

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

Jacques Genest MD¹, Ruth McPherson MD PhD², Jiri Frohlich MD³, Todd Anderson MD⁴, Norm Campbell MD⁴, André Carpentier MD⁵, Patrick Couture MD⁶, Robert Dufour MD⁷, George Fodor MD², Gordon A Francis MD³, Steven Grover MD¹, Milan Gupta MD⁸, Robert A Hegele MD⁹, David C Lau MD¹⁰, Lawrence Leiter MD¹¹, Gary F Lewis MD¹², Eva Lonn MD¹³, GB John Mancini MD¹⁴, Dominic Ng MD PhD¹¹, Glen J Pearson PharmD¹⁵, Allan Sniderman MD¹⁶, James A Stone MD PhD¹⁰, Ehud Ur MD¹⁴

J Genest, R McPherson, J Frohlich, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. *Can J Cardiol* 2009;25(10):567-579.

The present article represents the 2009 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult.

Key Words: Atherosclerosis; Cardiovascular risk factors; Cholesterol; Coronary artery disease; Dyslipidemia; Lipids; Secondary prevention

Cardiovascular disease (CVD) causes one-third of deaths in Canada – more than any other illness (1,2). The prevalence of CVD is expected to increase in Canada in the next decade, predominantly because of increasingly sedentary lifestyles and an attendant increase in the prevalence of obesity and diabetes mellitus. The economic cost of CVD represents approximately \$22 billion in direct and indirect health care costs and lost productivity annually. However, mortality from coronary artery disease (CAD) in Canada has decreased by nearly 40% in the past several decades (2). Intensive secondary prevention has resulted in a marked decrease in recurrent cardiovascular events in patients with established CAD, to a level approaching that of age- and sex-matched individuals without clinical CAD (at least in clinical trials). The decrease in cardiac mortality has been attributed to improvements in the control of CVD risk factors – especially cholesterol levels, smoking and blood pressure – and to improved medical management of patients with CVD. Despite these improvements, CVD still represents the major burden of disease in our society.

The incorporation of new data from clinical studies into clinical practice guidelines helps promote a standard of care that is current and uniform across Canada. Frequent updates are required to take this new information into account. The development of guidelines has undergone major changes to reduce bias by promoting a structured process that assesses and grades evidence, and highlights potential conflicts of

Les lignes directrices canadiennes 2009 de la Société canadienne de cardiologie pour le diagnostic et le traitement de la dyslipidémie ainsi que pour la prévention des maladies cardiovasculaires chez l'adulte – Des recommandations pour 2009

Le présent article contient la mise à jour 2009 des lignes directrices de la Société canadienne de cardiologie pour le diagnostic et le traitement de la dyslipidémie et pour la prévention des maladies cardiovasculaires chez l'adulte.

interest among contributors. Duality of interest of participants of guideline development has been the focus of much attention and debate, recognizing that individuals have many potential sources of bias. In common with documents prepared in other therapeutic areas, the present guidelines were developed by volunteer experts in lipid disorders and CVD, with full and open disclosure of their relationships with the pharmaceutical industry. There was no direct financial support for this guideline development from industry, nor was there any involvement by them in the guideline writing process.

While the major principles of screening and risk stratification in the 2006 Canadian lipid guidelines (3) have been retained, the process by which this updated version was developed took into account comments and criticisms by many stakeholders. The process changes include working under the Canadian Cardiovascular Society (CCS) guidelines process, and the establishment of primary and secondary review panels. In addition, members of the Canadian Vascular Coalition have had input in the guideline process. A systematic electronic PubMed search of original research published in the medical literature between January 1, 2006, and February 1, 2009, was performed. The following key words were used: lipid-lowering therapy (including generic names of medications), statins, fibrates, niacin, ezetimibe, diet, cardiovascular disease, prevention and clinical trials. Only blinded randomized controlled trials with cardiovascular outcome data were retained for evaluation. Meta-analyses of studies of the efficacy and safety of lipid-lowering therapies

¹McGill University Health Centre, Montreal, Quebec; ²University of Ottawa Heart Institute, Ottawa, Ontario; ³St Paul's Hospital, Vancouver, British Columbia; ⁴Libin Cardiovascular Institute of Alberta, Calgary, Alberta; ⁵Centre hospitalier universitaire de Sherbrooke, Sherbrooke; ⁶Centre Hospitalier Universitaire de Québec, Québec City; ⁷Institut de recherches cliniques de Montréal, Montreal, Quebec; ⁸Department of Medicine, McMaster University, Hamilton; ⁹Robarts Research Institute, London, Ontario; ¹⁰University of Calgary, Calgary, Alberta; ¹¹St Michael's Hospital, University of Toronto; ¹²University of Toronto, Toronto; ¹³Population Health Research Institute, McMaster University, Hamilton, Ontario; ¹⁴University of British Columbia, Vancouver, British Columbia; ¹⁵University of Alberta, Edmonton, Alberta; ¹⁶Edwards Professor of Medicine and Cardiology, McGill University, Montreal, Quebec

Correspondence: Dr Jacques Genest, Faculty of Medicine, McGill University, Division of Cardiology, McGill University Health Centre/Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1. Telephone 514-934-1934 ext 34642, fax 514-843-2813, e-mail jacques.genest@muhc.mcgill.ca

Received for publication August 2, 2009. Accepted August 12, 2009

TABLE 1
Patients whose plasma lipid profile should be screened

- Men ≥ 40 years of age, and women ≥ 50 years of age or postmenopausal
- All patients with the following conditions, regardless of age:
 - Diabetes
 - Hypertension
 - Current cigarette smoking
 - Obesity (Obesity Canada guidelines)
 - Family history of premature CAD (< 60 years in first-degree relatives)
 - Inflammatory diseases* (systemic lupus erythematosus, rheumatoid arthritis, psoriasis)
 - Chronic renal diseases (eGFR < 60 mL/min/1.73 m²)
 - Evidence of atherosclerosis
 - HIV infection treated with highly active antiretroviral therapy
 - Clinical manifestations of hyperlipidemias (xanthomas, xanthelasmas, premature arcus cornealis)
 - Erectile dysfunction
- Children with a family history of hypercholesterolemia or chylomicronemia

*Data on inflammatory bowel diseases are lacking. CAD Coronary artery disease; eGFR Estimated glomerular filtration rate

and on the predictive value of established and emerging risk factors were also reviewed. Strict criteria have been implemented for the incorporation of biomarkers of risk. **Novel biomarkers (4,5) must show improved risk prediction over the previously accepted markers and improved CVD risk stratification, and demonstrate that clinical decisions and outcomes are influenced by their measurement.**

The Canadian Vascular Coalition represents an informal group of stakeholders involved in CVD prevention under the banner of the Canadian Institutes of Health Research. Member organizations are listed in Supplementary Table 1. (Supplementary information begins on page 576.) The recommendations for the treatment of lipoprotein disorders are harmonized with those of the major Canadian stakeholders in CVD prevention. Areas of discordance between the various stakeholders and opinion leaders are highlighted and discussed. The CCS provided oversight and logistical support for the process. The recently released recommendations of the Canadian Heart Health Strategy and Action Plan (available at <http://www.chhs-scsc.ca/web/>) were also influential in writing these guidelines. The writing group used a widely accepted system to grade and assess the evidence behind the recommendations, based on consensus (Supplementary Table 2).

Since the previous publication of the recommendations for the management and treatment of dyslipidemia in 2006 (3), a number of new clinical studies have been published. When assessing interventions, the primary outcomes examined were cardiovascular death, nonfatal myocardial infarction (MI) and stroke as a combined end point, and total mortality as a secondary end point. Less emphasis was placed on the effects of biomarkers on cardiovascular risk or surrogate end points, such as invasive or noninvasive atherosclerosis assessment. The major changes in our recommendations since the 2006 guidelines are summarized in Supplementary Table 3. The high-risk population has been better defined, including patients with end-stage cardiac or renal disease (ie, severe heart failure or chronic kidney disease on hemodialysis, respectively). Improved, validated CVD event risk-stratification tools are provided. This is especially relevant in subjects at intermediate CVD risk for whom the justification of treatment, other than health behaviour interventions, is often extrapolated from studies of high-risk patients.

