Practical use of the Framingham risk score in primary prevention

Canadian perspective

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Abstract

Objective To review the 2009 Canadian Cardiovascular Society guidelines and provide practical recommendations for physicians.

Sources of information Initial review of the references provided with the guidelines led to a search of the PubMed, ACP Journal Club, and Cochrane databases using the key words primary prevention and statin for English-language clinical trials, randomized controlled trials, meta-analyses, and reviews conducted with human participants. References from appropriate retrieved articles were also reviewed.

Main message The guidelines outline low-density lipoprotein cholesterol (LDL-C) thresholds and targets to inform optimal use of statins in the primary prevention of cardiovascular disease (CVD). Family history of CVD and levels of high-sensitivity C-reactive protein (hsCRP) are risk modifiers in calculating the risk score with the new recommendations. An electronic calculator has been developed to facilitate increased uptake of these guidelines. Large numbers of asymptomatic people, particularly the elderly, will become eligible for statin therapy according to these new guidelines. Poor uptake by physicians and patients might result from the need for repeated testing of hsCRP and LDL-C levels in people who do not perceive themselves to be ill. Controversy persists concerning the role of hsCRP in the reclassification of CVD risk, and the concept of treating LDL-C to target has never been tested as an independent variable in a randomized trial. As two-thirds of the LDL-C lowering achieved by a statin occurs at the initial dose, it might be possible to achieve considerable CVD risk reduction for those at risk by treating initially with a mid-dose statin without LDL-C follow-up.

Conclusion A simplified approach might appeal to patients or physicians who find current guidelines too complex, cumbersome, or costly. Success in getting high-risk patients to take statins is key to achieving improved CVD mortality reduction.

Résumé

Objectif Revoir les directives 2009 de la Société canadienne de cardiologie et fournir des recommandations pratiques aux médecins.

Sources de l’information Une revue initiale des références fournies par les directives nous a amenés à consulter PubMed, l’ACP Journal Club et la base de données Cochrane à l’aide des rubriques primary prevention et statin pour repérer les essais cliniques, essais cliniques randomisés, méta-analyses et revues de langue anglaises portant sur des humains. On a également révisé les références des articles pertinents identifiés.

Principal message Les directives précisent les seuils et les cibles pour le cholestérol lié aux lipoprotéines de basse densité (LDL-C) afin de faire connaître l’utilisation optimale des statines dans la prévention primaire.

KEY POINTS The 2009 Canadian Cardiovascular Society (CCS) guidelines provide consistency and professional support in cardiovascular disease prevention, and the author has developed a free calculator (available at www.palmedpage.com) to facilitate their implementation. The treat-to-target approach leads to repetitive testing to determine if low-density lipoprotein cholesterol goals have been met, despite an absence of evidence that such goals are important. Adding high-sensitivity C-reactive protein testing on at least 2 occasions for selected subgroups, as the newer guidelines suggest, adds further to expense and complexity. Most outcome benefit is seen at the initial dose of statin therapy, and there is supporting evidence that when guideline uptake is suboptimal, patients derive substantial benefit from an empirical mid-dose statin without monitoring of low-density lipoprotein cholesterol levels.

