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Recommendations for the Management of Dyslipidemia and the Prevention of Cardiovascular Disease: 2006 Update

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There is ongoing evidence that lipid lowering is important in reducing cardiovascular risk. The first Canadian guidelines for dyslipidemia management were released in 1988 by the Working Group on Hypercholesterolemia and other Dyslipidemias,[1] with subsequent updates in 2000[2] and 2003.[3] The latest guidelines – to be published in 2006 – will reflect findings from recent clinical trials, as well as research on new markers of risk. These guidelines are the subject of this issue of *Cardiology Rounds*.

The proposed recommendations to the guidelines were designed to provide primary care physicians and internists with a tool for evaluating a patient's risk of coronary artery disease (CAD) as a component of a routine health assessment.

Like the 2003 guidelines, in the 2006 guidelines, patients are stratified into 3 different coronary artery risk categories using the Framingham Study equations (high, moderate, and low), with 2 treatment targets for each risk group (see Table 1 for Framingham calculations):[4]

- low-density lipoprotein cholesterol [LDL-C], and
- the total cholesterol:high-density lipoprotein cholesterol [HDL-C] ratio.

This is in contrast to the US National Cholesterol Education Panel (NCEP) Adult Treatment Panel III (ATP III) guidelines that use other non-HDL-C parameters (eg, sum of very low-density lipoprotein cholesterol [VLDL-C] and LDL-C levels) as its secondary therapeutic goal, especially in patients with the metabolic syndrome.[5] The new Canadian lipid target levels are outlined in Table 2.

The major changes from previous guidelines are in the highest risk category, where the new target LDL-C is <2.0, instead of <2.5, and in the lowest risk category, where the new target LDL-C is <5.0, instead of <4.5. As in the 2003 guidelines, there is no discrete target for serum triglyceride levels. The optimal plasma triglyceride concentration is <1.7 mmol/L. Treatment of hypertriglyceridemia is required in most patients to achieve the target total cholesterol:HDL-C ratio. Severe hypertriglyceridemia (>10.0 mmol/L) should be treated because it is a risk factor for pancreatitis.

The new Canadian guidelines are similar to the ATP III guidelines[6] that suggest medical therapy for high-risk cardiac patients, with an LDL-C goal of <2.6 mmol/L or, in very high-risk patients, ie, those with CAD and diabetes, an LDL-C goal of <1.8 mmol/L.

Screening guidelines

The following groups need to be screened (Class IIa, level C):

- Men aged >40 years; postmenopausal women aged >50 years)
- Patients with diabetes (DM), hypertension, abdominal obesity
- Patients with a family history of premature CAD
- Patients with a history of dyspnea, erectile dysfunction, kidney disease, systemic lupus erythematosus, or atherosclerosis

At the discretion of the physicians, patients of any age may be screened, especially if lifestyle changes are indicated. These screening guidelines have not been changed from 2003.

Risk assessment

A number of risk scores are available (PROCAM, Heartscore, Quebec Cardiovascular), but an adjusted Framingham equation is used in the Guidelines to calculate a given patient's 10-year risk of CAD. Since the 2003 guidelines revision, the Canadian guidelines have adopted the NCEP ATP-III's variation of the Framingham equations. It adjusts for certain risk factors, such as total cholesterol level,

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Table 1: Modified Framingham Risk Score

Model for estimating the 10-year risk of CAD in a patient without DM or clinically evident cardiovascular disease (CVD), using data from the Framingham Heart Study

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

smoking status, age, and the effect of treatment on blood pressure measurement.

Factors influencing risk assessment

Genetics

The genetics of CAD are complex. A recent study revealed that an unambiguous family history of premature CAD (defined as CAD at age <55 years for father and <65 years for mother), even when corrected for other risk factors, increases risk 2-fold in men and 1.7-fold in women.[7] Thus, a positive family history in a first-degree relative should alert the clinician to increase a patient's risk category to a higher level. This is the same as the 2003 guidelines.

