

# Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update

Jacques Genest, Jiri Frohlich, George Fodor, Ruth McPherson (the Working Group on Hypercholesterolemia and Other Dyslipidemias)

This article appears online only and is an appendix to *CMAJ* 2003;168(9):921-4.

Clinical practice guidelines require continual reassessment in response to new information and changes in the pattern of disease. Challenges in Canada, as in all industrialized countries, include the increasing size of the elderly population and the rising prevalence of obesity and diabetes mellitus. More than 20% of Canadians will be over 65 years of age by 2011; the fastest-growing age group is those over 80 years, expected to double by 2026 to 1.9 million.<sup>1</sup> Obesity, particularly abdominal adiposity, is associated with an increased prevalence of diabetes, hypertension and other features of the metabolic syndrome (hypertriglyceridemia, low levels of high-density lipoprotein cholesterol [HDL-C] and insulin resistance) as well as increases in a number of proinflammatory markers, including C-reactive protein and interleukin-6. Currently, 31% of Canadian adults are obese (defined as a body mass index greater than 27 kg/m<sup>2</sup>). Type 2 diabetes is a major risk factor for coronary artery disease, and its prevalence is reaching epidemic proportions.<sup>2</sup> The current incidence of new cases of diabetes is estimated at 60 000 per year, and the prevalence is projected to increase from 1.5 million in 1998 to 3 million in 2010.<sup>3</sup> The First Nations population, with a risk of diabetes 3 to 5 times higher than that of the general Canadian population, is at particular risk.<sup>4</sup>

Because of the burden of cardiovascular disease and the high rate of death from out-of-hospital acute myocardial infarction, preventive measures are essential in order to reduce health care costs and improve the health of Canadians. The Working Group on Hypercholesterolemia and other Dyslipidemias issued recommendations for the management of dyslipidemias in Canada in 2000.<sup>5</sup> Since the publication of these Canadian guidelines and of the US National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) report,<sup>6</sup> in 2001, the findings from several important clinical trials have been reported, including those from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study,<sup>7</sup> the Veterans Affairs High-Density

Lipoprotein Intervention Trial (VA-HIT)<sup>8</sup> and the Heart Protection Study (HPS).<sup>9</sup> As a result, the working group was reconvened to assess this new information and to address the increasing prevalence of the metabolic syndrome and its effect on the risk of cardiovascular disease. The main purpose of the recommendations is to provide primary care physicians and internists with a tool for evaluating a patient's risk of coronary artery disease as part of a routine health assessment.

The updated recommendations have been simplified and include 3 levels of risk of coronary artery disease (high, moderate and low) and 2 treatment targets (the low-density lipoprotein cholesterol [LDL-C] level and the total cholesterol:HDL-C ratio). The US NCEP ATP-III guidelines also provide 3 levels of risk based on the Framingham Study equation but, in contrast to the Canadian guidelines, recommend the use of non-HDL-C levels (i.e., the sum of very-low-density lipoprotein cholesterol [VLDL-C] and LDL-C levels) as its secondary therapeutic goal, especially in patients with features of the metabolic syndrome. Because the total cholesterol:HDL-C ratio is a more sensitive and specific index of cardiovascular risk than total cholesterol, the working group has chosen this simple lipid ratio as a secondary goal of therapy. Topics specifically addressed in the revised guidelines include the management of patients at high risk of coronary artery disease who have an LDL-C level at target (2.5 mmol/L), the management of patients who have combined dyslipidemia and low HDL-C levels, and the noninvasive assessment of cardiovascular disease and other risk factors, including the metabolic syndrome<sup>10</sup> and levels of apolipoprotein B, lipoprotein(a), homocysteine and C-reactive protein.

The revised guidelines attempt to harmonize cardiovascular risk assessment across North America using the Framingham Study equations published in the NCEP ATP-III report.<sup>6</sup> In addition, the guidelines will provide a background recommendation for Canadian specialty organizations such as the Canadian Hypertension Society, the Canadian Diabetes Association, the Dietitians of Canada

and the Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology. The guidelines were reviewed by 2 expert panels that included recognized specialists in the areas of cardiovascular disease prevention, lipid metabolism and diabetes as well as primary care physicians. In addition, several medical professional associations had an opportunity to review and comment on this document.

## Global risk assessment

For the 2000 Canadian guidelines, the Framingham Study risk equations used by the working group were those published by Grundy and colleagues.<sup>11</sup> The NCEP ATP-III used an adaptation of Framingham data based on the estimated 10-year risk of "hard cardiac endpoints." These included death from coronary artery disease and nonfatal myocardial infarction. The NCEP ATP-III risk estimate tables also adjust certain risk factors (e.g., total cholesterol level and smoking status) for age and correct for the effect of treatment on blood pressure measurement. This represents a refinement to the previously published risk assessment tables. For these reasons and in order to harmonize cardiovascular risk assessment across North America, the working group has used the NCEP ATP-III risk estimation algorithm<sup>6</sup> in the updated recommendations. The presence of diabetes is generally considered as a coronary artery disease risk equivalent. The Canadian Diabetes Association considers that an adult diabetic patient should be categorized as being at high risk. The working group agrees that a young patient whose diabetes is controlled by diet may still have a relatively low 10-year risk estimate, but the long-term risk is very high and should be considered when making treatment decisions.

### Risk assessment

A given patient's 10-year risk of coronary artery disease can be estimated using the model in Table 1.

