Lipid-lowering update 2001

Aggressive new goals

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abstract

OBJECTIVE To review the central role of cholesterol in coronary artery disease (CAD), underscore the need for identifying patients at high risk of CAD, and discuss treatment of dyslipidemias.

QUALITY OF EVIDENCE Current literature (1995-2000) was searched via MEDLINE using the MeSH headings "cholesterol," "risk reduction," and "statins." Recommendations in this paper are based mainly on the results of large randomized controlled trials. Preference was given to more recent articles, clinically relevant articles, and landmark clinical trials.

MAIN MESSAGE Lipid lowering, and specifically low-density lipoprotein lowering, has been repeatedly shown in large clinical trials to improve survival dramatically and reduce cardiac events in both primary and secondary prevention. Identifying those at highest risk for future cardiac events is critical because these patients will benefit most from aggressive modification of risk factors. The definition of high risk has been expanded to include patients with diabetes mellitus and peripheral vascular disease, as well as those with established CAD. A full lipid profile is required for these patients to assess risk and develop a lipid-lowering strategy with proven effectiveness.

CONCLUSION With the advent of powerful, efficacious, and well tolerated cholesterol-modifying therapies, lipid normalization should be a mandate for all physicians caring for patients with established CAD and patients at risk of developing CAD.

résumé

OBJECTIF Examiner le rôle déterminant du cholestérol dans les coronaropathies, insistant sur la nécessité d'identifier les personnes à risque élevé de coronaropathies, et discuter du traitement de la dyslipidémie.

QUALITÉ DES DONNÉES Une recension des ouvrages récents (1995-2000) a été effectuée dans MEDLINE à l'aide des rubriques MeSH en anglais pour « cholestérol », « réduction du risque » et la famille des « statines ». Les recommandations dans cet article se fondent principalement sur les résultats d'essais aléatoires contrôlés d'envergure. Nous avons accordé la préférence aux articles plus récents, aux articles pertinents sur le plan clinique et aux essais cliniques décisifs.

PRINCIPAL MESSAGE Il a été démontré à plusieurs reprises dans des essais cliniques d'envergure que la réduction de lipides, en particulier celle de lipoprotéines de basse densité, améliore considérablement les chances de survie et réduit les incidents cardiaques tant dans la prévention primaire que secondaire. Il est crucial d'identifier les personnes à risque le plus élevé de subir des incidents cardiaques futurs, puisque ces patients bénéficieront le plus d'une modification radicale des facteurs de risque. La définition de risque élevé a été élargie pour inclure les patients atteints de diabète sucré et d'acrosyndrome, ainsi que ceux ayant une coronaropathie diagnostiquée. Un profil lipidique complet est nécessaire pour évaluer le risque chez ces patients et élaborer une stratégie hypolipidémiante d'une efficacité éprouvée.

CONCLUSION Avec l'avènement de thérapies hypolipidémiantes puissantes, efficaces et bien tolérées, la normalisation du taux lipidique devrait constituer un devoir pour tous les médecins qui soignent des patients atteints de coronaropathie confirmée et ceux qui présentent un risque d'en souffrir.

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Cet article a fait l'objet d'une évaluation externe.
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Cardiovascular disease remains the number one cause of mortality in Canada, with more than 80 000 deaths yearly.[1] The global cardiovascular disease burden is increasing, causing more than 15 million deaths annually, and is projected to account for more than 40% of all deaths by the year 2020.[2]

Although advances in thrombolytic therapy and percutaneous revascularization continue to improve survival of patients with acute myocardial infarction, overall mortality remains more than 50%, underscoring the need for preventive strategies for this disease. Central to the pathogenesis of atherosclerosis is the lipid-rich plaque caused by deposition of cholesterol in arterial walls. Large clinical trials of both primary and secondary prevention have clearly demonstrated dramatic reductions in coronary events and cardiovascular mortality with lowering of serum low-density lipoprotein cholesterol (LDL-C)[3-7] (**Figure 1**[3-8]). Nonetheless, hyperlipidemia remains underdiagnosed and undertreated in Canada, with only one third of high-risk patients having lipids measured and fewer than 10% receiving treatment.[9] A more aggressive stance on lipid lowering is needed, particularly for high-risk patient groups.

