Guidelines for the detection of high-risk lipoprotein profiles and the treatment of dyslipoproteinemias

Canadian Lipoprotein Conference Ad Hoc Committee on Guidelines for Dyslipoproteinemias

Elevated plasma levels of cholesterol and triglycerides, low levels of high-density lipoproteins, hypertension, diabetes mellitus, smoking and abdominal obesity are risk factors for coronary heart disease (CHD) and stroke. Because of the preventable threat to life, well-being and productivity from perturbations of plasma lipoproteins (which affect about 60% of adults), we recommend a population-based strategy with public education on diet, exercise and the hazards of smoking and legislation for better food labelling. This should be combined with the medical guidelines we describe to detect and treat those at highest risk for CHD (including about 15% of adults), who merit priority for the medical, dietetic and laboratory services required. Among people aged 40 years or more this includes those with plasma total cholesterol levels greater than 7 mmol/L, fasting triglyceride levels greater than 3 mmol/L or cholesterol levels greater than 6 mmol/L when associated with CHD or other risk factors for CHD. For younger people the criteria for highest risk include cholesterol levels greater than 6.5 mmol/L for those aged 30 to 39 years, greater than 6 mmol/L for those aged 20 to 29 and greater than 5 mmol/L for those under age 20.

Les facteurs de risque à l'égard des coronaropathies et des accidents cérébrovasculaires sont l'hypercholestérolémie, l'hypertriglycéridémie, l'abaissement des lipoprotéines à haute densité, l'hypertension artérielle, le diabète sucré, l'habitude de fumer et l'obésité abdominale. Les perturbations des lipoprotéines plasmatiques affectent quelque 60% des adultes. Comme la menace qu'elles font peser sur leur vie, leur bien-être et leur productivité est susceptible de prévention, nous proposons une vaste action d'éducation populaire sur l'alimentation, l'exercice et les effets nocifs de la fumée de tabac, à sortie de lois portant un meilleur étiquetage des produits alimentaires. On y adjoindrait les directives que nous proposons au médecin pour le dépistage et le traitement des personnes les plus sujettes aux coronaropathies, ce qui comprend environ 15% des adultes, à qui on réserverait la priorité des services médicaux, diététiques et biologiques nécessaires. Parmi les sujets d'au moins 40 ans on compte les porteurs soit d'une cholestérolémie totale dépassant 7 mmol/L, soit d'une triglycéridémie à jeun dépassant 3 mmol/L, soit d'une cholestérolémie dépassant 6 mmol/L en présence de coronaropathie ou d'autres facteurs de risque à l'égard de celle-ci. Chez les sujets plus jeunes les critères du plus grand risque comprennent une cholestérolémie dépassant 6,5 mmol/L de 30 à 39 ans, 6 mmol/L de 20 à 29 ans et 5 mmol/L avant 20 ans.

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Myocardial infarction and underlying coronary heart disease (CHD) are the predominant causes of death and disability in Canada[1] and the United States[2] and account for the largest share of health care costs.[2] The main cause of myocardial infarction is the common, though biologically complex, degenerative process known as atherosclerosis, which in turn can be attributed to various genetic or environmental factors. The relative importance of the specific factors varies from person to person. However, regardless of the cause, sustained elevation of either low-density lipoprotein (LDL) or very-low-density lipoprotein (VLDL) levels above normal limits in susceptible people or animals is now known to result in atherosclerosis.[3,4] Elevated plasma levels of total cholesterol are clinically useful indicators of CHD risk, especially when combined with information on the plasma triglyceride levels and the composition and concentration of lipoprotein lipids and apolipoproteins. A recent long-term prospective study involving 350 977 subjects has shown that the plasma total cholesterol level is also an important predictor of thrombotic stroke.[5]

Besides dyslipoproteinemias there are other important primary risk factors for atherosclerosis, the most prevalent being hypertension, cigarette smoking, diabetes, physical inactivity and abdominal obesity.[6] Because of the synergistic interactions between these risk factors their deleterious effects on arteries are multiplied, so that the presence of more than one risk factor greatly increases the risk of CHD.[7]

Effective strategies to reduce illness and death from CHD require a multiple risk factor approach. Recent evidence has suggested that relatively small decreases in cigarette smoking, plasma cholesterol levels and blood pressure over a decade or more result in a significant reduction in the rates of CHD, along with a strong trend toward a decrease in all-cause mortality rates.[8] However, reductions in the rate of myocardial infarction are often demonstrable within only a few years after the start of effective prophylaxis. Demonstrated reductions in the rates of death from CHD — of at least 25% in Canada and other industrialized nations over the past two decades — and the apparent lag of one to two decades between dietary or medical intervention and such reductions[9,10] indicate the need for early prophylaxis for CHD and other atherosclerotic diseases.