### Screening

Routinely screen men over 40 years of age and women who are postmenopausal or over 50 years of age. In addition, screen those with: diabetes mellitus; risk factors such as hypertension, smoking or abdominal obesity; a strong family history of premature cardiovascular disease; manifestations of hyperlipidemia (e.g., xanthelasma, xanthoma or arcus corneae); or evidence of symptomatic or asymptomatic atherosclerosis.

Patients of any age may be screened at the discretion of the physician, particularly when lifestyle changes are indicated.

### Risk categories

Three categories of risk are recognized (Table 2). Patients at high risk include those with established coronary

artery disease, cerebrovascular disease or peripheral arterial disease; patients with chronic kidney disease; adult diabetic patients; and asymptomatic patients in whom the 10-year risk of death from coronary artery disease or nonfatal myocardial infarction is 20% or higher. Patients at moderate, or intermediate, risk include those with a 10-year risk greater than 10% but less than 20%.

The working group no longer recommends a discrete target for the plasma (or serum) triglyceride level. An optimal plasma triglyceride concentration is less than 1.7 mmol/L. Achievement of the target total cholesterol:HDL-C ratio will require treatment of significantly elevated triglyceride levels. Severe hypertriglyceridemia (triglyceride level greater than 10.0 mmol/L) should also be treated since it is a risk factor for pancreatitis. The preferred drug for the treatment of hypertriglyceridemia, in combination with diet and lifestyle changes, is a fibric acid derivative or niacin. In refractory cases, the addition of oils rich in omega-3 fatty acids derived from fish may be very effective.

## Factors influencing risk assessment

### Metabolic syndrome

The clustering of cardiovascular risk factors is recognized as being an important health issue. The metabolic syndrome is defined in qualitative terms and encompasses abdominal obesity, insulin resistance, elevated plasma triglyceride levels, low HDL-C levels and high blood pressure (Table 3).

### Role of abdominal obesity

Epidemiologic data have shown that abdominal obesity is associated with small, dense LDL particles, elevated apolipoprotein B levels, reduced plasma HDL-C levels, insulin resistance and hypertension. These features are observed in about half of patients with the metabolic syndrome. Adipose tissue synthesizes and secretes a variety of proteins, with important systemic effects. These proteins are collectively referred to as adipocytokines and include leptin, tumour necrosis factor, adiponectin, resistin, adipisin, angiotensinogen, plasminogen activator inhibitor-1 and C-reactive protein. Secretion of these cytokines and global changes in insulin sensitivity are in part contingent on adipose tissue mass and distribution. Although visceral fat accounts for only about 10% of total body fat, this depot is most strongly related to insulin resistance and dyslipidemia. Visceral adipocytes demonstrate higher lipolytic activity and release free fatty acids directly to the liver through the portal circulation. Waist circumference is a useful estimate of abdominal obesity and indicator of cardiovascular risk. The NCEP ATP-III has used cut-off values of waist circumference of 102 cm for men and 88 cm for women.

**Table 1: Model for estimating the 10-year risk of coronary artery disease in a patient without diabetes mellitus or clinically evident cardiovascular disease, using data from the Framingham Heart Study<sup>11</sup>**

MEN						WOMEN					
Risk factor	Risk points					Risk factor	Risk points				
<b>Age group, yr</b>						<b>Age group, yr</b>					
20–34	–9					20–34	–7				
35–39	–4					35–39	–3				
40–44	0					40–44	0				
45–49	3					45–49	3				
50–54	6					50–54	6				
55–59	8					55–59	8				
60–64	10					60–64	10				
65–69	11					65–69	12				
70–74	12					70–74	14				
75–79	13					75–79	16				
<b>Total cholesterol level, mmol/L</b>						<b>Total cholesterol level, mmol/L</b>					
	Age group, yr						Age group, yr				
	20–39	40–49	50–59	60–69	70–79		20–39	40–49	50–59	60–69	70–79
< 4.14	0	0	0	0	0	< 4.14	0	0	0	0	0
4.15–5.19	4	3	2	1	0	4.15–5.19	4	3	2	1	1
5.20–6.19	7	5	3	1	0	5.20–6.19	8	6	4	2	1
6.20–7.20	9	6	4	2	1	6.20–7.20	11	8	5	3	2
≥ 7.21	11	8	5	3	1	≥ 7.21	13	10	7	4	2
<b>Smoker</b>						<b>Smoker</b>					
No	0	0	0	0	0	No	0	0	0	0	0
Yes	8	5	3	1	1	Yes	9	7	4	2	1
<b>HDL-C level, mmol/L</b>						<b>HDL-C level, mmol/L</b>					
≥ 1.55	–1					≥ 1.55	–1				
1.30–1.54	0					1.30–1.54	0				
1.04–1.29	1					1.04–1.29	1				
< 1.04	2					< 1.04	2				
<b>Systolic blood pressure, mm Hg</b>						<b>Systolic blood pressure, mm Hg</b>					
	Untreated		Treated				Untreated		Treated		
< 120	0		0			< 120	0		0		
120–129	0		1			120–129	1		3		
130–139	1		2			130–139	2		4		
140–159	1		2			140–159	3		5		
≥ 160	2		3			≥ 160	4		6		
<b>Total risk points</b>						<b>Total risk points</b>					
	<b>10-year risk, %</b>						<b>10-year risk, %</b>				
< 0	< 1					< 9	< 1				
0–4	1					9–12	1				
5–6	2					13–14	2				
7	3					15	3				
8	4					16	4				
9	5					17	5				
10	6					18	6				
11	8					19	8				
12	10					20	11				
13	12					21	14				
14	16					22	17				
15	20					23	22				
16	25					24	27				
≥ 17	≥ 30					≥ 25	≥ 30				