The screening strategy is defined in Table 1. The importance of genetic factors and family history of premature CVD is taken into account in the determination of risk (6,7). The importance of obesity (especially abdominal obesity) as a major modifiable CVD risk factor (8,9) is emphasized by including the International Diabetes Federation (IDF) classification of the metabolic syndrome (10) (Table 2) and including overweight and obesity in the screening

TABLE 2
International Diabetes Federation classification of the metabolic syndrome

Central obesity	
	Waist circumference
Europids	Men ≥ 94 cm; women ≥ 80 cm
South Asians	Men ≥ 90 cm; women ≥ 80 cm
Chinese	Men ≥ 90 cm; women ≥ 80 cm
Japanese	Men ≥ 90 cm; women ≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
First Nations	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arabic) populations	Use European data until more specific data are available
Plus two of the following factors:	
Plasma triglycerides > 1.7 mmol/L	
High-density lipoprotein cholesterol	
Men < 1.03 mmol/L	
Women < 1.3 mmol/L	
Blood pressure $> 130/85$ mmHg (or treatment for hypertension)	
Fasting plasma glucose > 5.6 mmol/L	
<i>Data from reference 10</i>	

strategy. We have included risk stratification for several inflammatory diseases, including rheumatoid arthritis, psoriasis and systemic lupus erythematosus (SLE) (11-13). Such patients require comprehensive assessment and treatment of the traditional cardiovascular risk factors. The association between inflammatory bowel diseases (which share many commonalities with other inflammatory diseases) and CVD is less well established (14,15). The use of biomarkers of inflammation is now included in the guidelines based, in large part, on the epidemiology of high-sensitivity C-reactive protein (hs-CRP) and clinical trials of patients with high hs-CRP levels (4,5). Similarly, recommendations for patients with chronic HIV infection who are on highly active antiretroviral therapies are included (16).

We also provide simplified target lipid levels. The emphasis is once again focused on atherogenic lipoproteins, as reflected by the serum (or plasma) levels of low-density lipoprotein cholesterol (LDL-C) or apolipoprotein (apo) B. The evidence favouring LDL-C reduction for the prevention and treatment of atherosclerosis is strong and compelling, and is based on multiple randomized clinical trials (17). Whereas a specific target level for LDL-C will remain a matter of debate, the data indicate that a lower level of LDL-C is associated with reduced CAD risk (18). LDL-C therefore continues to constitute the primary target of therapy; the alternate primary target is apoB. A summary is provided of optional secondary therapeutic targets of potential relevance once the LDL-C (or apoB) is at target, including (in alphabetical order) the apoB to apoA1 ratio, the total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio, and the hs-CRP, non-HDL-C and serum (or plasma) triglyceride levels. Increased levels of all these parameters have been found to confer additional risk. However, clinical trial evidence is lacking on the importance of intervening on these variables to further reduce risk and thus, they are considered secondary and optional targets (19). We also provide further consideration for the noninvasive assessment of atherosclerosis in asymptomatic individuals, bearing in mind that data on cost effectiveness and outcomes are lacking.

While there is general agreement on the need for sustained, aggressive and multifactorial therapeutic interventions in the secondary prevention of CVD (18,20,21), controversy remains about the cost effectiveness and societal impact of primary prevention strategies. However, most heart attacks occur in subjects with relatively 'normal'

serum cholesterol levels (based on population distribution) but frequently suboptimal levels of cardiometabolic fitness in association with tobacco consumption. Many biomarkers, including levels of serum lipids, lipoproteins, apolipoproteins and various derived ratios, predict CVD risk (5). However, it is important to keep in mind that none of the traditional CVD risk factors or biomarkers reflect the actual presence or absence of atherosclerosis. They help to establish CVD event risk rather than the risk or presence of CVD itself. The inflammatory biomarker hs-CRP also predicts risk and identifies a population that responds particularly well to statin therapy. Importantly, however, our ability to predict CVD events does not always translate into our ability to prevent subsequent events. For instance, homocysteine level predicts CVD risk, but lowering an elevated homocysteine level with folic acid and other B vitamins to prevent recurrent cardiovascular events has proven to be unsuccessful (22). Therefore, we have focused on CVD risk factors whose measurement influences clinical decision making and for which there exists a proven effect on clinical outcomes.

CARDIOVASCULAR RISK FACTORS

Multiple epidemiological studies (23,24) have confirmed that the following risk factors account for the majority of CAD cases:

- Age (the major determinant of risk);
- Male sex;
- Cigarette smoking;
- Diabetes mellitus;
- Cholesterol (as assessed by TC, LDL-C or apoB);
- HDL-C;
- Blood pressure;
- Family history of premature CAD (younger than 60 years of age);
- Inflammatory biomarkers (especially hs-CRP); and
- Overweight and obesity.

Other variables conferring risk include poor nutrition, caloric excess resulting in overweight and obesity, physical inactivity and psychological stress. Because of the increase in prevalence of obesity in our society, the features of the metabolic syndrome (cardiometabolic risk) should be evaluated (Table 2), and should focus the physician's attention on anthropometric (ie, 'toxic waist') and metabolic abnormalities that can be improved or corrected by health behaviour interventions. Patients with chronic kidney disease (25,26), chronic autoimmune inflammatory diseases (rheumatoid arthritis, SLE and psoriasis) (11-13), as well as those with chronic HIV infection requiring highly active antiretroviral therapy (16), should be screened for the traditional CVD risk factors and treated according to their determined risk. Many novel and emerging risk factors have been demonstrated to improve risk prediction over and above the major risk factors considered in the Framingham risk score (FRS), albeit usually marginally, but these 'emerging' risk factors have not been shown to positively influence treatment outcomes. The measurement of hs-CRP, however, is being recommended in men older than 50 years and women older than 60 years of age who are at intermediate risk (10% to 19%) according to their FRS score and who do not otherwise qualify for lipid-lowering therapy (ie, if their LDL-C is less than 3.5 mmol/L).

The rationale for measuring hs-CRP specifically in these individuals is that we now have class I evidence (5) for the benefit of statin therapy in such individuals, if their hs-CRP is greater than 2.0 mg/L. Data from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (5) show that statin therapy reduces cardiovascular events (hazard ratio 0.56 [95% CI 0.46 to 0.69]; $P < 0.00001$). Importantly, because hs-CRP can be elevated during acute illness, clinical judgment should be exercised in the interpretation of any single measurement of hs-CRP.

Screening (Table 1)

Screening of the plasma lipid profile is recommended in adult men who are at least 40 years of age, and in women who are at least 50 years of age or postmenopausal (class I, level C). In addition, all subjects

TABLE 3
Target lipid levels

Risk level	Initiate treatment if:	Primary targets	
		LDL-C	Alternate
High CAD, PVD, atherosclerosis* Most patients with diabetes FRS $\geq 20\%$ RRS $\geq 20\%$	Consider treatment in all patients	<2 mmol/L or $\geq 50\%$ ↓ LDL-C Class I, level A	apoB <0.80 g/L Class I, level A
Moderate FRS 10%–19%	LDL-C >3.5 mmol/L TC/HDL-C >5.0 hs-CRP >2 mg/L Men >50 years Women >60 years Family history and hs-CRP modulates risk (RRS)	<2 mmol/L or $\geq 50\%$ ↓ LDL-C Class IIa, level A	apoB <0.80 g/L Class IIa, level A
Low FRS <10%	LDL-C ≥ 5.0 mmol/L	$\geq 50\%$ ↓ LDL-C Class IIa, level A	

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

with evidence of atherosclerosis in any vascular bed, irrespective of age, should be treated as being a high-risk patient (Table 3). Similarly, all adults with diabetes should have a complete lipid profile. Most adults with diabetes (men older than 45 years and women older than 50 years of age, as well as many younger patients who have diabetes with at least one additional traditional CVD risk factor) are considered to be at high risk for CVD events. Individuals with a family history of premature CVD (younger than 60 years of age) deserve earlier screening. Several medical conditions are associated with premature CVD. For instance, patients with arterial hypertension should be carefully assessed for concomitant metabolic disorders and dyslipidemias. Patients with abdominal obesity, as defined by an increased waist circumference or a body mass index (BMI) of greater than 27 kg/m² to 30 kg/m² (overweight), or greater than 30 kg/m² (obese) should also be screened. The metabolic syndrome classification recommended by the IDF classification is advocated because it most accurately reflects the diverse ethnic makeup of Canada (Table 2) (10). Autoimmune chronic inflammatory conditions such as rheumatoid arthritis, SLE and psoriasis are associated with increased CVD event risk. Patients with chronic kidney disease (estimated glomerular filtration rate of less than 60 mL/min/1.73 m²) are also at increased risk for CVD events.

