# Recommendations for the management and treatment of dyslipidemia

## *Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias*

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*Review*

*Synthèse*

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Despite the steady decline in the rate of death from coronary artery disease (CAD) during the past 25 years, cardiovascular disease remains the leading cause of death in Canada, accounting for 37% of total deaths.[1] Although the age-adjusted rate of death from cardiovascular disease is declining, the prevalence of cardiac conditions is increasing because of the growing number of elderly people, better acute care and improved survival.[1] People with heart disease often remain in the community, requiring long-term medical care. In quantitative terms, $7.3 billion (17%) of total direct health care costs and $12.3 billion (14.5%) of total indirect health care costs for all disease categories can be attributed to cardiovascular disease.[1]

The largest proportion of cardiovascular diseases is represented by CAD and cerebral and peripheral vascular disease. During the past 3 decades efficacious strategies have been developed for primary and secondary prevention of these diseases. These strategies involve general lifestyle changes (to promote healthy diet, optimal weight, physical activity, moderate or no alcohol consumption, and smoking cessation), treatment of high blood pressure, control of diabetes mellitus and, in particular, treatment of dyslipidemias.

The causal relation between hypercholesterolemia and atherosclerosis was established more than 80 years ago by Anitschkow.[2] Since the 1950s, there have been steady improvements in our ability to treat hypercholesterolemia through diet and the use of lipid-lowering drugs. The earliest angiographic and clinical studies demonstrated that intensive therapy to lower low-density lipoprotein cholesterol (LDL-C) levels slowed the progression of atherosclerosis and decreased the incidence of major coronary events;[3,4] however, these early studies did not have sufficient power to detect beneficial mortality trends. The results of these early clinical studies and the extensive epidemiological data on the relation between plasma lipoprotein levels and CAD, as well as experimental information from animal models of atherosclerosis, led to the development of policies to manage and treat lipid disorders. In Canada, guidelines for the management of hypercholesterolemia were first issued in 1988.[5]

Major clinical trials carried out over the past decade have shown a clear benefit of LDL-C reduction in terms of both CAD events and total mortality. A similar reduction in the relative risk of coronary events has been documented in patients with and without clinically evident CAD and in patients with mild or severe dyslipidemia.[6–16] These advances necessitated a re-evaluation of diagnostic and treatment policies. In 1995 the Working Group on Hypercholesterolemia and Other Dyslipidemias was established at the initiative of Health Canada. Its first report was drafted in October 1996; after review by committee members, modifications were made and the next draft document was released in March 1997. The committee continued to work during the next 2 years, collecting information from Canadian health care providers and the scientific community. An interim report was published in April 1998.[17] With the rapid progression of research in this area since then, a writing committee was convened to incorporate the most recent scientific

data and expert opinion from various organizations and individuals into this new set of recommendations.

## Recommendations

The following measures were recommended by the Working Group on Hypercholesterolemia and Other Dyslipidemias in light of the new scientific evidence that became available since the interim report was published. A summary of the changes in recommendations from the previous interim report appears in Table 1.

### *Routine screening*

Routinely screen the following patients to obtain a fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglyceride and calculated LDL-C levels): men over the age of 40; women over the age of 50; adults with 2 or more risk factors for CAD; patients with clinical evidence of CAD, peripheral vascular disease or carotid atherosclerosis (signs and symptoms of carotid vessel disease including bruits with transient ischemic attacks or carotid plaque visible by means of ultrasonography); patients with diabetes mellitus; patients with xanthomata or other stigmata of dyslipidemia; and patients with a family history of dyslipidemia or CAD.

Although there are no evidence-based recommendations regarding the optimal frequency for screening, it is reasonable to suggest that asymptomatic patients be screened every 5 years after the age of 40 for men and 50 for women. These ages have been chosen to initiate routine screening because they precede by about 5 years the accelerated rise in the incidence of clinically evident cardiovascular disease for men and women respectively. The frequency of repeat screening requires clinical judgement, but it is appropriate to repeat lipid measurements in patients who have acquired new risk factors or following lifestyle or pharmacological intervention.

