Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease

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Since the last publication of the recommendations for the management and treatment of dyslipidemia, new clinical trial data have emerged that support a more vigorous approach to lipid lowering in specific patient groups. The decision was made to update the lipid guidelines in collaboration with the Canadian Cardiovascular Society. A systematic electronic search of medical literature for original research consisting of blinded, randomized controlled trials was performed. Meta-analyses of studies of the efficacy and safety of lipid-lowering therapies, and of the predictive value of established and emerging risk factors were also reviewed. All recommendations are evidence-based, and have been reviewed in detail by primary and secondary review panels. Major changes include a lower low-density lipoprotein cholesterol (LDL-C) treatment target (lower than 2.0 mmol/L) for high-risk patients, a slightly higher intervention point for the initiation of drug therapy in most low-risk individuals (LDL-C of 5.0 mmol/L or a total cholesterol to high-density lipoprotein cholesterol ratio of 6.0) and recommendations regarding additional investigations of potential use in the further evaluation of coronary artery disease risk in subjects in the moderate-risk category.

Key Words: *Cardiovascular disease, Clinical practice guidelines, Dyslipidemia*

Document de principes de la Société canadienne de cardiologie : Recommandations pour diagnostiquer et traiter la dyslipidémie et prévenir la maladie cardiovasculaire

Depuis la dernière publication des recommandations pour prendre en charge et traiter la dyslipidémie, de nouvelles données d'essai clinique ont été colligées qui soutiennent une démarche hypolipidémiante plus vigoureuse dans des groupes de patients précis. Il a été décidé de mettre à jour les lignes directrices au sujet des lipides en collaboration avec la Société canadienne de cardiologie. On a effectué une recherche électronique systématique des publications médicales afin de trouver des recherches originales sous forme d'essais aléatoires et contrôlés en aveugle. Des méta-analyses d'études sur l'efficacité et l'innocuité des traitements hypolipidémiants et sur la valeur prédictive de facteurs de risque établis et émergents ont également été examinées. Les principaux changements incluent un traitement ciblé pour baisser davantage le cholestérol à lipoprotéines de basse densité (C-LDL) (à moins de 2,0 mmol/L) pour les patients très vulnérables, un point d'intervention légèrement plus élevé pour entreprendre la pharmacothérapie de la plupart des individus à faible risque (C-LDL de 5,0 mmol/L ou un ratio de 6.0 entre le cholestérol total et le cholestérol à lipoprotéines de haute densité) et la recommandation de mener des recherches supplémentaires sur l'utilité potentielle de mieux évaluer le risque de maladie coronarienne chez des sujets dans la catégorie de risque modéré.

Since the last publication of the recommendations for the management and treatment of dyslipidemia (1), new clinical trial data have emerged that support a more vigorous approach to lipid lowering in specific patient groups. Several of these recent studies, such as the Treatment to New Targets (TNT) (2), Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) (3) and PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) (4) studies, indicate that a lower low-density lipoprotein cholesterol (LDL-C) target is appropriate for high-risk individuals. Others, such as the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) (5), demonstrate treatment benefit for intermediate-risk groups, even in the absence of overt dyslipidemia. Based on some of these data, the National Cholesterol Education Program Adult Treatment Panel III updated their treatment recommendations (6). New information regarding the impact of abdominal obesity, family history of premature coronary artery disease (CAD), chronic kidney disease and presence of subclinical atherosclerosis on cardiovascular risk has been added. The value of nontraditional risk factors such as apolipoprotein (apo) B, high-sensitivity C-reactive protein (hsCRP), lipoprotein(a) (Lp[a]) and glycosylated hemoglobin in the prediction of cardiovascular risk, and the current status of homocysteine measurement or treatment have also been discussed.

This version of lipid guidelines differs from the previous not only in content, but also in the process by which it was developed. The changes include collaboration with the Canadian Cardiovascular Society, establishment of primary and secondary review panels, and adherence to the Appraisal of Guidelines Research and Evaluation principles for guideline formulation (www.agreecollaboration.org). A systematic electronic search of medical literature for original research from January 1, 1990, to December 31, 2005, was performed on PubMed using the following key words: statins or fibrates or niacin or ezetimibe or diet and clinical trials. Only blinded,

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TABLE 1
Criteria used for evaluation of evidence

Recommendation grade	
Class I	Evidence and/or general agreement that a given diagnostic procedure or treatment is beneficial, useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness and/or efficacy of the treatment
Class IIa	Weight of evidence in favour
Class IIb	Usefulness and/or efficacy less well established
Class III	Evidence that the treatment is not useful and, in some cases, may be harmful
Level of evidence	
Level A	Data derived from multiple randomized controlled trials or meta-analyses
Level B	Data derived from a single randomized controlled trial or large, nonrandomized studies
Level C	Consensus of opinion by experts and/or small studies, retrospective studies or registries

randomized controlled trials that had a minimum of 16 weeks of follow-up were retained for evaluation. Meta-analyses of studies on the efficacy and safety of lipid-lowering therapies, and on the predictive value of established and emerging risk factors were also reviewed. The system used to grade and assess the evidence behind the recommendations is summarized in Table 1. An effort has also been made to harmonize these guidelines with other expert-recommended lipid guidelines, such as those of the Canadian Diabetes Association, Canadian Hypertension Education Program and Canadian Association of Cardiac Rehabilitation.

HIGHLIGHTS OF THE 2006 LIPID GUIDELINES

Process

- Collaboration with the Canadian Cardiovascular Society;
- Primary and secondary review panels;
- Adherence to the Appraisal of Guidelines Research and Evaluation principles of guideline formation; and
- Grading of evidence for each recommendation.

Content

- LDL-C treatment target of lower than 2.0 mmol/L for high-risk patients;
- Intervention point for initiation of lipid-lowering therapy in most low-risk individuals changed to an LDL-C of 5.0 mmol/L or a total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio of 6.0; and
- Recommendations regarding potential additional investigations for the further evaluation of CAD risk in subjects in the moderate-risk category.

Age-specific mortality rates from CAD in Canada have decreased by almost 40% in the past several decades. It has been estimated that 50% to 75% of the decrease in cardiac deaths in western countries is due to population-wide improvements in the major CAD risk factors, particularly serum cholesterol concentrations, smoking and blood pressure; 25% to 50% is estimated to be due to improved acute and chronic treatments, including thrombolytics, acetylsalicylic acid, angiotensin-converting enzyme inhibitors and statins, as well as coronary artery bypass grafting and percutaneous coronary interventions (7,8). Nonetheless, CAD remains the major cause of death and morbidity in western countries, and the lifetime risk of developing CAD by the age of 40 years is approximately one in two for men and one in three for women (9,10). Although secondary prevention strategies have improved and are economically attractive, a substantial percentage of previously asymptomatic individuals die within minutes to weeks of their initial coronary event or are left with debilitating and life-limiting cardiac damage. Despite improved medical therapy, 59% of men and 45% of women die within five years of the onset of heart failure related to CAD (11).