**10-year risk:**  
 \_\_\_\_\_ %

**10-year risk:**  
 \_\_\_\_\_ %

## Apolipoprotein B

Each of the atherogenic particles — namely, VLDL, intermediate-density lipoprotein, LDL and lipoprotein(a) — contain 1 molecule of apolipoprotein B. Thus, the serum concentration of apolipoprotein B reflects the total number of these particles. Four recent prospective studies showed the apolipoprotein B concentration to be a better estimate of the risk of vascular events than the LDL-C level.<sup>12</sup> Risk is highest in people with an apolipoprotein B level of more than 1.2 g/L and a triglyceride level of more than 1.5 mmol/L. This profile is often associated with the presence of smaller, denser and more atherogenic LDL particles. Increased apolipoprotein B levels and high triglyceride concentrations are prevalent in patients with the metabolic syndrome and type 2 diabetes. Apolipoprotein B may be of particular value in assessing the adequacy of statin treatment. As shown in a number of statin trials, apolipoprotein B levels during treatment relate more strongly to clinical outcomes than do LDL-C levels during treatment.<sup>12</sup> Another advantage of measuring apolipoprotein B is that fasting samples are not required. In addition, Canadian population values have been established, apolipoprotein B has been standardized, and most laboratories have the equipment and expertise to measure it. For the Canadian population, an apolipoprotein B level of 0.9 g/L is about the 20th percentile, 1.05 g/L the 50th percentile and 1.2 g/L the 75th percentile.

In summary, apolipoprotein B concentration can be used to identify the risk category of patients with moderate hypertriglyceridemia and is a useful indicator of the adequacy of lowering the number of atherogenic particles. Plasma apolipoprotein B measurement may be of particular utility in determining cardiovascular risk and adequacy of treatment in people who have the metabolic syndrome. An optimal level of apolipoprotein B in a patient at high risk of coronary artery disease is less than 0.9 g/L.

**Table 2: Risk categories and target lipid levels**

Risk category	Target level	
	LDL-C level, mmol/L	Total cholesterol:HDL-C ratio
<b>High*</b> (10-year risk of coronary artery disease $\geq$ 20%, or history of diabetes mellitus† or any atherosclerotic disease)	< 2.5 <b>and</b>	< 4.0
<b>Moderate</b> (10-year risk 11%–19%)	< 3.5 <b>and</b>	< 5.0
<b>Low‡</b> (10-year risk $\leq$ 10%)	< 4.5 <b>and</b>	< 6.0

Note: LDL-C = low-density lipoprotein cholesterol.

\*Apolipoprotein B can be used as an alternative measurement, particularly for follow-up of patients treated with statins. An optimal level of apolipoprotein B in a patient at high risk is < 0.9 g/L, in a patient at moderate risk < 1.05 g/L and in a patient at low risk < 1.2 g/L.

†Includes patients with chronic kidney disease and those undergoing long-term dialysis.

‡In the “very low” risk stratum, treatment may be deferred if the 10-year estimate of cardiovascular disease is < 5% and the LDL-C level is < 5.0 mmol/L.

## Lipoprotein(a)

Lipoprotein(a) is an LDL particle in which apolipoprotein B is attached to apolipoprotein(a) protein by a disulfide bridge. The apolipoprotein(a) moiety has structural homology to plasminogen and may compete with plasminogen for binding to fibrin and plasminogen receptors on endothelial cells and thus impair fibrinolysis. Lipoprotein(a) has been identified as a potent predictor of premature atherosclerosis in most of the large prospective studies.<sup>13,14</sup> Elevated lipoprotein(a) levels occur in 15%–20% of people with premature atherosclerosis,<sup>15</sup> and most studies support lipoprotein(a) as an independent risk factor for coronary artery disease. A meta-analysis of 18 population-based cohorts indicated that the combined risk ratio for those in the upper versus lower tertile of the population distribution for lipoprotein(a) was 1.7.<sup>16</sup> There are accumulating data suggesting that the atherogenicity of lipoprotein(a) is aggravated by other risk factors.<sup>16</sup> Subgroup and post-ad-hoc analysis of published studies suggests that plasma lipoprotein(a) levels are no longer predictors of coronary artery disease once the LDL-C level has been markedly reduced.<sup>16</sup> Hopkins and associates<sup>17</sup> demonstrated a much greater effect of lipoprotein(a) on coronary artery disease risk in people with an elevated total cholesterol:HDL-C ratio or other risk factors for coronary artery disease than in people without such risk factors. The mechanism by which lipoprotein(a) interacts with plasma lipoproteins to increase the risk of atherosclerosis is unknown. Lipoprotein(a) may facilitate the proatherogenic effects of LDL. Lipoprotein(a) concentrations are determined by a single gene and are not responsive to dietary therapy. Measurement of lipoprotein(a) is not routinely recommended as part of lipid screening but may be useful in determining coronary artery disease risk in patients at moderate risk who have a family history of early coronary artery disease. A lipoprotein(a) concentration greater than 30 mg/dL in a patient who has a total cholesterol:HDL-C ratio greater than 5.5 or other major risk factors may indicate the need for earlier and more intensive therapy to lower the LDL-C level.

**Table 3: Clinical identification of the metabolic syndrome\***

Risk factor	Defining level
Abdominal obesity	
Men	Waist circumference > 102 cm
Women	Waist circumference > 88 cm
Triglyceride level	$\geq$ 1.7 mmol/L
HDL-C level	
Men	< 1.0 mmol/L
Women	< 1.3 mmol/L
Blood pressure	$\geq$ 130/85 mm Hg
Fasting glucose level	6.2–7.0 mmol/L

\*Criteria: 3 or more of the risk factors.