Detection of high-risk lipoprotein profiles

Importance of abnormal lipoprotein levels

There are convincing causal relations between lipoprotein disorders, or dyslipoproteinemias, and the development of CHD; in addition, there is evidence that lowering of lipid levels reduces the rates of death[11,12] and illness[13,14] from CHD and slows the disease's progression.[15] Lipoprotein disorders are therefore now being sought out for treatment.[16-18] CHD is common in North America, northern Europe and other prosperous regions. The incidence rate among British men aged 55 to 59 years, based on electrocardiographic evidence, approaches 20%.[19]

There is no longer any question about the atherogenic effects of severely elevated plasma levels of LDL, as observed in homozygous familial hypercholesterolemia. Rampant atherosclerosis develops in all such patients, and they usually die before age 30, some by age 3, unless aggressively treated.[20] In the more common syndrome of heterozygous familial hypercholesterolemia there is an 85% risk of myocardial infarction among men by age 60.[21] Plasma cholesterol levels of around 10 mmol/L are usually observed in untreated patients with the syndrome, although they may be as low as 6 mmol/L in early adulthood and below 5 mmol/L in childhood.

In people over 40 years of age plasma cholesterol levels of 7 mmol/L confer a risk of CHD three to four times that associated with levels below 5 mmol/L.[22] The definitive Multiple Risk Factor Intervention Trial, based on 6 years of follow-up of over 350 000 men in the United States, showed that the death rate among men with cholesterol levels of 8 mmol/L was almost six times that among men with levels of 4 mmol/L.[23,24] The steep, continuous, direct relation between elevated plasma total cholesterol levels and CHD risk is consistent with the findings in three earlier prospective studies.[23,25-29] The prevalence of CHD is closely related to the LDL concentration.[30] Although the LDL cholesterol (LDL-C) concentration is a better predictor of CHD risk in subjects under 50 years of age than in older subjects,[31] a direct relation has been observed in people aged 60 to 70 years.[32] Pathologically the extensiveness of fatty streak formation, as an early indication of atherosclerosis, is correlated with the antecedent LDL-C concentration, even in children and young adults.[33]

Despite the importance of hypercholesterolemia (e.g., sporadic or familial hypercholesterolemia) as an independent risk factor for CHD, a normal plasma level of total cholesterol or LDL cholesterol does not exclude the risk of CHD.[34,35] Other prevalent lipoprotein-related CHD risk factors that confer independent risk include (a) excessive Lp(a) lipoprotein, (b) hypertriglyceridemia with low levels of high-density lipoprotein cholesterol (HDL-C), (c) familial combined hyperlipoproteinemia or hyperapobetalipoproteinemia (hyperapo B), (d) low HDL-C

levels and (e) hypertriglyceridemia.[35-41] Determination of plasma total or LDL apo B levels can identify the many people at high risk for CHD owing to hyperapo B.[40,41] Apo B measurements quantify the actual numbers of LDL particles, whereas determination of LDL and total plasma cholesterol levels may reflect only cholesterol content, thereby underestimating the true LDL concentration. The lipid phenotype in hyperapo B may include hypertriglyceridemia, a low HDL level, hypercholesterolemia or normolipidemia in the presence of an elevated plasma apo B level. Hyperapo B and a low HDL-C level are important predictors of loss of function of saphenous vein bypass grafts and progression of atherosclerosis in coronary arteries.[42]

Testing for dyslipoproteinemias

The family history and the findings at physical examination often give clues to the presence of dyslipoproteinemia. Indications for selective screening of plasma lipoprotein lipids include (a) a history of myocardial infarction or ischemia before age 60 years, the presence of corneal arcus before age 50, or tendon or cutaneous xanthomas; (b) the presence of other risk factors for premature vascular disease, including diabetes mellitus, hypertension, smoking, obesity and gout; and (c) a family history (in a parent, sibling or offspring) of dyslipoproteinemia, myocardial infarction, or cerebral infarction or ischemia.[18] However, the family history fails to identify up to 20% of severely hypercholesterolemic children, which demonstrates the additional value of screening.[43]

Table 1 shows the lipid levels at which three independent national or international consensus conferences recommend medical assessment or intervention for dyslipoproteinemia in patients aged 30 years or more who lack other CHD risk factors.