Clearly, both primary and secondary prevention interventions are required to maximize the health of Canadians and reduce health care costs associated with the complications of CAD. These include identification of patients with asymptomatic CAD, early implementation of lifestyle factors and targeted use of proven pharmacological therapies, including statins, angiotensin-converting enzyme inhibitors and antiplatelet agents. Statins are widely recognized as highly effective for secondary prevention of myocardial infarction (MI), and there is increasing evidence that they provide safe and effective treatment for the primary prevention of CAD (12-15). Although consensus has been reached on the use of statins in high-risk patients (6,16), there remains considerable controversy regarding the appropriate use of statin therapy in patients without manifest atherosclerosis or diabetes mellitus (17-19).

Conventional CAD risk factors are present in 80% to 90% of patients who develop CAD (20,21). Among the best predictors of long-term risk is the TC/HDL-C ratio. A 40-year-old man in the Framingham study with a TC/HDL-C ratio of 5.8 or greater had a 20-year cumulative CAD risk of 20.1%, compared with only 5.4% for a 40-year-old man with a TC/HDL-C ratio of less than 3.8 (10,22). Importantly, the absence of established CAD risk factors at the age of 50 years is associated with a very low lifetime risk for cardiovascular disease and markedly longer survival (23). These data strongly support the regular reassessment of risk factor status and treatment of categorical risk factors, including plasma lipids.

SCREENING

- Physicians should screen all men 40 years or older and all women who are postmenopausal and/or 50 years or older with a full lipid profile (after a 9 h to 12 h fast) and other investigations as indicated every one to three years.
- Children should be investigated with a fasting lipid profile if there is a family history of a monogenic lipid disorder such as familial hypercholesterolemia or chylomicronemia.
- In addition, adult patients with the following additional risk factors should be screened at any age:
  - diabetes mellitus;
  - current or recent (within the previous year) cigarette smoking;
  - hypertension;
  - abdominal obesity, ie, waist circumference larger than 102 cm (men) or larger than 88 cm (women) (lower cut-offs are appropriate for South and East Asians);

- family history of premature CAD (especially in primary male relatives younger than 55 years and female relatives younger than 65 years);
- manifestations of hyperlipidemia (eg, xanthelasma, xanthoma or corneal arcus);
- exertional chest discomfort, dyspnea (24) or erectile dysfunction (25);
- chronic kidney disease (26,27) or systemic lupus erythematosus (28); or
- evidence of atherosclerosis.

- Patients of any age may be screened at the discretion of their physician, particularly when lifestyle changes are indicated.
- Fasting lipid levels (TC, triglycerides [TG], LDL-C and HDL-C) should be measured every one to three years, and other cardiovascular risk factors should be assessed for all men 40 years or older and all women who are postmenopausal and/or 50 years or older (class IIa, level C). More frequent testing should be performed for patients with abnormal values or if treatment is initiated.
- Screen, at any age, adult patients with major CAD risk factors (class IIa, level C).

RISK ASSESSMENT

Framingham Risk Score

Although a number of risk engines are available, calculation of the Framingham Risk Score (FRS) is recommended for the initial assessment of the majority of patients in the primary prevention category. The Framingham risk estimate tables adjust for certain risk factors such as TC and smoking status for age, and correct for the effects of treatment on blood pressure measurement (Tables 2 and 3). The FRS provides an estimate of the 10-year risk estimate of 'hard cardiac end points'. These include cardiac death and nonfatal MI. The Cardiovascular Life Expectancy Model was adjusted for the distribution of risk factors among Canadians and is available in both English and French at www.chiprehab.com. The Framingham risk engine is used to calculate the 10-year risk, while the Cardiovascular Life Expectancy Model is used to estimate changes in life expectancy or cardiovascular age associated with risk factor modification.

Other cardiovascular risk engines, such as the PROspective CArdiovascular Munster (PROCAM) study (29) and the HeartScore program (30), as well as data from the Quebec Cardiovascular Study (QCS) (31-33), have also been considered. The HeartScore algorithm includes fatal and nonfatal strokes, an important outcome in patients with hypertension and dyslipidemia, but does not incorporate HDL-C, an important negative risk factor for both stroke and CAD.

Short-term versus long-term risk

The FRS is applicable to a large percentage of the Canadian population and provides a reasonable estimate of the short-term risk of a major CAD event. However, many subjects at low or intermediate short-term (10-year) risk are at high risk in the long term due to the cumulative effects of single risk factors and/or changes in risk factors over time. In the Framingham study, men in the lowest tertile of the risk scores at 50 years of age experienced a 10-year cumulative risk of one

TABLE 2
Estimation of 10-year risk of nonfatal myocardial infarction or coronary death (Framingham Heart Study) in men

Age in years	Points
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Cholesterol level (mmol/L)	Age in years (points)				
	20–39	40–49	50–59	60–69	70–79
≤4.14	0	0	0	0	0
4.15–5.19	4	3	2	1	0
5.2–6.19	7	5	3	1	0
6.2–7.2	9	6	4	2	1
>7.21	11	8	5	3	1

Smoking status	Age in years (points)				
	20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

High-density lipoprotein cholesterol level (mmol/L)	Points
≥1.55	–1
1.30–1.54	0
1.04–1.29	1
<1.04	2

Systolic blood pressure (mmHg)	Untreated (points)	Treated (points)
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Points total	10-year risk (%)
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
17	>30

Estimation of 10-year risk can also be made at hin.nhlbi.nih.gov/atpiii/calculator.asp

TABLE 3
Estimation of 10-year risk of nonfatal myocardial infarction or coronary death (Framingham Heart Study) in women

Age in years	Points
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Cholesterol level (mmol/L)	Age in years (points)				
	20–39	40–49	50–59	60–69	70–79
≤4.14	0	0	0	0	0
4.15–5.19	4	3	2	1	1
5.2–6.19	8	6	4	2	1
6.2–7.2	11	8	5	3	2
>7.21	13	10	7	4	2

Smoking status	Age in years (points)				
	20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

High-density lipoprotein cholesterol level (mmol/L)	Points
≥1.55	–1
1.30–1.54	0
1.04–1.29	1
<1.04	2

Systolic blood pressure (mmHg)	Untreated (points)	Treated (points)
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Points total	10-year risk (%)
<9	1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	>30

Estimation of 10-year risk can also be made at hin.nhlbi.nih.gov/atpiii/calculator.asp

in 25, but a lifetime risk of nearly one in two. Women in the lowest tertile of risk at 50 years of age had a 10-year cumulative risk of one in 50, but a lifetime risk of one in four (10).

High risk

Individuals with a calculated 10-year risk of CAD-related death or nonfatal MI of 20% or greater are considered to be in the 'high-risk' category. Also included in this group is any patient with a diagnosis of CAD, peripheral artery disease or cerebrovascular disease, and most adult patients with type 1 or type 2 diabetes mellitus. Patients with chronic kidney disease (glomerular filtration rate of less than 30 mL/min/1.73 m^2) are also in the high-risk category (27), although the benefit of statin therapy in this group is less well established (34).