Clinical manifestations of genetic hyperlipidemias, including xanthomas, xanthelasmas and premature arcus cornealis, should be sought because they may signal the presence of a severe lipoprotein disorder, especially familial hypercholesterolemia – the most frequent monogenic disorder associated with premature CVD. Survival of patients with chronic HIV infection has improved, due largely to highly active antiretroviral therapies, which may be associated with accelerated atherosclerosis (27). The consensus of opinion is that HIV patients should also be evaluated for CVD risk and should be treated accordingly.

The screening of children must be based on sound clinical judgment. Children of patients with severe dyslipidemia (familial hypercholesterolemia or chylomicronemia) should be evaluated and followed in specialized clinics if affected. Similarly, premature CVD in first-degree relatives should prompt the screening of family members for significant lipoprotein disorders.

Family history

The etiology of CVD can be explained by conventional risk factors (24), which can have both genetic and environmental determinants. Importantly, 10% to 15% of patients with CAD have no apparent major CAD risk factors. However, CVD and CVD-related events occur along a continuum of risk, and persons with no apparent exposure to the traditional CVD risk factors may be exceptionally susceptible to the presence of apparently physiological levels of those risk factors. Family and twin studies suggest a strong genetic influence on premature CAD in particular. Results from the Framingham Offspring Study (6) demonstrate that, after correction for known risk factors, parental CVD was associated with a 1.7- and 2.0-fold increased risk for women and men, respectively.

The metabolic syndrome

The metabolic syndrome is defined as the association of several metabolic abnormalities including visceral adipose tissue mass (ie, toxic waist), dyslipidemia (elevated triglycerides and low HDL-C), elevated blood pressure and elevated serum glucose. Several classifications of the metabolic syndrome share common elements that emphasize the increase of cardiometabolic risk factors (8). However, a uniform classification of the metabolic syndrome remains elusive. The IDF classification (10) has more stringent waist circumference criteria than the National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) definition (3) and serves as the current diagnostic classification system recommended by the writing group (Table 2). Individuals with the metabolic syndrome are more likely to be at higher long-term CVD risk than estimated by the FRS alone. Currently, there is a paucity of data on the clinical usefulness of the new IDF definition of the metabolic syndrome to identify subjects with an intermediate FRS who may be at higher risk for cardiovascular events. A retrospective analysis of data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) suggests that determining the presence of the metabolic syndrome using the NCEP ATP-III definition identifies subjects with an FRS of less than 20% who have a similar risk to those without the metabolic syndrome with an FRS of 20% or greater. Results from meta-analyses (28) suggest that there is a 1.5-fold increase in risk when adjusted for other cardiovascular risk factors and that the increase in risk was higher among women than among men. Therefore, some subjects in the higher range of intermediate FRS with the metabolic syndrome may require lipid-lowering therapy to reduce their cardiovascular risk (class IIb, level C). However, no study has thus far demonstrated an improvement in outcome when subjects at intermediate risk were selected for lipid-lowering treatment on the basis of the metabolic syndrome. The measurement of hs-CRP may provide further help in the risk stratification of subjects with the metabolic syndrome (29). As a practical rule, an adult with the metabolic syndrome is extremely unlikely to truly be at low risk for CVD; most are either at intermediate or high

risk for CVD. The FRS is a good starting point for the global risk assessment of patients with the metabolic syndrome, as well as for those without the metabolic syndrome. We recommend that clinical judgement be used in some cases to move a patient up an FRS-determined risk score category based on his or her 'load' of metabolic risk factors or the 'severity' of the metabolic syndrome.

Other risk factors

Many other factors have been shown to be associated with increased CVD risk. These include specific lipoprotein subclasses, including lipoprotein(a) (30), inflammatory biomarkers such as lipoprotein-associated phospholipase A₂ (also called platelet-activating factor acetyl hydrolase) (31), cell adhesion molecules, homocysteine, uric acid, coagulation and a variety of thrombosis parameters, serum glycoproteins, and both anatomical and functional measures of vascular health available through an explosion of new imaging techniques, many of which are noninvasive (32). Despite an increasing number of new potential markers of risk, the traditional CVD risk factors remain the priorities for screening and treatment as appropriate. Unless a novel risk factor or marker has been proven to both influence clinical decision making and therapeutic approaches, and to change clinical outcomes, its use should remain within the specialized clinical and research setting (32).

RISK ASSESSMENT

Cardiovascular risk assessment remains imperfect. The FRS (Supplementary Tables 4A and 4B for men, and Supplementary Tables 5A and 5B for women) for total CVD is now recommended (33). The FRS has been shown to underestimate risk in specific categories of patients, especially in youth and women, and possibly in those with the metabolic syndrome (28). Arbitrarily, an FRS of 20% or greater at 10 years is considered to identify subjects at high risk for CVD events. The FRS has been validated in Canada with the Cardiovascular Life Expectancy Model (www.chiprehab.com) (34), and this model has been shown to increase adherence to therapeutic measures. The Reynolds Risk Score (RRS) constitutes an optional risk engine and includes the conventional CVD risk factors in addition to family history and hs-CRP (35,36) (<http://www.reynoldsriskscore.org>). It has been validated in men and women in an American population, but not yet in Canada. The Internet-based version of the RRS is now also available in mmol/L.

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 10-year risk of a major CVD event. A family history of premature CAD is considered to increase the risk by 1.7-fold in women and 2.0-fold in men. An elevated hs-CRP level is also a modulator of risk, especially in the moderate-risk category (6). Many subjects at low or moderate short-term (10-year) risk are at a high risk over the long term due to the cumulative effects of single but significant elevated risk factors (eg, severe systemic hypertension), the exponentially interactive effects of multiple but only moderately elevated CVD risk factors and/or changes in risk factors over time (for example, the young person with diabetes). In the Framingham study, men in the lowest FRS tertile at 50 years of age experienced a 10-year cumulative risk of one in 25, but a lifetime risk of nearly one in two. Women in the lowest FRS 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 (37,38). CVD risk should be reassessed every three years (class IIb, level C). European guidelines use a risk score based on total mortality (39).

Risk levels

High risk: Subjects are considered to be at high CVD risk if they have any of the following:

- Evidence of atherosclerosis – vascular bruits, an ankle-brachial index of less than 0.9, documented CAD by invasive or noninvasive

testing, coronary angiography, nuclear imaging, stress echocardiography, previous MI, coronary revascularization (percutaneous coronary intervention, coronary artery bypass graft surgery) and other arterial revascularization procedures, cerebrovascular accident, including transient ischemic attack, evidence of carotid disease by carotid ultrasonography or angiography, or peripheral vascular disease;

- Men older than 45 years and women older than 50 years of age with diabetes, as well as some younger people with diabetes who have an additional risk as per Canadian Diabetes Association guidelines (40); or
- A calculated FRS or RRS of 20% or greater for 10-year risk of CVD. These subjects should receive intensive lifestyle modification advice and benefit from a pharmacological approach aimed at lowering serum LDL-C.

Moderate risk: Many middle-aged Canadians will be in the moderate-risk category. The increase in obesity in the adult population, coupled with an increase in the prevalence of the individual components of the metabolic syndrome, has created a major health concern. This was recently addressed at the federal level in the Canadian Heart Health Strategy and Action Plan (<http://www.chhs-scsc.ca/web/>). Subjects are considered to be at moderate risk when their FRS is 10% to 19% at 10 years (33). This risk is further modulated by a family history of premature CAD and high hs-CRP.

Alternatively, the RRS, which combines the Framingham risk factors, family history and hs-CRP, can be considered for use to stratify risk (35,36). The indications for pharmacological interventions are based on primary prevention studies including AFCAPS/TextCAPS (41), the West of Scotland Coronary Prevention Study (WOSCOP) (42), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (43), the Heart Protection Study (HPS) (44) and JUPITER (5). Following the initiation of health behaviour interventions, pharmacological therapy is indicated if:

- the LDL-C is greater than 3.5 mmol/L (apoB higher than 1.00 g/L) (class IIa, level A);
- the TC/HDL-C ratio is higher than 5.0 (class IIa, level C); or
- the hs-CRP is higher than 2 mg/L in men older than 50 years and in women older than 60 years of age, irrespective of LDL-C (class IIa, level B).

The measurement of hs-CRP should not be performed on everyone. Men older than 50 years and women older than 60 years of age who are at moderate risk for CVD (determined by FRS) and whose level of LDL-C is less than 3.5 mmol/L are candidates because such individuals have been shown to benefit from statin therapy (5) (class IIa, level B). Subjects should be free of acute illness and the lower of two values, taken at least two weeks apart, should constitute the baseline value.