Quality of evidence

A MEDLINE search from 1995 to 2000 was conducted using the MeSH headings "cholesterol," "risk reduction," and "statins." The search was limited to English-language articles. In addition, bibliographies of the articles were used to find additional pertinent articles. Preference was given to more recent articles, clinically relevant articles, and landmark clinical trials. Recommendations in this paper are based mainly on results of large randomized controlled trials and expert consensus opinion and are compatible with recently published Canadian lipid guidelines.[10]

Identifying high-risk patients

Independent risk factors for coronary artery disease (CAD) are well established and include any cigarette smoking, elevated blood pressure, diabetes mellitus (DM), advancing age, high LDL-C and total cholesterol levels, and low serum high-density lipoprotein cholesterol (HDL-C) levels. "Predisposing" factors augment the major risk factors but lack an independent causative relation to CAD. These factors include premature family history (first-degree relative younger than 65 years for women and younger than 55 years for men), abdominal adiposity (waist more than 100 cm for men and more than 90 cm for women), sedentary lifestyle, postmenopausal status, and personality factors.

Risk levels for given patients can be calculated using the Framingham Tables to determine target lipid values,[11] which have been described in the latest report of the Canadian Working Group on Dyslipidemia.[10] No such calculations are necessary, however, for patients with established CAD, DM, or peripheral vascular disease (PVD), because they are automatically at high risk for the disease and require aggressive management of all cardiac risk factors, including hyperlipidemia.

It is vital that all patients with established CAD, including those who have had myocardial infarctions (MI), have a 12-hour fasting lipid profile measurement, including total cholesterol, LDL-C, HDL-C, and triglyceride (TG) levels. Because cholesterol levels are depressed for several weeks after onset of an acute coronary event, lipid measurements are often delayed or forgotten. To avoid having post-MI patients with hyperlipidemia "fall through the cracks," lipids should be measured within the first 24 hours of an acute coronary syndrome presentation. Taking this opportunity ensures both identification and treatment of high-risk patients with elevated LDL-C levels before they leave hospital. Enrolling post-MI patients in cardiac rehabilitation programs has been shown to reduce cardiovascular mortality by 25% and can help ensure compliance with therapy and achievement of target lipid levels.

Two patient subgroups with established CAD that have often been neglected in terms of risk reduction are women and the elderly. Cardiovascular disease remains the leading cause of death among North American women, with a higher mortality rate than among men.[12] Because landmark trials of statins for lipid lowering have shown similar survival benefits for both men and women with LDL-C reduction,[5-7,10] high-risk patients (regardless of sex) require the same aggressive approach to treatment of hyperlipidemia. Hormone replacement therapy in women with established CAD has not been shown to reduce mortality and is not recommended for secondary prevention in place of statin therapy.[13]

For the elderly, evidence-based medicine has clearly demonstrated survival benefits in starting lipid-lowering therapies for patients with established CAD up to age 75.[5,6,10] Cholesterol lowering stabilizes

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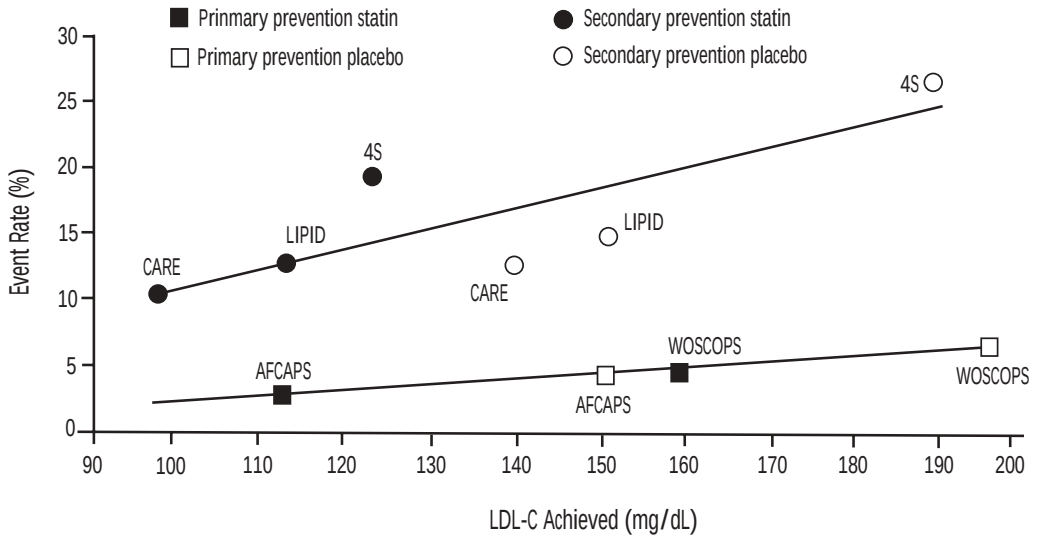
Figure 1. Low-density lipoprotein cholesterol and cardiac event rate: *In both primary and secondary prevention trials with clinical events as the primary end point, event rates decreased with successively lower concentrations of low-density lipoprotein cholesterol (LDL-C) achieved with either statin therapy or placebo.*