- High risk is defined as a 20% or greater 10-year risk of CAD-related death or nonfatal MI, and includes patients with a diagnosis of atherosclerotic vascular disease (CAD, cerebrovascular disease or peripheral artery disease), and most patients with chronic kidney disease or established diabetes mellitus.

Patients with diabetes mellitus

Most adult patients with established type 1 or type 2 diabetes are at high risk for vascular events and should be treated accordingly (35). In the Insulin Resistance Atherosclerosis Study (IRAS [36]), subjects with diabetes but without CAD were shown to have extensive carotid atherosclerosis by B-mode ultrasonography, similar in extent to that of nondiabetic subjects with CAD; this supports the aggressive management of cardiovascular risk factors in individuals with diabetes. Furthermore, CAD risk appears to be elevated in individuals at risk of future diabetes. Data from the Nurses' Health Study (NHS) showed a 3.7-fold RR of MI in the period before the diagnosis and a 4.6-fold RR of MI after the diagnosis in women with diabetes compared with women who remained free of diabetes (37). Although the vast majority of patients with established diabetes should be treated as high-risk, this does not apply to all patients with newly diagnosed diabetes. In the Third National Health And Nutrition Examination Survey (NHANES III) (38), in the small subset of patients (13%) with diabetes who did not also meet the criteria for the metabolic syndrome, the prevalence of CAD was comparable with that of individuals with neither diabetes nor the metabolic syndrome. Clinical assessment can identify those patients with diabetes who are at lower short-term risk for CAD. These include younger patients with a shorter duration of diabetes, without other risk factors for vascular disease (ie, without abdominal obesity, hypertension, dyslipidemia or cigarette smoking) and without other complications of diabetes. Even in this group, however, it is important to consider that the average patient with newly diagnosed type 2 diabetes may have had the disease for some time before diagnosis.

Although the Framingham tables are recommended for risk assessment in patients without diabetes, other software programs may better predict vascular risk in people with diabetes. The United Kingdom Prospective Diabetes Study (UKPDS [39]) risk engine, based on this study's cohort, provides such a calculation using not only traditional risk factors, but also the duration of diabetes and glycemic control (available online at www.dtu.ox.ac.uk/riskengine). However, it is important to note that recent studies suggest that both the Framingham and UKPDS risk engines underestimate CAD risk in patients with diabetes (40,41). In addition, all patients with diabetes have

an extremely high long-term risk of CAD, and thus, early intervention may be warranted, irrespective of the calculated short-term risk.

Intermediate risk

Patients in the intermediate- (moderate-) risk category have an FRS between 10% and 19%. Such individuals are candidates for treatment if their LDL-C level is 3.5 mmol/L or higher, or if their TC/HDL-C ratio is 5.0 or higher. Studies such as the ASCOT (5) demonstrate a significant reduction in clinical cardiovascular events with statin treatment for patients in the intermediate-risk category with lower baseline lipid values. Additional investigations, as discussed below, may be indicated to further establish the level of risk in individuals in this category.

Low risk

The low-risk category applies to individuals with a calculated FRS of less than 10%. Treatment is generally advised for low-risk subjects with categorical dyslipidemia (LDL-C level of 5.0 mmol/L or higher, or a TC/HDL-C ratio of 6.0 or higher). Clinical judgment may be used regarding the initiation of pharmacological therapy for patients in the lowest FRS category. In contrast, a family history of premature CAD (42,43) and/or the presence of additional risk factors, such as abdominal obesity, impaired fasting glucose or glucose intolerance, an hsCRP level higher than 3.0 mg/L or an Lp(a) level higher than 0.3 g/L (30 mg/dL) indicates a need for intervention at lower lipid values in selected individuals.

Racial differences in CAD risk

CAD rates vary among ethnic groups in Canada, being highest among individuals of South Asian ancestry and lowest among individuals of Chinese ancestry (44,45). The higher risk among South Asians is partly explained by an increased prevalence of abdominal obesity, glucose intolerance, hypertriglyceridemia, low HDL-C levels and elevated levels of Lp(a). Individuals of First Nations ancestry are also at markedly increased risk for diabetes and CAD (46).

TREATMENT TARGETS

Lipoprotein lipid and apo targets are determined according to available evidence from clinical trials and epidemiological studies (Table 4). Most studies have used the LDL-C level as a therapeutic goal, and targets are derived from these data. Secondary targets, including the TC/HDL-C ratio, non-HDL cholesterol and apo B levels (47), are based on post hoc analyses. The TC/HDL-C ratio is the best discriminator between CAD cases and controls (48), although some studies, such as the INTERHEART study (49), suggest that the apo B/apo A1 ratio can be a useful alternative.

Several recent randomized controlled trials with clinical end points, including the TNT (2), IDEAL (3) and PROVE-IT (4) studies, indicate that an LDL-C target of lower than 2.0 mmol/L is optimal for high-risk individuals with established CAD. This conclusion is further supported by two surrogate end point studies, REVERSal of Atherosclerosis with Lipitor (REVERSAL) (50) and A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID) (51). The REVERSAL study demonstrated slowing or halting of the progression of atherosclerosis, whereas ASTEROID documented significant regression of coronary artery atherosclerosis by assessing atheroma volume using intravascular ultrasound methodology.

TABLE 4
Risk categories and treatment recommendations

Risk level	10-year CAD risk	Recommendations	Grade, level of evidence
High*	≥20%	*Treatment targets*†:	
		Primary: LDL-C <2.0 mmol/L	Class I, level A
		Secondary: TC/HDL-C <4.0	Class IIa, level A
Moderate‡§	10% – 19%	*Treat when*:	
		LDL-C ≥3.5 mmol/L *or*	Class I, level A
		TC/HDL-C ≥5.0	Class I, level A
Low‡§	<10%	*Treat when*:	
		LDL-C ≥5.0 mmol/L *or*	Class IIa, level A
		TC/HDL-C ≥6.0	Class IIa, level A

**High risk includes coronary artery disase (CAD), peripheral artery disease, cerebrovascular disease (CVD) and most patients with diabetes. Individuals younger than 40 years with recent-onset diabetes, a normal lipid profile and no other risk factors for CVD are at lower short-term risk for CVD and may not require immediate lipid-lowering therapy. In patients with established atherosclerosis, treatment to lower low-density lipoprotein cholesterol (LDL-C) by at least 50% is generally appropriate; †Apolipoprotein B may be used to determine CAD risk, especially in hypertriglyceridemic patients, and to monitor adequacy of treatment. Optimal levels of apolipoprotein B are: less than 0.85 g/L in high-risk patients; less than 1.05 g/L in intermediate-risk patients; and less than 1.2 g/L in low-risk patients (47); ‡Treatment may be initiated at lower or higher levels if family history or other investigations indicate elevated or reduced risk. Patients with severe genetic lipoprotein disorders such as familial hypercholesterolemia or type 3 dyslipidemia should be treated because of their high risk of premature CAD; §Patients in the low- or moderate-risk categories may be at high long-term cardiovascular risk. This group includes many patients with abdominal obesity (the metabolic syndrome). The reduction in CAD and stroke events, and overall cost-effectiveness of therapy is proportional to the decrease in LDL-C (55). Thus, for those low- or moderate-risk subjects who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate. HDL-C High-density lipoprotein cholesterol; TC Total cholesterol*