Approximately one-quarter of the population of the United States and Canada over the age of 40 has cholesterol levels over 6 mmol/L,[44] and as many as 71% of middle-aged and elderly Canadians have at least one risk factor for CHD.[16] Table 2 shows plasma concentrations of total and LDL cholesterol in US and Canadian subjects, by age, grouped into normal values (below the 50th percentile), borderline high values (50th to 75th percentile), high values (75th to 90th or 95th percentile) and very high values (above the 90th or 95th percentile). These values describe the population and differ from target values much in the way that population body weights differ from desirable weights. The increase in the mean plasma cholesterol level of about 0.4 mmol/L among women 50 to 70 years of age may be related, at least in part, to deficiency of ovarian hormones.[45] Normal values for women are therefore based on the approximate mean value for those aged 45 to 54.[44] The levels at which the risk for CHD is considered to be high or very high are in general accord with earlier recommendations.[22] These criteria address the need for early recognition and treatment of young people at particular risk of CHD but avoid possible overtreatment in older patients. Because of the difficulty of remembering these numbers laboratories should provide age-related ranges for lipoprotein lipid levels in each report.

Strictly standardized quality control of the accuracy of lipid, lipoprotein and apolipoprotein determinations is mandatory. This may entail standardization against primary standards from the US Centers for Disease Control, Atlanta,[46] with adequate high and low control levels in each assay or the use of pure cholesterol and triglyceride standards for lipids that have been extracted from plasma and analysed chemically by means of standard reference chemical techniques or mass spectroscopy.

At least two, and in many cases three, measurements of the fasting plasma cholesterol and triglyceride levels should be made, at intervals of 1 to 2 months, along with at least one or two lipoprotein measurements to determine accurately the baseline LDL-C and HDL-C levels for each patient.[47,48] More lipoprotein lipid measurements are needed to document mild dyslipoproteinemia than to identify severe dyslipoproteinemia. Nonfasting plasma samples may be useful in the initial screening measurements of total plasma cholesterol (but not LDL-C or HDL-C); elevated triglyceride levels must be confirmed by measurements obtained after the patient

Table 1: Recommended indications for medical assessment or intervention for dyslipoproteinemia in patients aged 30 years or more

Region	Level, mmol/L			
	Total cholesterol	Triglycerides	Low-density lipoprotein cholesterol (LDL-C)	High-density lipoprotein cholesterol (HDL-C)
Canada[6]	6.2	2.3	3.4	0.9
Europe[7]	5.2	2.3	–	–
United States[8]	6.2	–	4.1	–

has fasted 12 or more hours. Patients should rest sitting for at least 5 minutes, and a tourniquet should be applied for the shortest time possible before venipuncture.[18] The need for several accurate determinations is underlined by the wide standard deviations (0.5 mmol for total cholesterol[49] and 0.4 mmol for LDL-C[50]) reported for repeated measurements in the same person over time. The measurement of cholesterol levels is as tricky as their reduction.[51]

Importance of LDL

The plasma total cholesterol level alone is not an accurate discriminator within a given population for risk of CHD.[31] As many as half of the patients with dyslipoproteinemia may be missed if only the total cholesterol and triglyceride levels are measured.[52] Furthermore, in a very small number of patients the plasma total cholesterol level is elevated because of a favourable increase in the HDL level.[53] Measuring or estimating the plasma LDL-C fraction may help the practitioner assess the risk of CHD and define therapeutic goals.[54]

Although practical considerations primarily favour the current measurement of LDL-C and total cholesterol levels in the management of dyslipoproteinemias, there is increasing evidence that other

Table 2: Medical management of cholesterol disorders in people screened for dyslipoproteinemias*

Step; age, yr				
1. Plasma total cholesterol level† on final screen, mmol/L				
≤ 19	≤ 4.0	> 4.0	> 4.5	> 5.0
20–29	≤ 4.5	> 4.5	> 5.0	> 6.0
30–39	≤ 5.0	> 5.0	> 5.5	> 6.5
≥ 40	≤ 5.5	> 5.5	> 6.0	> 7.0
2. Plasma LDL-C level, mmol/L				
≤ 19	≤ 2.5	> 2.5	> 2.8	> 3.2
20–29	≤ 3.0	> 3.0	> 3.5	> 4.0
30–39	≤ 3.5	> 3.5	> 4.0	> 4.5
≥ 40	≤ 4.0	> 4.0	> 4.5	> 5.0
3. Preliminary level of risk for coronary heart disease (CHD) based on 1 or 2	Normal	Borderline high	High	Very high
4. Amount of time before repeat testing	5 yr	< 6 mo	< 2 mo	< 2 mo
5. Rule out secondary dyslipidemia, measure levels of triglycerides and HDL-C (and possibly LDL-C), and confirm diagnosis	–	Yes	Yes	Yes
6. Advise preventive diet	Yes	Yes	Yes	Yes
7. Refer to dietitian for intensive therapy	–	If CHD or its risk present‡ plus high LDL-C level§	Yes	Yes
8. Amount of time before repeat testing and review of risk level	5 yr	6–12 mo	6 mo	< 6 mo
9. Prescribe appropriate medication‖	–	–	If CHD or its risk present‡ and total cholesterol or LDL-C level remains high or very high	If total cholesterol or LDL-C level remains high or very high
10. Target total cholesterol or LDL-C level	–	Normal value	Normal value	Normal value
11. Refer to specialist	–	–	–	If difficulty achieving target or if hypolipidemic drugs under consideration for children

