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Society Guidelines

2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

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ABSTRACT

Many developments have occurred since the publication of the widely-used 2009 Canadian Cardiovascular Society (CCS) Dyslipidemia guidelines. Here, we present an updated version of the guidelines, incorporating new recommendations based on recent findings and harmonizing CCS guidelines with those from other Societies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used, per present standards of the CCS. The total

RÉSUMÉ

De nombreux développements sont survenus depuis la publication communément utilisée des Lignes directrices 2009 de la Société canadienne de cardiologie (SCC) sur la dyslipidémie. Nous présentons ici une version mise à jour des lignes directrices, qui inclut des nouvelles recommandations fondées sur des résultats récents qui harmonisent les lignes directrices de la SCC à celles d'autres sociétés. La méthode GRADE (*Grading of Recommendations Assessment, Develop-*

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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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cardiovascular disease Framingham Risk Score (FRS), modified for a family history of premature coronary disease, is recommended for risk assessment. Low-density lipoprotein cholesterol remains the primary target of therapy. However, non-high density lipoprotein cholesterol has been added to apolipoprotein B as an alternate target. There is an increased emphasis on treatment of higher risk patients, including those with chronic kidney disease and high risk hypertension. The primary panel has recommended a judicious use of secondary testing for subjects in whom the need for statin therapy is unclear. Expanded information on health behaviours is presented and is the backbone of risk reduction in all subjects. Finally, a systematic approach to statin intolerance is advocated to maximize appropriate use of lipid-lowering therapy. This document presents the recommendations and principal conclusions of this process. Along with associated Supplementary Material that can be accessed online, this document will be part of a program of knowledge translation. The goal is to increase the appropriate use of evidence-based cardiovascular disease event risk assessment in the management of dyslipidemia as a fundamental means of reducing global risk in the Canadian population.

***ment and Evaluation*) a été utilisée selon les normes actuelles de la SCC. Le score de risque cardiovasculaire global de Framingham (SRF) total sur les maladies cardiovasculaires modifié pour tenir compte des antécédents familiaux de coronaropathie prématurée est recommandé pour l'évaluation du risque. Le cholestérol à lipoprotéines de faible densité demeure la cible principale du traitement. Cependant, le cholestérol non à lipoprotéines de haute densité a été ajouté à l'apolipoprotéine B comme autre cible. L'accent est davantage mis sur le traitement des patients exposés à un risque élevé, incluant ceux ayant une maladie rénale chronique et une hypertension à risque élevé. Le panel principal a recommandé une utilisation judicieuse d'examens secondaires des sujets chez qui la nécessité d'un traitement par des statines est incertaine. De plus en plus de renseignements sur les comportements en matière de santé sont présentés et sont les bases de la réduction du risque chez tous les sujets. Finalement, une approche systématique sur l'intolérance aux statines est recommandée pour optimiser l'utilisation de traitements hypolipidémiants. Ce document présente les recommandations et les conclusions principales de ce processus. Par les contenus complémentaires associés qui peuvent être consultés en ligne, ce document fera partie d'un programme d'application des connaissances. Le but est d'accroître l'utilisation appropriée de l'évaluation des risques d'événements cardiovasculaires fondée sur les preuves dans la prise en charge de la dyslipidémie en tant que moyen fondamental pour réduire le risque global dans la population canadienne.**

The 2009 Canadian Cardiovascular Society (CCS) Dyslipidemia guidelines have been updated in the current document to reflect new advances.[1] In addition, the **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation (GRADE) system was used as is now the standard established by the CCS.[2] The review was conducted under the direction of the CCS completely at arms length from industry.

Over the past decade, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors or statins have emerged as foundational therapy and have been shown to reduce an individual's relative cardiovascular disease (CVD) risk by 25%-35%.[3] They remain the first-line therapy for elevated low-density lipoprotein (LDL) cholesterol (LDL-C). Since the 2009 version of these Guidelines, new randomized trials have evaluated the potential role of combination lipid-lowering therapy to address residual risk. The **S**tudy of **H**eart **a**nd **R**enal **P**rotection (SHARP) was the first to demonstrate a beneficial role of lipid-lowering therapy in subjects with chronic kidney disease (CKD).[4] The important role of CKD as a significant cardiovascular risk factor is defined in the current document.[5]

The primary panel believed it important also to re-evaluate the method of risk assessment and definitions of cardiovascular risk, considering recent literature in this area and the publication of the new European dyslipidemia guidelines.[6] The panel has retained the concept of lipid thresholds and targets for treatment. However, it is important to recognize that overall cardiovascular risk is dependent on the phenotype of the patient with LDL-C being only 1 of those factors. Also, targets for treatment are somewhat arbitrary because none of the intervention studies have aimed for specific lipid targets. These targets are extrapolated from individual trial data and meta-analyses. The concept of non-high-density lipoprotein (HDL) cholesterol (HDL-C) was introduced and this variable has been added to apolipoprotein (apo) B as an alternate target to LDL-C. Its calculation is available from the standard lipid panel. A variety of blood- and imaging-based tests were evaluated for secondary assessment of individuals at risk in whom a clear decision to initiate pharmacotherapy is not obvious. The guideline balanced the emerging belief that many subjects might gain some benefit from lowering their LDL-C with pharmacotherapy, with the notion that secondary testing might help identify the best candidates for drug treatment.[7] The revised Guidelines provide expanded recommendations for health behaviours including diet and exercise. Finally, because statins have remained the cornerstone of therapy and use might expand based on recent analyses, we also reviewed new literature on the potential adverse effects of statin therapy.[8]

The Guidelines set forth by the primary panel were reviewed by a secondary panel of practitioners representing affiliated societies with a substantial interest in dyslipidemia treatment and cardiovascular risk reduction. Harmonization with recommendations from their representative societies and the **C**anadian **C**ardiovascular **Ha**rmonization of **N**ational **G**uidelines **E**ndeavour (C-CHANGE) was encouraged and supported.[9] The following document represents the result of this process and will be part of a program of knowledge translation that will also include slides, case-based learning, and downloadable applications. The goal is to increase the appropriate use of evidence-based CVD event risk assessment in the management of dyslipidemia as a fundamental means of reducing global risk in the Canadian population. The principal changes from the 2009 Guidelines are summarized in Table 1.

Whom to Screen for Lipids

Screening of plasma lipids is recommended in adult men $\geq$ 40 and women $\geq$ 50 years of age or postmenopausal (Fig. 1). The presence of modifiable CVD risk factors (smoking, diabetes, arterial hypertension, obesity) is taken into account in the decision to screen for lipids at any age. Adults with the following risk factors should also be screened at any age: rheumatoid arthritis,[10,11] systemic lupus erythematosus,[12-14] psoriatic arthritis,[12,15] ankylosing spondylitis,[12] inflammatory bowel dis-

Table 1. Major changes since 2009 Guidelines

Introduction of the concept of cardiovascular age
Recommending more frequent monitoring of patients with FRS ≥ 5%
Using apolipoprotein B or non-HDL-C as alternate lipid markers
Addition of chronic kidney disease as a high-risk feature
Reduced age for treatment in diabetes
Specific recommendations about health behaviours
New recommendation about statin adverse effects
Use of GRADE recommendations and process

apoB, apolipoprotein B; FRS, Framingham Risk Score; GRADE, **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation; HDL-C, high-density lipoprotein cholesterol.

eases,[12] chronic obstructive pulmonary disease,[16] chronic HIV infection,[17,18] CKD,[19] abdominal aneurysm, and erectile dysfunction.[20] Individuals of First Nations or of South Asian ancestry are at increased risk and consideration should be given to screening at an earlier age.[21]

Risk Assessment

Cardiovascular risk assessment has been shown to help primary health care providers identify patients most likely to benefit from primary prevention therapies such as the treatment of dyslipidemia or hypertension.[22] Several studies have also demonstrated that the potential benefits of risk assessment are maximized when the results are directly communicated to the patient to engage them in treatment decisions and increase their adherence with prescribed therapy.[23-26]

Despite the potential benefits of calculating and discussing patients' cardiovascular risk with them, a number of studies suggest that most health care providers do not routinely use these decision aids to guide primary prevention therapies.[27] The most commonly cited barrier to implementing cardiovascular guidelines was poor patient compliance. A recent Canadian survey also suggests that physician understanding and use of cardiovascular risk assessment is suboptimal.[28]