## Homocysteine

Elevated plasma concentrations of homocysteine are a strong predictor of adverse outcomes in patients with coronary artery disease and are prevalent in patients with renal impairment and those with cardiovascular disease. Several cross-sectional and retrospective studies have demonstrated a role for elevated homocysteine levels in determining coronary artery disease risk.<sup>18</sup> "Normal" plasma homocysteine levels range between 5 and 15  $\mu\text{mol/L}$ , and, although hyperhomocysteinemia refers to levels between 16 and 100  $\mu\text{mol/L}$ , even mildly elevated levels (greater than 10–15  $\mu\text{mol/L}$ ) are associated with an increased risk of cardiovascular disease.<sup>19</sup> Plasma homocysteine levels above the 90th to 95th percentile are associated with an increased risk of cardiovascular disease, stroke and deep vein thrombosis (odds ratio 1.7).<sup>20</sup>

Randomized controlled trials of the effect of lowering homocysteine levels on cardiovascular end points are under way and should be completed by 2004–2006. These trials involve a fixed dose of folic acid (1–2 mg) and vitamin B<sub>12</sub> (1 mg). A treat-to-target (9.0  $\mu\text{mol/L}$ ) homocysteine-lowering trial is still needed. The position of the working group, the Canadian Cardiovascular Society, the American Heart Association and the Heart and Stroke Foundation of Canada is that there is insufficient evidence to warrant broad homocysteine screening until these ongoing clinical trials show that vitamin supplementation to lower homocysteine levels decreases cardiovascular risk. However, there may be a specific indication for treatment with folic acid and vitamin B<sub>12</sub> in patients undergoing percutaneous coronary revascularization.<sup>21–23</sup> Similarly, the treatment of homocysteine concentrations greater than 10  $\mu\text{mol/L}$  with folic acid and vitamins B<sub>12</sub> and B<sub>6</sub> may be warranted in high-risk patients who have renal or cardiovascular disease.

## High-sensitivity C-reactive protein

The acute-phase concentration of C-reactive protein is a very sensitive, objective marker of inflammation, and the ability to measure C-reactive protein at very low concentrations may permit identification of asymptomatic patients at risk of acute coronary events. Recent data from the Women's Health Study<sup>24</sup> suggest that measurement of high-sensitivity C-reactive protein adds prognostic information to that provided by the Framingham Study risk score in terms of predicting coronary artery disease events. An elevated level of high-sensitivity C-reactive protein is associated with abdominal obesity and is another component of the metabolic syndrome.<sup>25</sup> In several studies, baseline levels in the upper quartile of the population distribution in people without cardiovascular disease were associated with a 3- to 4-fold increased incidence of subsequent coronary events.<sup>24,26,27</sup> Available data also suggest that measurement of the high-sensitivity C-reactive protein level may help target treatment to the population at risk;<sup>28</sup>

this is relevant, since about half of all coronary events occur in people without marked LDL-C elevations.

The working group does not currently provide firm recommendations regarding the use of the high-sensitivity C-reactive protein measurement in risk assessment. However, measurement may be clinically useful in identifying people who are at a higher risk of cardiovascular disease than that predicted by a global risk assessment, in particular those with a calculated 10-year risk between 10% and 20%. Fasting is not a requirement for measurement of high-sensitivity C-reactive protein. However, measurement should not be done during any acute illness and is not an index of cardiovascular risk in patients with chronic inflammatory conditions. Duplicate measurements, optimally 2 weeks apart, are recommended. The lower number should be considered the reliable value. Use of the high-sensitivity assay is essential when measurement of C-reactive protein is used for risk assessment; in most provinces, patients will be asked to pay for the analysis. Low risk is defined as a level less than 1 mg/mL, average risk as 1.0–3.0 mg/L and high risk as 3.0–10 mg/L. If the concentration is greater than 10 mg/L, the test should be repeated and the patient examined for sources of infection or inflammation.<sup>29</sup>

## Genetic risk

The genetic contribution to the risk of coronary artery disease cannot be quantified reliably on the basis of current knowledge. Familial aggregation can be primarily genetic (as seen in familial hypercholesterolemia) or can reflect a genetic predisposition to dyslipidemia, hypertension, diabetes, hypercoagulability or other cardiovascular risk factors. Shared household effect (diet, sedentary lifestyle) can also produce familial clustering of coronary artery disease. Despite these caveats, premature coronary artery disease (presenting before 55 years of age in men and before 65 years in women) in a first-degree relative (parent, sibling or child) should alert the clinician to increase the risk category to a higher level. When a family history of coronary artery disease can be ascertained unambiguously, the risk for first-degree relatives is increased by 1.7 to 2.0. This should be taken into account in risk stratification and may increase the risk category in individual patients.

## Hormone replacement therapy

New information from the Women's Health Initiative<sup>21</sup> and the Heart Estrogen/Progestin Replacement Study<sup>30,31</sup> has demonstrated that oral hormone replacement therapy (HRT) does not reduce and may increase cardiovascular disease risk. Most of the data available to make clinical recommendations are based on standard doses of orally administered conjugated equine estrogen plus medroxyprogesterone acetate. Information regarding the possible cardiovascular risks and benefits of transdermal use of estrogen, other progestins or selective estrogen receptor modulators is incomplete.