Table 2: Canadian risk categories and target lipid levels

Risk level*		LDL-C (mmol/L)	Total cholesterol: HDL-C ratio
High	10-year risk ≥20%	<2.0	<4.0
		Class I, Level A	Class IIa, Level C
Moderate**	10-year risk 10%-19%	<3.5	<5.0
		Class IIb, Level C	Class IIb, Level C
Low	10-year risk <10%	<5.0	<6.0
		Class IIb, Level C	Class IIb, Level C

* As calculated by the Framingham Study equations
** Excludes patients with family history

Metabolic syndrome

Currently, there is no unified definition for "metabolic syndrome." The American ATP III criteria[6] define metabolic syndrome if ≥3 of the following are present:

- waist circumference: men >102 cm, women >88 cm
- plasma triglycerides level ≥1.7 mmol/L
- HDL-C: men ≤1.03 mmol/L, women ≤1.30 mmol/L
- BP ≥130/85 mm Hg
- Serum glucose ≥6.1 (5.6) mmol/L

Tanko et al demonstrated that the presence of an enlarged waist (≥88 cm) and elevated triglycerides (≥1.45 mmol/L) in women was associated with a 4.7-fold (95% CI, 2.2-9.8; $P<0.001$) increased risk for fatal cardiovascular events. The presence of the metabolic syndrome, as defined above by the NCEP, was associated with a 3.2-fold (95% CI, 1.5-6.5; $P<0.001$) increased risk[8] (Figure 1).

In spite of these new data, it is felt that cardiovascular risk is reliably and adequately predicted by the Framingham equations. Furthermore, diagnosis of metabolic syndrome does not necessarily lead to intervention other than lifestyle-modifying therapies. Individual risk factors should thus be evaluated for global cardiovascular risk.

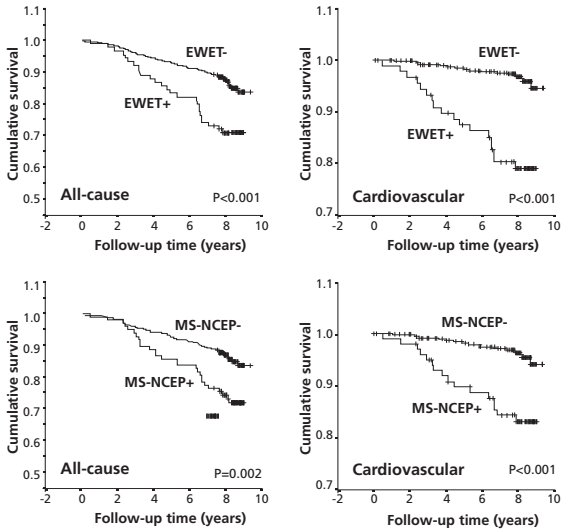
Obesity

Various definitions exist, including body mass index (BMI), waist circumference, and waist:hip ratio. It has been shown that abdominal obesity is associated with small dense LDL particles, elevated apolipoprotein B levels, reduced HDL-C, insulin resistance, and hypertension.[3] It is felt that the waist:hip ratio is the best predictor for CAD, with normal being <0.9 for men and <0.8 for women. The Canadian guidelines do not specifically recommend using waist:hip ratio as a clinical screening tool. The NCEP ATP-III uses these cut-off values for waist circumference: 102 cm for men and 88 cm for women.[6]

Novel risk markers

Currently, there are inadequate data to support routine measurements of apolipoprotein B (ApoB), ApoB/ApoA1, lipoprotein a (Lp(a)), homocysteine, and high-sensitivity C-reactive protein (hsCRP). This is a change from the 2003 guidelines, which stated that ApoB concentrations could be used to identify patients with moderate hypertriglyceridemia.

Figure 1: Enlarged waist and elevated triglycerides (EWET) and metabolic syndrome as defined by NCEP (MS-NCEP) predicts cardiovascular risk[8]



Epidemiological data have demonstrated a role for elevated homocysteine levels in determining risk of CAD,[9] but randomized controlled trials examining homocysteine-lowering therapies were not available at the time of the 2003 guidelines. Three new trials have been published since then.