4S—Scandanavian Simvastatin Survival Study,[3] AFCAPS—Air Force/Texas Coronary Atherosclerosis Prevention Study,[7] CARE—Cholesterol and Recurrent Events trial,[4] LIPID—Long-term Intervention with Pravastatin in Ischemic Disease study,[6] WOSCOPS—West of Scotland Coronary Prevention Study.[5]

Adapted with permission from Ballantyne.[8]

lipid-laden plaques by reducing the likelihood of rupture and subsequent thrombus formation. Because the absolute risk of CAD rises with age, the number of coronary events prevented by cholesterol-lowering therapy could be higher in older patients than in younger patients. As well, statin therapy has been shown to be well tolerated and safe for older patients.[14] Therefore, although the benefit of lipid lowering in terms of life years saved could be less when therapy is started later in life, lipid normalization remains important for all patients with established CAD, even the very elderly.

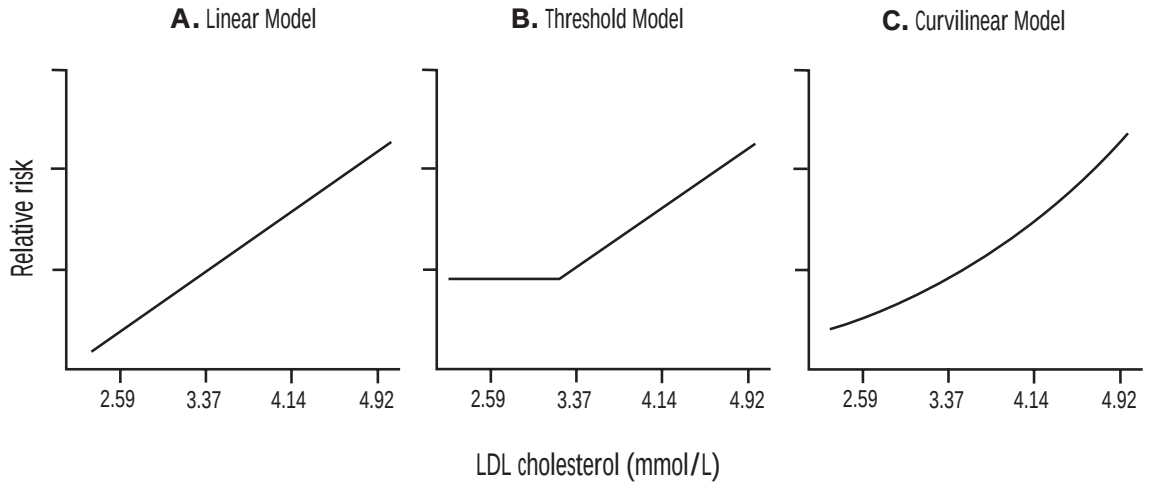
Primary prevention of MI with statin therapy has been well established, particularly in high-risk groups, such as patients with PVD and DM, which are both considered CAD risk equivalents. Peripheral vascular disease is a marker of extensive, generalized atherosclerosis, with a prevalence of more than 10% in older people.[15] Risk of cardiovascular mortality is increased nearly five times in symptomatic patients with a low ankle-brachial index, and more than 10 times in those with symptomatic PVD.[16] As well, angiography shows that improvement in plasma lipid levels reduces development and progression of atherosclerotic lesions, underscoring the need for aggressive lipid management in these patients.[17] Likewise, DM is a high-risk marker for CAD, because diabetic patients with no history of CAD have a similar incidence of fatal and nonfatal MI, as do patients without diabetes but with established CAD.[18]