**Table 1: Summary of changes in the recommendations for the management of dyslipidemia by the Working Group on Hypercholesterolemia and Other Dyslipidemias***

- Patients with diabetes mellitus over the age of 30 years are now classified as being at very high risk for CAD
- The target LDL-C level for people classified as being at high risk for CAD (10-year calculated risk 20%–30%) has been decreased from 3.5 mmol/L to 3.0 mmol/L
- The assessment of risk factors has been simplified
- All categorical risk factors should be treated, if possible by nonpharmacological means
- For patients at high and very high risk whose lipid concentrations are above target levels, pharmacological treatment should be initiated concomitantly with diet
- For patients at low and moderate risk, pharmacological treatment should be initiated if target lipid levels are not met after 3 and 6 months, respectively, of lifestyle therapy

Note: CAD = coronary artery disease, LDL-C = low-density-lipoprotein cholesterol.
*Changes since the committee's interim report, published in April 1998.[17]

### *Physical examination*

Conduct a physical examination, with particular attention to evidence of cholesterol disorders (cutaneous eruptions, tendon xanthomas, arcus cornealis) and evidence of atherosclerosis (abdominal bruits, carotid bruits, diminished peripheral pulses, ankle–brachial index < 0.9).

### *Risk assessment*

Patients with clinically evident atherosclerosis (i.e., CAD, peripheral vascular disease or carotid vascular disease including ischemic stroke) are categorized as being at very high risk for a cardiovascular event. Those with diabetes (fasting blood glucose level of 7.0 mmol/L or greater) who are over the age of 30 are classified as being at very high risk for CAD. For patients without clinical evidence of cardiovascular disease or diabetes, calculate their short-term risk level using the Framingham risk tables (Table 2).

Other predisposing risk factors contribute directly or indirectly to a high CAD risk. Lipoprotein(a) levels greater than 40 mg/dL increase CAD risk by as much as four-fold in patients with 2 or more other CAD risk factors or with a total cholesterol:HDL-C ratio greater than 5.8.[19,20] A family history of CAD in any first-degree relative increases CAD risk, as does abdominal obesity (waist measurement greater than 100 cm in men and greater than 90 cm in women);[21] a body mass index greater than 25;[18,22] sedentary lifestyle (less than 20 minutes of vigorous exercise 3 times per week or less than 30 minutes per day of moderate exercise);[23] postmenopausal status; ethnic background (absolute risk among South Asian people living in Western society appears to be twice that of white people, even when matched for major risk factors[18]).

### *Target lipid levels*

Determine target lipid levels according to the patient's level of risk. An elevated LDL-C level is a major risk factor for CAD in both men and women. Recent clinical studies[24–26] provide supporting evidence for LDL-C target levels of less than 2.5 mmol/L for the secondary prevention of CAD.[27] Aggressive reduction of LDL-C levels has been shown to slow significantly the progression of atherosclerosis in grafts of patients who have undergone coronary artery bypass graft surgery.[25]

Patients over the age of 30 who have diabetes are now classified as being at "very high risk" for CAD (CAD risk equivalent). The recent United Kingdom Prospective Diabetes Study Group demonstrated that intensive blood glucose control in patients with type 2 diabetes reduced the incidence of retinopathy and nephropathy but had less of an impact on CAD risk;[28] therefore, lipid lowering and blood pressure control are major priorities for these high-risk patients. Haffner and colleagues[29] showed that patients with diabetes without previous myocardial infarction were at as

high a risk of coronary events as nondiabetic patients with previous myocardial infarction.