*Modified from references 16 and 44.
†Serum cholesterol = plasma cholesterol × 1.03.
‡Assumes physician is of the opinion that CHD or important risk of it is present. Examples of important risk factors for CHD or recurrent myocardial infarction other than elevated total cholesterol or LDL-C level include HDL-C level below the 10th percentile, triglyceride level above the 90th percentile, hypertension, smoking, family history of CHD in a first-degree relative, diabetes mellitus and severe abdominal obesity. See Table 3 and sections of text on importance of HDL and treatment of dyslipoproteinemias (Goals) for cut-off points and target values.
§Indicates high risk of CHD or recurrent myocardial infarction.
‖Hypocholesterolemic drugs are not used in pregnant women and are rarely used in children (and then cautiously).

lipid or lipoprotein fractions as well as apolipoprotein fractions may provide additional, alternative or more accurate information about the risk of CHD, possibly at less cost. For example, patients with elevated levels of intermediate-density lipoprotein (IDL) due to type III hyperlipoproteinemia,[55] chronic renal failure[56] or unknown causes[57] are known to exhibit accelerated atherogenesis. Furthermore, the severity of CHD in women has been correlated with IDL levels.[58,59]

Importance of triglycerides

Hypertriglyceridemia appears to be an independent risk factor for CHD in both older and younger women.[60] Recent evidence from the Framingham study has indicated that elevated plasma triglyceride levels are also an independent risk factor in men with low HDL-C levels.[61] However, the association of triglycerides with CHD could be largely explained by elevated levels of IDL, which transports appreciable amounts of triglyceride. Triglyceride-rich lipoprotein fractions in VLDLs and chylomicrons are of clinical interest primarily because they may cause life-threatening acute pancreatitis when present in great excess (triglyceride level greater than 20 mmol/L). Table 3 shows fasting plasma total triglyceride levels, by age, considered to be elevated (above the 90th percentile).

There is increasing evidence that hypertriglyceridemic patients with elevated levels of LDL apo B who have hyperapo B[62,63] are particularly at risk for CHD. Recent cross-sectional studies involving relatives of patients with established CHD have indicated that the measurement of plasma total or LDL apo B levels, combined with the measurement of apolipoprotein AI or AII (to detect low HDL levels), may be more sensitive and specific than the measurement of the plasma level of total cholesterol or triglycerides for the detection of CHD risk.[64-72] However, prospective studies of the efficacy of these tests are needed, along with improved standardization.

Table 3: Fasting plasma triglyceride levels* suggestive of disordered lipoprotein transport† and risk of myocardial infarction or stroke

Age, yr	Level, mmol/L
≤ 19	> 1.5
20–29	> 2.0
30–39	> 2.5
≥ 40	> 3.0

*Modified from reference 44.
†Includes such conditions as hypoalphalipoproteinemia, hyperapobetalipoproteinemia and familial combined hyperlipidemia.[62]

Importance of HDL

Low HDL-C levels have been found to be associated with increased risk of CHD[73-77] and stroke[78] in many, but not all, studies,[79] whereas a gemfibrozil-induced increase in HDL-C levels was reported to be associated with a decrease of 34% in the rate of illness from CHD.[80] However, no increase in risk of CHD was detected when HDL-C levels decreased in hyperlipidemic patients treated with a combination of probucol and clofibrate, conceivably owing to the specific properties of probucol.[81] The fasting plasma HDL-C levels indicative of markedly increased risk of myocardial infarction (corresponding approximately to the 10th percentile in North American women and men) are less than 1.0 mmol/L and less than 0.8 mmol/L respectively.[44]