Those with DM have a fourfold increase in incidence of CAD and a sevenfold increase in CAD mortality over patients without DM. Women with diabetes lose their premenopausal protection against developing CAD and manifest heart disease at an earlier age than women without DM. In the United Kingdom Prospective Diabetes Study (UKPDS), a 30% reduction in risk of MI for patients with DM was shown for every 1-mmol reduction in LDL-C levels.[19] Therefore, lipid lowering for patients with either DM or PVD needs to be as aggressive as for patients with established CAD.

Interventions

Once high-risk patients with hyperlipidemia have been identified, a lipid-lowering strategy is needed. Although the greatest clinical benefits of lipid lowering have been demonstrated to be associated with the

Figure 2. Theoretic models of the relationship between low-density cholesterol and relative risk for coronary heart disease: *A) Linear model, B) Threshold model, C) Curvilinear model.*



Adapted with permission from Grundy.[21]

greatest LDL-C reductions,[20] the extent to which we should lower LDL-C levels remains controversial.

The precise relationship between LDL-C lowering and the relative risk of recurrent CAD is unknown (**Figure 2**[21]). The Framingham data[22] and post hoc analysis of the CARE trial[4] suggest a limit to the benefit of lipid lowering beyond which no further survival advantage is obtained (threshold relationship). Post hoc analysis of the Scandinavian Simvastatin Survival Study (4S) data,[3] as well as evidence from the Atorvastatin versus Revascularization Treatment (AVERT) trial,[23] however, suggest an extended benefit with more aggressive LDL-C lowering (curvilinear relationship). The Treat-to-New-Targets (TNT) trial involving more than 8500 patients randomized to high- versus low-dose atorvastatin over a 5-year period is currently under way to see whether marked reduction in LDL-C is associated with an incremental cardiovascular survival benefit.[24] One subgroup that might benefit from an aggressive lipid-lowering strategy is patients who have had coronary artery bypass grafting surgery, because saphenous vein grafts have been shown to be exquisitely susceptible to development of atherosclerosis, with more than 50% graft closure at 10 years.[25] Although the optimal LDL-C level remains controversial, current guidelines recommend a target LDL-C level of less than 2.5 mmol/L in very high-risk patients (**Table 1**[10]).

Nonpharmacologic lipid-lowering interventions in the form of diet and exercise are important for all patients with elevated serum lipids, but become all the more crucial for patients receiving statin therapy because the proportion of dietary cholesterol is greater when cholesterol biosynthesis is impaired. The Step II diet recommended by the National Cholesterol Education Program (NCEP) has been shown to decrease LDL-C concentrations from 8% to 15% in long-term studies.[26] The Lyon Diet Heart Study demonstrated a 70% reduction in the cardiac event rate in the treatment group using the Mediterranean diet, which emphasizes higher amounts of monounsaturated fats, as found in fish and olive oil, and low amounts of trans-fatty acids, as found in stick margarine.[27] Nonetheless, for high-risk patients, diet and exercise are often insufficient to achieve target LDL-C levels, and concomitant pharmacologic therapy is recommended.

Table 1. Target lipid values based on risk level

RISK LEVEL	10-YEAR RISK OF CORONARY ARTERY DISEASE (%)	TARGET LOW-DENSITY LIPOPROTEIN CHOLESTEROL (MMOL/L)	TRIGLYCERIDE (MMOL/L)	TOTAL CHOLESTEROL–HIGH-DENSITY LIPOPROTEIN RATIO
Very high	>30	<2.5	< 2	<4
High	20-30	<3.0	<2	<5
Moderate	10-20	<4.0	<2	<6
Low	<10	< 5.0	< 3	<7

Adapted with permission from Fodor et al.[10]

Drugs of the statin class effectively lower LDL-C concentrations by acting as competitive inhibitors of β-hydroxy–methylglutaryl-coenzyme A (HMG-CoA), the rate-limiting step in cholesterol synthesis. All of the six statins currently available have been shown to reduce LDL-C by approximately 20% to 60% at equipotent doses.[28] The dose required to lower serum LDL-C concentrations to a similar degree varies among the statins, but in general, doubling the dose decreases LDL-C by an additional 6%.[29] Other beneficial effects of statins have been reported to include reduced TG levels, decreased fibrinogen levels and viscosity, activation of endothelial nitric oxide synthase, suppression of tissue factor release, and increased immune tolerance. These effects could account for some of the clinical benefits seen beyond those expected with LDL-C reduction alone, including stroke reduction.[30]