A major consideration in terms of pharmacological therapy for patients in the low- to intermediate-risk categories is cost (19). However, analyses of cost efficacy in primary prevention have generally been based on data from early statin intervention studies (19,52,53). In a recent meta-analysis of 14 randomized trials, the Cholesterol Treatment Trialists' (CTT) Collaborators reported that each mmol/L reduction in LDL-C resulted in a 25% decrease in major coronary events, a 19% decrease in coronary mortality and a 12% reduction in all-cause mortality (54). In contrast to the relatively moderate degree of cholesterol reduction achieved in the early statin trials, it is now generally feasible and common clinical practice to lower patient LDL-C levels by 2 mmol/L to 2.5 mmol/L with proportionately greater efficacy in reducing clinical events. As noted by Law et al (55), after five years of continuous treatment, an LDL-C reduction of 1.8 mmol/L is estimated to reduce CAD events by 61%. Clearly, the number needed to treat, or cost efficacy, of statin therapy is contingent not only on the absolute level of risk, but on the LDL-C-lowering efficacy of the intervention chosen. Thus, for those individuals in the low- and intermediate-risk categories, who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate.

Therapeutic targets

- The primary target of therapy is the LDL-C level (class I, level A).
- The secondary target is the TC/HDL-C ratio (class IIa, level A).

FAMILY HISTORY

Much of the susceptibility to CAD can be explained by conventional risk factors, but these are both genetically and environmentally determined (20,21,49). Importantly, 10% to 15% of patients with CAD do not have any major CAD risk factors (20,21). Family and twin studies are consistent with premature CAD being strongly influenced by genetic factors (56,57). Among identical twins, premature cardiac death confers an eightfold increase in risk to the surviving male siblings and a 15-fold increase in risk to female siblings. The corresponding risk is far lower in fraternal twins, indicating that genetic variation strongly affects CAD susceptibility (58,59). Results from the Framingham Offspring Study (FOS [42]) demonstrate that after correction for known risk factors, parental cardiovascular disease led to a 1.7- to twofold increased risk for women and men, respectively. The incremental increased risk associated with a positive family history of CAD may be even greater in women with a 'low-risk' FRS (60).

- For patients with a family history of CAD in a first-degree relative younger than 55 years (men) or 65 years (women), the calculated 10-year CAD risk should be multiplied by a factor of 2.0 (class I, level C).

ADDITIONAL INVESTIGATIONS OF POTENTIAL USE IN RISK ASSESSMENT

For patients with a low FRS (10-year risk less than 10%), no indicators of possible subclinical atherosclerosis and no family history of early CAD, additional investigations are not usually indicated. Individuals in the intermediate-risk category (FRS between 10% and 20%) may be moved to a higher or lower risk category based on additional investigations. Investigations of possible clinical use include:

- laboratory measurements such as apo B, hsCRP, Lp(a) and, for individuals with elevated plasma glucose, glycated hemoglobin (HbA1c);
- assessment of exercise capacity (metabolic equivalent [MET] level achieved) by graded exercise stress testing (61-64); and
- noninvasive assessment of atherosclerosis such as determination of ankle-brachial index (ABI) (65) and carotid imaging (66,67).

Apo B

Each of the atherogenic lipoprotein particles (very LDL, intermediate-density lipoprotein, LDL and Lp[a]) contains one molecule of apo B. Thus, the serum concentration of apo B reflects the total number of these particles. Several recent prospective studies found apo B to be a better estimate of the risk of vascular events than LDL-C (32,47). Risk is highest in individuals with apo B levels higher than 1.2 g/L and TG levels higher than 1.5 mmol/L (33). This profile is often associated with the presence of smaller, denser LDL particles, which are more atherogenic. Increased apo B levels and high TG levels are prevalent in patients with the metabolic syndrome and type 2 diabetes. Apo B measurement may be of particular value in assessing the adequacy of statin treatment. In a number of statin trials, on-treatment levels of apo B related more strongly to clinical outcomes than on-treatment levels of LDL-C (68). Canadian population values have been established; apo B has been standardized, and most laboratories have the equipment and expertise to measure it. An apo B level of 0.9 g/L is approximately the 20th percentile, 1.05 g/L the 50th percentile and 1.2 g/L the 75th percentile for the Canadian population.

Overall, apo B separates higher and lower risk patients with moderate hypertriglyceridemia, and is a useful indicator of adequacy of treatment to lower the number of atherogenic particles. Plasma apo B measurement may be of particular use in determining CAD risk and adequacy of treatment in subjects with the metabolic syndrome (47). Most patients who achieve target values for both the LDL-C level and the TC to HDL-C ratio can be expected to also achieve optimal apo B concentrations.

- Optimal plasma apo B concentrations are less than 1.2 g/L in low-risk patients, less than 1.05 g/L in intermediate-risk patients and less than 0.85 g/L in high-risk patients (class IIa, level C).

hsCRP

The acute-phase CRP is produced by the liver in response to inflammatory cytokines such as interleukin-6. Although CRP does not appear to be directly atherogenic (69,70), when measured using a high-sensitivity assay, hsCRP is a stable and objective marker of inflammation, and may potentially identify asymptomatic individuals at risk for acute coronary events. Adipocytes produce both interleukin-6 and CRP, and an elevated hsCRP level is associated with abdominal obesity and is another component of the metabolic syndrome (71). Recent data from the Women's Health Study (WHS) suggest that hsCRP measurement adds prognostic information to that provided by the FRS in terms of predicting future CAD events. After correction for other risk factors, women in the upper quintile of the population distribution for hsCRP had a threefold increased hazard ratio for future CAD events compared with those in the lowest quintile (48,71,72). To date, more than 20 prospective epidemiological studies have demonstrated that hsCRP independently predicts vascular risk, six cohort studies have confirmed that hsCRP evaluation adds prognostic information beyond that available from the FRS, and eight cohort studies have demonstrated additive prognostic value for all levels of the metabolic syndrome or in the prediction of type 2 diabetes, as recently reviewed by Ridker and Cook (73). In contrast, Miller et al (74) recently reported that the relationship of CRP to CAD risk in subjects in the NHANES III study was largely explained by other risk factors, although this study did not use the hsCRP assay. Although debate remains regarding the incremental value of hsCRP testing in risk assessment in clinical practice (75-77), the majority of data support the judicious use of hsCRP measurement to further stratify risk (higher or lower than that predicted by the FRS) for individuals in the intermediate-risk category.

- hsCRP measurement may be useful in the further definition of CAD risk for patients with an FRS between 10% and 19% (class IIb, level C).