Although abnormal HDL and LDL levels are independent risk factors for CHD in people over age 50 years, there is a much stronger association of CHD with the total cholesterol:HDL ratio.[31] Furthermore, a decreased plasma phosphatidylcholine:free cholesterol ratio has been identified as a novel independent risk factor for CHD.[82] A decrease in this ratio may signal supersaturation of the vascular system with cholesterol.[83,84] The apo E4 phenotype has recently been found to contribute significantly to the elevation of plasma cholesterol levels.[85] As a group, patients at risk for CHD tend to exhibit a spectrum of metabolic abnormalities.[35-37,86-88]

Secondary lipid disorders

Before one treats dyslipoproteinemia it is important to make a correct diagnosis, including the identification of secondary or aggravating factors underlying lipid disorders that may be related to other diseases, medication, lifestyle or nutrition.[89] Such factors frequently include excessive nutritional intake, especially of saturated fats and cholesterol,[90] hypothyroidism, ovarian failure (e.g., menopause),[45] nephrotic syndrome, diabetes, obstructive liver disease,[91] alcoholism, certain antihypertensive drugs,[92] glucocorticoids, obesity,[90] oral contraceptives[93] and retinoids.[94] Secondary dyslipoproteinemias often respond favourably to specific measures and may not respond to other hypolipidemic therapy. This can result in the loss of valuable therapeutic time.

Treatment of dyslipoproteinemias

Goals

Age-related target or normal values for fasting plasma total and LDL cholesterol based on approxi-

mate 50th percentiles in the population[18,26,44,47] are in Table 2. Most patients whose levels are above the target values can be expected to lower their risk of CHD by adhering to public health measures (smoking cessation, prudent diet, obesity control and alcohol restriction) that do not necessitate physician-intensive therapy.[95,96] However, a primary objective in the treatment of hypercholesterolemia should be to lower the plasma LDL (or total) cholesterol level substantially, generally to within normal limits for the patient's age group, when feasible. Since children with elevated LDL-C levels tend to maintain them over many years,[97] early prophylaxis could prove to be more important than intensive treatment later in life. When well-standardized measurements of the total or LDL apo B level are available the goal of therapy for hyperapo B should be to lower the LDL apo B level to the same percentile as the LDL-C level. Acceptable target levels for plasma HDL-C corresponding to the 50th percentile are 1.1 mmol/L for men and 1.5 mmol/L for women.[44]

General principles

The main clinical objectives in the treatment of lipoprotein disorders are to reduce the rates of illness and death from CHD, to lower health care costs and to reduce the loss of earnings and productivity due to premature disease. Given the importance of patient compliance with therapy these goals should be kept in mind and emphasized to the patient when necessary.

Because of the high prevalence of risk factors for CHD in the Canadian population,[16,98-100] including elevated levels of LDL-C and triglycerides and low HDL levels in about 60% of adults in Nova Scotia, and the scarcity of medical, dietetic and laboratory services required to provide the necessary care, there is an urgent need to concentrate these limited diagnostic and therapeutic resources among patients with the most serious types of dyslipoproteinemia-related CHD risk. Public health measures may be expected to achieve a mean lowering of the plasma cholesterol level of about 1.2% to 4.1%,[95,96] thereby complementing the dyslipoproteinemia case-finding strategy.

Physicians should direct initial patient counselling toward correcting underlying disorders, reducing intake of saturated fats and cholesterol, correcting serious obesity (over 20% above ideal weight), revising medication that may be inducing dyslipoproteinemia, treating hormonal abnormalities and increasing exercise in sedentary patients. Although therapy early in life may afford the most successful prophylaxis, treatment should not be denied to interested older people who could reasonably expect to benefit without exorbitant costs. Guidelines are necessary and useful, but in no way can they substitute for judgement by personal physicians. They see the patient in context and are best qualified to assess the risk and make therapeutic decisions after considering the complexity of information derived from clinical evaluation. It cannot be overemphasized that the family history is a most useful indicator in risk assessment. Genetic counselling should be offered to patients with potentially grave hereditary disorders. For instance, patients of childbearing age with heterozygous familial hypercholesterolemia should be advised that if they marry a similarly affected person there is one chance in four that their offspring will have homozygous familial hypercholesterolemia.

Dietary therapy

Diet modification remains the mainstay of the initial therapy for primary dyslipidemias.[101] There is evidence that fat-modified diets can reduce plasma cholesterol levels[102] and CHD risk.[103-105] The lowering of cholesterol levels has been shown to reduce overall rates of death from CHD[11,12] and to retard progression or induce regression of atherosclerosis in peripheral arteries,[106] coronary arteries[80,107-112] and coronary artery bypass grafts.[113] The American Heart Association's phase I fat-modified diet[114] has been widely adopted as a first step to achieve this purpose. Recent research has suggested a possible role for the long-term substitution of protein for carbohydrate to lower the plasma levels of total cholesterol, LDL-C and triglycerides and to raise the HDL-C level in conjunction with low-fat, low-cholesterol diets.[115] A summary of the principles of diet modification for the prevention of CHD based largely on the final report of the Canadian Consensus Conference on Cholesterol[16] and current nutritional practice is in Table 4.