The urgency for initiating lipid-lowering therapy after acute coronary events remains controversial. The landmark 4S[3] and CARE[4] trials included patients 6 months and 3 months following an acute event, respectively. Because cholesterol lowering can produce rapid improvement in endothelial function following an acute coronary event,[31] some suggest lipid-regulating drugs should be initiated sooner after MI. The MIRACL study is currently under way to help provide an answer, enrolling patients to statin therapy versus placebo at the time of their acute presentation.[32]

Side effects

Historically, doubts were raised about the safety of lipid-lowering interventions because the early primary-prevention trials, conducted before the introduction of statin therapy, suggested incidence of non-CAD deaths increased in treatment groups.[33] Data on the long-term safety of statin therapy accumulated over the past 20 years have largely put these concerns to rest.[34] Common adverse effects with statins include gastrointestinal upset; muscle aches; peripheral neuropathy; rash, and insomnia (**Table 2**). A statin without central nervous system penetration, such as pravastatin, is preferred for patients who have difficulty sleeping.

The statins undergo hepatic transformation and can elevate aminotransferase concentrations 1.5 to 2 times the upper limit of normal. Higher elevations can indicate development of hepatitis and require prompt discontinuation of the drug. It is recommended that serum aminotransferases be measured within the first 3 months after treatment initiation, and every 6 months during long-term therapy.[35]

Table 2. Potential side effects of statins

COMMON
Nausea
Diarrhea
Muscle cramps
Sleep disturbance
SERIOUS
Hepatitis
Myositis
Rhabdomyolysis
Peripheral neuropathy

Myopathy, defined as muscle pain with serum creatine kinase (CK) concentrations above 1000 U/L, has been reported with statins, particularly in elderly, small-framed people with renal dysfunction or when a combination of statin and fibrate or nicotinic acid therapies are used.[36] In the CARE trial, however, higher CK levels occurred more often in the placebo group than in pravastatin-treated patients, and no cases of rhabdomyolysis were reported.[4] Because statins (with the exception of pravastatin) are metabolized by the cytochrome P-450 system, hepatotoxicity and myotoxicity are also more common among patients who are receiving drugs with similar metabolisms, such as erythromycin, ketoconazole, cyclosporin, and human immunodeficiency virus protease inhibitors.[37]

Complete lipid profile

In addition to a serum LDL-C concentration, a full lipid profile is required to assess CAD risk and determine appropriate therapy. Treatment should centre first on LDL-C lowering, then on raising HDL-C levels, and last on lowering TG levels. Observational studies have implicated low HDL-C levels as an independent risk factor for CAD, supporting the current understanding that HDL-C exerts an antiatherogenic effect by transporting cholesterol from peripheral tissues back to the liver for excretion. Low HDL-C levels, without elevated LDL-C levels, characterize 20% to 30% of North American patients with CAD, and often occur in the context of abdominal adiposity, insulin resistance, and hypertension.[38]

Although smoking cessation, regular aerobic exercise, and nicotinic acid therapy have been shown to increase HDL-C levels, studies using these approaches have not shown a benefit on mortality. As well, nicotinic acid is poorly tolerated because of flushing, and this drug has been implicated in worsening glycemic control among diabetic patients.[39] The recently published Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated that the fibric acid gemfibrozil markedly reduced the risk of death, MI, and stroke in men with CAD and HDL-C levels lower than 1.0 mmol/L.[40] Therefore, for patients with isolated low HDL-C levels, fibric acid therapy is well tolerated and has been proven effective for this indication in high-risk patients. The TC–to–HDL-C ratio, which takes into account both TG and HDL-C levels, is a powerful predictor of future coronary events and should be kept below 4 in very high-risk patients (**Table 1**[10]).