The HOPE-too trial randomly assigned 5522 patients, aged >55 years with vascular disease or diabetes, to 2.5 mg folate, 50 mg vitamin B_6, and 1 mg vitamin B_{12} versus placebo for an average of 5 years.[10] Mean plasma homocysteine levels decreased by 2.4 mmol/L in the treatment group, but did not significantly decrease the risk of cardiovascular death (RR 0.96, 95% CI, 0.81-1.13).

The VISP trial recruited 3680 stroke patients to receive either a high dose regimen of 25 mg vitamin B_6, 0.4 mg vitamin B_{12}, and 2.5 mg folate, or a low-dose regimen of 200 µg vitamin B_6, 6 µg vitamin B_{12}, and 20 µg of folate.[11] Mean plasma homocysteine levels decreased by 2 mmol/L in the high-dose group, but there was no treatment effect on any endpoint at 2 years.

The NORVIT trial included 3749 patients within 7 days of an acute myocardial infarction (MI) and patients were randomized to 4 groups:

- 0.8 mg folate, 0.4 mg vitamin B_{12}, and 40 mg vitamin B_6
- 0.8 mg folate and 0.4 mg vitamin B_{12}
- 40 mg vitamin B_6
- placebo.[12]

The mean total homocysteine level was lowered by 27% in the group given folate and vitamin B_{12}, but it did not affect the primary endpoint at 40 months of recurrent MI, stroke, and sudden death due to CAD. In the group given folate, vitamin B_{12}, and vitamin B_6, there was a trend towards increased risk (RR 1.22, 95% CI, 1.00-1.50, P=0.005).

In view of the above neutral results, the new guidelines no longer recommend the routine use of folate (1-2 mg) and vitamin B_{12} (1 mg) to lower homocysteine levels in patients with hyperhomocysteinemia. For patients in the moderate-risk categories, there may still be a role for further risk stratification by examining their genetic markers (eg, Lp(a) and hsCRP).

Table 3: Major statin studies

Study	4S[15]	CARE[16]	LIPID[17]	HPS[13]	TNT[14]	IDEAL[20]
N	4444	4159	9014	20536	10001	8888
% men	81	86	83	75	81	81
Age	35-69	21-75	31-75	40-80	29-76	30-80
% smokers	26	21	10	14	13	20
% HTN	26	43	41	41	54	33
% DM	4.5	14	9	29	15	12
Medications:						
ASA	37	83	82	63	88	79
ß-blocker	57	40	47	26	55	75
Ca-blocker	31	39	35	–	26	19
LDL-C (mmol/L)	4.9	3.6	3.9	3.4	2.5	3.1

Recent lipid trials

Trials in the modern era recruit patients who are already being treated adequately with other therapies (Table 3), to the point where no treatments are beginning to reach the "asymptote" of benefit. It appears that absolute reductions in LDL-C correlate with reductions in major coronary events; however, all-cause mortality does not change. Recent clinical trials indicate that, for every 1% decrease in LDL-C, there is a relative risk reduction in major coronary heart disease events by approximately 1%.[6] This relationship holds true for LDL-C levels below 2.6 mmol/L, as suggested by the Heart Protection Study (HPS) data[13] (Figure 2).

A number of new clinical trials support "the-lower-the-better" therapy for LDL-C. In the Treating to New Targets (TNT) study,[14] 10,001 patients with clinically evident coronary heart disease (CHD) and LDL-C <3.4 mmol were assigned to 10 mg or 80 mg of atorvastatin per day, with a median follow-up of 4.9 years. The aggressive lipid-lowering group had a 2.2% absolute reduction in the rate of major cardiovascular events (defined as death from CHD, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) and a 22% relative reduction in risk was observed (HR 0.78, 95% CI, 0.69-0.89, P<0.001), with a mean LDL-C of 2 mmol/L vs. 2.6 mmol/L (Figure 3).