Although widespread pharmacological therapy for those at low risk is not recommended, subjects whose 10-year risk for CVD is estimated to be between 5% and 9% have been shown in randomized controlled trials (5) to achieve the same RR reduction from statin therapy as those at a higher 10-year risk (25% to 50% reduction in events). However, the absolute benefit of therapy is estimated to be smaller (in the order of 1% to 5% reduction of CVD), the numbers needed to treat to prevent one cardiac event are higher and the cost/benefit ratio of therapy is less favourable than for those at a higher risk for CVD events. For individuals in this category, the physician is advised to discuss these issues with the patient and integrate the patient's beliefs regarding the benefits and risks of long-term preventive cholesterol-lowering therapy into the final individualized treatment decision.

Low risk: The low-risk category applies to individuals with an FRS of less than 10%. Pharmacological lipid-lowering treatment is advised for low-risk subjects with severe dyslipidemia (LDL-C of 5.0 mmol/L or greater), usually reflecting a genetic lipoprotein disorder, especially familial hypercholesterolemia (class I, level C). Consideration for lipid-lowering therapy may also be indicated in subjects at low risk with a TC/HDL-C ratio of greater than 6.0 (class IIb, level C). This especially applies to patients

with severe hypertriglyceridemia, in whom treatment may be indicated to reduce the risk of pancreatitis. The need for treatment of subjects with isolated HDL-C is a subject of debate because evidence that pharmacological treatment will reduce cardiovascular risk is lacking and currently available therapies may not increase HDL-C to a clinically significant extent. Clinical judgment should be used concerning the proper timing for the initiation of pharmacological therapy in these patients. A careful family history should be taken and the presence of additional CVD risk factors may indicate the need for intervention in selected individuals. The RRS has the potential to reclassify low-risk patients according to the FRS when there is a family history and elevated hs-CRP.

Ethnic differences in CAD risk

CAD rates vary among ethnic groups in Canada, with the highest incidence among individuals of South Asian ancestry and the lowest among individuals of Chinese ancestry (45). The higher risk among individuals of South Asian ancestry is partly explained by an increased prevalence of abdominal obesity, glucose intolerance, hypertriglyceridemia and low HDL-C. Individuals of First Nations ancestry are also at markedly increased risk for diabetes and CAD (46). For these reasons, the risk stratification approach provides an opportunity for greater focus on overweight and obese individuals, as well as patients with other related metabolic features, which should help ensure identification of modifiable CVD risks, even within those populations unique to the Canadian sociocultural milieu.

TREATMENT TARGETS

Cholesterol treatment target levels are derived from clinical trials. Nearly all studies have measured the serum (or plasma) level of LDL-C as an indicator of response to therapy (Table 3). The Cholesterol Treatment Trialists (CCT) meta-analysis (17) of 14 statin trials showed a dose-dependent relative reduction in CVD with LDL-C lowering. Every 1.0 mmol/L reduction in LDL-C is associated with a corresponding 20% to 25% reduction in CVD mortality and nonfatal MI. Data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) (47), Treating to New Targets (TNT) (48), Aggrastat to Zocor (A to Z) (49), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) (50) and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) (18) trials have confirmed that lowering LDL-C to a mean of 2.0 mmol/L or less is associated with the lowest risk of recurrent CVD events in secondary prevention patient populations (51). Extrapolating from the available data, a 2.0 mmol/L absolute reduction or a 50% relative reduction in LDL-C provides optimal benefit in terms of CVD reduction (52). Thus, for high-risk subjects, the target levels should be an LDL-C of less than 2.0 mmol/L, or a 50% or greater reduction from baseline LDL-C (class I, level A). In the majority of patients, this is achievable with statin monotherapy. Furthermore, because apoB levels have so frequently been measured in outcome studies in parallel with LDL-C, apoB can be substituted for LDL-C (53,54). The present version of the guidelines recommends apoB as the primary alternate target to LDL-C. Based on the available evidence, many experts have concluded that apoB is a better marker than LDL-C for the risk of vascular disease and a better index of the adequacy of LDL-lowering therapy than LDL-C (53). Also, there now appears to be less laboratory error in the determination of apoB than LDL-C, particularly in patients with hypertriglyceridemia, and all clinical laboratories could easily and inexpensively provide standardized measurements of apoB. However, not all experts are fully convinced that apoB should be measured routinely and, in any case, apoB is not presently being measured in most clinical laboratories. Consequently, a substantial educational effort for patients and physicians would be required for the most effective introduction of apoB into widespread clinical practice. Nevertheless, all would agree that physicians who wish to use apoB in their clinical care should be encouraged to do so. Furthermore, the present compromise approach represents a positive transitional phase in the assessment of lipid parameters to improve the prevention of CVD through the

clinical measurement of apoB. The apoB target for high-risk subjects is less than 0.80 g/L (class I, level A).

Targets other than LDL-C (or apoB)

Secondary targets have been determined in post hoc analyses or as part of prespecified analyses in a number of clinical trials. These secondary targets include a TC/HDL-C ratio of less than 4.0, a non-HDL-C level of less than 3.5 mmol/L, an apoB/apoAI ratio of less than 0.80, a triglyceride level of less than 1.7 mmol/L and an hs-CRP level of less than 2.0 mg/L. Adjusting lipid-lowering therapy to optimize one or more of these secondary targets may be considered in the high-risk patient after achieving a target LDL-C or apoB, but the clinical advantages of this approach, with respect to patient outcomes, remain to be proven.

The specific target for non-HDL-C should be less than 3.5 mmol/L (33). A TC/HDL-C ratio of less than 4.0 or an apoB/apoAI ratio of less than 0.8 is inferred from clinical trials and epidemiological data to convey reduced CVD event risk in high-risk subjects. To date, no specific targets for HDL-C or triglyceride levels have been determined in clinical trials, although increases in HDL-C predict atherosclerosis regression (55) and low HDL-C is associated with excess events and mortality in CAD patients, even when LDL-C is lower than 1.8 mmol/L (56). A specific target for hs-CRP in secondary prevention is based on the predetermined analysis (51) of the PROVE-IT and A to Z studies, which showed that patients with CAD who have reached both an LDL-C level of less than 2.0 mmol/L and an hs-CRP level of less than 2.0 mg/L had the lowest CVD event rate (class IIa, level B). Similarly, an analysis (57) of the JUPITER trial showed that the lowest cardiovascular event rate was achieved in subjects who attained both an LDL-C level of less than 2.0 mmol/L and an hs-CRP level of less than 2.0 mg/L. To date, no clinical trial has addressed the issue of treating the secondary targets of therapy more aggressively, including hs-CRP, once LDL-C (or apoB) is at target. Presently, hs-CRP as a secondary target of therapy is not recommended based on the lack of clinical trial evidence that targeting a particular hs-CRP level results in clinical benefit. Thus, clinicians must exercise expert judgment and caution when considering further treatment intensification in secondary prevention or in high-risk primary prevention. Although several clinical trials are ongoing, to date, no statin-based combination therapy has been shown to improve clinical outcomes.

The target level for subjects at moderate risk are extrapolated from high-risk clinical studies, especially ASCOT (43), HPS (44), AFCAPS/TexCAPS (41), WOSCOP (42) and JUPITER (5). The 2006 recommendations also focused on LDL-C as the primary target of therapy in these patients, with a treatment trigger LDL-C level of 3.5 mmol/L and a recommended 40% reduction (as was obtained in the ASCOT trial [43]), thus reaching a level close to 2.0 mmol/L. Based in large part on the JUPITER trial (5), in which a 50% reduction in LDL-C was achieved, we recommend the same targets of an LDL-C level of lower than 2.0 mmol/L (apoB lower than 0.80 g/L) or a 50% reduction from baseline LDL-C (class IIa, level A) when the baseline level is known. For the above reasons, secondary targets of therapy in the moderate-risk category are based on data extrapolation and therefore, clinical judgment is required before a final treatment plan is implemented (class IIb, level C). These revised recommendations are more stringent than the previous set (3). Clinicians should exercise judgement to avoid premature or unnecessary implementation of lipid-lowering therapy. Health behaviour interventions will have an important long-term impact on health and the long-term effects of pharmacotherapy must be weighed against potential side effects. A meta-analysis of statin trials (17) has demonstrated that for each 1.0 mmol/L decrease in LDL-C, there is a corresponding RR reduction of 20% to 25%. Intensive LDL-C lowering therapy is associated with a decreased risk of CVD events (18).