The primary focus of CVD risk assessment should be to reassure low-risk (LR) individuals without any treatable risk factors and a healthy lifestyle that they are doing well, to advise individuals with treatable risk factors or unhealthy behaviours to address these factors, and to identify subjects most likely to benefit from pharmacotherapy. We are recommending that the initial risk assessment be completed using the FRS to estimate the 10-year risk of developing "total" cardiovascular events.[29] Among individuals 30-59 years of age without diabetes, the presence of a positive history of premature CVD (men <55 and women <65 years of age

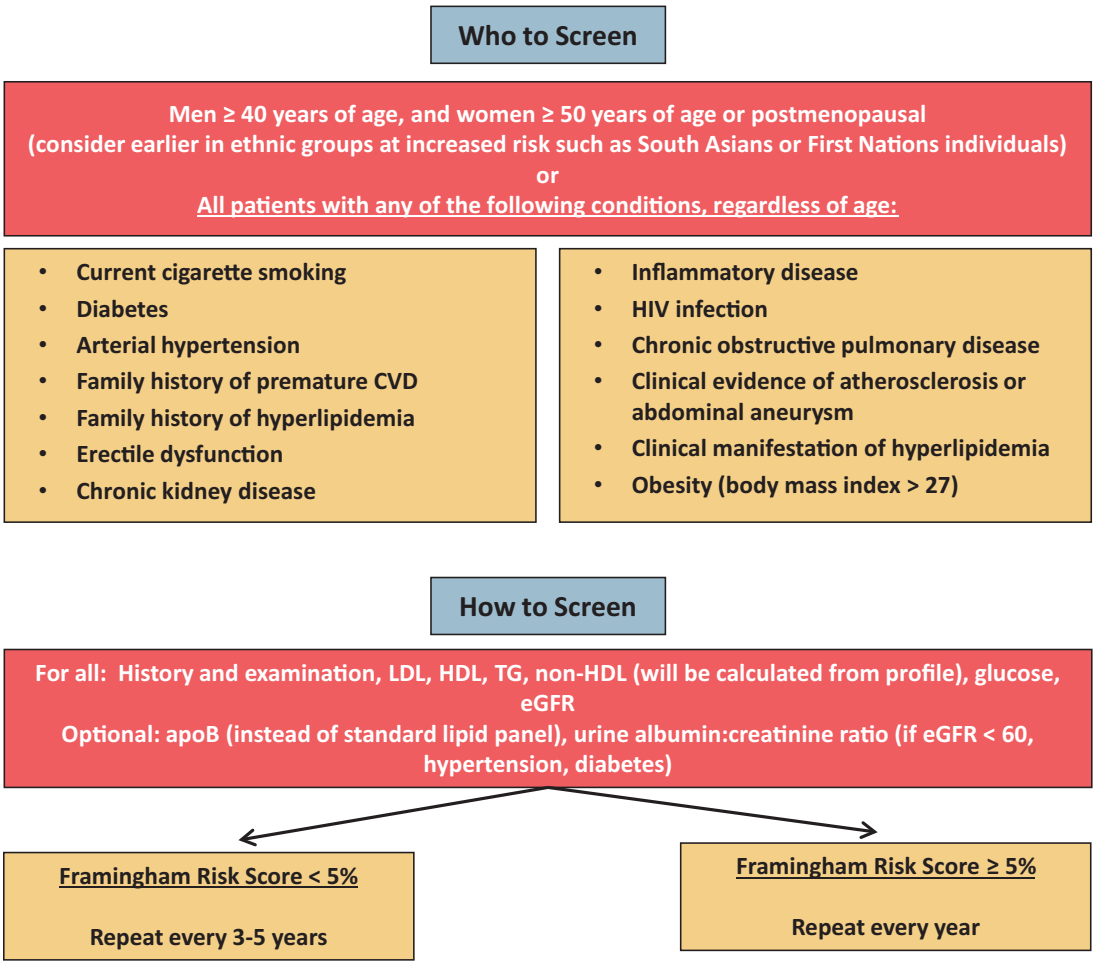

Figure 1. Approach on who and how to screen for dyslipidemia. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

in first-degree relatives) increases an individual's calculated Framingham percent risk by approximately 2-fold.[30] The 10-year Framingham risk percent doubled for family history of premature CVD will be referred to as the modified FRS.

Despite the significant improvement in identifying high-risk individuals several shortcomings must be recognized with all risk assessment strategies including those based on the Framingham Heart Study risk equations. First, short-term risk estimates over 10 years are extremely sensitive to the patient's age such that older individuals are more likely to be targeted for therapy. Second, cardiovascular risk scoring strategies tend to be more accurate among younger individuals because traditional cardiovascular risk factors such as dyslipidemia, hypertension, and cigarette smoking are most strongly associated with premature CVD.[31,32] Third, with increasing age, the increasing risk of other age-related fatal diseases such as cancer reduces the accuracy of risk assessment scoring (the concept of "competing risk"). Finally, there are no randomized trials showing optimal outcomes based on FRS for guiding therapy. Furthermore, no risk equation is perfect. Though an individual whose risk is 30% at 10 years is clearly at increased risk compared with someone whose risk is 10%, one cannot predict with certainty that either individual will or will not develop a CVD event. It must also be recognized that the risk categories that are widely used internationally (LR <10%, intermediate risk (IR) 10%-19%, and high risk 20% or more) are completely arbitrary and have been chosen by consensus rather than by scientific evidence. Accordingly, clinical judgement is essential.

In addition, recent analyses using population data demonstrate that the vast majority of individuals will be identified as being at LR (<10%) over the short term of 10 years.[33] Considering the importance of age as a risk factor, most men younger than 50 years of age and women younger than 70 years of age were classified as LR over the next 10 years.[34]

Despite the limitations of 10-year risk estimates, a number of studies have demonstrated that assessing an individual's total CVD risk can have a positive effect on the management of blood pressure and/or blood lipid levels. Studies that showed the greatest reduction in risk factors were those in which the risk profile was actually given to the patient, thereby supporting patient-centred care. Accordingly, there is increasing interest in finding the better clinical decision aids to help patients understand their risk status.

A systematic review of clinical trials to communicate cardiovascular risk to patients identified metrics such as Cardiovascular Age, Vascular Age, or Heart Age to be particularly meaningful, engaging, and easy to understand.[35] Research using focus groups also suggests that providing individuals with statistical probabilities might be insufficient for motivating change. However, understanding one's cardiovascular risk-adjusted age was shown to be relevant. The basic idea is if you are at high risk compared with your peers, then your vascular system is aging faster than you. This might be particularly useful for individuals whose short-term risk is low but in whom the long-term benefits of risk factor modification might be substantial such as in higher risk young men, and women. Indeed, a "Heart Age" score has been shown to have more of an emotional impact than presenting an estimated CVD risk score to younger individuals at increased risk of CVD.[36]

Considering the recognized limitations of 10-year risk models, existing risk engines, including the FRS, have been adapted to estimate "Cardiovascular Age," "Vascular Age," or "Cardiovascular Age Risk."[6,29,37,38] Cardiovascular age is calculated as the patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex.[24] For example, a 50-year-old with a life expectancy of 25 more years (vs 30 more years for the average Canadian male who lives to be 80 years) would be assigned a cardiovascular age of 55 years. Having primary health care providers engage Canadian patients in discussing their "cardiovascular age" has been shown to reduce uncertainty surrounding prescribed therapy and improve the management of dyslipidemia and hypertension.[24,39]

If the adjusted FRS is used primarily for guiding physician treatment decisions surrounding statin therapy, how should health professionals incorporate Cardiovascular Age into clinical practice? First it should be recognized that the risk factors used for calculating Cardiovascular Age are identical to those used for the adjusted FRS. No additional measurements are required. Cardiovascular Age can be used as a clinical decision aid to inform the patient of their risk status, and underscore the need for healthy lifestyle changes (including weight reduction, regular physical activity, smoking cessation) or adherence with recommended statin therapy. After a change in blood lipids and other risk factors, the patient's Cardiovascular Age can then be recalculated to emphasize the positive effect of following treatment and improve the likelihood of treatment adherence.