Elevated serum TG levels are associated with increased risk of CAD, particularly in women and diabetics.[41] Given the established metabolic link between LDL-C and TG, it makes sense to treat elevated TG levels in high-risk patients, even though epidemiologic data are disparate in terms of reduction in coronary events or survival benefit.[42] Triglyceride levels can be lowered to a certain extent with weight reduction, with increased aerobic exercise, and with improvement in blood pressure levels and glycemic control. Statins can lower TG levels in proportion to the degree of TC lowering; the greater the reduction in TC, the greater the effect on TG levels.[40]

If the predominant lipid abnormality is hypertriglyceridemia or if the TG level is elevated to such a degree that the LDL-C level cannot be properly measured (ie, TG > 4.6 mmol/L), then treatment with fibric acid therapy is indicated. Once the TG level has been lowered sufficiently, the lipid profile can be remeasured in 6 to 8 weeks to assess the LDL-C level. The recommended target for TG lowering is a serum concentration of 2.0 mmol/L or less, since higher values are associated with a doubling of CAD risk[42] (**Table 1**[10]). High-risk patients with combined hyperlipidemia (elevated LDL-C and TG) might not experience adequate improvement in their lipid profile with either statin or fibric acid alone, and combined therapy could be warranted. The combination has been shown to be generally safe and effective for patients with normal hepatic and renal function, although serial measurement of aminotransferase, creatinine, and CK levels are recommended every 6 months while receiving chronic therapy.[43]

Editor's key points

- Lipid lowering, particularly low-density lipoprotein (LDL) lowering, reduces cardiac events in primary and secondary prevention.
- High-risk patients now include those with diabetes and peripheral vascular disease in addition to those with established coronary artery disease.
- Benefits of lipid lowering are seen in women as well as in men, and in seniors at least until age 75.
- Diet and exercise can reduce lipid levels moderately, but statins are most often used for larger reductions, especially of LDL.
- Use of gemfibrozil has led to reductions in coronary artery events in patients with isolated low high-density lipoprotein levels.

Points de repère du rédacteur

- La baisse du taux lipidique, particulièrement celle des lipoprotéines de basse densité, réduit les incidents cardiaques dans la prévention primaire et secondaire.
- Les patients à risque élevé incluent maintenant les patients atteints de diabète et d'acrosyndrome en plus de ceux qui souffrent de coronaropathie diagnostiquée.
- Les bienfaits de la baisse du taux lipidique se remarquent autant chez la femme que chez l'homme ainsi que chez les aînés, et ce au moins jusqu'à 75 ans.
- Le régime alimentaire et l'exercice peuvent modérément réduire les taux de lipides, mais les agents de la famille des « statines » sont plus souvent utilisés en vue de plus importantes réductions, en particulier pour les lipoprotéines de basse densité.
- L'utilisation du gemfibrozil s'est traduite par des réductions du nombre d'incidents coronariens chez des patients ayant de faibles taux isolés de lipoprotéines de haute densité.

Conclusion

Evidence from more than 30 years of experimental, epidemiologic, and clinical studies shows elevated serum cholesterol is undeniably a critical contributor to development of CAD in humans. In light of the overwhelming clinical trial data on cholesterol lowering, and with the advent of efficacious and well tolerated lipid-modifying therapies, cholesterol normalization should be standard for all patients with established CAD and for those at risk for developing CAD. Future trends in lipid management will include improved accuracy of risk assignment with newer noninvasive measurements of atherosclerosis, such as B-mode carotid ultrasonography, and incorporation of emerging risk factors, such

as homocysteine levels and estrogen deficiency, into risk estimation equations. To reduce the burden of CAD meaningfully, physicians should adopt a more aggressive stance on lipid lowering, particularly for high-risk patients.