Lp(a)

Lp(a) is an LDL particle in which apo B is attached to the apo (a) protein by a disulfide bridge. The apo (a) moiety has structural homology to plasminogen, and may compete with plasminogen for binding to fibrin and plasminogen receptors on endothelial cells, thus impairing fibrinolysis. Lp(a) has been identified as a potent predictor of premature atherosclerosis in most (78), but not all, large, prospective studies (79). Elevated

Lp(a) levels occur in 15% to 20% of those with premature atherosclerosis, and most studies support Lp(a) as an independent risk factor for CAD. Results from a meta-analysis of 18 population-based cohorts indicate that the combined risk ratio for those in the upper versus lower tertiles of the population distribution for Lp(a) was 1.7 (80). There are accumulating data that suggest that the atherogenicity of Lp(a) is aggravated by other risk factors. Subgroup and post hoc analyses of published studies suggest that plasma Lp(a) levels are no longer predictors of coronary disease once the LDL-C level has been markedly reduced. Hopkins et al (81) and Sevlin et al (82) demonstrated a much greater impact of Lp(a) on CAD risk in subjects with an elevated TC/HDL-C ratio or other CAD risk factors. Plasma levels of Lp(a) are determined by a single gene, and heritability is approximately 90%. Repeat measurement is not required because levels are very stable. The only therapy with quantitatively significant effects on Lp(a) is high-dose niacin. Measurement of Lp(a) is not routinely recommended, but may be useful in further assessment of CAD risk in patients in the intermediate-risk category or with a family history of early CAD.

- An Lp(a) concentration higher than 0.3 g/L in an individual with a TC/HDL-C ratio higher than 5.0 or other major risk factors indicates a need for earlier and more intensive LDL-C lowering (class IIa, level C).

Measurements of glycemia

Chronic hyperglycemia is believed to contribute to premature atherosclerosis in individuals with diabetes (83,84). Nondiabetic individuals with impaired glucose tolerance also have an elevated risk of CAD. Fasting plasma glucose (FPG) should be measured every one to three years in adults over the age of 40 years and in younger adults with risk factors for diabetes, including abdominal obesity or a family history of type 2 diabetes. In patients with an FPG level higher than 6.0 mmol/L, HbA1c measurement may be indicated. In persons without diabetes, a number of studies have shown that the HbA1c level predicts cardiovascular events independently of other known risk factors (85-88). In the Atherosclerosis Risk In Communities (ARIC) study, in adults with diabetes, the RR of CAD was 2.37 for the highest (8.2% or greater) versus lowest (less than 5.2%) quintiles of HbA1c (89). In the European Prospective Investigation into Cancer – Norfolk (EPIC-Norfolk) study (90), nondiabetic subjects with an HbA1c level between 6.0% and 6.5% had a more than twofold increase in CAD risk compared with those with an HbA1c level of less than 5.0%.

- FPG should be measured every one to three years in adults over the age of 40 years, and in younger adults with abdominal obesity and/or a family history of type 2 diabetes.
- Measurement of HbA1c is not recommended unless FPG is elevated.
- Moderate elevations in HbA1c may indicate increased CAD risk (class IIa, level C).

The metabolic syndrome

The metabolic syndrome, defined according to National Cholesterol Education Program Adult Treatment Panel III criteria (16), incorporates many of the risk factors considered in the calculation of global risk using the FRS, as well as other risk factors discussed above (hyperglycemia, and elevated apo B and hsCRP levels). Individuals who meet the definition of the metabolic syndrome by the criteria listed in Table 5 are often at higher risk than estimated by the FRS, and additional investigations as listed above may be appropriate to further define short-term CAD risk.

TABLE 5
Criteria used to define the metabolic syndrome (three or more of the following criteria)

Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm
Women	>88 cm
Triglyceride	≥1.7 mmol/L
High-density lipoprotein cholesterol	
Men	<1.0 mmol/L
Women	<1.3 mmol/L
Blood pressure	>130/85 mmHg
Fasting glucose	5.7–7.0 mmol/L

Homocysteine

Elevated plasma concentrations of homocysteine are a strong predictor of adverse outcomes in patients with CAD, and are prevalent in patients with renal impairment or peripheral vascular disease. Plasma homocysteine levels above the 90th to 95th percentile are associated with an increased risk of all types of atherosclerotic vascular disease (OR=1.7) (91). Homocysteine measurement is expensive, and it is not generally recommended because recent randomized clinical trials do not indicate a benefit in treating CAD patients with folic acid and vitamin B_{12} supplements (Heart Outcomes Prevention Evaluation – The Ongoing Outcomes [HOPE-TOO] [92], NORwegian VItamin Trial [NORVIT] [93]). Clinical judgment should be used for patients with marked elevations in plasma homocysteine concentrations (higher than 20 μmol/L).

- Treatment with vitamin supplements to lower homocysteine concentrations is not currently recommended (class III, level A).

Assessment of exercise capacity

Exercise stress testing in asymptomatic men over the age of 40 years can also be useful in risk stratification. Gibbons et al (61) studied 25,927 healthy men (mean age 43 years). In this group of asymptomatic men, a positive exercise test was associated with an age-adjusted RR of CAD death ranging from 21 (in subjects with no CAD risk factors) to 80 (in subjects with three or more risk factors) compared with subjects with a normal test. Earlier reports from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and Multiple Risk Factor Intervention Trial (MRFIT) also demonstrated that a positive exercise stress test strongly predicted future CAD risk (94). Thus, as reviewed by Greenland and Gaziano (64), a positive exercise stress test (1 mm or greater ST depression within 6 min using the Bruce treadmill protocol) can move a middle-aged man from the intermediate-risk to high-risk secondary prevention categories. In contrast, a negative stress test and good exercise tolerance (more than eight METs) carries a good prognosis and may move the same man to a lower risk category (64). Similarly, in women, exercise capacity has been shown to be a good predictor of future CAD risk. In a cohort of 5721 asymptomatic women (63), the

FRS-adjusted hazard ratio of death increased from 1.0 for women achieving more than eight METs to 1.9 for those achieving five to eight METs to 3.1 for those achieving less than five METs on a symptom-limited stress electrocardiogram using the Bruce protocol. Similar findings were reported for women in the LRC Prevalence Study (95).

Noninvasive assessment of atherosclerosis

Modalities include determination of the ABI (65), carotid imaging (66,67), coronary computed tomography (96) and multislice computed tomography angiography (97,98). The ABI is the ratio of systolic blood pressure in the dorsalis pedis or posterior tibial artery to the systolic blood pressure in the brachial artery. An ABI less than 0.90 is a reliable index of peripheral vascular disease, with a sensitivity of 90% and specificity of 98% for detecting greater than 50% stenosis. Such patients have a high likelihood of concomitant coronary atherosclerosis. Carotid B-mode ultrasonography is also useful in assessing preclinical atherosclerosis. In asymptomatic individuals over 50 years of age, a number of studies have demonstrated an up to fivefold increase in future CAD risk in those with intimal medial thickness of more than 1 mm (67). Although intimal medial thickness quantification is not yet a standard measure, evidence of early carotid atherosclerosis by routine carotid ultrasonography is an indication for statin therapy. Electron beam computed tomography can be used to quantify coronary calcium. It is important to note that not all plaques are calcified, and calcium cannot be used to reliably identify plaques at risk for rupture. Nonetheless, emerging data suggest that coronary calcium scores above or below 80 add predictive value to the FRS (64,96). Although increasingly popular in the United States, electron beam computed tomography is not widely available in Canada.