Figure 2: Event rates plotted against LDL cholesterol levels during statin therapy in secondary-prevention studies[13]

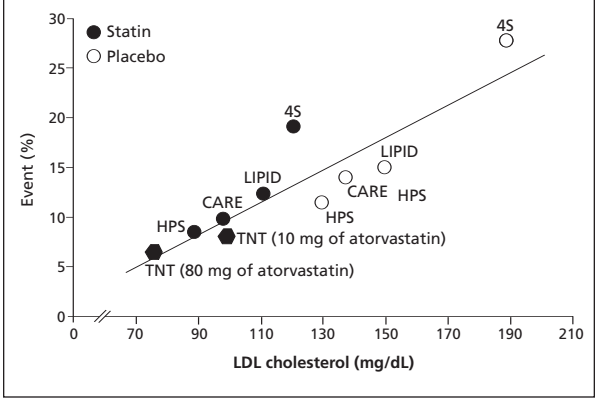


Figure 3: Event rate in TNT trial[14]

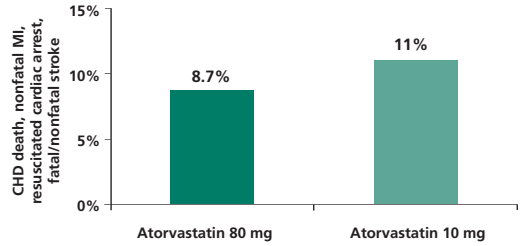
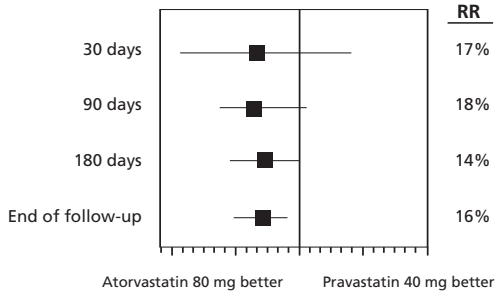


Figure 4: Primary endpoint over time in PROVE-IT[18]



The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT TIMI-22)[18] enrolled 4162 patients recently hospitalized with acute coronary syndrome (ACS), with a mean follow-up of 24 months. They were randomized to either 80 mg atorvastatin or 40 mg pravastatin. The primary endpoint was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The median LDL-C level achieved during treatment was 2.46 mmol/L in the standard-dose pravastatin group and 1.60 mmol/L in the high-dose atorvastatin group ($P<0.001$). Aggressive lipid-lowering with 80 mg atorvastatin versus 40 mg pravastatin provided a 3.9% absolute reduction and 16% relative reduction in death, cardiovascular events, and stroke at 2 years ($P=0.005$) (Figure 4). Prior trials have demonstrated that pravastatin 40 mg reduces the risk for major coronary events by approximately 27%.[19] The results of PROVE-IT suggest that more intensive LDL-C lowering therapy (ie, an optional target LDL-C of <1.8 mmol/L) may be beneficial in patients with ACS. However, it must be noted that, in the subgroup with LDL-C <3.22 mmol/L, the benefit of atorvastatin over pravastatin was not statistically significant.

The Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL)[20] trial recruited 8888 patients aged <80 years with a previous MI; median follow-up was 4.8 years. Treatment with 80 mg atorvastatin was associated with a directional, but nonsignificant ($P=0.07$), reduction in the primary composite endpoint of major coronary events (defined as coronary death, confirmed nonfatal AMI, or cardiac arrest with resuscitation) compared with 20 mg simvastatin at 5-year follow-up.[20] However, atorvastatin 80 mg did reduce the risk of other secondary endpoints such as nonfatal AMI (HR 0.83, 95% CI, 0.71-0.98, $P=0.02$), major cardiovascular events (HR 0.87, 95% CI, 0.77-0.98, $P=0.02$), and any coronary event (HR 0.84, 95% CI, 0.76-0.91, $P<0.001$).

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA), which was stopped early after 3.3 years of follow-up, 10,305 hypertensive patients, aged 40-79 years with ≥3 cardiovascular risk factors, and nonfasting total cholesterol 6.5 mmol/L, who were not currently taking a fibrate or a statin, were randomly assigned to atorvastatin (10 mg) or placebo. Atorvastatin 10 mg reduced nonfatal MI or CHD death by 1.1% with a relative risk reduction of 36% (HR 0.64, 95% CI, 0.50-0.83, $P=0.0005$).[21] This benefit was apparent within the first year of follow-up. Atorvastatin lowered total serum cholesterol by about 1.3 mmol/L compared with placebo at 12 months, and by 1.1 mmol/L after 3 years of follow-up. The authors concluded that LDL lowering with atorvastatin may potentially reduce risk for cardiovascular disease (CVD) in primary prevention in patients with multiple CVD risk factors.