For all people classified as being at high risk (10-year calculated risk of CAD 20%–30%), the LDL-C target level has been decreased from 3.5 mmol/L to 3.0 mmol/L. Supportive evidence from the recent Air Force/Texas Coronary Atherosclerosis Prevention Study demonstrated a 36% reduction in major coronary events among patients without CAD who were at moderately high risk and treated to achieve an LDL-C level below 3.0 mmol/L.[16]

In 1998 Wilson and associates[30] published a simple coronary disease prediction algorithm to assist physicians in predicting multivariate CAD risk in patients without overt CAD. This particular prediction model, as well as the recently published global risk assessment scores,[18] integrates continuous variables from prior CAD prediction models and categorical approaches, or various treatment guidelines, including the guidelines of the Working Group on Hypercholesterolemia and Other Dyslipidemias. Using these tables, a person's 10-year risk of symptomatic CAD can be estimated and lipid target levels determined (Tables 2 and 3). The calculated risk is based on information in available databases; however certain caveats apply. For instance, the risk prediction is relatively short term (10 years), and many patients at moderate short-term risk are at high long-term risk for CAD.[31] The Framingham data do not apply to people with extreme or unusual risk factors such as severe familial hypercholesterolemia or those with very low levels of HDL-C (familial hypoalphalipoproteinemia). The impact of ethnic background and family history on CAD risk also requires further study. Finally, there are many emerging risk factors for CAD such as elevated levels of lipoprotein(a), fibrinogen, C-reactive protein and homocyst(e)ine that are likely to be incorporated into risk-calculation equations in the future.

With regard to triglyceride levels as

**Table 2: Model for calculating the 10-year risk of CAD in a patient without diabetes mellitus or clinically evident cardiovascular disease,* using Framingham data[18,30]**

**STEP 1: DETERMINE RISK POINTS[18]†**

| Risk factor | Risk points Men | Women |
|---|---|---|
| **Age, yr** | | |
| 30–34 | –1 | –9 |
| 35–39 | 0 | –4 |
| 40–44 | 1 | 0 |
| 45–49 | 2 | 3 |
| 50–54 | 3 | 6 |
| 55–59 | 4 | 7 |
| 60–64 | 5 | 8 |
| 65–69 | 6 | 8 |
| 70–74 | 7 | 8 |
| **Total cholesterol level, mmol/L** | | |
| < 4.14 | –3 | –2 |
| 4.15–5.17 | 0 | 0 |
| 5.18–6.21 | 1 | 1 |
| 6.22–7.24 | 2 | 2 |
| ≥ 7.25 | 3 | 3 |
| **HDL-C level, mmol** | | |
| < 0.90 | 2 | 5 |
| 0.91–1.16 | 1 | 2 |
| 1.17–1.29 | 0 | 1 |
| 1.30–1.55 | 0 | 0 |
| ≥ 1.56 | –2 | –3 |
| **Systolic blood pressure, mm Hg** | | |
| < 120 | 0 | –3 |
| 120–129 | 0 | 0 |
| 130–139 | 1 | 1 |
| 140–159 | 2 | 2 |
| ≥ 160 | 3 | 3 |
| **Smoker** | | |
| No | 0 | 0 |
| Yes | 2 | 2 |
| **Record the points** | | |
| Age | ____ | ____ |
| Total cholesterol | ____ | ____ |
| HDL-C | ____ | ____ |
| Blood pressure | ____ | ____ |
| Smoker | ____ | ____ |
| **Add total risk points** | ____ | ____ |

**STEP 2: CALCULATE RISK[30]‡**

| Total risk points | 10-year risk, % Men | Women |
|---|---|---|
| 1 | 3 | 2 |
| 2 | 4 | 3 |
| 3 | 5 | 3 |
| 4 | 7 | 4 |
| 5 | 8 | 4 |
| 6 | 10 | 5 |
| 7 | 13 | 6 |
| 8 | 16 | 7 |
| 9 | 20 | 8 |
| 10 | 25 | 10 |
| 11 | 31 | 11 |
| 12 | 37 | 13 |
| 13 | 45 | 15 |
| 14 | ≥ 53 | 18 |
| 15 | | 20 |
| 16 | | 24 |
| 17 | | > 27 |