The following noninvasive investigations may be useful for patients in the intermediate-risk category to detect subclinical atherosclerosis and/or to further define future CAD risk:

- ABI (class IIa, level C);
- carotid ultrasound (class IIa, level C);
- graded exercise testing (class IIa, level C); and
- electrocardiogram (class IIb, level C).

TREATMENT

Lifestyle

Lifestyle interventions remain the cornerstone of CAD prevention strategies (99-101), and are the first step in risk factor intervention for individuals in the low- and intermediate-risk categories. Of particular importance are smoking cessation, achievement and maintenance of ideal body weight, regular exercise, and reductions in the intake of saturated fat and simple sugars.

Although smoking prevalence has declined among Canadian men, from a high of 60% in 1960 to 27% today, and among women, from 40% in 1974 to 23% today (Statistics Canada [102]), further improvements are required, particularly in smoking deterrent programs for young people. A review of recent studies indicates that smoking cessation results in a 36% reduction in the RR of mortality from CAD (103).

Dietary intervention should be part of a strategy of lifestyle changes aimed at increasing exercise, decreasing intake of saturated and trans fats, and increasing fruit and vegetable intake, as well as increasing the proportion of monounsaturated and polyunsaturated fats in the diet. Since 1960, mean serum cholesterol concentrations in North America have decreased in middle-aged men from 5.9 to 5.5 mmol/L and in women from 6.8 to 5.6 mmol/L (104). This improvement has occurred despite increased rates of obesity, and is primarily related to reciprocal changes in the intake of saturated fat, cholesterol and polyunsaturated fat (105). In contrast, an attempted simple reduction in total fat intake had little effect on cholesterol levels or CAD incidence in the WHS (106).

Obesity has increased dramatically in Canada over the past 20 years. In 1985, the overall prevalence of obesity (body mass index [BMI] greater than 30 kg/m^2) in Canada was less than 7%. By 2004, this figure had increased to greater than 15% (107). Obesity is a major risk factor for CAD. In the Pathological Determinants of Atherosclerosis in Youth (PDAY) study, McGill et al (108) demonstrated a strong correlation between BMI, subcutaneous abdominal fat and coronary atherosclerosis in young men aged 15 to 34 years dying of external causes. BMI (109), waist circumference and waist-to-hip ratio (110) are important determinants of CAD risk. Much of the increased CAD risk in obese individuals is mediated by an increased prevalence of type 2 diabetes and features of the metabolic syndrome, including hypertension, elevated plasma TG levels and low levels of HDL-C. Individuals of South Asian ancestry are at higher risk for these metabolic abnormalities, and optimal BMI and waist circumference differ by ethnicity (111-113). Low-fat diets may not be sufficient to achieve and maintain weight loss (114). An important focus should be on decreasing caloric consumption in particular by reducing intake of refined carbohydrates and sugar to achieve and maintain an optimal level and distribution of body fat.

Physical activity is another important component of prevention. A number of recent studies (reviewed in [115]) have demonstrated that physically active subjects have CAD rates one-half those of sedentary individuals. Regular exercise has beneficial effects on the risks of diabetes (116), hypertension (117) and hypertriglyceridemia, and improves plasma levels of HDL-C (118). In several studies (119,120), a lower frequency of CAD was noted in physically active individuals, independent of known CAD risk factors. A general recommendation for healthy individuals is at least 30 min of moderate physical activity on a daily basis.

Lifestyle recommendations

All individuals should be encouraged to adopt a healthy lifestyle to lower their risk of CAD as described below (class I, level A).

- Refrain from smoking.
- Adopt healthy eating habits:
  - limit intake of saturated and trans fatty acids, simple sugars, refined carbohydrates; and
  - emphasize a diet rich in vegetables, fruit, whole-grain cereals, and polyunsaturated and monounsaturated oils, including omega-3 fatty acids.
- Achieve and maintain a healthy weight:
  - waist circumference of, optimally, less than 94 cm for men and 80 cm for women (a lower cut-off is appropriate for South and East Asian men [less than 90 cm] [111]); and
  - BMI of less than 27 kg/m^2 as a minimum goal and, optimally, less than 25 kg/m^2.

- Engage in regular physical activity:
  - 60 min of light, 30 min to 60 min of moderate or 20 min to 30 min of vigorous activity four to seven days per week.

Medication

Target lipid levels: In high-risk individuals, treatment should be started immediately, concomitant with diet and therapeutic lifestyle changes. The primary target of therapy is to achieve an LDL-C level of less than 2.0 mmol/L. For patients with established CAD, a reduction in LDL-C of at least 50% is generally required to prevent progression or elicit regression of atherosclerosis (50,51). An LDL-C level of less than 2.5 mmol/L may represent adequate control for patients placed into the high-risk category by FRS without established diabetes or vascular disease, and for a small subset of patients with stable CAD who do not have diabetes or saphenous vein bypass grafts. The secondary treatment target is achievement of a TC/HDL-C ratio of less than 4.0. Table 6 lists the lipid-lowering medications that are currently available on the market.

Achievement of target LDL-C concentrations: The majority of patients, including those with the metabolic syndrome, diabetes mellitus and combined dyslipidemia, are able to achieve target levels of LDL-C on statin monotherapy. However, a significant minority of patients may require combination therapy with an agent that inhibits cholesterol absorption (ezetimibe) or bile acid reabsorption (cholestyramine). These combinations are generally safe and can decrease LDL-C levels by an additional 10% to 20%. Clinical outcome data on the incremental benefit of combination therapy with a statin plus ezetimibe versus statin monotherapy are not yet available.

Achievement of the target TC/HDL-C ratio: The TC/HDL-C ratio is a robust predictor of CAD risk (48,121). Particularly for high-risk patients with low levels of HDL-C, achievement of the target TC/HDL-C ratio (less than 4.0) can be difficult. The following approaches are recommended.

Lifestyle therapy to lower TGs and/or increase HDL-C: For patients with hypertriglyceridemia, intensify dietary therapy and exercise, with a focus on weight loss, restriction of refined carbohydrates and alcohol, and an increase in the intake of omega-3 fatty acids. For patients with low levels of HDL-C, increased aerobic exercise, increased intake of monounsaturated fats, moderate alcohol intake (if TGs are not significantly elevated), weight loss and smoking cessation are beneficial (reviewed in [122]).

Increased statin dose: For patients with low HDL-C levels or mild hypertriglyceridemia, the recommended TC/HDL-C ratio may often be achieved by a further increase in statin dose, even if the target LDL-C level has been reached.

