 million Canadians classified as low risk would require treatment.

Interpretation

The 1998 lipid screening guidelines discriminate more accurately between people at high risk for CAD and those at low risk for CAD than the old CCCC guidelines.[16,20] This increased accuracy is largely due to a lower false-positive rate. However, the associated higher false-negative rate means more people, who would eventually die from cardiac-related causes, would be falsely assured that they did not require treatment. This problem could be overcome in part by recalibrating the treatment guidelines to more aggressively treat those at the lower levels of risk for CAD. For instance, lipid target levels for each risk level could be lowered so that more individuals would be eligible for treatment. Unfortunately, this would increase the false-positive rate as well.

Because the LRC data included only fatal coronary events, it was necessary to substitute death due to CAD for total CAD risk when evaluating the diagnostic performance of the 1998 guidelines. Nonetheless, this approach can be used to compare the relative accuracy of different lipid screening guidelines, given that the risk factors for death due to CAD have been shown to also predict CAD events.[25] We also note that some risk factors specified in the guidelines were not available in the CHHS data for evaluation. However, these risk factors, including family history and left ventricular hypertrophy were also not identified as independent risk factors in the recent Framingham analyses.[25] Finally, we emphasize that we focused on primary prevention screening only and did not consider the current guidelines for secondary prevention lipid treatment.

The 1998 screening guidelines also demonstrate marginally superior discriminating ability when compared with their American counterparts.[17,18] It is not readily apparent why this is so, given that they all consider lipid parameters and non-lipid risk factors. However, it has been shown that the ratio of total cholesterol to HDL-cholesterol level is the best lipid discriminator for increased risk for CAD;[27] the 1998 Canadian guidelines incorporate this important lipid risk factor, whereas the American guidelines focus primarily on LDL-cholesterol levels, with a more minor role for HDL cholesterol.[18]

If the 1988 guidelines are applied to the CHHS data and extrapolated to the Canadian population, approximately 5% of Canadian adults eligible for screening would ultimately be targeted for some form of lipid therapy. These results are consistent with a similar analysis by Haq and colleagues[28] in which British Health Survey data and Framingham equations were used to estimate the proportion of the British adult population that would be eligible for lipid

Table 5: Projected number of Canadian men and women eligible for lipid screening at each level of risk for CAD using the 1998 screening guidelines

Level of risk	No. of risk factors	Projected no. (and %) of Canadians in each risk group					
		Men		Women		Total	
Very high	≥ 4	18 646	(0.5)	7 591	(0.3)	26 237	(0.4)
High	3	231 412	(6.3)	125 064	(5.7)	356 476	(6.1)
Moderate	2	1 179 073	(32.2)	697 243	(31.6)	1 876 316	(32.0)
Low	≤ 1	2 237 684	(61.0)	1 373 548	(62.3)	3 611 232	(61.5)
Total		3 666 815	(100)	2 203 446	(100)	5 870 261	(100)

Table 6: Projected treatment status at each level of risk using lipid threshold values in the 1998 lipid screening guidelines

Level of risk	Projected treatment status, no. (and %) of Canadians screened				Projected total no. (and %) of those eligible for screening	
	No treatment required		Treatment required			
Very high	14 333	(0.3)	11 904	(0.2)	26 237	(0.4)
High	276 906	(4.7)	79 570	(1.4)	356 476	(6.1)
Moderate	1 661 331	(28.3)	214 985	(3.7)	1 876 316	(32.0)
Low	3 594 986	(61.2)	16 246	(0.3)	3 611 232	(61.5)
Total	5 547 556	(94.5)	322 705	(5.5)	5 870 261	(100)

therapy. Among men with no cardiovascular disease between 40 and 69 years of age, they estimated 0.6% would have a 10-year risk of CAD of over 45%, 6.8% would have a risk of over 30%, and 32% would have a risk of 15% or more. In our analysis of Canadian men we estimate that 0.5% would have a risk of 40% or more, 6.3% would have a risk of 20%–39%, and 32.2% would have a risk of 10%–19%. For women between 50 and 70 years of age, the British study estimated that 0% would have a risk of 45% or more, 0.8% would have a risk of 30% or more and 17.9% would have a risk of 15% or more. The estimates for Canadian women are: 0.3% with a 10-year risk of over 40% or more, 5.7% would have a risk of 20%–39%, and 31.6% would have a risk of 10%–19%.

These consistent results indicate that the overall 10-year risk for CAD for most people with hyperlipidemia in our society is below 10%. Accordingly, treatment decisions based on short-term risk estimates will result in a substantial portion of the population not receiving therapy for blood lipid levels that are significantly abnormal. These data underscore the need to develop primary prevention strategies on the basis of not only short-term risk but also the potential long-term benefits of treatment over a lifetime.[29]

Previous analyses of the CCCC guidelines indicated that over 50% of the Canadian population would be targeted for lipid therapy if only blood lipids levels were considered.[16] However, when applying the 1998 guidelines approximately 5% of the population would require lipid therapy. Which is more correct? Clinical trial data alone cannot dictate who should be treated. The long-term benefits, the associated risks and the net cost of treatment must also be considered when these decisions are made. Also, if we are to improve long-term compliance, patients' preferences must not be ignored.

Clearly, the 1998 lipid screening guidelines represent an ongoing effort to formulate a clinically reasonable, scientifically sound and affordable strategy to treat hyperlipidemia in Canadians. This study was conducted to provide a systematic evaluation of the guidelines, which was needed to advance the development of this primary prevention policy. The updated 2000 guidelines for the management and treatment of dyslipidemia[30] have incorporated many of our observations including the importance of accurately assessing the risk for a coronary event.

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Reprint requests to: *Dr. Steven A. Grover, The Montreal General Hospital, Division of Clinical Epidemiology, 1650 Cedar Ave., Montreal QC H3G 1A4*