Diabetes

Eighty per cent of the total mortality in patients with diabetes can be attributed to atherosclerosis and, of this 80%, 75% is attributed to CHD and 25% to cerebral or peripheral vascular disease. More than 75% of all hospitalizations for diabetic complications are related to atherosclerosis and >50% of patients with newly diagnosed type 2 diabetes have CHD. Taking data from the FIELD,[22] CARDS,[23] and UKPDS[24] studies, the 5-year CV risk is ~5%-10%, which extrapolates into a ~10%-20% 10-year risk.

In the FIELD trial, 9795 patients with type 2 diabetes with total cholesterol levels of 3-6.5 mmol/L and total cholesterol: HDL-C ratios of ≥4 or plasma triglycerides of 1-5 mmol/L were assigned to 200 mg of micronized fenofibrate or placebo and were followed for over 5 years.[22] Patients assigned to fenofibrate had a nonsignificant reduction in coronary events (defined as CHD death or nonfatal MI) (HR 0.89, 95% CI, 0.75-1.05, $P=0.16$), less progression to albuminuria ($P=0.002$), and less retinopathy needing laser treatment (5.2% vs. 3.6%, $P=0.0003$). Total mortality was higher in the fenofibrate group (7.3% versus 6.6%, $P=0.18$). This was considered a neutral study and the results do not support the use of fibrates for CAD prevention in diabetics.

The CARDS[23] trial enrolled 2838 patients with diabetes who had no history of CVD, an LDL-C of ≤4.14 mmol/L, triglycerides ≤6.78 mmol/L, and at least one of the following: retinopathy, albuminuria, smoking, or hypertension. The trial was stopped 2 years early after a median follow-up of 3.9 years. Patients were randomized to atorvastatin 10 mg daily or placebo. The treatment group had a 37% relative risk reduction in major vascular events (95% CI, 7% to 52%, $P=0.001$) and a nonsignificant 27% relative risk reduction in death rate (95% CI, -48% to 1%; $P=0.059$). The authors concluded that atorvastatin was safe and efficacious for the primary prevention of CVD events in patients with type 2 diabetes who do not have high LDL-C.

Table 4: Lipid-lowering medications

Generic name	Trade name	Recommended dose range
Statins		
Atorvastatin	Lipitor	10-80 mg
Fluvastatin	Lescol	20-80 mg
Lovastatin	Mevacor	20-80 mg
Pravastatin	Pravachol	10-40 mg
Rosuvasatin	Crestor	10-40 mg
Simvastatin	Zocor	10-80 mg
Bile acid sequestrants		
Cholestyramine	Questran	2-24 g
Colestipol	Colestid	5-30 g
Cholesterol absorption inhibitors		
Ezetimibe	Ezetrol	10 mg
Fibrates*		
Bezafibrate	Bezalip	400 mg
Fenofibrate	Lipidil	67-200 mg
Gemfibrozil	Lopid	600-1200 mg
Niacin†		
Nicotinic acid		1-3 g

* Avoid in patients with renal insufficiency
† Use with caution in patients with diabetes or glucose intolerance

With few exceptions, all adult patients with diabetes should be stratified into the moderate-to-high 10-year CV risk category; this is a new recommendation in the 2006 guidelines.

Treatment options

All patients should begin with diet, exercise, and smoking cessation, followed by lipid-lowering medications as outlined in Table 4. Most patients should be able to achieve target LDL-C levels with statin monotherapy. However, some may need combination therapy, including bile acid sequestrants and cholesterol absorption inhibitors. Figure 5 compares the relative efficacy of 4 common statins at various doses.