Approximately 50% of patients will discontinue lipid therapy within 1 year of starting and as few as 25% of those treated for primary prevention will still continue therapy after 2 years.[40] One of the most common reasons for stopping is that the patient remains unconvinced of the need for treatment.[41] Accordingly, discussing the patient's Cardiovascular Age and the change in their Cardiovascular Age after therapy is an important use for CVD risk assessment in clinical practice. Cardiovascular Age can be estimated from Supplemental Figure S1 or calculated concurrently with the adjusted FRS at www.chiprehab.com.

FRS can also be obtained based on Supplemental Table S2. There is increasing interest in the concept of cardiometabolic risk considering that unhealthy behaviours including excess body weight or lack of regular physical activity increases the risk of diabetes and CVD.[42,43] Moreover, diabetes is 1 of the strongest risk factors for CVD. It might therefore be helpful when trying to motivate patients to lose weight or become more physically active to consider their cardiovascular risk and their diabetes risk (www.myhealthywaist.org or www.chiprehab.com). Not only will weight reduction or exercise improve the lipid profile and reduce blood pressure thereby reducing one's cardiovascular risk, but there are consistent clinical trial data demonstrating that these positive lifestyle changes can reduce the risk of developing diabetes by as much as 60%.[44]

In conclusion, CVD risk assessment should make intuitive sense to patients and health care professionals. It might prove to be most clinically useful when it is used to guide diagnostic and treatment decisions rather than simply defining treatment targets leaving little room for clinical judgement or patient preferences. Considering the suboptimal long-term adherence with lipid pharmacotherapy, communicating the benefits of treatment to pa-

tients in terms of a reduction in CVD risk or cardiovascular age might also have a positive effect on the overall effectiveness of clinical prevention strategies.

RECOMMENDATION

1. We recommend that a cardiovascular risk assessment, using the "10-Year Risk" provided by the Framingham model be completed every 3-5 years for men age 40-75, and women age 50-75 years. This should be modified (percent risk doubled) when family history of premature CVD is positive (ie, first-degree relative <55 years for men and <65 years of age for women). A risk assessment might also be completed whenever a patient's expected risk status changes. Younger individuals with at least 1 risk factor for premature CVD might also benefit from a risk assessment to motivate them to improve their lifestyle (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend calculating and discussing a patient's "Cardiovascular Age" to improve the likelihood that patients will reach lipid targets and that poorly controlled hypertension will be treated (Strong Recommendation, High-Quality Evidence).

Values and preferences. The primary evaluation of risk is the modified 10-year FRS. Considering the overlap in risk factors for diabetes, a simultaneous evaluation of cardiometabolic risk for diabetes might be useful to motivate lifestyle changes. It is well known that a 10-year risk does not fully account for risk in younger individuals. In these individuals, the calculation of a Cardiovascular Age has been shown to motivate subjects to achieve risk factor targets.

Practical tip. For patients older than 75 years of age, the Framingham model is not well validated.[45] Though clinical studies are currently under way to address this group, at this point clinical judgement is required in consultation with the patient to determine the value of pharmacotherapy. One approach is extrapolation of the modified FRS, and this approach identifies most subjects as having intermediate- to high-risk based on age.

Levels of Risk

LR

The LR category still applies to individuals with a modified 10-year FRS <10% (Fig. 2). Pharmacologic lipid-lowering treatment is still advised for LR subjects with severe dyslipidemia (LDL-C > 5.0 mmol/L), a level that usually reflects a genetic lipoprotein disorder, especially familial hypercholesterolemia. Clinical judgement should be used concerning the proper timing for the initiation of pharmacological therapy in such patients. The recent meta-analysis of studies of primary prevention in traditionally defined LR subjects (<10%) suggests that the LDL-C threshold for intervention can even be lower.[46] The judicious use of secondary testing in FRS 5%-9% group might be of value to help guide therapy.

Though there are no prospective randomized control trial data supporting a 50% LDL-C reduction in LR patients specifically, the recommendation is unchanged from 2009.[46] At that time, the recommendation was based primarily on extrapolation of the findings in the **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study[47] in primary prevention, within which a mean 50% LDL-C reduction was achieved with rosuvastatin and was associated with approximately a 40% reduction in major cardiovascular events. A 50% reduction in LDL-C is often achievable with single-agent therapy with moderate to high doses of the most widely prescribed statins. Less aggressive LDL-C lowering will still result in risk reduction (to a lesser degree) considering the linear relationship between LDL-C lowering and event reduction.

More frequent monitoring of individuals with adjusted 5%-9% FRS, but not necessarily treatment. The recommendation to reconsider treatment of individuals with lower modified FRS was based on the 2012 **C**holesterol **T**reatment **T**rialists (CTT) collaboration meta-analysis of 27 randomized trials of statin therapy in people with 5-year risk of major vascular events <10%. This study reported that for individuals with a 5%-9% FRS, a 1 mmol/L of reduction in LDL-C was associated with an absolute reduction in major vascular events of approximately 11 per 1000 over 5 years. The CTT argued that this degree of benefit greatly exceeds any known hazards of statin therapy.[46] Balanced against this high quality evidence was the realization that expanding the IR definition to a lower limit of FRS would represent a substantial change from 2006 and 2009, and would markedly expand the proportion of Canada's population who would be eligible for treatment. In addition, the number needed to treat to achieve the demonstrated relative benefits would be high. And finally, the panel is advocating use of modified FRS to more consistently take into account a family history of premature CVD, a change which in itself will expand the treatment group but in those wherein the treatment for genetic risk is well justified (see above). Accordingly, the panel decided to make no change in the percent strata that define IR for now. However, in recognition of the findings of this meta-analysis, we recommend that the modified FRS 5%-9% risk level, which was traditionally considered as "LR," should prompt more frequent, yearly assessment, judicious use of secondary testing, encouragement for aggressive nonpharmacologic risk factor modification, and consideration of pharmacologic therapy only as outlined in the section on LR.

RECOMMENDATION

1. We recommend pharmacotherapy in LR individuals with LDL-C ≥ 5.0 mmol/L, or if there is evidence of genetic dyslipidemia (such as familial hypercholesterolemia) (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend ≥ 50% reduction of LDL-C in LR individuals for whom treatment is initiated (Strong Recommendation, Moderate-Quality Evidence).

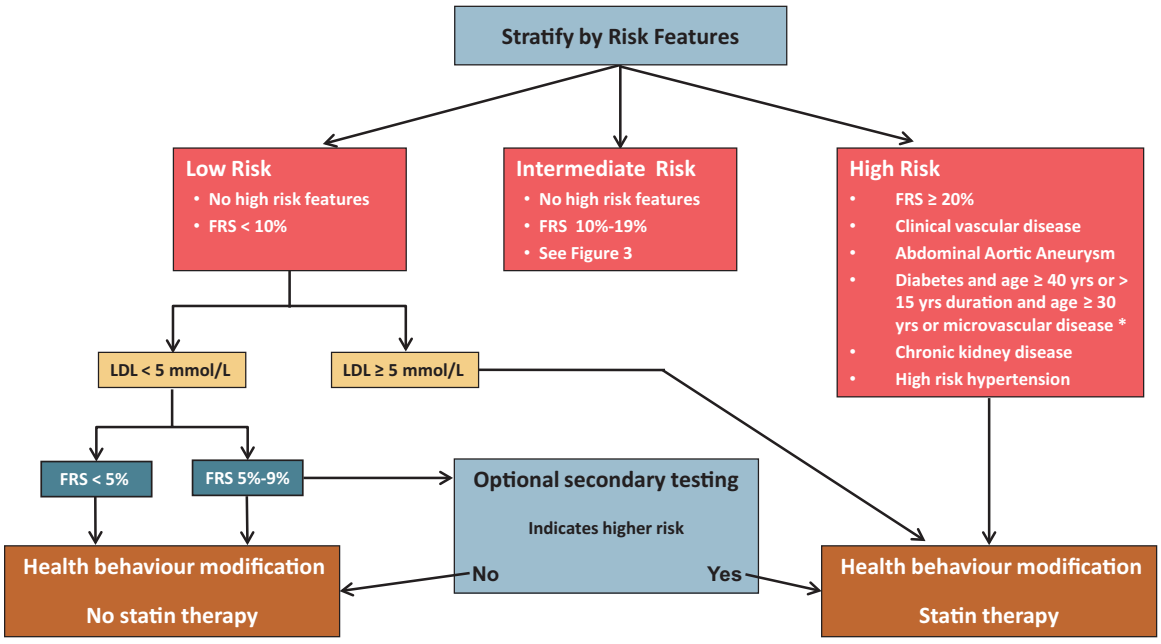

Figure 2. Risk stratification by Framingham Risk Score (FRS) and phenotype.*Not all subjects with diabetes are at high 10-year risk; included for treatment based on randomized studies and high long-term risk.