Phase II or even phase III of the American Heart Association diet may be indicated if the plasma LDL, IDL or VLDL level remains elevated with the phase I diet.[116] Reductions in cholesterol levels attained with these diets have fallen somewhat short of the expected decreases of 0.8 to 1.0 mmol/L extrapolated from metabolic studies by means of standard equations.[102,117] The combination of an increase in the polyunsaturated:saturated fat ratio to 0.8 and a reduction of the daily cholesterol intake to 400 mg has been reported to reduce the plasma total cholesterol level by about 0.4 mmol/L.[111] However, the use of fat-modified diets, especially when combined with the synergistic effects of smoking cessation, increased exercise and other improvements in lifestyle, can usefully lower the plasma cholesterol level as well as the CHD risk.[102-104,107] When advising patients to decrease their fat intake physicians

should strongly emphasize a reduction in foods that contain substantial amounts of the saturated fatty acids known to increase cholesterol levels in humans: lauric acid (C-12), myristic acid (C-14) and especially palmitic acid (C-16).[114,118] Subjects with elevated triglyceride levels may require special emphasis on restriction of energy, alcohol and fat intake.

It is frequently necessary for physicians to devote 3 to 6 months to dietary counselling and monitoring of plasma lipid levels before they can decide whether dietary intervention alone is sufficient.[47] Other risk factors, such as hypertension, smoking and diabetes, should be detected and treated. The presence of such risk factors often indicates a need to treat the dyslipoproteinemia aggressively with medication instead of using diet alone.

Drug therapy

Hypercholesterolemia: Failure of dietary measures alone over 3 to 6 months to lower very high LDL (or total) cholesterol levels to normal or target values (Table 2) is an indication to begin drug therapy, especially in adults. This period may be extended if diet modification results in a favourable downward trend in the LDL-C level. Drug therapy may also be started in patients whose fasting plasma LDL-C level remains high despite dietary therapy,[15,113] particularly in men and in the presence of CHD or other important risk factors for CHD (e.g., a low HDL-C level). The potential benefits, the need for compliance for clinical and biochemical follow-up and the known side effects of each drug should be explained to patients.

Table 4: Minimum dietary prescription for hypercholesterolemia*

Reduce intake of fats, especially saturated fats, from both animal and plant sources by substituting complex carbohydrates from a variety of foods containing dietary fibre. Goal of less than 30% of energy from fat and less than 10% from saturated fat.

Polyunsaturated fats may provide up to 10% of energy intake.

Reduce cholesterol intake by restricting foods high in cholesterol, such as egg yolks, butter, organ meats and shrimp; cholesterol intake less than 300 mg/d in selected patients.

Gradually reduce total energy intake to correct obesity, if present.

The following is a partial list of the most important specific recommendations for desirable foods and their preparation.

- Consume low-fat milk, meats and cheeses instead of high-fat products.
- Consume whole-grain breads, muffins, brown rice, split peas, kidney beans and lentils instead of white bread, white rice, donuts, cookies and other commercially prepared foods.
- Consume soft margarine instead of butter, yoghurt instead of sour cream and egg whites instead of whole eggs.
- Bake, broil, microwave, barbeque or roast instead of frying, and substitute vegetable oils for lard in cooking or baking.
- Consume fresh and dried fruits such as prunes, raisins and apricots instead of canned fruits.

*Modified from reference 16.

Bile-acid-binding resins have a long record of efficacy and safety in lowering cholesterol levels[111,113,119] but are often hard to tolerate because of gastrointestinal symptoms. Drugs such as warfarin, digoxin and thyroxine, whose absorption can be affected by bile-acid-binding resins, should be taken 1 hour before or 2 hours after these agents. Nicotinic acid is inexpensive, lowers LDL and triglyceride levels and elevates HDL levels[15,113,120] but may be difficult to tolerate owing to flushing and gastrointestinal symptoms. The new HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (e.g., lovastatin and pravastatin) generally appear to be readily tolerable and effective;[119] however, data on long-term safety are required, and liver function needs to be monitored closely during the first 15 months of therapy and periodically thereafter. Caution is advised about the concurrent use of lovastatin with cyclosporine, nicotinic acid or gemfibrozil because of the risk of elevated creatine kinase levels or even rhabdomyolysis. Combination drug therapy with bile-acid-binding resins and HMG-CoA reductase inhibitors can markedly lower the LDL level.[121] Combined therapy may be cheaper and have fewer side effects than a large dose of a single drug.