**STEP 3: COMPARE RISK WITH THAT OF AVERAGE PERSON OF SAME AGE[30]**

| Age, yr | Average risk, % | Low risk,§ % |
|---|---|---|
| **Men** | | |
| 30–34 | 3 | 2 |
| 35–39 | 5 | 3 |
| 40–44 | 7 | 4 |
| 45–49 | 11 | 4 |
| 50–54 | 14 | 6 |
| 55–59 | 16 | 7 |
| 60–64 | 21 | 9 |
| 65–69 | 25 | 11 |
| 70–74 | 30 | 14 |
| **Women** | | |
| 30–34 | < 1 | < 1 |
| 35–39 | < 1 | < 1 |
| 40–44 | 2 | 2 |
| 45–49 | 5 | 3 |
| 50–54 | 8 | 5 |
| 55–59 | 12 | 7 |
| 60–64 | 12 | 8 |
| 65–69 | 13 | 8 |
| 70–74 | 14 | 8 |

Note: the Framingham tables underestimate CAD risk if the LDL-C level is > 6.0 mmol/L.

*For example, a 55-year-old man who has a total cholesterol level of 5.43 mmol/L, an HDL-C level of 1.23 mmol/L and a systolic blood pressure of 148 mm Hg and who smokes would have a total risk score of 9. His 10-year risk for CAD would therefore be 20%; the average risk for an average person of his age in the Framingham study population is 16%.

†This section of the table was reprinted, with permission, from Grundy et al.[18]

‡Risk of CAD outcomes including angina pectoris, unstable angina, nonfatal myocardial infarction and coronary death over subsequent 10 years for a Framingham Study participant with that specific risk score.

§Risk of a patient with "optimal" risk factors.

a risk factor, 2 issues are relevant: severe hypertriglyceridemia (triglyceride level greater than 10.0 mmol/L), which poses a significant risk for pancreatitis, and moderate hypertriglyceridemia (triglyceride level of 1.7 to 5.0 mmol/L). In many patients with marked hypertriglyceridemia it may not be feasible to achieve target triglyceride concentrations or total cholesterol:HDL-C ratios, but a goal should be to maintain fasting triglyceride levels below 5.0 mmol/L. Moderate hypertriglyceridemia is a much more common clinical abnormality. This deviation in lipid concentration is a component of the "metabolic syndrome," which is a cluster of risk factors including insulin resistance, elevated fasting and postprandial plasma triglyceride concentrations, and small dense LDL and low HDL-C levels (less than 1.0 mmol/L in men and less than 1.2 mmol/L in women).[18,31] The metabolic syndrome is associated with a marked increase in CAD risk; in people with this condition it is especially important to normalize plasma triglyceride levels and manage contributing risk factors such as abdominal obesity.

All categorical risk factors should be treated, preferably by nonpharmacological means. Excess risk, accumulated over many years, cannot be eliminated by the introduction of intensive short-term prevention strategies.[9,12,18,30,32–34] Although there are several medications that can significantly lower risk, they cannot reinstate the low-risk status of youth.

### *Secondary causes of hyperlipidemia*

Identify and treat secondary causes of hyperlipidemia such as hypothyroidism, renal disease, diabetes and excessive alcohol intake, and assess whether medications taken by the patient are affecting lipid levels.

### *Therapy*

The therapeutic strategy for patients with dyslipidemia depends on both the short-term (10-year) and long-term risk for CAD. For patients at very high or high risk, start drug therapy immediately and promote specific healthy lifestyle changes. For those at moderate risk, promote specific healthy lifestyle changes and, if target lipid levels are not achieved after 3 months, begin drug therapy. For patients at low risk, promote specific healthy lifestyle changes and, if target lipid levels are not reached after 6 months, begin drug therapy.

Recommend lifestyle changes. Specific healthy lifestyle recommendations with respect to diet, ideal body weight, physical activity, moderate alcohol consumption and smoking cessation are summarized in Table 4.

For drug therapy, the lipid-lowering drug of choice depends on the major lipid abnormality. Recommended drug therapies for the different types of lipid disorders are outlined in Table 5. A summary of currently used lipid-lowering medications is shown in Table 6.