Values and preferences. This recommendation is unchanged from previous guidelines. Considering relatively less trial evidence in this group of subjects, individual practice will vary and will be dependent on the wishes of the patient and evaluation of the treating clinician. Subjects with a risk in the higher end of this category can have the risks/benefits of statin therapy discussed and might be offered statin therapy based on patient wishes and/or the judicious use of secondary testing.

IR

The IR group encompasses a significant proportion of the Canadian population and is the most difficult to evaluate. Based on the present guidelines, many will be candidates for pharmacotherapy (Fig. 3). If statin therapy is not clearly indicated after evaluating risk with the modified FRS, the clinician can consider the use of the alternate target of apo B or non-HDL-C or secondary testing to refine risk assessment and treatment (see subsequent sections).

In IR patients, the main lipid trigger for treatment is LDL-C ≥ 3.5 mmol/L. Indications for pharmacotherapy are based on primary prevention studies including the **A**ir **F**orce/**Tex**as **C**oronary **A**therosclerosis **P**revention **S**tudy (AFCAPS/TexCAPS),[48] the **W**est **o**f **S**cotland **Co**ronary **P**revention **S**tudy (WOSCOPS),[49] the **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial (ASCOT),[50] and JUPITER.[47] Although clinicians should exercise judgement, pharmacologic therapy is recommended after initiation and compliance with health behaviour modifications among individuals with LDL-C that remains ≥ 3.5 mmol/L because the absolute benefit of therapy is estimated to be significant in these patients.

Apo B and non-HDL-C as alternate targets. Pervasive pharmacologic therapy for IR patients with LDL-C <3.5 mmol/L is not routinely recommended because of the smaller estimated absolute benefit of therapy. However, some of these patients might have an atherogenic dyslipidemia as reflected by plasma apo B and calculation of non-HDL-C might be helpful. In IR patients with LDL-C <3.5 mmol/L, the presence of an apo B ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L identifies patients at increased CVD risk who might benefit from pharmacotherapy.

Moreover, growing evidence indicates the risk of these CVD events during therapy correlates more strongly with the level of apo B or non-HDL-C than with LDL-C.[51] LDL-C is a suboptimal indicator of low-density lipoprotein (LDL) particle number, in particular when triglycerides are higher than 1.5 mmol/L, at which point cholesterol in LDL particles is replaced by triglyceride.[52] One molecule of apo B is present in all atherogenic lipoproteins, including LDL, very-LDL and very-LDL remnants, and lipoprotein (a), and this does not change with variation in LDL cholesterol or triglyceride content. Non-HDL-C is derived from the simple calculation of total cholesterol minus HDL-cholesterol, and is the sum of all the cholesterol transported in atherogenic lipoproteins, regardless of triglyceride level. Apo B was introduced in the 2009 Canadian dyslipidemia guidelines as an alternate primary target of therapy.[1] However, apo B is not yet uniformly available as a funded laboratory test in many provinces. Considering the higher predictive value of non-HDL-C for cardiovascular risk, including for reduction of additional events after statin treatment when compared with LDL-C,[53] plus the ability of laboratories to report non-HDL-C from the standard lipid profile at no additional cost, non-HDL-C is now introduced as an alternate primary target. Non-HDL-C, like apo B, also has the advantage of being applicable in a nonfasting state.

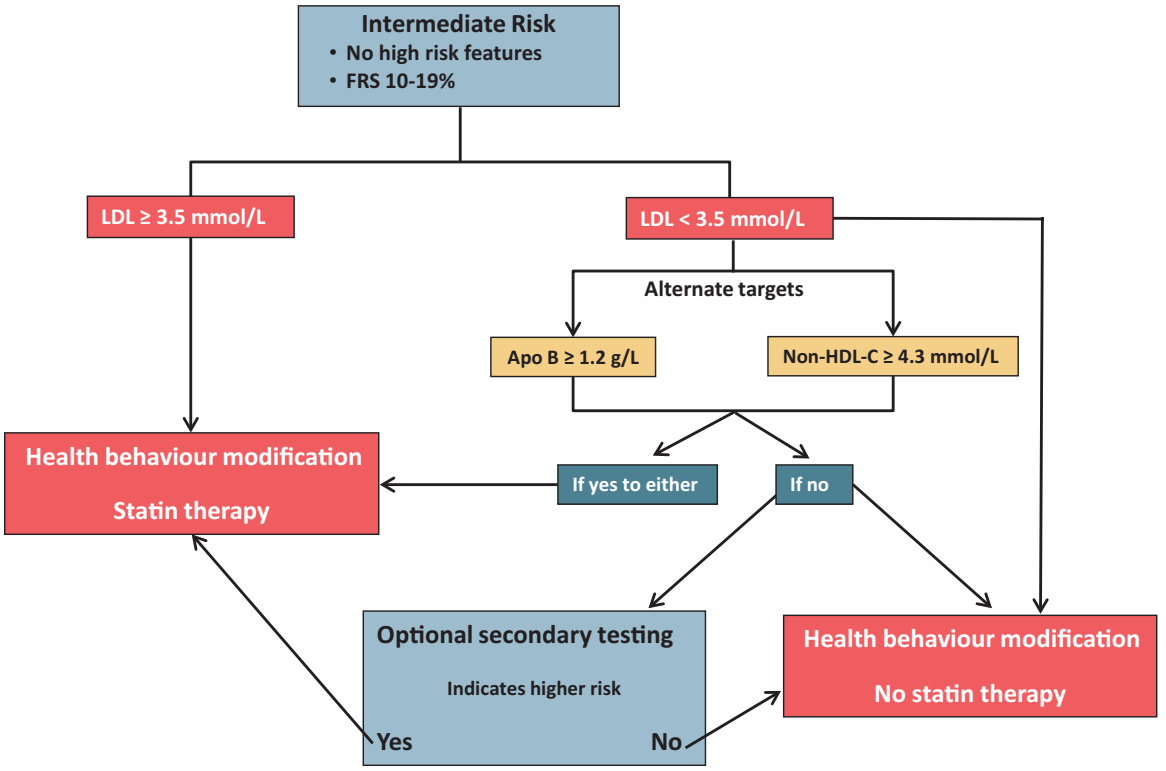

Figure 3. Risk stratification for intermediate risk subjects; subjects with intermediate risk and low-density lipoprotein (LDL) <3.5 mmol/L have the option of health behaviour modification or additional risk stratification based on alternate targets (apolipoprotein [Apo] B or non-high-density lipoprotein cholesterol [HDL-C]) or secondary testing.

Treatment targets in IR. When pharmacologic treatment is initiated in IR patients, the primary target remains LDL-C ≤ 2.0 mmol/L or ≥ 50% reduction of LDL-C from untreated baseline. Alternate targets in IR patients include apo B ≤ 0.8 g/L (unchanged) or non-HDL-C ≤ 2.6 mmol/L (new). Cholesterol treatment target levels are derived from clinical trials. Nearly all studies have measured LDL-C as an indicator of response to therapy. The 2005 CTT meta-analysis of 14 statin trials showed a dose-dependent relative reduction in CVD with LDL-C-lowering.[54] Every 1.0 mmol/L reduction in LDL-C is associated with a corresponding 20% to 25% reduction in CVD mortality and nonfatal myocardial infarction (MI). Data from the **Pr**avastatin **o**r Ator**v**astatin **E**valuation and **I**nfection **T**herapy (PROVE-IT),[55] **T**reating to **N**ew **T**argets (TNT),[56] **A**ggrastat **to** **Z**ocor (A to Z),[57] **I**ncremental **D**ecrease in **E**nd Points Through **A**ggressive **L**ipid Lowering (IDEAL),[58] and the **S**tudy of the **E**ffectiveness of **A**dditional **R**eductions in **C**holesterol and **H**omocysteine (SEARCH)[59] trials have confirmed that lowering LDL-C to a mean of 2.0 mmol/L or less is associated with the lowest risk of recurrent CVD events in secondary prevention patient populations. Extrapolating from the available data, a 2.0 mmol/L absolute reduction or a 50% relative reduction in LDL-C provides optimal benefit in terms of CVD reduction.[60] Thus, when pharmacotherapy is initiated in IR patients, target levels should be an LDL-C ≤ 2.0 mmol/L, or a 50% or greater reduction of LDL-C from baseline. Furthermore, because apo B and non-HDL-C have been suggested to be more accurate markers than LDL-C of CVD risk, particularly during pharmacotherapy, apo B or non-HDL-C can be substituted for LDL-C.[51] The apo B target for IR patients is ≤ 0.80 g/L and the non-HDL-C target is ≤ 2.6 mmol/L.