Type III hyperlipoproteinemia: Type III hyperlipoproteinemia is uncommon and involves excessive amounts of IDL in the plasma. The initial objective of therapy should be to reduce elevated levels of fasting plasma cholesterol and triglycerides, bringing them within the target or normal limits by dietary means. However, if dietary measures, including weight loss, fail to lower the levels effective therapy can generally be accomplished with fibric acid derivatives such as gemfibrozil.[18,122]

Hypertriglyceridemia: Failure of diet modification, with concomitant restriction of alcohol intake to less than 50 ml/d, substitution of complex carbohydrates for simple sugars and weight loss (if there is obesity) to lower triglyceride levels below 4 mmol/L in a patient with CHD, a strong family history of CHD, elevated LDL-C levels, low HDL-C levels or other risk factors for CHD is an indication for prescribing triglyceride-lowering drugs (e.g., gemfibrozil). However, weight loss,[123] like hypotriglyceridemic drugs,[124] sometimes elevates previously low levels of LDL-C in hypertriglyceridemic pa-

tients. This could lead to the need for simultaneous therapy to lower LDL levels.

Therapy for hypoalphalipoproteinemia

The causes of hypoalphalipoproteinemia have been summarized by Stein.[125] Therapeutic options for increasing the plasma HDL cholesterol level include hygienic and pharmacologic means,[126] such as changing or stopping treatment with the offending medication (e.g., certain antihypertensives,[92] oral contraceptives[93] and retinoids[94]), weight loss, smoking cessation, regular vigorous exercise, treatment with hypotriglyceridemic drugs if the triglyceride level is greater than 4 mmol/L and hormonal replacement therapy among postmenopausal women. Hormonal replacement therapy among estrogen-deficient and progesterone-deficient postmenopausal women may also lower the risk of CHD,[127-130] in part by lowering LDL levels and raising HDL levels. Oral contraceptive and hormonal replacement therapy should be aimed at minimizing undesirable effects on lipoproteins (such as depression of HDL and elevation of LDL levels) through the use of the lowest effective dosage of triglyceride-lowering progestin.[93,131]

Therapy for hyperapo B

The variable lipid phenotype of hyperapo B primarily necessitates measures to reduce the number of apo B particles. This can be achieved with niacin or lovastatin combined with colestipol. Such therapy has also been found to elevate the HDL-C level, to cause regression in atherosclerosis and to reduce illness from CHD.[120]

Patient follow-up

The success of any lipid-regulating therapy that entails significant changes in lifestyle necessarily depends on adequate patient follow-up and continuing motivational support. Initially, physicians may have to examine patients as often as every few weeks to establish the correct therapy by assessing the response of the plasma lipids to the chosen regimen. Subsequently, follow-up every 6 to 12 months (or even every 2 years in compliant patients) may be sufficient.[132] However, follow-up should be indefinite to allow the earliest possible implementation of the safest, simplest and most efficacious therapy.

Summary

Table 2 summarizes our recommendations for detecting and treating patients with high-risk lipoprotein profiles and synthesizes them with those of the Canadian Consensus Conference on Cholesterol[16] to provide a comprehensive approach. In accord with others[16,22,133] we recommend age-related diagnostic and therapeutic criteria to accommodate the increase in lipoprotein levels with increasing age and the observation that lipoprotein levels tend to track in the same quartile over time.[97] The most appropriate criteria available are needed for the careful targeting of patients to identify those most susceptible to CHD, those most likely to benefit from therapy and the otherwise naturally concerned family members (expected to be 50% of the family) who have not inherited dyslipoproteinemia despite a family history of myocardial infarction attributable to such disorders as familial hypercholesterolemia[20,21] or familial combined hyperlipidemia.[35,37] It is appropriate to test children and both young men and women under 35 years of age for these disorders without additional evidence of risk beyond the family history. Heterozygous familial hypercholesterolemia is known to increase the risk of myocardial infarction about 20-fold.[35] The diagnosis and treatment of such a devastating disorder should occur in its presymptomatic stage.[134] Timely therapy could save thousands of lives annually, prevent much of the illness intrinsic to CHD, coronary artery bypass surgery and heart transplantation, and save many millions of dollars in earnings and industrial production in Canada alone.