Combination therapy: In patients with combined dyslipidemia and low HDL-C levels, the combination of a statin with niacin is very effective, and was reported to significantly reduce CAD events in the HDL-Atherosclerosis Treatment Study (HATS) (123) and to halt progression of carotid atherosclerosis in the ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 2 (ARBITER-2) study (124). Niacin is more effective than fibrates in increasing HDL-C concentrations. Side effects are most manifest with crystalline niacin, and include flushing, dry skin and gastrointestinal irritation. Crystalline niacin should be taken two to three times daily after meals, and the dose should be increased slowly. 'Flush-free' niacin preparations are ineffective because they contain little bioavailable niacin (1125). Extended-release niacin (available in Canada as Niaspan [Oryx Pharmaceuticals Inc, Canada]) is taken once daily at bedtime and has a better tolerability profile. NSAIDs, including acetylsalicylic acid, attenuate the vasodilatory side effects in most patients. There is a small but significant risk of hepatotoxicity with niacin monotherapy or combined niacin and statin treatment, so transaminase levels should be monitored. Niacin can impair insulin sensitivity and may raise blood glucose levels in susceptible individuals in a dose-dependent fashion, although this effect may be transient (126). Glycemic control should be monitored in patients with diabetes who are treated with niacin.

For patients who do not tolerate or are not candidates for niacin and exhibit significant hypertriglyceridemia despite statin monotherapy, a combination of a statin with a fibrate may be used with close patient follow-up. Fibrates may increase serum creatinine and homocysteine levels. It should be noted that the recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD [127]) study demonstrated that fenofibrate monotherapy did not significantly reduce nonfatal MI or CAD death in patients with diabetes and mild hypertriglyceridemia. Statin and fibrate combination therapy should not be used in patients with renal impairment, but fibrates alone may be used with caution at low doses in cases of mild renal impairment. Available data suggest that fenofibrate is reasonably safe in combination with a statin (127,128). Studies are underway to determine whether addition of fenofibrate to a statin regimen alters CAD risk. Gemfibrozil is associated with a higher risk of myotoxicity and should not be used in combination therapy (129). For patients with moderate hypertriglyceridemia, the addition of salmon oil (1 g to 2 g three times daily) to statin therapy is safe, and may be useful in lowering TG levels and thus achieving the target TC/HDL-C ratio.

Elevated TG levels: Epidemiological evidence suggests that the optimal plasma TG concentration is less than 1.5 mmol/L. The current recommendation is to first implement and maintain lifestyle changes rather than to attempt to lower TG levels by pharmacological means. Achievement of the target TC/HDL-C ratio generally entails modification in TG levels when elevated. Severe hypertriglyceridemia imposes a significant risk for pancreatitis, and patients with a TG level higher than 10 mmol/L on optimal lifestyle therapy require drug treatment. Available options include a fibrate, niacin and salmon oil supplementation.

Safety issues

Statins are generally well tolerated by most individuals. Significant increases in hepatic transaminase levels, defined as alanine aminotransferase (ALT) levels more than three times the upper limit of normal, occur in 0.3% to 2.0% of patients and are generally dose-related. Although underlying liver disease is considered a contraindication to statin therapy, there is no evidence of worsening of liver function in subjects with fatty liver (130), chronic hepatitis C (131) or primary biliary cirrhosis (132) treated with statins. Niacin therapy, in the form of crystalline niacin or extended-release niacin, can result in persistent significant elevations in ALT in approximately 1% of patients. The risk of hepatotoxicity is much greater with slow-release niacin, and these products are not recommended (133). A general recommendation is to measure

TABLE 6
Currently available lipid-lowering medications

Generic name	Trade name	Recommended dose range
Statins*		
Atorvastatin	Lipitor (Pfizer Canada Inc)	10 mg – 80 mg
Fluvastatin	Lescol (Novartis Pharmaceuticals Canada Inc)	20 mg – 80 mg
Lovastatin	Mevacor (Merck Frosst Canada)	20 mg – 80 mg
Pravastatin	Pravachol (Bristol-Myers Squibb, Canada)	10 mg – 40 mg
Rosuvastatin	Crestor (AstraZeneca Canada)	5 mg – 40 mg
Simvastatin	Zocor (Merck Frosst Canada)	10 mg – 80 mg
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Generic	2 g – 24 g
Colestipol	Colestid (Pfizer Canada Inc)	5 g – 30 g
Ezetimibe	Ezetrol (Merck Frosst/Schering Pharmaceuticals Canada)	10 mg
Fibrates†		
Bezafibrate	Bezalip (Hoffman-La Roche Limited, Canada)	400 mg
Fenofibrate	Lipidil Micro/Lipidil Supra/Lipidil EZ (Fournier Pharma Inc, Canada)	100 mg, 145 mg, 160 mg, 200 mg
Gemfibrozil‡	Lopid (Pfizer Canada Inc)	600 mg – 1200 mg
Niacins§		
Nicotinic acid	Generic cystalline niacin	1 g – 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g – 2 g

**Use lower dose ranges in persons of South and East Asian origin; †In patients with renal insufficiency (creatinine clearance between 20 mL/min and 100 mL/min), fibrates should be initiated at the lowest available dose and increased only after re-evaluation of renal function and lipid parameters; ‡Do not use gemfibrozil in combination with a statin. §In patients with diabetes or glucose intolerance, initiate therapy at 500 mg/day to 1000 mg/day and monitor glycemic control*

ALT levels at baseline, and between one and three months after initiating statin or niacin therapy.

Statin-induced myopathy is a well-established but rare side effect. The incidence of myalgia (muscle discomfort without significant increases in creatine phosphokinase) is approximately 3% to 4% in statin-treated patients versus 2% in placebo-treated individuals. In randomized controlled trials, approximately 1% of patients have been withdrawn from study because of muscle discomfort (134). In particular, there has been no evidence of increased myopathy in patients achieving very low levels of LDL-C (1.0 mmol/L to 1.5 mmol/L) on high-dose atorvastatin treatment (135). Myositis occurs in fewer than 0.1% of treated patients and is defined as muscle discomfort or weakness accompanied by plasma creatine kinase levels higher than 10 times the upper limit of normal. Drug therapy should be discontinued promptly, because there are risks of significant muscle damage (rhabdomyolysis), myoglobinuria and acute renal failure. Persons at increased risk for myositis are elderly patients and those with multiple comorbidities, such as diabetes, hypertension and organ transplants. Myositis may occur with statin monotherapy, but is more commonly associated with the concomitant administration of other drugs, including cyclosporine, gemfibrozil, certain antifungal drugs and macrolide antibiotics (129). The incidence of rhabdomyolysis in patients receiving statin therapy was reported to be approximately one in 23,000 (136). In patients at risk for myopathy, creatine kinase levels should be measured at baseline, and patients should be advised to stop their statin immediately and report for blood and urine testing if significant symptoms develop.

Increases in plasma creatinine of 15% to 20% are common in fibrate-treated patients (128), and more significant increases can occur in patients with underlying renal disease (137). In patients with renal insufficiency (creatinine clearance between 20 mL/min and 100 mL/min), fibrates should be initiated at the lowest available dose, and increased only after re-evaluation of renal function and lipid parameters. Fenofibrate therapy also results in elevations in serum homocysteine levels, which are of uncertain significance (138).