Competing interests

None declared

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References

1. Statistics Canada. *Mortality—summary list of causes 1994.* Ottawa, Ont: Statistics Canada; 1994. Catalogue no. 84-209-XPB,199.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-504.
3. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
4. Sacks FM, Pfeffer MA, Moye LA, Rouleau J, Rutherford J, Cole T, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. The Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 1996;335:1001-9.
5. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
6. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels for the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349-57.
7. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al, for the AFCAPS/TexCAPS Research Group. 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.
8. Ballantyne CM. Low-density lipoproteins and risk for coronary artery disease. *Am J Cardiol* 1998;82:3Q-12Q.
9. Teo KK. Coronary artery disease prevention: better management of dyslipidemias required. *Can J Cardiol* 1997;13(2):127-8.
10. Fodor G, Frohlich J, Genest J Jr, McPherson R. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *Can Med Assoc J* 2000;162(10):1441-7.
11. 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.
12. Kannel WB, Abbott RD. The incidence and prognosis of myocardial infarction in women. The Framingham Study. In: Eaker ED, Packand B, Wenger NK, editors. *Coronary heart disease in women*. New York, NY: Haymakers Doyma; 1997. p. 208-14.
13. Hulley S, Grady D, Bush T. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;208:605-13.
14. Santanello N, Barber B, Applegate W, Elam J, Curtis C, Hunninghake B, et al. Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the Cholesterol Reduction in Seniors Program (CRISP) Pilot Study. *J Am Geriatr Soc* 1997;45:8-14.
15. Vogt M, Cauley J, Newman A, Kuller L. Hulley S. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993;270:465-9.
16. Criqui M, Langer R, Fronek A. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326:381-6.
17. Buchwald H, Bourdages H, Campos C, Nguyen P, Williams S, Campbell G, et al. Impact of cholesterol reduction on peripheral arterial disease in the program on the surgical control of the hyperlipidemias (POSCH). *Surgery* 1996;120:672-9.
18. Haffner S, Legto S, Onnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.
19. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Mathews DR, for the United Kingdom Prospective Diabetes Group. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS 23). *BMJ* 1998;316(7134):823-8.
20. Leiter LA. Low density lipoprotein cholesterol: is lower better? *Can J Cardiol* 2000;16(Suppl A):1A-3A.
21. Grundy SM. Statin trials and goals of cholesterol-lowering therapy. *Circulation* 1998;97:1436-9.
22. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;241:2035-9.
23. Pitt B, Waters D, Brown W, Van Boven A, Schwartz L, Title L, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;341(2):70-6.
24. La Rosa JC. Effect of lowering LDL-C beyond currently recommended minimum targets—the Treating to New Targets (TNT) study, TNT Steering Committee [abstract]. XIII International Symposium on Drugs Affecting Lipid Metabolism. 1998 May 30 to June 3; Florence, Italy.
25. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;336:153-62.
26. Walden C, Retzall B, Buck B, McCann B, Knopp R. Lipoprotein lipid response to the National Cholesterol Education Program Step II diet by hypercholesterolemic and combined hyperlipidemic women and men. *Arterioscler Thromb Vasc Biol* 1997;17:375-82.
27. DeLorgeril M, Salen P, Martin JN. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. Final report of the Lyon Diet Heart Study. *Circulation* 1999;99(6):779-85.
28. Stein E, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 1998;81(14A):66-9B.
29. Knopp R. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498-511.
30. Vaughan C, Murphy M, Buckley B. Statins do more than just lower cholesterol. *Lancet* 1996;348:1079-82.
31. Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation* 1999;99:3227-33.
32. Schwartz G, Oliver M, Ezekowitz M, Ganz P, Waters D, Kane J, et al. Rationale and design of the myocardial ischemia reduction with aggressive cholesterol lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non–Q-wave acute myocardial infarction. *Am J Cardiol* 1998;81:578-81.
33. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;301:309-14.
34. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* 1998;97:946-52.
35. Bradford RH, Shear CL, Chremos AN. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med* 1991;151:43-9.
36. Feher MD, Foxton J, Banks D, Lant AF, Wray R. Long-term safety of statin-fibrate combination treatment in the management of hypercholesterolemia in patients with coronary artery disease. *Br Heart J* 1995;74:14-7.
37. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498-511.
38. Goldbourt U, Yaari S, Medalie J. Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality: a 21-year follow-up of 8000 men. *Arterioscler Thromb Vasc Biol* 1997;17:107-13.
39. Knopp R, Ginsberg J, Albers J. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism* 1985;34:642-50.
40. Rubins H, Robbins S, Collins D, Fye C, Andersen J, Elam M, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: for the Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.
41. Stampfer MJ, Kraus RM, Ma J. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996;276:882-8.
42. Kesaniemi YA. Serum triglycerides and clinical benefit in lipid-lowering trials. *Am J Cardiol* 1998;81(4A):70-3B.
43. Ellen R, McPherson R, Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81(4A):60-5B.

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