POINTS DE REPÈRE Les directives 2009 de la Société canadienne de cardiologie (SCC) assurent une cohérence et un soutien professionnel pour la prévention des maladies cardiovasculaires, et l’auteur a développé un calculateur (disponible gratuitement sur www.palmedpage.com) pour faciliter leur mise en pratique. L’approche qui consiste à traiter en fonction de cibles requiert de nombreux examens pour vérifier si le niveau du LDL-cholestérol (LDL-C) a atteint la valeur visée, malgré l’absence de preuve de l’importance d’un tel objectif. L’addition d’au moins 2 dosages de la protéine C-réactive à haute sensibilité pour des sous-groupes choisis, comme le suggèrent les nouvelles directives, ajoute encore aux coûts et à la complexité. C’est à la dose initiale qu’on observe la plupart des avantages d’un traitement par les statines, et certaines données indiquent qu’en cas d’adhésion sous-optimale aux directives, les patients bénéficient grandement d’une dose moyenne empirique de statine sans monit orage des niveaux du LDL-C.
des maladies cardiovasculaires (MCV). Une histoire familiale de MCV et des niveaux élevés de la protéine-C réactive hautement sensible (hsCRP) sont des éléments qui interviennent dans le calcul du score de risque selon les nouvelles recommandations. Un calculateur électronique a été développé pour faciliter une meilleure adhésion à ces directives. D’après ces directives, bon nombre de sujets asymptomatiques, notamment les personnes âgées, vont devenir candidats pour un traitement aux statines. Une adhésion insuffisante de la part du médecin ou du patient pourrait être due à la nécessité de répéter les dosages de la hsCRP et du LDL-C chez des sujets qui ne se considèrent pas malades. Le rôle de la hsCRP dans la détermination du risque de MCV demeure controversé et le concept de traiter le LDL-C en fonction de cibles n’a jamais été testé en tant que variable indépendante dans un essai randomisé. Étant donné que, dans une proportion de deux sur trois, la réduction du LDL-C causée par une statine survient à la dose initiale, on pourrait peut-être obtenir une réduction considérable du risque de MCV chez les personnes à risque en commençant par une dose de statine intermédiaire, sans suivi du LDL-C.

Conclusion Une approche simplifiée pourrait s’avérer intéressante pour les patients ou les médecins qui trouvent les directives actuelles trop complexes, trop exigeantes ou trop coûteuses. Il est crucial de convaincre les patients à risque élevé de prendre des statines si on veut obtenir une meilleure réduction de la mortalité par MCV.

Case description
Ms M.E. is a 61-year-old recently retired real estate agent who presents with general health concerns, as she feels she is unfit and somewhat overweight. Her body mass index is 28 kg/m². Blood pressure is 145/95 mm Hg, and she is not taking any medication. Findings of physical examination are otherwise unremarkable. She has never smoked and gives no personal or family history of diabetes. Two uncles were known to have heart disease, but both parents died in their eighties of other causes.

Results of laboratory work include a fasting blood sugar level of 5.6 mmol/L, total cholesterol of 6.50 mmol/L, a high-density lipoprotein cholesterol (HDL-C) level of 1.25 mmol/L, a low-density lipoprotein cholesterol (LDL-C) level of 3.26 mmol/L, a triglyceride level of 2.65 mmol/L, and a ratio of total cholesterol to HDL-C of 5.2 mmol/L.

You explore her motivation to begin a meaningful commitment to exercise, and she agrees to a referral to a diettitian. Your old Framingham calculator indicates a 13% risk for all cardiovascular events and a threshold LDL-C level of 4.13 mmol/L for initiation of lipid-lowering therapy. You discuss the modest benefit of acetylsalicylic acid (ASA) for primary prevention and resolve to become familiar with the new Canadian dyslipidemia guidelines before her next visit.

Sources of information
References provided with the 2009 Canadian Cardiovascular Society (CCS) guidelines were initially reviewed. PubMed was searched using the key words primary prevention and statin, restricted to English-language clinical trials, randomized controlled trials, meta-analyses, and reviews conducted with human subjects. The ACP Journal Club and Cochrane databases were searched using the same key words. References from appropriate retrieved articles were also reviewed.

Risk score derivation
The Framingham risk score (FRS) has evolved in North America as a validated means of predicting cardiovascular disease (CVD) risk in asymptomatic patients. More recently, tables have been developed to help predict all aspects of CVD risk. Input variables are easily obtained from office history, physical examination findings, and basic laboratory evaluations. A 10-year risk score can be derived as a percentage, which can then be used to inform the decision about initiating lipid-lowering therapy for primary prevention. Risk is considered low if the FRS is less than 10%, moderate if it is 10% to 19%, and high if it is 20% or higher.

Decisions based on the Framingham tables are made every day in office practice. In 2009 the CCS published a new set of guidelines, which coupled the new Framingham algorithms with enhanced modifiers for subsets of patients. These modifiers included family history of coronary artery disease before age 60 in a first-degree relative, and evaluation of high-sensitivity C-reactive protein (hsCRP) levels in older patients at moderate 10-year risk of CVD. The FRS has been validated in Canada.