## Interpretation

Since the 1988 Canadian Consensus Conference on Cholesterol,[5] there has been enormous progress in our understanding of the pathological basis of atherosclerosis and its complications. Over this same period, many large clinical trials have provided clear evidence that dyslipoproteinemia is a major treatable risk factor for CAD and that lowering LDL-C levels results in a prompt and significant decrease in cardiovascular events, including transient ischemic attacks and stroke. This is true for people at various levels of risk, with and without pre-existing CAD.[37] Although identification and treatment of elevated LDL-C levels may be of benefit to many patients, the short-term benefit is clearly the greatest for people at highest risk for CAD. Thus, the most intensive interventions are advised for people with clinically evident cardiovascular disease or diabetes. These patients require an aggressive approach to reach LDL-C and total cholesterol:HDL-C ratio targets and to modify other risk factors.

Recent studies in Canada and the United States have shown that the majority of patients at very high risk for CAD do not achieve and maintain recommended target lipid levels. This failure is rarely accounted for by severe treatment-resistant dyslipidemia but more often by inadequate lifestyle and pharmacological interventions. Simple procedures such as standing orders for lipid measurement within 12 hours after admission to coronary care units and standard hospital or clinic discharge orders stipulating the appropriate lipid treatment for patients with cardiovascular disease and diabetes could be expected to have a major impact on standard of care. General rec-

**Table 3: Target lipid values by level of risk**

| Level of risk (definition) | Target values | | |
|---|---|---|---|
| | LDL-C level, mmol/L | Total cholesterol: HDL-C ratio | Triglyceride level, mmol/L |
| **Very high*** (10-year risk of CAD > 30%, or history of cardiovascular disease or diabetes) | < 2.5 | < 4 | < 2.0 |
| **High*** (10-year risk 20%–30%) | < 3.0 | < 5 | < 2.0 |
| **Moderate†** (10-year risk 10%–20%) | < 4.0 | < 6 | < 2.0 |
| **Low‡** (10-year risk < 10%) | < 5.0 | < 7 | < 3.0 |

*Start medication and lifestyle changes concomitantly if values are above target values.
†Start medication if target values are not achieved after 3 months of lifestyle modification.
‡Start medication if target values are not achieved after 6 months of lifestyle modification.

ommendations for managing patients at high and very high risk include prompt intervention with both diet and medication, using an initial drug dose calculated to achieve the necessary reduction in LDL-C levels, and modification of the drug regimen as necessary to achieve and maintain target lipid levels. Inclusion of the patient in decision-making is essential, and a "know your LDL-C level" strategy is likely to improve long-term patient compliance.

For people without clinically evident cardiovascular disease or diabetes, the cost:benefit ratio of lipid-lowering therapy depends on their risk of cardiovascular disease; a comprehensive evaluation of short-term risk is advised using multiple risk-assessment equations such as those provided by the Framingham Heart Study. Although more time-consuming than counting risk factors, risk calculation has a number of advantages, including greater accuracy in the assignment of risk, especially for women. Risk calculation takes into account the relative contribution of individual risk factors to overall risk of cardiovascular disease, the severity of individual risk factors and the sex-specific relative risk. For example, the 10-year risk of a coronary event is much higher for a 55-year-old man with an LDL-C level of 4.5 mmol/L than for a 55-year-old woman with the same LDL-C level. However, a 55-year-old woman with an HDL-C level of 0.9 mmol/L has the same 10-year risk of a major coronary event as a 55-year-old man with a similar HDL-C concentration.[38] Risk calculation also provides an opportunity for the physician to review modifiable risk factors with the patient and motivate the patient to make lifestyle changes that will reduce his or her overall risk.