Therapy appropriate based on clinical trials. Finally, despite the fact that high-sensitivity C-reactive protein (hsCRP) is not believed to be causative in the development of atherosclerosis based on recent genetic data, those subjects who meet JUPITER criteria (men > 50 years and women > 60 years of age and CRP ≥ 2 mg/L and LDL <3.5 mmol/L) could be considered for treatment based on the results of that study. Most of those subjects were in the low-IR category.

RECOMMENDATION

1. We recommend that the IR category include individuals with adjusted FRS ≥ 10% and <20% (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend treating IR individuals with LDL-C ≥ 3.5 mmol/L (Strong Recommendation, Moderate-Quality Evidence).
3. In IR individuals with LDL-C <3.5 mmol/L, apo B ≥ 1.2 g/L, or non-HDL-C ≥ 4.3 mmol/L is suggested to identify patients who might benefit from pharmacotherapy (Strong Recommendation, Moderate-Quality Evidence).

4. We recommend a target LDL-C ≤ 2.0 mmol/L or ≥ 50% reduction of LDL-C for IR individuals in whom treatment is initiated (Strong Recommendation, Moderate-Quality Evidence). Alternative target variables are apo B ≤ 0.8 g/L or non-HDL-C ≤ 2.6 mmol/L (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. Non-HDL-C has been added as a second alternate treatment target because apo B is not available in some jurisdictions. Non-HDL-C is available without any additional cost or testing and there are increasing data to demonstrate its potential value. Therefore, it was decided to increase its profile in the guidelines. It is particularly useful where apo B is not available and in patients whose triglyceride level is greater than 1.5 mmol/L.

High risk

Definition of high risk for ischemic CVD. Individuals are considered to be at high risk of major ischemic cardiovascular events and thus the principle beneficiaries of statin therapy if they have clinical evidence of atherosclerosis, previous MI, or coronary revascularization by percutaneous coronary intervention or coronary artery bypass graft surgery, other arterial revascularization procedures, or cerebrovascular disease including transient ischemic attack, or peripheral arterial disease. The current guidelines have also added the presence of abdominal aortic aneurysm as a condition indicating high CVD risk, because atherosclerosis is the primary aetiology of this type of aneurysm.[61] Thoracic aortic aneurysm is more frequently associated with medial degeneration than atherosclerosis, and risk estimation in patients with this type of aneurysm should be based on the presence of other risk modifiers rather than the aneurysm itself.[62] An FRS of ≥ 20% also constitutes high risk.

There are also a number of conditions that might not necessarily have a 20% 10-year risk but are included in this category becaue treatment is indicated based on clinical trials. The presence of type 1 or type 2 diabetes mellitus in any patient older than 40 years of age, or younger patients with diabetes of more than 15 years duration and age older than 30 years, or with documented silent or clinically apparent CVD or microvascular complications of diabetes should be considered for statin treatment. Individuals with CKD are at increased risk of CVD risk depending on their levels of both estimated glomerular filtration rate (eGFR) and urinary albumin excretion. Anyone with an eGFR ≤ 45 mL/min/1.73 m^2 or albumin:creatinine ratio (ACR) of ≥ 30 mg/mmol (≥ 300 mg/day) is considered high risk (Supplemental Table S5). Those with an eGFR ≤ 60 mL/min/1.73 m^2 and an ACR of ≥ 3 mg/mmol are also at higher risk. In a recent population-based study, the risk from CKD was similar to that of diabetes.[5] In the SHARP study, there was benefit of lipid-lowering therapy with a combination of statin and ezetemibe in this patient population. High risk is also defined by hypertension plus 3 of the following risk factors: male, age > 55 years, smoking, total cholesterol/HDL-C ratio > 6, left ventricular hypertrophy, family history of premature CVD, electrocardiogram (ECG) abnormalities, or microalbuminuria. Patients with these characteristics were shown to gain benefit from statin therapy.[50]

Treatment targets in high risk individuals. It is the high risk group that achieves the greatest absolute benefit from pharmacotherapy and statins remain the primary first-line therapy. In determining what LDL-C target to set for high risk individuals, our panel reviewed all randomized clinical trials and meta-analyses of lipid-lowering agents published since 2009. This includes the second cycle of the CTT published in 2010, a meta-analysis of 26 large, long-term outcomes studies of more vs less intensive statin regimens or statin vs control.[3] Based on this analysis, we conclude that an LDL-C of ≤2.0 mmol/L remains a suitable target for most high risk individuals. In the presence of more severe baseline dyslipidemia or in patients in whom therapy is limited by drug intolerance and who fail to achieve an LDL-C ≤2.0 mmol/L, a 50% or greater reduction of LDL-C from baseline is recommended. In some individuals with recurrent vascular disease or very high risk on the basis of established vascular disease and multiple major coronary risk factors, an LDL-C target of <1.8 mmol/L is justified based on the finding in this CTT analysis that individuals achieving this target with a standard statin regimen showed additional definite benefit and no increase in major side effect rates. This is also in keeping with other current international guidelines for very high risk individuals.[63,64]

The need for combination treatment of subjects with low HDL-C and/or high triglycerides remains unproven considering recent evidence that niacin or fibrates in addition to statins showed neutral results with respect to CVD outcomes.[65,66] There continues to be ongoing work in this area.

It is recommended for those using the alternate targets that pharmacotherapy be used to achieve the non-HDL-C target of ≤2.6 mmol/L. For practitioners with experience and access to apo B measurements, the target of apo B for high risk patients is ≤0.8 mmol/L (Fig. 4).

RECOMMENDATION

1. We recommend that high risk be defined in subjects who have clinical atherosclerosis, abdominal aortic aneurysm, or an adjusted FRS of ≥ 20% (Strong Recommendation, High-Quality Evidence). We have also included diabetes of > 15 years duration and age older than 30 years, diabetes with age older than 40 years, or the presence of microvascular disease, high risk kidney disease, or high risk hypertension (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend a target LDL-C ≤ 2.0 mmol/L or ≥ 50% reduction of LDL-C for IR individuals in whom treatment is initiated (Strong Recommendation, Moderate-Quality Evidence).
3. We recommend that apo B ≤ 0.80 g/L or non-HDL-C ≤ 2.6 mmol/L be considered as alternative treatment targets for optimal risk reduction (Strong Recommendation, High-Quality Evidence).

Values and preferences. Our decision to add CKD to the high risk category was based on significant emerging epidemiology data and the recently published SHARP data. The treatment of dyslipidemia in subjects on hemodialysis remains controversial and individual judgement is required.

Risk level	Initiate therapy if	Primary target LDL C	Alternate target
High FRS ≥ 20%	Consider treatment in all (Strong, High)	≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, High)	➢ Apo B ≤ 0.8 g/L ➢ Non HDL-C ≤ 2.6 mmol/L (Strong, High)
Intermediate FRS 10%-19%	➢ LDL-C ≥ 3.5 mmol/L (Strong, Moderate) ➢ For LDL-C < 3.5 consider if: Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 4.3 mmol/L (Strong, Moderate)	≤ 2 mmol/L or ≥ 50% decrease in LDL-C (Strong, Moderate)	➢ Apo B ≤ 0.8 mg/L ➢ Non HDL-C ≤ 2.6 mmol/L (Strong, Moderate)
Low FRS < 10%	➢ LDL-C ≥ 5.0 mmol/L ➢ Familial hypercholesterolemia (Strong, Moderate)	≥ 50% reduction in LDL-C (Strong, Moderate)	

Figure 4. Summary of treatment thresholds and targets based on Framingham Risk Score (FRS), modified by family history. HDL-C, high-density lipoprotein C; LDL-C, low-density lipoprotein cholesterol.