Value of primary prevention
Secondary prevention of CVD with statins is effective. Absolute risk is high and relative numbers of events are also high. Primary prevention using statins is a more population-based strategy; a lower absolute risk of CVD exists among these asymptomatic individuals, but numerous cardiovascular events still occur. Patients with the highest risk scores benefit most from statin therapy. There is, however, a 20% reduction in relative mortality risk for every 1-mmol/L reduction in LDL-C levels, no matter how high the initial lipid level might be. This implies that treating patients who have high risk scores and normal lipid levels can reduce mortality, and this has been demonstrated. Screening of appropriate patients (Box 1) is therefore important in order to identify those who might benefit from preventive measures.
Evolving importance of risk factors

Differences in risk scoring between the 2006 and 2009 CCS guidelines reflect, in part, the inclusion of all vascular end points in the risk equation. In addition to cardiac death and infarction, end points also include stroke, peripheral vascular disease, and heart failure. Risk scores expressed as percentages over 10 years are therefore going to be higher. Table 1 outlines the changes in risk scoring assigned to various risk factors.

Patients with diabetes are not automatically considered to be at high risk of CVD according to statin guidelines. Many can be scored the same as patients without diabetes, but the presence of at least 1 cardiac risk factor, or age older than 45 years in men and 50 years in women, does move them to high-risk status.

Problem of LDL-C targets

Target LDL-C levels comprise the new treatment goals, and, although they are simplified, they are more ambitious (Table 2). They represent a “treat to LDL-C target” approach, which has been criticized because no statin trial to date has demonstrated that lowering LDL-C to target levels improves CVD outcomes. Randomization in statin trials has been by type of statin treatment not by LDL-C targets. Further, use of LDL-C targets disregards nonlipid effects of statins on inflammation, thrombosis, and oxidation. All-or-nothing targets coupled with performance measures provide strong incentives for overtreatment, not only with high-dose statins, but also with drugs with unproven mortality benefits such as ezetimibe.

Treatment thresholds for LDL-C have been identified for the 3 levels of 10-year risk. The threshold of 3.4 mmol/L for those at moderate risk comes from the ASCOT study (Anglo-Scandinavian Cardiac Outcomes Trial), which studied only patients with 3 or 4 CVD risk factors and cannot reflect the needs of the many people in this category who are at lower risk.

It has been shown that two-thirds of the lipid-lowering effect of any statin is realized at the starting dose. Thereafter, doubling the dose of a statin will only lower LDL-C levels by a further 4% to 7%. While it is acknowledged that patients with established CVD, or those at high risk of CVD, will benefit from high-intensity statin therapy, there is no good evidence for treating to a specific LDL-C target. To ascertain optimal dosing, Hayward and colleagues used a simulated model of population-level effects of statin therapy, using 40 mg of simvastatin for patients at 5% to 15% CVD risk and 40 mg of atorvastatin for patients at greater than 15% risk. Compared with a treat-to-target approach, this strategy resulted in a considerable saving of life-years at lower cost, while treating fewer patients with high-dose statins. In view of the lack of evidence for LDL-C targets, laboratory follow-up was only suggested to assure medication safety, reducing time and expense in follow-up.

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**Box 1. Patients who require screening for cardiovascular disease**

<table>
<thead>
<tr>
<th>Screen the following patients for cardiovascular disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Men aged 40 y and older</td>
</tr>
<tr>
<td>• Women aged 50 y and older or postmenopausal women</td>
</tr>
<tr>
<td>• Children with a family history of hypercholesterolemia or chylomicronemia</td>
</tr>
</tbody>
</table>

Screen all patients with the following conditions regardless of age:

| • Diabetes |
| • Hypertension |
| • Current cigarette smoking |
| • Obesity |
| • Family history of premature CAD (< 60 y in first-degree relative) |
| • Inflammatory disease (SLE, rheumatoid arthritis, psoriasis) |
| • Chronic renal disease (eGFR < 60 mL/min/1.73 m²) |
| • Clinical atherosclerosis |
| • HIV infection treated using highly active retroviral therapy |
| • Clinical manifestations of hyperlipidemia (xanthomas, xanthalasmas, premature arcus cornealis) |
| • Erectile dysfunction |


The concept that relative risk reduction with statins is similar for patients all the way down to those at 5% 10-year CVD risk (with much larger numbers needed to treat) comes from the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), which has generated many concerns related to its methodology. Most guidelines apply a higher treatment threshold to try to achieve an acceptable risk-benefit ratio and to avoid treating patients who might have very small absolute event reductions from statin therapy.