Physicians must realize that this set of recommendations is a general guide and that clinical judgement is required. Many patients at low short-term risk are at high long-term risk for cardiovascular disease. Modifiable risk factors must be addressed at any age, and patients' risk factors should be reassessed periodically. Certain caveats apply to risk calculation. The major prospective population studies such as the Framingham Heart Study[38] and the PROCAM Experience[39] included a relatively small number of patients with

**Table 4: Recommendations for healthy lifestyle**

| |
|---|
| **Eat a healthy diet** |
| *Canada Food Guide*[35] |
| 5–10 servings of grain products per day (emphasize whole grain) |
| 5–10 servings of fruits and vegetables per day |
| 2–4 servings of low-fat milk products per day |
| 2–3 servings of low-fat meat and alternatives per day |
| *Low fat diet*[5,35] |
| < 30% of total calories from fat |
| < 10% of total calories from saturated fat and trans fatty acids |
| < 300 mg cholesterol per day |
| *High-fibre diet*[36] |
| > 25–35 g of fibre per day |
| **Get regular physical activity**[32] |
| 30–60 min of endurance (cardiovascular) activities (e.g., brisk walking, jogging, cycling) 4–7 days a week |
| **Maintain ideal body weight**[21] |
| Patients with dyslipidemia who are overweight (body mass index [BMI] > 25) or have a waist circumference > 90 cm (women) or > 100 cm (men) should be advised to reduce their weight |
| Patients should be encouraged to attain and maintain a healthy body weight (BMI of 20–25) |
| **Consume alcohol in moderation** |
| Patients who choose to drink should limit their alcohol consumption to 2 or fewer standard drinks per day |
| Patients with elevated triglyceride levels should be advised to decrease or eliminate alcohol consumption |
| **Stop smoking** |
| Patients who smoke should be advised to quit, and young people should be encouraged not to smoke |
| Patients who are unable to quit on their own should be provided with information on smoking-cessation programs, nicotine replacement therapy and drug therapy where indicated |

**Table 5: Drugs of choice for different abnormal lipid profiles**

| Lipid profile | Drug of choice |
|---|---|
| Elevated LDL-C level | |
| Alone | Statin with or without resin |
| With a moderately elevated triglyceride level | Statin |
| With a low HDL-C level | Combination therapy may be required (e.g., statin plus fibrate or statin plus niacin) |
| Normal LDL-C level | |
| With an elevated triglyceride level | Niacin or fibrate,* or combination therapy |
| With a low HDL-C level | Niacin or fibrate, or combination therapy |

*Modify dose of fibrate for patients with reduced creatinine clearance.

**Table 6: Current lipid-lowering medications**

| Drug | Available dose |
|---|---|
| **Statins** | |
| Atorvastatin (Lipitor) | 10–80 mg |
| Cerivastatin (Baycol) | 0.2–0.4 mg |
| Fluvastatin (Lescol) | 20–80 mg |
| Lovastatin (Mevacor) | 20–80 mg |
| Pravastatin (Pravachol) | 10–40 mg |
| Simvastatin (Zocor) | 10–80 mg |
| **Resins** (bile acid sequestrants) | |
| Cholestyramine (Questran) | 4–24 g |
| Colestipol (Colestid) | 5–30 g |
| **Fibrates*** | |
| Bezafibrate (Bezalip) | 200–400 mg |
| Fenofibrate (Lipidil) | 67–200 mg |
| Gemfibrozil (Lopid) | 600–1200 mg |
| **Niacin†** | |
| Nicotinic acid | 1–3 g |

*Use with caution in patients with renal insufficiency.
†Use with caution in patients with diabetes.

severe dyslipidemias such as familial hypercholesterolemia. Adults with an LDL-C level greater than 5.0 mmol/L are at very high risk of CAD and, even in the absence of other CAD risk factors, are likely to require early pharmacological intervention. The accuracy and precision of risk calculation will continue to evolve. Future data sets are likely to include more detailed information on emerging CAD risk factors such as lipoprotein(a), fibrinogen, homocyst(e)ine, plasminogen activator inhibition-1 (PAI-1) and C-reactive protein; assessment of these factors may further improve the accuracy of risk assessment. Finally, noninvasive assessment of preclinical atherosclerosis, including exercise stress testing, nuclear perfusion scans and B-mode carotid ultrasonography, may aid in the early identification of patients at high risk for cardiovascular events.

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