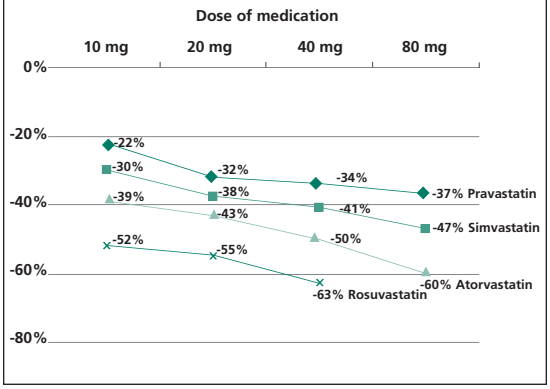
HDL therapy

The clinical trials outlined in Table 5 demonstrate the rationale for increasing HDL-C. Niacin also increases HDL; however, the evidence for this effect is weak and niacin is associated with intolerable side effects (eg, flushing, peptic ulcers, hepatic toxicity, and glucose intolerance). Statins and fibrates are weakly efficacious for increasing HDL. Other drugs in development include cholesteryl ester-transfer protein (CETP) inhibitors (torcetrapib), LxR/RxR agonists (ABCA1), PPAR-agonists, and SR-B1 modulators.

Table 5: Trials that increased HDL-C

Trial	Treatment	Endpoints	N	% HDL-C change	Relation to CV endpoints
4S[25]	Simvastatin 20-40 mg	Total mortality	4444	+8%	P= 0.001
CARE[26]	Pravastatin 40 mg	CHD mortality, nonfatal MI	4159	+5%	NS
LIPID[27]	Pravastatin 40 mg	CHD mortality	9014	+5%	NS

Figure 5: Efficacy of currently available statins



Prevention of CAD

There are 5 main therapeutic options:

- Lifestyle changes, including smoking cessation, diet, target BMI<25, and exercise
- LDL-C lowering: target LDL <2 mmol/L in high risk patients
- ASA
- Beta-blockers
- ACE inhibitors in high-risk patients, especially those with decreased ejection fraction.

Currently there is no evidence to support the use of neutraceuticals and fish oils for CAD prevention.

Conclusion

Patients should be individually risk-stratified to determine their needs and therapeutic goals. The 2006 guidelines are more aggressive in treating high-risk patients with pharmacotherapy. Patients at intermediate risk require better risk stratification, while, for low-risk subjects, drug therapy should be avoided except for those with genetic lipoprotein disorders. Lifestyle changes, such as smoking cessation, diet, weight loss, and exercise, should be emphasized for all patients.

These Rounds were originally presented by Dr. Jacques Genest at St. Michael's Hospital Cardiology Rounds, April 10th 2006

References

1. Canadian Consensus Conference on Cholesterol: final report. The Canadian Consensus Conference on the Prevention of Heart and Vascular Disease by Altering Serum Cholesterol and Lipoprotein Risk Factors. *CMAJ* 1988;139:1-8.
2. Fodor JG, Frohlich JJ, Genest JJ, Jr., McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000;162:1441-7.
3. Genest J, Frohlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ* 2003;169:921-4.

4. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100:1481-92.
5. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm.2006. Accessed May 30, 2006.
6. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
7. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., Levy D, Murabito JM, Wang TJ 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.
8. Tanko LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation* 2005;111:1883-90.
9. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002;288:2015-22.
10. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567-77.
11. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565-75.
12. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354: 1578-88.
13. 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.
14. 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.
15. Grodos D, Tonglet R. Scandinavian simvastatin study (4S). *Lancet* 1994;344:1768.
16. Sacks FM, Pfeffer MA, Moye L, et al. Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the Cholesterol and Recurrent Events trial (CARE). *Am J Cardiol* 1991;68:1436-46.
17. LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002;359:1379-87.
18. 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.
19. Sacks FM, Tonkin AM, Shepherd J, et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: The Prospective Pravastatin Pooling Project. *Circulation* 2000;102:1893-900.
20. Pedersen TR, Faergeman O, Kastelein JJ, 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.
21. 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.
22. 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.
23. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96.
24. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-53.
25. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97:1453-60.
26. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
27. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349-57.

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