Treating larger numbers of patients at lower absolute risk also requires that statin therapy have few side effects. Although statins seem to be relatively safe, there are emerging concerns, such as those over increased myalgia with exercise and increased vascular events on sudden discontinuation of the medication.

The success of lipid-lowering therapy in primary prevention of CVD is similar for patients all the way down to those at 5% 10-year CVD risk (with much larger numbers needed to treat) comes from the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), which has generated many concerns related to its methodology. Most guidelines apply a higher treatment threshold to try to achieve an acceptable risk-benefit ratio and to avoid treating patients who might have very small absolute event reductions from statin therapy.

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Most reviews support the use of statins in the primary prevention of CVD. Benefit has recently been questioned in women and in the elderly, however, and a recent meta-analysis was unable to show overall mortality reduction in primary prevention trials in which patients with existing CVD had been carefully excluded. It seems reasonable, therefore, to direct statin therapy in primary prevention toward patients with higher FRSSs rather than those who simply have high lipid levels.
This model reduces the number of patients treated with high-dose, high-potency statins while reducing cardiovascular mortality at least as effectively. The concept requires prospective controlled trials for validation.

**Problem of hsCRP**

Physician compliance with lipid guidelines has in the past been suboptimal in Canada. Adding another test along with a complex algorithm incorporating appropriate use is unlikely to improve this situation. Besides being an acute-phase reactant, hsCRP, much like blood pressure, shows considerable within-subject variability, with a standard deviation of 1.2 mg/L. Such variation is sufficient in itself to reassign a patient to a different level of treatment according to current guidelines. Even accepting the values obtained, adding hsCRP to the standard FRS produces changes that are small and inconsistent, and it seems unlikely that the increase in cost and complexity is warranted. There is also prospective evidence that hsCRP level is significantly related to risk factors already in use, including smoking status, blood pressure, and glucose and cholesterol levels.

It was shown in the JUPITER trial that treating older patients at moderate risk, with LDL-C levels below 3.4 mmol/L and hsCRP levels greater than 2 mg/L, reduced the number of CVD end points. The trial did not compare hsCRP testing with no testing, nor did it compare outcomes of those with high versus low levels of hsCRP. There is at present poor evidence of the contribution of hsCRP to the reduction of CVD events.

**Problem of evaluation**

Many of the trials used to derive cardiovascular end points also involve secondary prevention. Treatment recommendations for primary prevention in patients at lower risk might be inappropriate if they are derived from secondary prevention trials.

As guidelines start to use more subgroup analyses and cost-benefit considerations, it becomes difficult to remember age cutoffs and targets for such variables as sex, presence of diabetes, hsCRP levels, and family history. Framingham tables and text are adequate guides, but they are time-consuming and difficult to retrieve.
Table 2. Target lipid levels