Congestive heart failure due to systolic dysfunction or end-stage renal disease

Recent studies (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA] [58] and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure [GISSI-HF] [59])

have addressed the issue of statin treatment in end-stage heart failure (left ventricular ejection fraction of less than 30%). These studies suggest that statin therapy does not reduce CVD morbidity or mortality in advanced heart failure of ischemic or nonischemic etiology. Similarly, the Deutsche Diabetes Dialyse Studie (4D) (60) and A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events (AURORA) (61) trials examined statin treatment in hemodialysis subjects (who were not considered to be candidates for statin therapy by their physicians) and found no effect on CVD outcomes. Clinical judgement must be applied when considering the modest baseline elevation of LDL-C in these trials (approximately 3.5 mmol/L) and also the observation that patients on dialysis awaiting renal transplantation may still benefit from statins.

Surrogate markers of CVD risk – testing for atherosclerosis

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. An ankle-brachial index value of less than 0.90 is a reliable index of peripheral arterial disease, with a sensitivity of 90% and a specificity of 98% for detecting greater than 50% stenosis. Such patients have a high likelihood of concomitant CVD (62).

Exercise stress testing in asymptomatic men older than 40 years of age can also be useful in risk stratification (63). A positive stress test is highly predictive of CAD and future cardiovascular events. However, the likelihood of detecting asymptomatic CAD remains low when the pretest probability is low. Furthermore, a negative stress test has a low negative predictive value, particularly in patient populations with a higher pretest probability of CVD.

Carotid B-mode ultrasonography is also useful in assessing preclinical atherosclerosis. In asymptomatic individuals 50 years of age or older, several studies have demonstrated up to a fivefold increase in future risk of CAD events when the carotid intima-media thickness (CIMT) is greater than 1 mm, although a better measurement would be a CIMT of greater than the 75th percentile for age, sex and ethnic background (64). A screening strategy, based on carotid ultrasonography, was recently proposed (64). Although CIMT quantification is not yet a standard measure, evidence of early carotid atherosclerosis (visible arterial wall plaques or IMT of 1.5 mm or greater) by routine carotid ultrasonography is probably an indication for statin therapy. Some believe that noninvasive imaging, especially in the moderate-risk category, may be useful to identify patients with undiagnosed, subclinical atherosclerosis. The presence of atherosclerosis places the individual in the high-risk category (class IIa, level C).

Cardiac computed tomography (electron-beam computed tomography) and multidetector computed tomography coronary angiography quantify the burden of coronary artery calcium and can be useful in risk prediction. Importantly, not all plaques are calcified and calcium cannot be used to reliably identify plaques at risk for rupture (65). Even so, the negative predictive value of a coronary artery calcium score of 0 remains very high (greater than 98%) for ruling out significant coronary atherosclerosis or the development of coronary events (65). Noninvasive imaging of the coronary arteries requires computerized gated images of the heart, frequently with pharmacologically induced bradycardia to improve image quality. While not as sensitive as coronary angiography (66), it may be useful for the differential diagnosis of chest pain in highly selected patients. It is not recommended for screening in asymptomatic subjects.

TREATMENT

Health behaviours

Health behaviour interventions remain the cornerstone of chronic disease prevention, including CVD prevention. They should be universally applied for the prevention of chronic diseases such as obesity, type 2 diabetes, atherosclerosis, cancer and neurodegenerative diseases. The major recommended health behaviour interventions are:

- Smoking cessation, including the use of pharmacological therapy as required;

- A diet low in sodium and simple sugars, with substitution of unsaturated fats for saturated and trans fats, as well as increased consumption of fruits and vegetables;
- Caloric restriction to achieve and maintain ideal body weight;
- Moderate to vigorous exercise for 30 min to 60 min most (preferably all) days of the week;
- Psychological stress management; and
- Alcohol consumption in moderation is not contraindicated if there are no metabolic or clinical contraindications (67).

Smoking cessation: Smoking cessation is probably the most important health behaviour intervention for the prevention of CVD. There is a linear and dose-dependent association between the number of cigarettes smoked per day and CVD risk (24). Pharmacological therapy is associated with an increased likelihood of smoking abstinence.

Diet: Recommendations regarding the type of diet favouring health maintenance have been fraught with controversy. Most authorities agree that reducing saturated fats and refined sugars in the diet, while increasing fruits, vegetables and fibres, is associated with increased health. For patients with hypertriglyceridemia, a reduction in the intake of alcohol and refined carbohydrates, in conjunction with increased consumption of omega-3 and omega-6 polyunsaturated fats, is indicated. Most important is the restriction of caloric intake to achieve and maintain a healthy body weight. In Caucasians, a BMI of less than 25 kg/m² is considered optimal, while in subjects of Asian, Chinese and Japanese descent, a lower BMI (less than 23 kg/m²) may be indicated. The dietary content (percentage of protein, carbohydrate and fat) required to maintain a healthy weight does not appear to matter as long as caloric intake is reduced (68). A diet suited to the individual that provides adequate nutrition with a balance between caloric intake and energy expenditure, is best. Often, a professional dietician is of value to provide advice and follow-up. Moderate alcohol intake is acceptable (one drink per day for women and two drinks per day for men) if no metabolic or clinical contraindications are present (67).

Exercise: Physical activity is another important component of prevention. Many studies have shown the benefits of regular exercise in maintaining health and preventing CVD. Regular exercise also has beneficial effects on diabetes risk, hypertension and hypertriglyceridemia, and improves plasma levels of HDL-C. In several studies, a lower frequency of CVD was noted in physically active individuals independent of known CVD risk factors. A general recommendation for healthy individuals is at least 30 min to 60 min of moderate to vigorous physical activity on most, but preferably all, days of the week.

Psychological factors: The INTERHEART study (69) confirmed the importance of stress as a CVD risk factor. Following MI, patients with depression have a worse prognosis, but it remains unclear whether pharmacological treatment reduces this risk (70).

Pharmacotherapy (Table 4)

LDL-C: In high-risk individuals, treatment should be started immediately, concomitant with health behaviour interventions with respect to appropriate diet, physical activity, weight management and the cessation of tobacco consumption. The primary target of therapy is to achieve an LDL-C of less than 2.0 mmol/L, an apoB of less than 0.8 g/L or a 50% reduction in LDL-C from baseline values (class I, level A).

The majority of patients will be able to achieve target LDL-C levels 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, colestipol), or the concomitant use of niacin. These combinations are generally safe and can decrease LDL-C by an additional 10% to 15% for bile acid resins and up to 20% for ezetimibe and niacin. Clinical outcome data on the incremental benefit of combination therapy with statin plus ezetimibe, niacin or fibrate, versus statin monotherapy are lacking, although clinical trials are underway to examine this issue.

Triglycerides: A specific target for triglyceride levels in high-risk subjects or for the primary prevention of CAD has not been established.

TABLE 4
Lipid-lowering medications

Generic name	Trade name (manufacturer)	Recommended dose range (daily)
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 Ltd)	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 Ltd)	10 mg – 80 mg*
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Questran (Bristol-Myers Squibb, USA)	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 (Actavis Group PTC EHF, Iceland)	400 mg
Fenofibrate [†]	Lipidil Micro/Supra/EZ (Fournier Pharma Inc, Canada)	48 mg – 200 mg
Gemfibrozil ^{††}	Lopid (Pfizer Canada Inc)	600 mg – 1200 mg
Niacin		
Nicotinic acid	Generic crystalline niacin	1 g – 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g – 2 g

*Increased myopathy on 80 mg; [†]Reduce dose or avoid in renal impairment; ^{††}Should not be used with a statin because of an increased risk of rhabdomyolysis

Epidemiological studies show that lower triglyceride levels are associated with decreased CVD risk, and drugs that lower triglycerides have demonstrated a reduction of CVD events in the Helsinki Heart Study (71) and the Veterans Administration HDL Intervention Trial (VA-HIT) (72). In both cases, the drug used was the fibric acid derivative gemfibrozil. Gemfibrozil should not be used with a statin because of the increased risk of rhabdomyolysis. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (73) in diabetic patients using fenofibrate failed to meet its primary end point in terms of CAD prevention. In patients with hypertriglyceridemia, dietary therapy, exercise and weight loss, with a focus on restriction of refined carbohydrates and reduced alcohol intake, in association with increased intake of omega-3 fatty acids, are first-line therapies. The use of fibrates as first-line agents is warranted in patients with extreme hypertriglyceridemia (triglyceride levels greater than 10 mmol/L) to prevent pancreatitis. For patients with moderate hypertriglyceridemia (triglyceride levels of 5 mmol/L to 10 mmol/L), fibrates may be useful, but the impact on CAD prevention is less clear. In high-risk patients already on a statin, elevated triglyceride levels (2 mmol/L to 5 mmol/L) may be further treated with a fibrate or niacin. However, it has not been established whether the addition of a fibrate or niacin to a statin further reduces CAD events once the LDL-C is at target (class IIb, level C).