Atherosclerosis prevention is a field in rapid evolution. More specific and sensitive diagnostic tests under evaluation[63-72] may replace current tests. More tolerable and effective medication for lowering LDL levels whose safety is currently being tested may become first-line therapy for patients unable to achieve target levels of lipoprotein lipids with diet alone.

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Conferences

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Oct. 11-12, 1990: Histopathologic Diagnosis of Inflammatory and Neoplastic Skin Diseases: Assessment of Patterns and Silhouettes
Halifax Sheraton
Dr. Noreen Walsh, Department of Pathology, Victoria General Hospital, Rm. 721, D.J. MacKenzie Building, 1278 Tower Rd., Halifax, NS B3H 2Y9; (902) 428-3897

Oct. 11-14, 1990: Canadian Pain Society (IASP Chapter) Annual Meeting
London, Ont.
Ms. Inese Kramins, Local Arrangements Committee, Department of Psychology, University of Western Ontario, London, Ont. N6A 5C2

Oct. 12-14, 1990: Freud and the History of Psychoanalysis
Trinity College, University of Toronto
Dr. Andrew Brink or Herma Joel, 300 Larkin Building, Trinity College, 6 Hoskin Ave., Toronto, Ont. M5S 1H8; (416) 978-8454

Oct. 16-20, 1990: Canadian Cardiovascular Society 43rd Annual Meeting
World Trade and Conference Centre, Halifax
Secretariat, 401-360 Victoria Ave., Westmount, PQ H3Z 2N4; (514) 482-3407

Oct. 17-20, 1990: Canadian Group Psychotherapy Association 11th Annual Conference
Minto Place Suite Hotel, Ottawa
Dr. Allen A. Surkis, 675-1650 Cedar Avenue, Montreal, PQ H3G 1A4; (514) 934-8010

Le 18-20 oct. 1990: 11e congrès annuel de la Société québécoise de biochimie clinique
Hôtel Château Mont Sainte-Anne, Beaupré, PQ
Pierre Douville, président du Comité organisateur, Service de biochimie, Hôtel-Dieu de Québec, 11 Côte du Palais, Québec, PQ G1R 2J6; (418) 691-5135

Oct. 19-20, 1990: Canadian Art Therapy Association Conference
Academy of Medicine, Toronto
Abstract deadline is July 30, 1990.
Canadian Art Therapy Association Conference Committee, 216 St. Clair Ave. W, Toronto, Ont. M4V 1R2; (416) 924-6221

Oct. 22-24, 1990: Institute for the Prevention of Child Abuse 5th National Conference — Focus on Child Abuse: Stop the Hurt
Delta Chelsea Inn, Toronto
Note: originally scheduled for Sept. 24-26, 1990
Consultation and Conferences Services, Institute for the Prevention of Child Abuse, 25 Spadina Rd., Toronto, Ont. M5R 2S9; (416) 921-3151, FAX (416) 921-4997

Oct. 26-28, 1990: Canadian Sex Research Forum 17th Annual Meeting
Whistler Conference Centre, Whistler, BC
Shirley A. Halliday, executive director, Canadian Sex Research Forum, Sexual Medicine Unit, University Hospital-Shaughnessy Site, 4500 Oak St., Vancouver, BC V6N 3N1; (604) 875-2027

Oct. 31-Nov. 3, 1990: American Medical Writers Association 50th Annual Conference
Biltmore Hotel, Los Angeles
American Medical Writers Association, 9650 Rockville Pike, Bethesda, MD 20814; (301) 493-0003

Nov. 1-4, 1990: Quebec Association of Urologists 15th Annual Meeting
Four Seasons Hotel, Montreal
Ms. Jacqueline Deschênes, Quebec Association of Urologists, 2 Complexe Desjardins (East Tower), Door 3000, PO Box 216, Stn. Desjardins, Montreal, PQ H5B 1G8; (514) 844-9523

Dec. 1-2, 1990: Society of Toxicology of Canada 23rd Annual Symposium
Holiday Inn Crowne Plaza, Montreal
Dr. Gordon Krip, executive director, Society of Toxicology of Canada, PO Box 517, Beaconsfield, PQ H9W 5V1

Feb. 26-Mar. 2, 1991: 7th International Hypoxia Symposium — High Altitude Physiology and Medicine (sponsored by McMaster University and the Arctic Institute of North America in conjunction with the International Society for Mountain Medicine)
Chateau Lake Louise, Lake Louise, Alta.
Abstract deadline is Nov. 1, 1990.
Ingrid Ellis, conference coordinator, Rm. 1M10, McMaster University, 1200 Main St. W, Hamilton, Ont. L8N 3Z5; (416) 525-9140, ext. 2182