<table>
<thead>
<tr>
<th>RISK LEVEL</th>
<th>INITIATE TREATMENT IF:</th>
<th>PRIMARY TARGETS</th>
<th>ALTERNATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Consider treatment in all patients</td>
<td>LDL-C &lt; 2 mmol/L or ≥50% ↓ LDL-C</td>
<td>apoB &lt; 0.80 g/L</td>
</tr>
<tr>
<td>CAD, PVD, atherosclerosis* Most patients with diabetes FRS ≥20% RRS ≥20%</td>
<td></td>
<td>Class I, level A*</td>
<td>Class I, level A*</td>
</tr>
<tr>
<td>Moderate</td>
<td>LDL-C &gt; 3.5 mmol/L TC/HDL &gt; 5.0 hs-CRP &gt; 2 mg/L Men &gt; 50 years Women &gt; 60 years Family history and hs-CRP modulates risk (RRS)</td>
<td>LDL-C &lt; 2 mmol/L or ≥50% ↓ LDL-C</td>
<td>apoB &lt; 0.80 g/L</td>
</tr>
<tr>
<td>FRS 10%-19%</td>
<td></td>
<td>Class IIa, level A*</td>
<td>Class IIa, level A*</td>
</tr>
<tr>
<td>Low</td>
<td>LDL-C ≥ 5.0 mmol/L</td>
<td>≥50% ↓ LDL-C</td>
<td>Class IIa, level A*</td>
</tr>
<tr>
<td>FRS &lt; 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grades and levels of evidence for each target are shown in bold. Classes and levels of evidence are summarized below. Clinicians should exercise judgement when implementing lipid-lowering therapy. Lifestyle modifications will have an important long-term impact on health and the long-term effects of pharmacotherapy must be weighed against potential side effects. Meta-analysis of statin trials show that for each 1.0 mmol/L decrease in low-density lipoprotein cholesterol (LDL-C), there is a corresponding RR reduction of 20% to 25%. Intensive LDL-C lowering therapy is associated with decreased cardiovascular risk. Those whose 10-year risk for cardiovascular disease (CVD) is estimated to be between 5% and 9% have been shown in randomized clinical trials to achieve the same RR reduction from statin therapy as those at a higher 10-year risk (25% to 50% reduction in events), but the absolute benefit of therapy is estimated to be smaller (in the order of 1% to 5% reduction in CVD), the numbers needed to treat to prevent one cardiac event are higher and the cost/benefit ratio of therapy is less favourable than for those at higher risk for CVD. For individuals in this category, the physician is advised to discuss these issues with the patient and, taking into account the patient’s desire to initiate long-term preventive cholesterol-lowering therapy, to individualize the treatment decision. *Atherosclerosis in any vascular bed, including carotid arteries. apoB Apolipoprotein B level; CAD Coronary artery disease; FRS Framingham risk score; HDL-C High-density lipoprotein cholesterol; hs-CRP High-sensitivity C-reactive protein; PVD Peripheral vascular disease; RRS Reynolds Risk Score; TC Total cholesterol

A search of the Internet found no electronic tool appropriate for the new CCS guidelines. The Reynolds risk score (RRS) includes the more recently added factors of family history and hsCRP levels, but yields different values when compared with the new CCS guidelines based on the FRS. The RRS is validated in the United States but has not yet been validated in Canada.†

The treat-to-target approach leads to repetitive testing to determine if LDL-C goals have been met, despite an absence of evidence that such goals are important. Adding hsCRP testing on at least 2 occasions for selected subgroups adds further to expense and complexity.

Problems of advocacy and adherence

As guidelines evolve and the population ages, large numbers of patients without known disease will be identified as being at risk and will have indications for statin therapy. Age is by far the largest contributor to the FRS.

The cost of statins will become an increasing burden to individuals and to society, having long-term financial consequences for both. It has been shown even at current levels of advocacy that fewer than 50% of patients take 80% or more of their prescribed statin dosages.‡ Thus, we need to continue to clarify which people actually derive net benefit from statin therapy so that we can advocate more effectively and, perhaps, achieve improved compliance.

Practical alternatives

Practical application of statin therapy can follow 2 courses, one supported by guidelines, the other by expediency (Table 3):

Treat-to-target approach using LDL-C as a surrogate goal. The best evidence and clinical support comes from the 2009 CCS guidelines. Complex new guidelines should be accompanied by accessible application tools available electronically. This should comprise electronic decision support as well as simple calculation. I have developed a tool for use with the 2009 CCS guidelines that is available for use until an authorized version appears. It will calculate risk scores using the new...
algorithms. It will also flag patients with diabetes who become high risk, patients who might benefit from ASA therapy, and patients who might be reclassified by measuring hsCRP levels, although hsCRP entry is optional. Family history is included in the calculation. Treatment thresholds and targets are specified. This allows rapid use of statin and ASA guidelines without reference to tables. It runs in Firefox, Google Chrome, or Internet Explorer and requires that JavaScript be enabled. It is available at www.palmedpage.com. Files can be downloaded for use on local computers. With use of this calculator it quickly becomes clear that large numbers of people, particularly the elderly, become candidates for statin therapy.