HDL-C: Smoking cessation, weight loss, exercise and moderate alcohol intake all increase HDL-C. These favourable health behaviours stand on their own merit in terms of benefit over the long term and HDL-C may be a marker of cardiovascular health. There is considerable controversy regarding the treatment of a low HDL-C, in part because there are many genetic forms of HDL-C deficiency that do not increase (or increase only slightly) CVD risk (74). Furthermore, the treatment of a genetic HDL-C deficiency is often difficult with currently available medications (75). Statins have little effect on HDL-C and fibrates only modestly raise HDL-C (5% to 10%) in most cases. Niacin can increase HDL-C by 15% to 25%.

Novel approaches to raise HDL-C are being tested clinically. Despite early disappointing results (76), the data indicate that raising HDL-C may still prove to be a valuable therapeutic target (77).

Combination therapy: The combination of a statin with niacin is effective in improving the lipid profile of patients with combined dyslipidemia and low HDL-C. Niacin is more effective than fibrates in increasing HDL-C concentrations. Side effects are most manifest with crystalline niacin, and include flushing, dry skin, gastritis and worsened glycemic control in persons with diabetes mellitus. Crystalline niacin should be taken two to three times daily after meals and the dose should be increased slowly. Extended-release niacin (Niaspan; Oryx Pharmaceuticals Inc, Canada) is taken once daily and is better tolerated. The use of acetylsalicylic acid (325 mg) 30 min to 60 min before niacin attenuates the flushing in most patients. There is a small but significant risk of hepatotoxicity with niacin monotherapy or niacin plus statin combination treatment and therefore, serum transaminase levels should be followed. Until the results of the Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) (78) and Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) (79) trials using combined statin/niacin in high-risk patients are available, the data supporting the use of niacin are based on small studies not powered for major adverse CVD end points. Gradual titration of niacin and the use of acetylsalicylic acid to decrease flushing symptoms are recommended.

The combination of a statin with a fibrate may be used with close patient follow-up. Because fibrates may increase serum creatinine, the dose must be adjusted in patients with kidney impairment. Fibrates may also increase serum homocysteine levels. It should be noted that the recent FIELD study (73) demonstrated that fenofibrate monotherapy did not significantly reduce CVD events in patients with diabetes and mild hypertriglyceridemia. Available data suggest that fenofibrate is reasonably safe in combination with a statin. Studies are underway to determine whether the addition of a fenofibrate to a statin regimen alters CVD risk. Gemfibrozil is associated with a higher risk of myotoxicity and should not be used in combination therapy. For patients with moderate hypertriglyceridemia, the addition of omega-3 fatty acids (2 g to 4 g three times daily) to statin therapy is safe, and may lower triglycerides and help achieve the TC/HDL-C ratio target.

Safety and laboratory monitoring

Before initiation of pharmacological therapy for dyslipidemias, a baseline lipoprotein profile should be obtained after a 10 h to 12 h fast, preferably with the subject refraining from alcohol for 24 h to 48 h. The lipoprotein profile should include TC, HDL-C and triglycerides. The LDL-C is derived from the Friedewald formula and is considered accurate for triglyceride levels of less than 5 mmol/L. A fasting glucose level should also be obtained at baseline to identify the presence of impaired fasting glucose or diabetes. ApoB and apoAI measurements should be made at the discretion of the physician. Important issues for these newer biochemical analytes include standardization of laboratory measurement proficiency and reimbursement, both of which, at present, vary widely across Canada. ApoB measurement may also be useful for differentiation between familial hypertriglyceridemia and familial combined hyperlipidemia, and in subjects with a low HDL-C. A baseline thyroid-stimulating hormone level helps uncover the occasional hypothyroid-induced hyperlipidemia. Baseline transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase), creatinine and creatine kinase (CK) are useful to monitor potential side effects associated with therapy. The frequency of follow-up measurements is debated but should probably be performed semiannually, or with any changes in lipid-lowering therapy.

Statin are well tolerated by most individuals. Myalgias represent the most common side effect of statins and may occur in approximately 5% of patients, although similar rates are often seen in the placebo groups in clinical trials. Statin-related myalgias are characterized by dull muscle aches and can be made worse by exercise, although they may occur in

sedentary patients. Serum levels of CK may remain normal. The diagnosis should be based on drug cessation and re-challenge. Myositis is an inflammation of skeletal muscles and the diagnosis is based on muscle discomfort and elevation of CK to more than three times the upper limit of normal. This is a potentially serious condition and may be caused by strenuous exercise. Dose reduction and close monitoring of CK levels or discontinuation of the statin are often required. Of note, a genetic predisposition to myositis is thought to underlie a number of cases. Rhabdomyolysis is a potentially life-threatening condition with a prevalence of less than 1:100,000 statin-treated patients. It is characterized by severe muscle pains, myoglobinuria and possibly, acute renal failure and a CK level of greater than 10,000 U/L. The discontinuation of statins and prompt hospitalization for supportive treatment is required. Significant increases in hepatic transaminase levels, defined as an ALT level of greater than three times the upper limit of normal, occur in 0.3% to 2.0% of patients and are generally dose related.

Both crystalline niacin and extended-release niacin preparations can result in persistent significant elevations in ALT in approximately 1% of patients. A general recommendation is to measure ALT at baseline, and between one and three months after initiating niacin therapy. Fasting blood glucose and glycosylated hemoglobin should be monitored every six to 12 months in patients treated with niacin, in view of its tendency to raise blood glucose levels. If these parameters deteriorate significantly in patients treated with niacin, consideration should be given to dose reduction or withdrawal of niacin therapy. Uric acid levels should be monitored in patients taking niacin.

Reversible increases in plasma creatinine of 15% to 20% are common in fibrate-treated patients and more significant increases can occur in patients with underlying renal disease. In patients with renal insufficiency (estimated glomerular filtration rate of less than 60 mL/min/1.73 m²), fibrates should be initiated at the lowest available dose and increased only after re-evaluation of renal function and lipid parameters.

Referral to a specialty clinic, advanced laboratory tests and genetic testing

Physicians are often confronted with issues of drug intolerance, complex diagnostic cases, lack of laboratory resources, seemingly 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 academic centres across Canada have specialized lipid clinics and the laboratory resources required for more extensive testing. In extreme cases, therapeutic modalities, such as extracorporeal LDL apheresis techniques, are available. We recommend that lipoprotein disorder specialists be available in each province to provide care for more difficult patients referred from primary care physicians.

Genetic testing for severe lipoprotein disorders is available in a few highly specialized centres. However, a molecular genetic diagnosis is not necessary for the majority of patients with severe dyslipidemia; the biochemical and clinical data usually suffice to make a diagnosis. As a research tool, however, the molecular study of extreme lipoprotein disorders has provided considerable scientific insight including the identification of potential future therapeutic targets.

ACKNOWLEDGEMENTS: The authors thank the external reviewers, Dr Philip Barter, Sydney Heart Institute (Sydney, Australia) and Dr David Waters, Professor Emeritus, University of California (San Francisco, USA), for their criticisms and comments.

CONFLICTS OF INTEREST: These guidelines were developed without financial or logistical support from pharmaceutical companies. Under no circumstances were funds requested or received for work related to these recommendations by members of the writing group or review panelists. A full disclosure of the conflicts of interest can be found on the CCS Web site (www.ccs.ca).

CANADIAN CHOLESTEROL GUIDELINES 2009: SUMMARY OF RECOMMENDATIONS

SCREENING FASTING LIPID PROFILE

- Screen men who are at least 40 years of age, and women who are at least 50 years of age or postmenopausal.
- Adults with the following risk factors should be screened at any age:
 - Diabetes;
 - Cigarette smoking;
 - Hypertension;
 - Obesity (body mass index greater than 27 kg/m²);
 - Family history of premature coronary artery disease;
 - Clinical signs of hyperlipidemia;
 - Evidence of atherosclerosis;
 - Rheumatoid arthritis, systemic lupus erythematosus, psoriasis;
 - HIV infection on highly active antiretroviral therapy;
 - Estimated glomerular filtration rate of less than 60 mL/min/1.73 m²; or
 - Erectile dysfunction.
- Screen children with a family history of hypercholesterolemia or chylomicronemia.