### Primary prevention

- HRT should not be initiated for the primary prevention of cardiovascular disease.
- Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary risks and patient preference.
- Unless otherwise indicated for osteoporosis treatment or severe menopausal symptoms, efforts should be made to stop or taper HRT in women over the age of 55 years who have been treated with HRT for more than 5 years.

### Secondary prevention

- HRT should not be initiated for the secondary prevention of cardiovascular disease.
- If a woman experiences an acute cardiovascular event or is scheduled for coronary artery bypass grafting, a percutaneous coronary intervention or other surgery, consideration should be given to stopping HRT.

### Findings from new trials

The Heart Protection Study<sup>9</sup> was a landmark study involving 20 556 men and women aged 40–80 years who had a total cholesterol level above 3.5 mmol/L and were at high risk of coronary artery disease. The study subjects included patients with established coronary artery disease, those who had had a myocardial infarction, those with peripheral or cerebral vascular disease, and patients with diabetes or hypertension or both. The study added to a recent body of data demonstrating no cardiovascular benefit with oral antioxidant vitamin therapy. The main finding was that the use of simvastatin (40 mg/d) decreased the death rate by 13% and reduced the rate of all cardiovascular end points by 24%. With adjustment for lack of compliance in the simvastatin group and for patients in the placebo group who took a statin, the actual effect may be increased by 1.5-fold. Predefined subgroup analysis showed benefit in men and in women, in young and old, and in patients with and without established disease. More important, benefits extended across all ranges of total cholesterol and LDL-C levels. Indeed, subjects with a baseline LDL-C level of less than 2.6 mmol/L demonstrated the same magnitude of risk reduction as those with higher LDL-C levels. In light of these data, the working group now suggests that people at high risk of coronary artery disease be treated with the equivalent of 40 mg/d of simvastatin and that the minimum target of therapy be an LDL-C level of less than 2.5 mmol/L and a total cholesterol:HDL-C ratio of less than 4.0. Controversy still exists as to the optimal LDL-C level in people at high risk of a cardiovascular event. Large clinical trials are under way to examine clinical outcomes in patients with cardiovascular disease treated to reach a

target LDL-C level of less than 1.8 mmol/L versus the conventional target of less than 2.6 mmol/L. Until the results of these trials are published, available evidence suggests that a patient at high risk should be treated with the equivalent of 40 mg/d of simvastatin and that an LDL-C level of less than 2.5 mmol/L should be achieved.

In the MIRACL Study,<sup>7</sup> atorvastatin (80 mg/d) was compared with best treatment and angioplasty in patients with stable coronary artery disease. There was a reduction in the rate of cardiovascular events of 16%, most of the benefit being attributable to admission to hospital because of recurrent angina. The study showed that high-dose atorvastatin is safe and may acutely reduce the rate of cardiovascular events. The VA-HIT investigators<sup>8</sup> examined patients with established coronary artery disease and a normal LDL-C level but a reduced HDL-C level. The use of gemfibrozil (1200 mg/d) was associated with a 22% decrease in the rate of recurrent coronary events. The Diabetes Atherosclerosis Intervention Study<sup>32</sup> was an angiographic trial of fenofibrate in patients with diabetes and dyslipidemia. Although the change in the prespecified primary end point did not reach statistical significance, one angiographic measure of coronary disease progression was reduced with fenofibrate. A reduction in clinical end points was also noted, although the study was not powered to evaluate clinical events. The HDL-Atherosclerosis Treatment Study<sup>33</sup> was an angiographic trial of low-dose simvastatin (10–20 mg/d) plus niacin (1500 mg/d) with or without antioxidant vitamins or placebo. In this small trial, there was angiographic reduction of coronary artery disease and a 90% reduction in the rate of major cardiovascular events with the combination treatment. Antioxidants had no effect.

The Anglo-Scandinavian Cardiac Outcomes Trial<sup>34</sup> investigators compared the effects of atorvastatin (10 mg) versus placebo on the combined outcome of nonfatal myocardial infarction (including silent myocardial infarction) and fatal coronary artery disease in 9000 hypertensive patients with total cholesterol levels of less than 6.5 mmol/L. These patients had other risk factors for coronary artery disease but no evidence of pre-existing coronary artery disease. The study was stopped after 3 years because of significant apparent benefit in the treatment group. There was a reduction of 36% in the rates of fatal and nonfatal myocardial infarction, together with significant reductions in the rates of stroke (27%), all cardiovascular events and procedures (21%) and total coronary events (29%). This study provides strong support for statin therapy in patients at high risk in the primary prevention category.

These studies provide new information relevant to risk stratification algorithms, the target LDL-C levels in patients at high risk, the use of high-dose statin therapy and better recommendations for managing people at high risk who have low HDL-C levels.

## Diagnosis of asymptomatic atherosclerosis

Atherosclerosis may be detected and the diagnosis of cardiovascular disease confirmed using the following methods:

- *Recommended*: physical examination; ankle-brachial index
- *Possibly useful in subjects at moderate risk*: carotid ultrasonography (may detect clinically unapparent atherosclerosis); electrocardiography; graded exercise testing in men over 40 years who have risk factors
- *Not currently recommended, based on available evidence*: flow-mediated vasodilatation, plethysmography, arterial compliance; electron beam CT scanning; MRI scanning; intravascular ultrasonography