Practical tip. LDL-C remains the primary target in the guidelines. Clinicians are encouraged to be familiar with the use of LDL-C and 1 of the 2 alternate targets. We are not advocating using all 3 indices regularly or testing for both LDL-C and apo B in subjects. For clinicians who have apo B available and are comfortable with using it, there are advantages that were previously addressed.

Secondary Testing in Risk Stratification

In a subset of patients who do not exhibit significant dyslipidemia (LDL-C <3.5 mmol/L, apo B <1.2 g/L, or non-HDL-C <4.3 mmol/L), it might be unclear whether to offer or withhold therapy when the adjusted FRS falls between 5% and 19%. Secondary testing might be considered in such patients, and might help direct decision-making regarding the need for lipid-lowering therapy.[67,68] Secondary testing is optional, and left to the discretion of the clinicians in discussion with the individual patient. Conversely, secondary testing is not recommended in patients with high risk or very LR (<5%) (Supplemental Table S3).

Emerging evidence suggests that at a population level a more liberal statin use policy would decrease cardiovascular events, thus obviating the need for any additional testing. The relative risk reduction with statins appears to be independent of baseline risk or cholesterol levels, however the absolute risk reduction is smaller in a LR population.[46] As such the number needed to treat is quite high in a LR population (near 100). Others believe that a personalized risk stratification approach is more appropriate and the biomarkers discussed could be used to aid in this evaluation. Although the biomarkers referenced add incremental risk discrimination to standard FRS, this does not guarantee that such an approach will lead to treatment decisions which will lower cardiovascular risk. Considering the lack of randomized trial evidence that a biomarker strategy reduces cardiovascular events, except for hsCRP,[47] or eGFR (SHARP), one must be cautious. In addition, we are not advocating multiple tests. Clinicians should minimize the number of additional tests and only use those most appropriate based on the individual's risk profile and local availability and expertise. When using more than 1 secondary test the estimated increase in risk is not incremental.

Biomarkers

Lipoprotein (a). Lipoprotein (Lp) (a) is an LDL-like particle in which apo B is covalently bound to a plasminogen-like molecule "apo (a)." Lp(a) proatherogenic and might also inhibit the fibrinolytic action of plasminogen. Plasma concentrations of Lp(a) are controlled by a single gene, *LPA*, and are highly (> 90%) heritable. Lp(a) levels exhibit a skewed distribution with median values of approximately 90 mg/L and are generally stable throughout life. Measurement of Lp(a) might be of value in additional risk assessment particularly in individuals with a family history of premature vascular disease and familial hypercholesterolemia. Mendelian randomization studies have clearly demonstrated that genetic variants regulating Lp(a) levels are robustly associated with coronary heart disease (CHD) risk, supporting a causal role for Lp(a) in atherosclerosis.[69] The Copenhagen Heart Study determined the risk of MI by Lp(a) concentrations in the general population including 7524 subjects, followed for 17 years.[70] They reported a stepwise increase in MI risk after adjustment for conventional risk factors. Subjects with an Lp(a) concentration between 300 and 760 mg/L had a 1.7-fold hazard ratio. The Emerging Risk Factors Collaboration[71] similarly demonstrated that Lp(a) concentrations greater than 300 mg/L were associated with a progressive increase in risk.

hsCRP. Compared with the 2009 guidelines, hsCRP was removed from the main treatment table of routine measurement in selected IR patients with LDL-C <3.5 mmol/L. C-reactive protein is an inflammatory biomarker, the levels of which are associated with risk for both coronary artery disease (CAD) and stroke. CRP is primarily produced in the liver in response to the inflammatory cytokine, interleukin-6 but CRP is also synthesized in adipose tissue and by arterial smooth muscle cells and endothelial cells. The Emerging Risk Factors Collaboration[72] demonstrated a stepwise increase in CAD risk for hsCRP levels between 0.5 and 20 mg/L. A CRP > 2.0 mg/L was associated with a hazard ratio for CVD of 1.5; this was attenuated after correction for age, sex, body mass index, diabetes mellitus, and plasma triglyceride and HDL-C concentrations. Mendelian randomization studies have demonstrated that

CRP is not causally related to CVD risk and thus CRP is not a target of therapy.[47,73] Adding hsCRP to the standard FRS produces changes in risk classification that are inconsistent and is generally of small magnitude.[74] However, the JUPITER study, despite some limitations, demonstrated that a population of men older than 50 and women older than 60 years of age with a LDL-C <3.5 mmol/L and a hsCRP > 2.0 mg/L clearly benefitted from 20 mg daily rosuvastatin therapy with a 50% reduction in major coronary events. hsCRP is not recommended as a routine test for risk stratification outside these patient characteristics.

Hemoglobin A1c. Large prospective studies have demonstrated a relationship between hemoglobin A1c (A1c) and CVD risk in subjects without diabetes. The **E**uropean **P**rospective **I**nvestigation **I**nto **C**ancer (EPIC) study[75] followed 4662 men and 5570 women, 45 to 79 years of age at baseline for 7 years. In this population, an A1c <5.0% was associated with the lowest rates of CVD and mortality. For each 1% point increase in A1c, the relative risk of death was 1.24 (1.14-1.34) for men and 1.28 (1.06-1.32) for women (P <0.001). Similarly in the **A**therosclerosis **R**isk **i**n **C**ommunities (ARIC) study,[76] among 11,092 black or white subjects without a history of diabetes or CVD at enrolment, CHD risk increased with levels of A1c > 5.0%. For subjects with an A1c between 6.0% and 6.5%, the hazard ratio was 1.78 (1.48-2.15). CHD risk discrimination improved with addition of A1c to models including fasting glucose. Measurement of fasting glucose is recommended for individuals older than the age of 40 years and earlier in those with a family history of diabetes or obesity. Further measurement of hemoglobin A1c might be of value especially in subjects with fasting glucose > 5.6 mmol/L for both CVD risk stratification and diagnosis of diabetes.

ACR

Some might consider eGFR as a biomarker for secondary testing, however it was believed that eGFR should be routinely tested as part of risk assessment. Albuminuria is associated with several CVD risk factors including hypertension and diabetes. In a meta-analysis of 26 cohort studies with 169,949 participants,[77] microalbuminuria (defined as 30-300 mg/d) was associated with a 2.17 (1.87-2.52)-fold increased CAD risk. Similarly in the Cardiovascular Health Study,[78] among subjects with a FRS of 5%-10%, the 5-year CAD event rate was 6.3% for those with negative urinary protein and 20.1% for those with an ACR > 3 mg/mmol. The ACR was shown to improve the net risk reclassification index. In asymptomatic adults at IR for CVD, especially those with hypertension or in some patients with diabetes, measurement of microalbuminuria might be considered for cardiovascular risk assessment.

A summary of biomarker use for CVD risk assessment is presented in Supplemental Table S4.

Noninvasive Testing

There is much interest in the use of noninvasive testing and imaging to identify subclinical atherosclerosis and its physiological consequences. Though there is strong support for this approach, this strategy has not been yet tested in a randomized fashion in a large prospective cohort. However, emerging data that demonstrate favourable effects on discrimination and reclassification have been obtained (Supplemental Table S5).

Graded exercise stress testing

A positive stress test is highly predictive of obstructive and hemodynamically significant CAD and future cardiovascular events. Conversely, a negative stress test has a low negative predictive value in identifying the likelihood of future CVD events. Importantly, low exercise capacity (<6 metabolic equivalents [METs]) is predictive of risk for future cardiac events in the absence of ECG changes.[79] In the Framingham Heart Study offspring cohort, 3043 subjects without CAD at baseline (1431 men and 1612 women; age 45 ± 9 years) underwent a graded exercise test with follow-up for 18.2 years.[80] In addition to ST depression, failure to reach a target heart rate and exercise tolerance (METs achieved) strongly predicted future CAD risk in women and men after adjustment for FRS. Evidence for incremental value beyond FRS has been provided by multiple studies.[80-83] An exercise ECG might be considered for cardiovascular risk assessment in asymptomatic adults, particularly those embarking on an exercise program.