CARDIOVASCULAR RISK ASSESSMENT

Determine risk using the Framingham risk score modified for family history (double the cardiovascular disease risk percentage if any cardiovascular disease is present in a first-degree relative before 60 years of age). In men older than 50 years or women older than 60 years of age, of intermediate risk whose low-density lipoprotein cholesterol does not already suggest treatment, high-sensitivity C-reactive protein can be used for risk stratification.

TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High	<2 mmol/L or Most patients with diabetes FRS ≥20% RRS ≥20%	Class I, level A
Moderate	<2 mmol/L* or LDL-C >3.5 mmol/L TC/HDL-C >5.0 hs-CRP >2 mg/L in men >50 years and women >60 years of age Family history and hs-CRP modulate risk	Class IIa, level A
Low	≥50% ↓ LDL-C	Class IIa, level A

*Clinicians should exercise judgement when implementing statin therapy. Meta-analysis of statin trials show that for each 1.0 mmol/L decrease in low-density lipoprotein cholesterol (LDL-C), there is a corresponding 20% to 25% RR reduction. Those whose 10-year risk for cardiovascular disease is 5% to 9% have been shown in randomized clinical trials to achieve the same RR reduction from statin therapy as those at higher 10-year risk, but the absolute benefit of therapy is estimated to be smaller. apoB Apolipoprotein B; CAD Coronary artery disease; FRS Framingham risk score; HDL-C High-density lipoprotein cholesterol; hs-CRP High-sensitivity C-reactive protein; PVD Peripheral vascular disease; RRS Reynolds Risk Score; TC Total cholesterol

Secondary (optional) targets (once low-density lipoprotein cholesterol is at goal)

- Total cholesterol to high-density lipoprotein cholesterol ratio of less than 4.0;
- Non-high-density lipoprotein cholesterol of less than 3.5 mmol/L;
- Triglycerides of less than 1.7 mmol/L;
- Apolipoprotein B to apolipoprotein AI ratio lower than 0.80; and
- high-sensitivity C-reactive protein of less than 2 mg/L.

Clinical trial evidence is lacking for secondary targets; clinical judgements are warranted.

TREATMENT

Health behaviours

- Smoking cessation;
- Diet (reduced saturated fats and refined sugars);
- Weight reduction and maintenance;
- Exercise (daily); and
- Stress management.

Medication

In high-risk patients, pharmacological therapy should be considered concomitantly with lifestyle changes. In moderate-risk patients, lifestyle changes should be implemented first, followed by medications if the targets are not reached.

Generic name	Trade name (manufacturer)	Dose range (daily)
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 Ltd)	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 Ltd)	10 mg – 80 mg*
Bile acid and/or cholesterol absorption inhibitors		
Cholestyramine	Questran (Bristol-Myers Squibb, USA)	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 (Actavis Group PTC EHF, Iceland)	400 mg
Fenofibrate [†]	Lipidil Micro/Supra/EZ (Fournier Pharma Inc, Canada)	48 mg – 200 mg
Gemfibrozil ^{††}	Lopid (Pfizer Canada Inc)	600 mg – 1200 mg
Niacin		
Nicotinic acid	Generic niacin	1 g – 3 g
	Niaspan (Oryx Pharmaceuticals Inc, Canada)	0.5 g – 2 g

*Simvastatin 80 mg has a higher incidence of rhabdomyolysis; [†]Reduce dose or avoid in renal impairment; ^{††}Should not be used with a statin because of an increased risk of rhabdomyolysis

Other risk factors/risk markers

The clinical usefulness of other risk factors or markers of risk has not been evaluated in large-scale clinical trials.

Noninvasive assessment of atherosclerosis

The determination of the ankle-brachial index, carotid plaque, coronary calcium score or multidetector computed tomography coronary angiography will detect asymptomatic atherosclerosis not always predicted by the cardiovascular risk assessment algorithms.

Follow-up

Most lipid-lowering medications are well tolerated. Serum transaminases and creatine kinase should be followed regularly (every six to 12 months) or when symptoms develop. Follow-up is not required if levels are consistently normal and the patient has no symptoms.

Referral to specialized clinics

Most Canadian universities have a specialized lipid clinic. Cases of unexplained atherosclerosis, severe dyslipidemias, genetic lipoprotein disorders and patients refractory to pharmacological treatment should be referred.

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY TABLE 1

Stakeholders in the elaboration of the Canadian lipid guidelines

Canadian Cardiovascular Harmonization of National Guidelines Endeavor (C-Change). Putting Prevention into Practice

- Canadian Association of Cardiac Rehabilitation
- Canadian Cardiovascular Society
- Canadian College of Family Physicians of Canada
- Canadian Council for Tobacco Control
- Canadian Council of Cardiovascular Nurses
- Canadian Diabetes Association
- Canadian Hypertension Society
- Canadian Medical Association
- Canadian Obesity Network
- Canadian Pharmacists Association
- Canadian Society for Exercise Physiology
- Canadian Stroke Network
- Canadian Working Group on Dyslipidemias
- Obesity Canada
- Public Health Agency of Canada
- Royal College of Physicians and Surgeons of Canada
- Canadian Institutes of Health Research

SUPPLEMENTARY TABLE 2

Criteria used for evaluation of evidence

Recommendation grade

Class I

Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective

Class II

Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment

Class IIa Weight of evidence in favour

Class IIb Usefulness/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 clinical trials or meta-analysis

Level B

Data derived from a single randomized clinical trial or large nonrandomized studies

Level C

Consensus of opinion by experts and/or small studies, retrospective studies and registries

SUPPLEMENTARY TABLE 3

Major changes since the 2006 recommendations

Involvement of the Canadian Vascular Coalition and the Canadian Institutes of Health Research

Secondary and high-risk prevention

Strategy better defined

Clinical studies on end-stage disease (advanced heart failure and hemodialysis)

Primary prevention

Cardiovascular risk evaluation tools

Framingham risk score includes cardiovascular diseases

Intermediate risk defined as a Framingham risk score of 10% to 19% for 10-year risk

Family history part of risk stratification

High-sensitivity C-reactive protein part of risk stratification in intermediate-risk subjects whose low-density lipoprotein cholesterol level does not already suggest treatment (men older than 50 years and women older than 60 years of age)

Targets

Simplified target levels

Apolipoprotein B role defined

Secondary targets evaluated according to available evidence

SUPPLEMENTARY TABLE 4A

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

POINTS	Age	HDL-C	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
-2		>1.6		<120				
-1		1.3-1.6						
0	30-34	1.2-1.3	<4.1	120-129	<120	NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9	5.2-6.2	140-159	120-129			
3			6.2-7.2	160+	130-139		YES	
4			>7.2		140-159	YES		
5	40-44				160+			
6								
7	45-49							
8	50-54							
9								
10	55-59							
11	60-64							
12								
13	65-69							
14	70-74							
15	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

SUPPLEMENTARY TABLE 4B

Cardiovascular disease risk for men

Points	Risk, %	Points	Risk, %	Points	Risk, %
-3 or less	<1	5	3.9	13	15.6
-2	1.1	6	4.7	14	18.4
-1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	>30
3	2.8	11	11.2		
4	3.3	12	13.3		

SUPPLEMENTARY TABLE 5A

Estimation of 10-year risk of total cardiovascular disease in women (Framingham Heart Study)

POINTS	Age	HDL-C mmol/L	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
-3				<120				
-2		>1.6						
-1		1.3-1.6			<120			
0	30-34	1.2-1.3	<4.1	120-129		NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9		140-149	120-129			
3			5.2-6.2		130-139	YES		
4	40-44		6.2-7.2	150-159			YES	
5	45-49		>7.2	>160	140-149			
6					150-159			
7	50-54				160+			
8	55-59							
9	60-64							
10	65-69							
11	70-74							
12	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

SUPPLEMENTARY INFORMATION – CONTINUED

SUPPLEMENTARY TABLE 5B
Cardiovascular disease risk for women

Points	Risk, %	Points	Risk, %	Points	Risk, %
-2 or less	<1	6	3.3	14	11.7
-1	1.0	7	3.9	15	13.7
0	1.2	8	4.5	16	15.9
1	1.5	9	5.3	17	18.51
2	1.7	10	6.3	18	21.5
3	2.0	11	7.3	19	24.8
4	2.4	12	8.6	20	27.5
5	2.8	13	10.0	21+	>30