The *ankle-brachial index* is the ratio of systolic blood pressure in the dorsalis pedis or posterior tibial artery to the systolic blood pressure in the brachial artery. Requirements include a blood pressure cuff and Doppler ultrasonic sensor. Measurement of the ankle-brachial index can be of particular utility in assessing asymptomatic vascular disease in middle-aged or elderly patients with other risk factors. An index of less than 0.90 in either leg is a reliable indicator of peripheral vascular disease, with a sensitivity of 90% and specificity of 98% for detecting stenosis of greater than 50%. Symptomatic peripheral vascular disease is associated with a marked increase in the risk of cardiovascular disease.<sup>35</sup>

*Carotid B-mode ultrasonography* can also be of use in assessing asymptomatic atherosclerosis. Most of the published literature pertains to the measurement of intimal-medial thickness. Measurements are obtained bilaterally on the distal 1 cm of the common carotid, the carotid bifurcation and the proximal 1 cm of the internal carotid. Among asymptomatic people over the age of 50, several studies have shown up to a 5-fold increase in the risk of cardiovascular disease for those with increased intimal-medial thickness.<sup>36-38</sup> Measurement of intimal-medial thickness is a useful tool in cardiovascular risk assessment but is not yet a standard measure in routine carotid ultrasonography. Although these measurements are not routinely available, patients with evidence of nonstenotic carotid lesions or sessile plaque on routine carotid Doppler ultrasonography similarly are candidates for secondary prevention strategies. The degree of stenosis required for a high-risk approach has not been determined in clinical trials.

*Exercise stress testing* in asymptomatic men over the age of 40 years can also be useful in risk stratification. Gibbons and coworkers<sup>39</sup> studied 25 927 healthy men with a mean age of 43 years. In this group of asymptomatic men, a positive stress test result was associated with a 21-fold increased relative risk of coronary artery disease among those with no risk factors and an 8- to 10-fold increase in relative risk among those with risk factors. Earlier reports from the Lipid Research Clinics Coronary Primary Prevention Trial<sup>40</sup> and the Multiple Risk Factor Intervention Trial (MRFIT)<sup>41</sup> also showed that a positive result of exercise stress testing strongly predicted risk of coronary artery dis-

ease. Thus, a positive exercise stress test result (1 mm or more of ST-segment depression within 6 minutes on the Bruce protocol) can move a middle-aged man from the moderate-risk to the high-risk secondary prevention category. In contrast, a negative stress test result and good exercise tolerance (greater than 8 metabolic equivalents) carries a good prognosis in this group. Fewer data are available to support exercise stress testing as part of risk assessment for women, although there may be a role for nuclear perfusion scanning in the presence of risk factors and possible angina symptoms.

## Treatment

### Diet

Although there have been significant improvements in dietary composition in the past 4 decades, particularly decreases in intake of saturated fat and cholesterol, these gains have been partly offset by a continuing increase in the prevalence of obesity. Dietary intervention should be part of a strategy of lifestyle changes aimed at increasing exercise, increasing fruit and vegetable intake and increasing the proportion of mono- and polyunsaturated fats in the diet while decreasing the proportion of saturated fats and trans-fatty acids to less than 7% of total calories. An increase in the intake of omega-3 fatty acids from fish and plant sources is also recommended. An important focus should be on decreasing energy consumption, in particular by reducing intake of refined carbohydrates and sugar to achieve and maintain a body mass index of less than 25 kg/m<sup>2</sup>.

### Medication

#### Target lipid levels

In people at high risk of coronary artery disease, treatment should be started immediately, concomitant with diet and therapeutic lifestyle changes. The priority for treatment is reduction of the LDL-C level to less than 2.5 mmol/L and the total cholesterol:HDL-C ratio to less than 4.0. In light of the new data from the Heart Protection Study,<sup>9</sup> the working group recommends that people at high risk be treated with the equivalent of 40 mg/d of simvastatin, with a minimum target level for LDL-C of 2.5 mmol/L. A summary of currently used lipid-lowering medications is shown in Table 4.

#### Achievement of target LDL-C levels

Most patients, including those with the metabolic syndrome, diabetes and combined dyslipidemia, will be able to achieve target LDL-C levels with statin monotherapy. A substantial minority of patients will, however, require combination therapy with a bile acid sequestrant (cholestyramine or colestipol). New cholesterol absorption inhibitors

(ezetimibe) are available and are better tolerated than bile acid sequestrants. These combinations are safe and can decrease LDL-C levels by an additional 10% to 20%.

### Achievement of target total cholesterol:HDL-C ratio

Particularly for patients at high risk, the target total cholesterol:HDL-C ratio (less than 4.0) may be more difficult to achieve than the target LDL-C levels. The following approaches are recommended.

**Lifestyle therapy:** For patients with hypertriglyceridemia, intensify dietary therapy and exercise, with a focus on weight loss and restriction of refined carbohydrate and alcohol. For patients with low HDL-C levels, increased aerobic exercise, increased intake of monounsaturated fats, moderate alcohol intake (only if the triglyceride level is within normal limits) and weight loss are beneficial.

**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 reduce cardiovascular events significantly in the HDL-Atherosclerosis Treatment Study.<sup>33</sup> Niacin is the only available agent that significantly increases HDL-C concentrations. Side effects, which may be significant, include flushing, dry skin and gastrointestinal irritation. Niacin should be taken 2 to 3 times daily, after meals, and the dose should be increased slowly. NSAIDs, including ASA, attenuate the vasodilatory side effects in most patients. There is a small but significant risk of hepatotoxic effects with niacin–statin treatment, and transaminase levels should be monitored. Niacin may also impair insulin sensitivity, and drug regimens may have to

be modified for patients with diabetes or impaired glucose tolerance. For patients who do not tolerate or are not candidates for niacin therapy, a combination of a statin with a fibrate may be used, with close patient follow-up. Fibrates increase serum creatinine and homocysteine levels, and fibrates alone or statin–fibrate combination therapy should not be used in patients with renal impairment (or should be used under carefully monitored conditions). In general, the smallest available doses of both fibrate and statin are recommended for initial treatment. Available data suggest that fenofibrate is reasonably safe in combination with either simvastatin or pravastatin.<sup>42</sup> Gemfibrozil is associated with a higher risk of myotoxic effects and should not be used in combination therapy. For patients with moderate hypertriglyceridemia, the addition of salmon oil (1–3 g three times daily) to statin therapy is safe and may be useful in lowering triglyceride levels and thus achieving the target total cholesterol:HDL-C ratio.