Carotid ultrasound imaging

Carotid ultrasound, including measurement of carotid intimal media thickness (CIMT) where technical expertise exists, provides an assessment of subclinical atherosclerosis. In a meta-analysis of 8 studies, consisting of 37,197 subjects, Lorenz et al.[84] demonstrated that each 0.1 mm increase in CIMT is associated with a 10% increased risk for MI and a 13% increased risk for stroke. In the ARIC study, for any CIMT category, the presence of visible plaque was associated with significantly increased CVD risk.[85] Visible arterial wall plaques defined as a CIMT > 1.5 mm or in the absence of plaque, CIMT values > 75% for age and sex (generally > 1.0 mm) are considered as evidence of subclinical atherosclerosis and are generally an indication for statin therapy. In a recent meta-analysis which was limited to imaging of the common carotid artery, but did not evaluate the bifurcation and internal carotid artery segments or the presence or absence of plaques, carotid intima media measurements added only little to risk reclassification after adjustment for conventional risk factors. CIMT measurements used to enhance CVD risk assessment should be restricted to centres with specific expertise.[86]

Ankle brachial index

The ratio of ankle to brachial blood pressure (ankle brachial index [ABI]) is a reliable measure of peripheral arterial disease and can be measured in the office setting with a hand-held Doppler device. Normal ABI values are between 1.0 and 1.2. Higher values (> 1.3) might indicate arterial calcification and noncompressible blood vessels and are associated with increased CVD risk and lower values indicate obstructive disease of peripheral arteries. The Ankle Brachial Index Consortium[87] reported on the meta-analysis of 16 studies including 480,325 years of follow-up of 24,955 men and 23,339 women. Overall there was a 2.0-fold increase in CVD risk for subjects with an ABI <0.9 and a 4.3-fold increased CVD risk for those with an ABI <0.60, across all FRS categories. Measurement of ABI might be useful in further CVD risk assessment especially in smokers. An ABI <0.90 is associated with a high probability of concomitant CAD and is normally an indication for statin therapy.

Coronary artery calcium

An abnormal coronary artery calcium (CAC) score (Agatston score) is a strong predictor of CAD risk and provides predictive

information beyond conventional risk factors. This has been demonstrated by multiple studies and pooled analyses in women and men.[88-91] A normal CAC score is 0, anything other than 0 is abnormal, and CAC increases with age. Younger individuals might harbour significant noncalcified plaque and thus a CAC of 0 is reassuring (negative predictive value of 95%-98%) but does not always indicate negligible risk of future MI. Evidence for improved C-statistic/net reclassification index after adjustment for standard risk factors (FRS) has been provided by multiple studies including the South Bay Heart Watch Study,[92,93] Rotterdam Study,[94] and the Heinz Nixdorf Recall Study.[95]

In IR subjects, a CAC of 100-399 is associated with a 4-fold increased risk of CAD death or MI, and a CAC > 400 with a 6-fold increased risk, relative to subjects with a CAC <100. Repeat measures more frequently than every 5 to 10 years are not indicated. A CAC > 300 places the patient in a very high risk category with a 10-year risk of MI/CVD death of approximately 28%.[88] Coronary calcium score has demonstrated the greatest change in discrimination (C-statistic) and reclassification of all of the biomarkers that have reported these data to date.[96] Based on these findings the presence of a CAC score > 100 is generally an indication for statin therapy.

RECOMMENDATION

1. We recommend that secondary testing be considered for further risk assessment in "IR" patients (10%-19% FRS after adjustment for family history) who are not candidates for lipid treatment based on conventional risk factors or for whom treatment decisions are uncertain (Strong Recommendation, Moderate-Quality Evidence).
2. We suggest that secondary testing be considered for a selected subset of "LR to IR" patients (5%-9% FRS after adjustment for family history) for whom further risk assessment is indicated (eg, strong family history of premature CAD, abdominal obesity, South Asian ancestry, or impaired glucose tolerance) (Weak/Conditional Recommendation, Low-Quality Evidence).

Values and preferences. It is important to note that use of these tests should be viewed as optional and only to be used where decision-making will be directly affected (ie, not in those in the high risk or lower risk groups [<5%]). The choice of which test to use depends on the clinical situation (Supplemental Tables S4 and S5) and local expertise. In appropriate situations, A1c, urine ACR, and hsCRP can be helpful, are safe and inexpensive, and should be considered. For noninvasive testing a clinical suspicion of peripheral vascular disease should prompt ABI testing. Individuals who have been inactive and wish to exercise could have an exercise stress test. Finally, recent evidence would suggest that CAC testing with computed tomography is superior to carotid ultrasound. However, given its expense and radiation exposure until further data are available it cannot be widely advocated.

Health Behaviours

Health behaviour interventions remain the cornerstone of chronic disease prevention, including CVD. They should be universally applied for the prevention of chronic diseases such as obesity, type 2 diabetes, atherosclerosis, cancer, and neurodegenerative diseases. Data from the INTERHEART study indicate that, in addition to the traditional risk factors (abnormal lipids, hypertension, and diabetes), abdominal obesity, dietary patterns, alcohol consumption, physical inactivity, psychosocial factors, and smoking are modifiable risk factors for MI worldwide in both sexes and at all ages.[97]

Nutrition therapy

Nutrition therapy is an integral component of health behaviour interventions and its goals are to improve the lipid profile and importantly reduce the risk of cardiovascular events. A meta-analysis of 37 trials using the US National Cholesterol Education Program Step I (<30% total energy as fat, <10% of energy as saturated fat), and Step II (<7% of energy as saturated fat, dietary cholesterol <200 mg/d) diets confirmed significant lowering of plasma lipids and lipoproteins, and CVD risk factors. LDL-C levels decreased by an average of 12% with the Step I diet (dietary cholesterol <300 mg/d) and 16% with the Step II diet (dietary cholesterol <200 mg/d).[98] Dietary therapy augments drug therapy with statins and remains an important therapeutic tool with few side effects and little harm. Supplemental Table S7 summarizes the evidence-based inclusionary and exclusionary nutrition recommendations for dyslipidema management. Nutrition practice guidelines for the prevention and management of atherosclerosis are cited elsewhere.[99]

For detailed information about specific dietary modifications, see Supplementary Material.

Nutrition therapy is also the cornerstone of weight management programs to achieve and maintain healthy body weights. A diet suited to the individual that provides adequate nutrition with a balance between caloric intake and energy expenditure, is best. Often, a professional dietician is of value to provide advice and follow-up.

Exercise

Physical activity is another important component of prevention. Many studies have shown the benefits of regular exercise in maintaining health and preventing CVD.[100,101] Regular exercise also has beneficial effects on diabetes risk, hypertension, and hypertriglyceridemia, and improves plasma levels of HDL-C.[102] In several studies, a lower frequency of CVD was noted in physically active individuals independent of known CVD risk factors.[103] Adults should accumulate at least 150 minutes of moderate to vigorous aerobic activity per week in bouts of 10 minutes or more. It is also beneficial to add muscle- and bone-strengthening activities at least 2 days per week. A greater amount of activity will be associated with greater benefits.[100,104]

Psychological factors

The INTERHEART study confirmed the importance of stress as a CVD risk factor.[97] After MI, patients with depression have a worse prognosis, but it remains unclear whether pharmacologic treatment reduces this risk. Health care providers can explore stress management techniques with this population to optimize quality of life.

Smoking cessation

Smoking cessation is probably the most important health behaviour intervention for the prevention of CVD. Smoking also has an adverse effect on lipids. There is a linear and dose-dependent association between the number of cigarettes

smoked per day and CVD risk. Pharmacologic therapy is associated with an increased likelihood of smoking abstinence.

RECOMMENDATION

1. We suggest that all individuals be encouraged to adopt healthy eating habits to lower their CVD risk: (1) moderate energy (caloric) intake to achieve and maintain a healthy body weight; (2) emphasize a diet rich in vegetables, fruit, whole-grain cereals, and polyunsaturated and monounsaturated oils, including Ω-3 fatty acids particularly from fish; (3) avoid trans fats, limit saturated and total fats to <7% and <30% of daily total energy (caloric) intake, respectively; (4) increase daily fibre intake to > 30 g; (5) limit cholesterol intake to 200 mg daily for individuals with dyslipidemia or at increased CVD risk (Conditional Recommendation, Moderate-Quality Evidence).
2. We recommend the Mediterranean, Portfolio, or Dietary Approach to Stop Hypertension (DASH) diets to improve lipid profiles or decrease CVD risk (Strong Recommendation, High-quality Evidence), and for cholesterol-lowering consider increasing phytosterols, soluble fibre, soy, and nut intake.
3. We recommend that adults should accumulate at least 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of 10 minutes or more to reduce CVD risk (Strong Recommendation, High-Quality Evidence).
4. We recommend smoking cessation (Strong Recommendation, Moderate-Quality Evidence), and limiting alcohol intake to 30 g or less per day (1-2 drinks) (Conditional Recommendation, Moderate-Quality Evidence).