REFERENCES

- Heart and Stroke Foundation of Canada. The Growing Burden of Heart Disease and Stroke in Canada 2003. <<http://www.cvdinfobase.ca/cvdbook/En/Index.htm>> (Version current at August 13, 2009).
- Statistics Canada. CANSIM. <<http://cansim2.statcan.ca>> (Version current at August 13, 2009).
- McPherson R, Frohlich J, Fodor G, Genest J; Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement – recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006;22:913-27.
- Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B-100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005;294:326-33.
- Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.
- Lloyd-Jones DM, Nam BH, D'Agostino RB, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults – a prospective study of parents and offspring. *JAMA* 2004;291:2204-11.
- Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998;97:155-60.
- Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;444:881-7.
- Katzmarzyk PT, Mason C. Prevalence of class I, II and III obesity in Canada. *CMAJ* 2006;174:156-7.
- Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;366:1059-62.
- Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:338-46.
- Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009;68:1131-5.
- Thorburn CM, Ward MM. Hospitalizations for coronary artery disease among patients with systemic lupus erythematosus. *Arthritis Rheum* 2003;48:2519-23.
- Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: Results from a systematic review and meta-analysis. *Am J Gastroenterol* 2007;102:662-7.
- Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: A population-based study. *Clin Gastroenterol Hepatol* 2008;6:41-5.
- DAD Study Group; Friis-Møller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007;356:1723-35.
- Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
- The SEARCH Study. <<http://www.ctsu.ox.ac.uk/~search/>> (Version current at August 13, 2009).
- Fruchart JC, Sacks F, Hermans MP, et al. The residual risk reduction initiative: A call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol* 2008;102(10 Suppl):1K-34K.
- Johnson C, Waters DD, DeMicco DA, et al. Comparison of effectiveness of atorvastatin 10 mg versus 80 mg in reducing major cardiovascular events and repeat revascularization in patients with previous percutaneous coronary intervention (post hoc analysis of the Treating to New Targets [TNT] Study). *Am J Cardiol* 2008;102:1312-7.
- Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007;356:2388-98.
- Lonn E, Yusuf S, Arnold MJ, et al; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567-77.
- Smith SC Jr, Allen J, Blair SN, et al; AHA/ACC; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363-72.
- Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* 2004;364:937-52.
- Go AS, Chertow GM, Fan DJ, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
- Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease – a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;108:2154-69.
- Barbaro G, Iacobellis G. Metabolic syndrome associated with HIV and highly active antiretroviral therapy. *Curr Diab Rep* 2009;9:37-42.
- Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: A meta-analysis. *Am J Med* 2006;119:812-9.
- Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. *Circulation* 2003;107:391-7.
- Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease – meta-analysis of prospective studies. *Circulation* 2000;102:1082-5.
- Davidson MH, Corson MA, Alberts MJ, et al. Consensus panel recommendation for incorporating lipoprotein-associated phospholipase A2 testing into cardiovascular disease risk assessment guidelines. *Am J Cardiol* 2008;101:51F-57F.
- NACB LMPG Committee Members; Myers GL, Christenson RH, Cushman M, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Emerging biomarkers for primary prevention of cardiovascular disease. *Clin Chem* 2009;55:378-84.
- D'Agostino RB, Ramachandran SV, Pencina MJ, et al. General cardiovascular risk profile for use in primary care. The Framingham Heart Study. *Circ* 2008;117:743-53.
- Grover SA, Lowensteyn I, Joseph L, et al; Cardiovascular Health Evaluation to Improve Compliance and Knowledge Among Uninformed Patients (CHECK-UP) Study Group. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: The CHECK-UP study: A randomized controlled trial. *Arch Intern Med* 2007;167:2296-303.
- Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds Risk Score. *JAMA* 2007;297:611-9.

36. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: The Reynolds Risk Score for men. *Circulation* 2008;118:2243-51.
37. Michos ED, Blumenthal RS, Becker LC. Women with a Framingham risk score < 10 and a family history of premature CHD have a high prevalence of subclinical coronary atherosclerosis. *Circulation* 2004;110:790.
38. Lloyd-Jones DM. Short-term versus long-term risk for coronary artery disease: Implications for lipid guidelines. *Curr Opin Lipidol* 2006;17:619-25.
39. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007;14(Suppl 2):S1-113.
40. Leiter L, Genest J, Harris SB, et al. Dyslipidemia. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008;32(Suppl 1):S107-S114.
41. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels – results of AFCAPS/TexCAPS. *JAMA* 1998;279:1615-22.
42. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart-disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
43. Sever PS, Dahlof B, Poulter NR, et al. 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.
44. Heart Protection Study Collaborative Group. 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.
45. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: The Study of Health Assessment and Risk in Ethnic Groups (SHARE). *Lancet* 2000;356:279-84.
46. Kaler SN, Ralph-Campbell K, Pohar S, King M, Laboucan CR, Toth EL. High rates of the metabolic syndrome in a First Nations Community in western Canada: Prevalence and determinants in adults and children. *Int J Circumpolar Health* 2006;65:389-402.
47. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
48. Larosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
49. Wiviott SD, de Lemos JA, Cannon CP, et al. A tale of two trials: A comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. *Circulation* 2006;113:1406-14.
50. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial. *JAMA* 2005;294:2437-45.
51. Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 trials). *Am J Cardiol* 2007;100:1047-51.
52. Thompson GR, Hollyer J, Waters DD. Percentage change rather than plasma level of LDL-cholesterol determines therapeutic response in coronary heart disease. *Curr Opin Lipidol* 1995;6:386-8.
53. Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: Report of the Thirty-Person/Ten-Country Panel. *J Intern Med* 2006;259:247-58.
54. van der Steeg WA, Boekholdt SM, Stein EA, et al. Role of the apolipoprotein B-apolipoprotein A-I ratio in cardiovascular risk assessment: A case-control analysis in EPIC-Norfolk. *Ann Intern Med* 2007;146:640-8.
55. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;297:499-508.
56. Kini AS, Muntner P, Moreno PR, et al. Relation of high-density lipoprotein cholesterol to mortality after percutaneous coronary interventions in patients with low-density lipoprotein <70 mg/dL. *Am J Cardiol* 2009;103:350-4.
57. Ridker PM, Danielson E, Fonseca FA, et al; on behalf of the JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: A prospective study of the JUPITER trial. *Lancet* 2009;373:1175-82.
58. Kjekshus J, Apetrei E, Barrios V, et al; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248-61.
59. GISSI-HF Investigators; Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:1231-9.
60. Wanner C, Krane V, März W, et al; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353:238-48.
61. Fellström BC, Jardine AG, Schmieder RE, et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360:1395-407.
62. Ankle Brachial Index Collaboration; Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: A meta-analysis. *JAMA* 2008;300:197-208.
63. Greenland P, Gaziano JM. Clinical practice. Selecting asymptomatic patients for coronary computed tomography or electrocardiographic exercise testing. *N Engl J Med* 2003;349:465-73.
64. Stein JH, Korcarz CE, Hurst RT, et al; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;21:93-111.
65. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 2007;115:402-26.
66. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324-36.
67. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. *Circulation* 2007;116:1306-17.
68. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859-73.
69. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation* 2008;118:1768-75.
70. Lespérance F, Frasrance-Smith N, Koszycki D, et al; CREATE Investigators. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007;297:367-79.

71. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.
 72. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.
 73. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* 2005;366:1849-61.
 74. Frikke-Schmidt R, Nordestgaard BG, Stene MC, et al. Association of loss-of-function mutations in the *ABCA1* gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *JAMA* 2008;299:2524-32.
 75. Alrasadi K, Awan K, Ruel I, et al. Comparison of treatment of severe high-density lipoprotein cholesterol deficiency in men with daily atorvastatin (20 mg) versus fenofibrate (200 mg) versus extended-release niacin (2 g). *Am J Cardiol* 2008;102:1341-7.
 76. Barter PJ, Caulfield M, Eriksson M, et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109-22.
 77. Barter P, Gotto AM, LaRosa JC, et al; Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;357:1301-10.
 78. Brown BG, Zhao XQ. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. *Am J Cardiol* 2008;101:58B-62B. <<http://clinicaltrials.gov/ct/show/NCT00120289>>.
 79. ClinicalTrials.gov. <<http://clinicaltrials.gov/ct2/results?term=NCT00461630>> (Version current at August 13, 2009).
-