Expedient approach when adherence or persistence is a problem. The most important issue is that a patient at considerable 10-year risk be given a statin, with the realization that most of the benefit will be achieved at the initial dose. If the physician or patient resists repeated hsCRP testing or follow-up LDL-C testing, or therapy is discontinued because of cost or complexity, the evidence does support submaximal dosing with less intensive LDL-C monitoring. The FRS could be calculated without hsCRP testing, and, if statin therapy were indicated, 40 mg of simvastatin (if the FRS were <15%) or 40 mg of atorvastatin (if the FRS were >15%) could be given. Starting with higher doses seems to be well tolerated, and repeat visits for dose adjustment, which are so often met with reduced compliance, are avoided. Because doses are not maximized, the 80-mg formulations can be split, leading to an almost 50% reduction in costs, as the prices of 80-mg and 40-mg tablets are very similar. This strategy could result in more patients beginning and remaining on statin therapy, which is the outcome most likely to improve mortality.

Conclusion
New CCS guidelines provide consistency and professional support in CVD prevention. A calculator has been developed to facilitate implementation. Evidence and opinion vary in their support of treating to target LDL-C levels and use of hsCRP measurement in risk evaluation. Because most outcome benefit is seen at the initial dose, there is supporting evidence that when guideline uptake is suboptimal, patients derive substantial benefit from an empirical mid-dose statin without LDL-C monitoring.

Case revisited
Ms M.E. returns in 3 weeks. She has seen the dietitian and is restricting salt and calories. She is walking 2 km each day and complains about her knees. Her weight is unchanged. Blood pressure is 140/90 mm Hg and several home blood pressure readings are below 135/85 mm Hg.

You have found the new CCS guidelines and ordered her hsCRP level be tested; results show levels of 5.25 mg/L and 5.70 mg/L taken 2 weeks apart. Her 10-year CVD risk using the new tables was 13.7%. It is now 13.0% with a lower blood pressure. Being older than 60 and having a high hsCRP level places her at moderate risk. Despite her moderate LDL-C level of 3.26 mmol/L, guidelines recommend further LDL-C lowering to 2.0 mmol/L. She is also a candidate for ASA therapy, although evidence for this is not robust.

You discuss this with Ms M.E., and she indicates that she is willing to take ASA but that she is not ready to take a statin. She believes that she can continue the diet and exercise program and perhaps reach her lipid goal with this lifestyle modification. You agree on a 6-month trial of diet and exercise and further consideration of the need for statin therapy at that time. You point out that if medication is eventually needed, a moderate dose of a generic drug might suffice, provided that she adheres to her diet and exercise program.

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Competing interests
None declared.

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Table 3. Treatment options

<table>
<thead>
<tr>
<th>TREATMENT APPROACH</th>
<th>PATIENT COHORT</th>
<th>LDL-C TARGETS</th>
<th>hsCRP TESTING</th>
<th>BENEFITS</th>
<th>RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline-based (treat to target)</td>
<td>High FRS or High LDL-C level</td>
<td>Yes</td>
<td>Selected groups</td>
<td>Peer support, Consistency, Optimization of benefits</td>
<td>Suboptimal physician uptake, Suboptimal patient compliance, Reliance on surrogate markers and targets</td>
</tr>
<tr>
<td>Expedient</td>
<td>High FRS</td>
<td>No</td>
<td>No</td>
<td>Simplicity, Lower cost, Two-thirds of benefit realized</td>
<td>Maximal benefit not realized, No prospective validation studies exist</td>
</tr>
</tbody>
</table>

FRS—Framingham risk score, hsCRP—high-sensitivity C-reactive protein, LDL-C—Low density lipoprotein cholesterol.
Framingham risk score for primary prevention | Clinical Review

References