**Increase statin dose:** For patients with low HDL-C levels or mild hypertriglyceridemia (triglyceride level less than 5.0 mmol/L) the recommended target total cholesterol:HDL-C ratio may often be achieved by a further increase in statin dose even if the target LDL-C level has been reached.

### Achievement of target triglyceride levels

Epidemiologic evidence suggests that the optimal triglyceride level is less than 1.7 mmol/L.<sup>43,44</sup> Current recommendations are to first implement and maintain lifestyle changes rather than to attempt to lower triglyceride levels by pharmacologic means. Achievement of the target total cholesterol:HDL-C ratio usually entails modification of triglyceride levels when elevated. Severe hypertriglyceridemia poses a significant risk for pancreatitis, and patients with triglyceride levels of more than 6.0 mmol/L despite optimal lifestyle therapy require drug treatment. Available options include a fibrate, niacin and salmon oil supplementation.

### Follow-up

Large-scale clinical trials such as the Heart Protection Study<sup>9</sup> have shown that the statin class of drugs is very well tolerated. After drug therapy is started, plasma levels of lipids and lipoprotein lipids are expected to reach a steady state within 6 weeks. Long-term follow-up after the initial titration period can be performed every 6–12 months. More frequent monitoring of transaminases and creatinine kinase is warranted in subjects receiving maximum doses of medications and those receiving combination therapy (especially statins and fibrates).

### Referrals

Physicians are often confronted with difficult cases, lack of laboratory resources, unexplained atherosclerosis, ex-

**Table 4: Current lipid-lowering medications**

Drug	Recommended daily dose
<b>Statins</b>	
Atorvastatin (Lipitor)	10–80 mg
Fluvastatin (Lescol)	20–80 mg
Lovastatin (Mevacor)	20–80 mg
Pravastatin (Pravachol)	10–40 mg
Rosuvastatin (Crestor)	10–40 mg
Simvastatin (Zocor)	10–80 mg
<b>Resins (bile acid sequestrants)</b>	
Cholestyramine (Questran)	2–24 g
Colestipol (Colestid)	5–30 g
<b>Cholesterol absorption inhibitors</b>	
Ezetimibe (Ezetrol)	10 mg
<b>Fibrates*</b>	
Bezafibrate (Bezalip)	400 mg
Fenofibrate (Lipidil)	67–200 mg
Gemfibrozil (Lopid)	600–1200 mg
<b>Niacin†</b>	
Nicotinic acid	1–3 g

\*Avoid in patients with renal insufficiency. Do not use gemfibrozil in combination with statins.  
†Use with caution in patients with diabetes or glucose intolerance.

tremes 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 in Canada have specialized lipid clinics and the laboratory backup for extensive testing. In extreme cases therapeutic modalities such as extracorporeal LDL precipitation techniques are available. The working group recommends that specialists in lipoprotein disorders in each province be available for consultation for difficult cases.

Some patients may present with unexplained atherosclerosis. In these cases, the degree of atherosclerosis is not explained by conventional risk factors. The evaluation of such patients should include measurement of concentrations of apolipoprotein B, lipoprotein(a), homocysteine and high-sensitivity C-reactive protein. Even in the presence of a normal LDL-C level, such cases warrant treatment with ASA and a statin if the total cholesterol level is greater than 3.5 mmol/L.

This article has been peer reviewed.

Dr. Genest is with the Royal Victoria Hospital, McGill University, Montréal, Que. Dr. Frohlich is with St. Paul's Hospital, University of British Columbia, Vancouver, BC. Drs. Fodor and McPherson are with the University of Ottawa Heart Institute, Ottawa, Ont.

**Competing interests:** The authors did not receive financial support from pharmaceutical companies for their work in developing these recommendations and producing this report. All have received speaker fees from various drug companies, including those that manufacture drugs used to treat dyslipidemia and cardiovascular disease; Drs. Genest, Frohlich and McPherson have been members of advisory boards of various drug companies; and Drs. Fodor, Frohlich and McPherson have received travel expenses from one or more drug companies to attend scientific meetings.

**Contributors:** Each of the authors contributed substantially to the drafting and reviewing of the article. All approved the final version submitted for publication.

**Acknowledgements:** We acknowledge the following for their advice and comments on the recommendations: Dr. Jean Bergeron, Laval, Que.; Dr. Ross Feldman, Robarts Research Institute, London, Ont.; Dr. Milan Gupta, Hamilton, Ont.; Dr. Lawrence Leiter, University of Toronto, Toronto, Ont.; Dr. Garry Lewis, University of Toronto, Toronto, Ont.; Dr. G.B. John Mancini, University of British Columbia, Vancouver, BC; and Dr. Bruce Sussex, Memorial University, St. John's, Nfld. We also thank Dr. Helen Stokes, University of Ottawa, Ottawa, Ont., and Kristi Adamo and Penlope Turton, Ottawa Heart Institute, Ottawa, Ont., for their help in writing the manuscript.