SPECIALTY CLINIC REFERRALS

Physicians are often confronted with difficult cases, lack of laboratory resources, unexplained atherosclerosis, extremes of lipoprotein disorders or a lack of response to conventional therapies. In such cases, referral to a specialized centre may be warranted. Most medical schools across Canada have specialized lipid clinics and the laboratory backup for extensive testing. In extreme cases, therapeutic modalities, such as extra-corporeal LDL apheresis techniques, are available. The working group recommends that specialists in lipoprotein disorders be available in each province for consultation with primary care physicians concerning difficult cases.

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CONFLICT OF INTEREST: Dr Ruth McPherson has received honoraria from AstraZeneca, GlaxoSmithKline, Merck Frosst, Pfizer and Schering for conferences or advisory boards, with no ownership of stock or options. Dr Jiri Frohlich has received honoraria from AstraZeneca, Merck Frosst, Pfizer and Schering for conferences or advisory boards, with no ownership of stock or options. Dr George Fodor has received honoraria from AstraZeneca, Merck Frosst, Pfizer and Schering for conferences or advisory boards, with no ownership of stock or options. Dr Jacques Genest has received honoraria from Merck Frosst Canada, Schering-Plough, Pfizer, Novartis and AstraZeneca for conferences, advisory boards and consultant work, with no ownership of stock or options. The elaboration of these guidelines was done entirely without financial or logistical support from government agencies or pharmaceutical companies. Under no circumstances were funds requested nor received for work related to these recommendations by members of the Writing Group or Review Panels.

APPENDIX

2006 GUIDELINES FOR THE MANAGEMENT AND TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

SUMMARY OF RECOMMENDATIONS

Ruth McPherson, Jiri Frohlich, George Fodor, Jacques Genest

GLOBAL RISK ASSESSMENT

Framingham Risk Factor score screening

- Screen with a full lipid profile, every one to three years, all men who are 40 years of age or older and all women who are postmenopausal or 50 years of age or older.
- In addition, adults with the following risk factors should be screened at any age:
  - diabetes mellitus;
  - current or recent (within past year) cigarette smoking;
  - hypertension;
  - abdominal obesity (metabolic syndrome) – waist circumference of greater than 102 cm for men and greater than 88 cm for women (lower cut-offs are appropriate for South and East Asians);
  - family history of premature coronary artery disease (CAD);
  - stigmata of hyperlipidemia (eg, xanthoma);
  - exertional chest discomfort, dyspnea, erectile dysfunction, claudication, chronic kidney disease; or
  - evidence of atherosclerosis.
- Screen children who have a family history of severe hypercholesterolemia or chylomicronemia.
- Other patients may be screened at the discretion of their physician, particularly when lifestyle changes are indicated.

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets*: Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% – 19%	*Treat when*: LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when*: LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes. HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; TC Total cholesterol

OTHER FACTORS INFLUENCING CAD RISK

Apolipoprotein B

Plasma apolipoprotein B measurement may be used to determine CAD risk, especially in hypertriglyceridemia, and to monitor treatment. Optimal levels of apolipoprotein B are less than 0.85 g/L in high-risk patients, less than 1.05 g/L in moderate-risk patients and less than 1.2 g/L in low-risk patients.

Lipoprotein(a)

A lipoprotein(a) concentration greater than 0.3 g/L in an individual with a total cholesterol to high-density lipoprotein cholesterol ratio of greater than 5.5 or other major risk factors indicates the need for earlier, more intensive low-density lipoprotein cholesterol (LDL-C) lowering.

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein may be clinically useful in identifying individuals who are at higher risk for CAD than that predicted by a global risk assessment, in particular in patients with abdominal obesity or a calculated 10-year risk between 10% and 20%. A high-sensitivity C-reactive protein level of less than 1.0 mg/L indicates low risk for cardiovascular disease, between 1.0 mg/L to 3.0 mg/L indicates moderate risk and more than 3.0 mg/L indicates high risk.

Indexes of glycemia

Fasting glucose should be measured every one to three years in adults 40 years of age or older and in younger adults with abdominal obesity and/or a family history of type 2 diabetes. Measurement of glycated hemoglobin is not recommended unless fasting glucose is elevated. Moderate elevations in glycated hemoglobin may indicate increased CAD risk.

Homocysteine

Although it is a marker of CAD risk, treatment with vitamins to lower homocysteine is not recommended.

NONINVASIVE INVESTIGATIONS

After a careful history review and physical examination, noninvasive investigations that may be useful for patients in the moderate-risk category to detect subclinical atherosclerosis and/or to further define future CAD risk are the ankle-brachial index, carotid ultrasound and graded exercise testing.

TREATMENT

Lifestyle

An important focus should be to decrease caloric consumption by decreasing saturated and trans fat intake, reducing intake of sugar and refined carbohydrates, and by increasing exercise (to more than 200 min per week) as needed to achieve and maintain a body mass index of less than 27 kg/m^2 (ideally less than 25 kg/m^2).

Medication

- In high-risk individuals, treatment should be started immediately and concomitantly with diet and exercise. The treatment goal for most high-risk patients is first to achieve an LDL-C of less than 2.0 mmol/L; an optimal reduction in LDL-C for most CAD patients is at least 50%. Once the LDL-C target has been reached, attempts should be made to achieve a total cholesterol to high-density lipoprotein cholesterol ratio ratio of less than 4.0 by further lifestyle modification. Adjuvant lipid-modifying therapy may also be considered.
- Patients in the low- or moderate-risk categories may be at high long-term cardiovascular risk. This group includes many patients with abdominal obesity. The reduction in CAD and stroke events and overall cost-effectiveness of therapy is proportional to the decrease in LDL-C.
- For those low- and moderate-risk individuals who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate.

Generic name	Trade name	Recommended dose range
Statins		
Atorvastatin	Lipitor (Pfizer Canada Inc)	10 mg – 80 mg
Fluvastatin	Lescol (Novartis Pharmaceuticals Canada Inc)	20 mg – 80 mg
Lovastatin	Mevacor (Merck Frosst Canada)	20 mg – 80 mg
Pravastatin	Pravachol (Bristol-Myers Squibb, Canada)	10 mg – 40 mg
Rosuvastatin	Crestor (AstraZeneca Canada)	5 mg – 40 mg
Simvastatin	Zocor (Merck Frosst Canada)	10 mg – 80 mg
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Generic	2 g – 24 g
Colestipol	Colestid (Pfizer Canada Inc)	5 g – 30 g
Ezetimibe	Ezetrol (Merck Frosst/Schering Pharmaceuticals Canada)	10 mg
Fibrates*		
Bezafibrate	Bezalip (Hoffman-La Roche Limited, Canada)	400 mg
Fenofibrate	Lipidil Micro/Lipidil Supra/Lipidil EZ (Fournier Pharma Inc, Canada)	100 mg, 145 mg, 160 mg, 200 mg
Gemfibrozil	Lopid (Pfizer Canada Inc)	600 mg – 1200 mg
Niacins		
Nicotinic acid	Generic cystalline niacin	1 g – 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g – 2 g

**Fibrates should be generally be reserved if triglyceride levels are greater than 10 mmol/L despite lifestyle changes; follow creatinine levels*

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