Practical tip. Some groups suggest a 0-5-30 approach to counselling patients on health behaviours. This is zero cigarettes, 5 servings of vegetables/fruits, and 30 minutes of exercise daily.

Statin Intolerance and Adverse Effects

The main intolerance issues with statins pertain to adverse muscle effects, but there are many other purported effects that are either uncommon or difficult to relate conclusively to statin therapy. Baseline transaminases (alanine aminotransferase; ALT), creatinine, and creatine kinase are useful to monitor potential side effects associated with therapy. There is however no indication for routine repeat measures of ALT and creatine kinase in patients using statin therapy unless symptoms develop. Statins are not contraindicated in patients with mild to moderate elevations in ALT because of hepatic steatosis, chronic hepatitis C, or primary biliary cirrhosis. The following updates a recent, comprehensive review of these issues.[8]

Adverse effects

Drug interactions. There are many commonly reported drug interactions including those which result in an increased risk of myopathy with statins and gemfibrozil; therefore, this combination is not recommended.[8] It is prudent to check for interactions when adding new medication for patients using statin therapy. Additional concerns regarding drug interactions with simvastatin have been raised.[105] Simvastatin is particularly prone to drug-drug interactions, in part because it is extensively metabolized by the CYP3A4 enzyme system. It is recommended that practitioners no longer use the 80 mg dose because of the increased risk of myopathy. Most of this risk has been seen with concomitant use of amiodarone, diltiazem, and amlodipine. With amlodipine, simvastatin should not exceed 20 mg; and it should not exceed 10 mg if amiodarone, verapamil, or diltiazem are being used. Simvastatin should not be used at all with antifungal agents, gemfibrozil, cyclosporine, or the macrolide antibiotics.

Neurologic effects. The US Food and Drug Administration has recently mandated label changes warning of memory loss and confusion. These adverse effects claimed on the basis of anecdotal reports have not emerged as consistent signals in large clinical trials. There is no clear association with type or dose of statins or with fixed or progressive dementia such as Alzheimer's disease. In contrast, other groups have suggested a potential beneficial effect of statins on depression in patients with CHD[106] and perhaps even a reduction in risk of Parkinson disease.[107] Thus, it is believed that though memory loss is exceedingly rare with statin therapy it should be monitored by history.

The association of subarachnoid hemorrhage and lipid-lowering therapy has been re-evaluated in a meta-analysis of 31 randomized controlled trials incorporating more than 180,000 patients. Active statin therapy was not associated with significant increase in intracranial hemorrhage. A significant reduction in all strokes and even all-cause mortality was observed.[108] The CTT meta-analysis suggested a very small increased risk of hemorrhagic stroke, but this again was offset by a clear reduction in overall stroke risk.

Diabetes. An increased risk of new onset, type 2 diabetes has been described with several drugs including thiazide diuretics, β-blockers, glucocorticoids, niacin, and protease inhibitors. This risk might also apply to statin therapy and has recently led the Food and Drug Administration to mandate addition of this adverse effect to statin labels. Mechanistic studies are conflicting but a recent review of the existing data suggest that potential mechanisms include increased insulin levels, reduced insulin sensitivity, and the potential for survivor selection bias to influence the development of new onset diabetes in those taking statin therapy.[109-111] However, the overall data available strongly suggests that the reduction in CVD events outweighs the minor effect on glucose homeostasis.[112] For patients with impaired glucose tolerance who are using statin therapy, blood sugars should be monitored as they would be for evaluation of cardiometabolic risk.

A recent analysis of 3 large trials emphasizes that fasting glucose levels and features of the metabolic syndrome are more consistent determinants of type 2 diabetes.[113] A specific adverse effect on glucose levels with concomitant use of pravastatin and paroxetine was noted in the Food and Drug Administration's Adverse Event Reporting System which was not seen when either was given separately nor was it seen with other selective serotonin reuptake inhibitors and statins.[114]

Therapy for statin intolerance

Statin-based strategies. Evidence for lipid-lowering efficacy of intermittent doses of high potency statins continues to emerge. Alternate day statin therapy can sometimes be useful in this situation to reduce side effects and increase compliance. In addition, LDL lowering of more than 10% was achieved with weekly 5-10 mg of rosuvastatin in a small, randomized, double-blind trial in patients with a history of statin-associated myalgia.[115]

Treatments targeting muscle symptom relief. Vitamin D deficiency is a cause of myopathy and unrecognized, mild deficiencies might represent a rare but potentially reversible cause of statin-associated myalgia or myositis.[116] Placebo controlled trials of this intervention either in patients with low serum vitamin D or in the more general population of statin-intolerant patients are lacking, as are trials for other types of vitamins or other types of supplements, such as coenzyme Q10.

RECOMMENDATION

1. Because overall risk/benefit favours therapy in patients meeting criteria for lipid lowering therapy and cardiovascular risk reduction, we recommend that: (1) despite concerns about a variety of other possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, re-initiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use (Strong Recommendation, Very Low-Quality Evidence); and (2) statins not be withheld on the basis of a potential, small risk of new-onset diabetes mellitus emerging during long-term therapy (Strong Recommendation, Very Low-Quality Evidence).
2. We do not recommend vitamins, minerals, or supplements for symptoms of myalgia perceived to be statin-associated (Strong Recommendation, Very Low-Quality Evidence).

Practical tip. Patients should be advised to stop statin therapy and contact the prescribing health care provider if worrisome symptoms develop. The amount of effort spent persevering with statin therapy in subjects with adverse effects should be directly related to the level of risk for an individual patient. In those at highest risk all options should be exercised before changing to alternative lipid-lowering therapy or withdrawing all lipid-lowering treatment. Lower dose combination therapy remains an option for these subjects. Strong emphasis should be put on a more aggressive nonpharmacologic approach such as diet modulation and exercise. For subjects at lower risk who do not tolerate statin therapy, a re-evaluation of the need for lipid lowering therapy should precede a change to alternative therapy because outcomes studies are not as robust.

Nonstatin Pharmacotherapy

No new formal recommendations are presented because this topic was not reviewed in detail (see 2009 Guidelines for detail).[1] No studies to date have demonstrated a decrease in CVD event rate with the addition of lipid modulating drugs to statin therapy. The SHARP study did however demonstrate that simvastatin and ezetimibe decreased CVD events in subjects with CKD compared with placebo. A statin-only arm was not tested.[4]

For subjects who do not tolerate statin therapy or only at low dose, favourable effects on LDL-C can be achieved with ezetimibe, bile acid resins, or niacin. Niacin therapy alone has been shown to decrease CVD events.[117] Fibrates have a favourable effect on triglyceride levels with minimal change on LDL-C, and gemfibrozil decreased CVD events in subjects with established CAD.[118] Subgroup analyses in other trials suggest possible benefit from fibrates in people with elevated triglyceride and low HDL-C even when treated with a statin. However, these should not be viewed as conclusive. Ongoing studies with ezetimibe, niacin, and new cholesterol-modifying medications will give us further insights into the value of strategies beyond statin monotherapy.

Practical Approach to the Guidelines

For those wishing a simple approach, one would identify risk based on the phenotype of the patient, use LDL-C as the predominant threshold, and target and forego any secondary testing or use of alternate targets. Patients will separate into those in whom treatment is clearly not indicated (lower end of lower risk) and those in whom treatment is indicated (Fig. 2). For the others, a discussion with the patient would determine the desire for pharmacotherapy most of the time. Emerging evidence suggests that a more liberal use of statins in those with a risk of 5%-19% can be justified if deemed acceptable to the patient and health care provider. Regular re-evaluation of the approach of treating or not treating should be undertaken.

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Supplementary Material

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