## References

- Canadian Institute for Health Information. *Health conditions: heart disease and stroke*. Ottawa: The Institute; 2002. Available: [http://secure.cihi.ca/cihiweb/disPage.jsp?cw\\_page=statistics\\_results\\_topic\\_heartdisease\\_e&cw\\_topic=Health%20Conditions&cw\\_subtopic=Heart%20Disease%20and%20Stroke](http://secure.cihi.ca/cihiweb/disPage.jsp?cw_page=statistics_results_topic_heartdisease_e&cw_topic=Health%20Conditions&cw_subtopic=Heart%20Disease%20and%20Stroke) (accessed 2003 Oct 10).
- Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 2001;286(10):1195-200.
- Meltzer S, Leiter L, Daneman D, Gerstein D, Lau S, Ludwig JF, et al. Clinical practice guidelines for the management of diabetes in Canada. *CMAJ* 1998;159(Suppl 8):S1-29.
- First Nations and Inuit Health Branch, Health Canada. *Aboriginal Diabetes Initiative* [consultation summary report]. Ottawa: Health Canada; 2001. Available: [www.hc-sc.gc.ca/fnihb/cp/adi](http://www.hc-sc.gc.ca/fnihb/cp/adi) (accessed 2003 Oct 10).
- Fodor JG, Frohlich JJ, Genest JG Jr, McPherson PR, for the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management and treatment of dyslipidemia: report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000;162(10):1441-7.
- Grundy SM, Becker D, Clark LT, on behalf of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)* (Adult Treatment Panel III). Bethesda (MD): National Institutes of Health; 2001. Available: [www.nhlbi.nih.gov/guidelines/cholesterol/index.htm](http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm) (accessed 2003 Sept 26).
- Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al, on behalf of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285(13):1711-8.
- Robins SJ, Collins D, Rubins HB. Relation of baseline lipids and lipid changes with gemfibrozil to cardiovascular endpoints in VA-High-Density Lipoprotein Intervention Trial (VA-HIT). *Circulation* 1999;100(18)(Suppl 1):I-238.
- MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287(3):356-9.
- Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100(13):1481-92.
- Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 2003;361:777-80.
- Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PW, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger: a prospective study. *JAMA* 1996;276(7):544-8.
- Ridker P, Hennekens C, Meir M, Stamfer M. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 1993;270(18):2195-9.
- Jenner J, Ordovas J, Lamon-Fava S, Schaefer MM, Wilson PW, Castelli WP, et al. Effects of age, sex and menopausal status on plasma lipoprotein(a) levels. The Framingham Offspring Study. *Circulation* 1993;87(4):1135-41.
- Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation* 2000;102(10):1082-5.
- Hopkins PN, Wy LL, Hunt SCX, James BC, Vincent GM, Williams RR. Lipoprotein(a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol* 1997;17(11):2783-92.
- Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002;288(16):2015-22.
- Pahor M, Elam M, Garrison R, Kritchevsky S, Applegate W. Emerging non-invasive biochemical measures to predict cardiovascular risk. *Arch Intern Med* 1999;159(3):237-45.
- Boushey C, Beresford S, Omenn G, Motulsky A. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;274(13):1049-57.
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-33.
- Schnyder G, Roffi M, Pin R, Flammer Y, Lange H, Eberli FR, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001;345(22):1593-600.
- Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B(12), and vitamin B(6) on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. *JAMA* 2002;288(8):973-9.
- Ridker PM, Rifai NF, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347(20):1557-65.
- Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 2003;107(3):391-7.
- Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relationship of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996;144(6):537-47.
- Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984-1992. *Circulation* 1999;99(2):237-42.
- Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, et al, on behalf of the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344(26):1959-65.
- Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107(3):499-511.

30. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280(7):605-13.
31. Herrington DM, Vittinghoff E, Lin F, Fong J, Harris F, Hunninghake D, et al, on behalf of the HERS Study Group. Statin therapy, cardiovascular events and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 2002;105(25):2962-7.
32. Steiner G, and Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001;357(9260):905-10.
33. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345(22):1583-92.
34. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al; for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
35. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326(6):381-6.
36. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340(1):14-22.
37. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 1997;146(6):483-94.
38. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;128(4):262-9.
39. Gibbons LW, Mitchell TL, Wei M, Blair SN, Cooper KH. Maximal exercise test as a predictor of mortality from coronary heart disease in asymptomatic men. *Am J Cardiol* 2000;86(1):53-8.
40. Ekelund LG, Suchindran CM, McMahan RP, Heiss G, Leon AS, Romhilt DW, et al. Coronary heart disease morbidity and mortality in hypercholesterolemic men predicted from an exercise test: the Lipid Research Clinics Coronary Primary Prevention Trial. *J Am Coll Cardiol* 1989;14(3):556-63.
41. Rautaharju PM, Prineas RJ, Eifler WJ, Furberg CD, Neaton JD, Crow RS, et al. Prognostic value of exercise electrocardiogram in men at high risk of future coronary heart disease: Multiple Risk Factor Intervention Trial experience. *J Am Coll Cardiol* 1986;8(1):1-10.
42. Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81(4A):60B-65B.
43. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996;276(11):882-8.
44. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation* 2001;104(25):3046-51.

---

**Correspondence to:** Dr. Jacques Genest, Division of Cardiology, McGill University Health Centre, Royal Victoria Hospital, 687 Pine Ave. W, Montréal QC H3A 1A1; fax 514 843-2813; jacques.genest@muhc.mcgill.ca