Cholesterol Management and Risk Reduction – Current Guidelines and Barriers to Goal Attainment

a report by

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Cardiovascular disease (CVD), a major cause of morbidity and mortality worldwide, is predicted to result in 20 million deaths by 2015.[1–4] Coronary heart disease (CHD) is the most common clinical manifestation of CVD.[5,6] A major, modifiable risk factor for CVD is hypercholesterolaemia, particularly elevated low-density lipoprotein cholesterol (LDL-C).[7–13] Clinical trials with angiographic end-points have consistently shown that lowering cholesterol levels slows the progression of atherosclerotic lesions and reduces end-points such as myocardial infarction and sudden death.[14–16]

Various epidemiological studies have correlated the intake of specific types of fat with plasma cholesterol levels and, consequently, CHD incidence.[17] However, intervention studies have shown that dietary modification can reduce cholesterol levels only by about 10%.[18–20] Accordingly, the management of hypercholesterolaemia is often a step-wise approach incorporating lifestyle modification with eventual pharmacotherapy. Several drug classes are available for reducing plasma cholesterol levels, including early agents such as bile acid sequestrants, fibrates and nicotinic acid.[21] These first-generation antilipid agents are associated with mild efficacy or poor tolerance as a result of adverse effects.[22] The introduction of the statins represented a major advance in lipid-lowering therapy.[23]

The statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is responsible for mediating the feedback suppression of cholesterol biosynthesis,[24] and have become the mainstay for the treatment of elevated plasma cholesterol levels because of their efficacy in reducing LDL-C, as well as their excellent tolerability and safety.[23] The benefits of statin therapy have been established in several landmark clinical trials and include reduced morbidity and mortality from CHD, decreased progression of atherosclerosis, regression of atherosclerotic lesions and decreased coronary artery revascularisation.[25–30] This article will review the current guidelines for cholesterol management and cardiovascular risk reduction. It will also focus on the treatment gap that exists between what the guidelines recommend and what is actually seen in clinical practice, and will discuss the barriers responsible for this gap.

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Cholesterol Management and Cardiovascular Risk Reduction Guidelines

Professional guidelines have consistently identified LDL-C as the primary target of lipid-lowering therapy,[31] focusing on either primary or secondary disease prevention strategies (see *Tables 1* and *2* and *Figures 1* and *2*). The current World Health Organization (WHO), European and American guidelines also stress the need for appraisal of total CVD risk and appropriate risk stratification.[4,12,32–35] In terms of lipid targets for high-risk individuals, the Adult Treatment Panel (ATP) III guidelines recommend an LDL-C target of <2.6mmol/l (<100mg/dl),[33] the WHO recommends an LDL-C target of <3.0mmol/l in high-risk individuals and LDL-C targets for high-risk individuals recommended by the Fourth Joint Task Force (JTF4) of the European Society of Cardiology (ESC) and other societies are <2.5mmol/l (<100mg/dl), or <2mmol/l if feasible.[4,32]

Guideline–Clinical Practice Treatment Gap

Despite the availability of several professional guidelines for cholesterol management and cardiovascular risk reduction, there exists a wide gap between what the guidelines recommend and what is actually seen in clinical practice.[21,36–42] Several studies and surveys have shown that many individuals with established CHD,[43] those at high risk of CHD[43] or those at high risk coupled with diabetes or previously diagnosed hypercholesterolaemia[44] do not achieve target plasma cholesterol (total cholesterol or LDL-C) levels. For instance, a multicentre survey reported that only 38% of patients receiving lipid-lowering therapy achieved their National Cholesterol Education Program (NCEP)-specified LDL-C targets.[43] Most people usually require lipid-lowering therapy to reach optimal cholesterol levels, particularly those with established CVD or individuals at high risk of this disease.[35] However, published data from 12 studies (n=68,446) indicated that only 35% (range 6–62%) of patients with established CHD received therapy with a lipid-lowering agent.[45–56] Additional data are available in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, which has collected data on atherosclerosis risk factors and treatment from >68,000 outpatients 45 years of age or older with either established atherothrombotic disease or ≥3 risk factors for atherothromobosis. The registry confirmed that patients were generally undertreated with statins: only 69.4% of all patients were prescribed statins, including 56.4% for coronary artery disease, 67.2% for cerebrovascular disease, 64.2% for peripheral arterial disease and 71.6% for ≥3 risk factors. Furthermore, only a minority of patients were found to achieve the target goals for cholesterol.[39]

The European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) surveys set out to determine the extent to which the European JTF4 recommendations on risk factor documentation and management in patients with established CHD were being incorporated into clinical practice.[57,58] EUROASPIRE I (1995–1996) and II

(1999–2000) showed that many patients with dyslipidaemia and either established CHD or high risk of CHD were not treated to their LDL-C goal, which suggested that guidelines were being poorly implemented.[57,58] Researchers from EUROASPIRE II reported that 58.3% of patients did not reach the total cholesterol goal of <5.0mmol/l despite the fact that 60.6% of patients were being treated with statins.[58,59] Recently, the EUROASPIRE III survey (2006–2007) showed that lipid control was completely inadequate, with most patients not achieving the targets defined in the European guidelines.[60] EUROASPIRE III also showed that 79% of the patients had total cholesterol ≥4.5mmol/l, which exceeded the recommended European targets.[61] Furthermore, the high-risk individuals in primary prevention programmes were not being managed effectively, with too few of these patients following the European guidelines and more than 80% never having received any advice or direction about the importance of following a heart-healthy lifestyle programme.[60] EUROASPIRE III also showed that statins were underprescribed.[60] Other recent surveys have investigated the extent to which the ATPIII[62] and European guidelines (based on recommendations by JTF3)[63] were incorporated into clinical practice. These surveys have shown that the treatment gap still exists, despite the continuing improvement in guidelines, with many patients not reaching target cholesterol levels.

Barriers to Goal Attainment

The treatment gap may be due to the presence of certain barriers to goal attainment. These barriers can be vaguely divided into three categories: physician-related, patient-related and healthcare-system-related.

Physician-related Barriers

The Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey identified numerous physician-related barriers,[64] including lack of time, prescribing costs, too many guidelines, lack of guideline awareness and lack of physician motivation. Lack of time could result in physicians not properly informing their patients about their treatment regimen, leading to patient non-compliance due to improper understanding of their therapy.[65] The cost of pharmacotherapy may also be a barrier; however, the effect of this factor on clinical practice has not been well documented.[66,67]

Although physicians have knowledge of hypercholesterolaemia and its link to CHD, they are not suitably motivated to implement correct treatment.[65] This requires a change in behavioural practice and also new policies from health services to ensure better physician understanding and implementation of the guidelines; for example, a payment-by-results scheme could give physicians the incentive to implement more wide-ranging treatment regimens.

Another strategy to improve guideline implementation is to use powerful information technology (IT) systems that encompass up-to-date medical knowledge and the medical history of patients.[68,69] With some systems, the physicians can actually input and access the information in realtime.[69,70] In this manner, the knowledge management system can automatically check the physician's decision (order of a medicine or laboratory test) against a large clinical database, as well as the patient's own medical record, and make queries or recommendations.[69,70] Thus, this system helps the physician to provide treatment tailored to the patient and also considers all of the patient's health needs at the same time.[69] Health IT and knowledge management systems have been shown to be a valuable tool for physicians in improving the quality of both their decision-making and the health of their patients.[69,71–73] However, the main barrier to thorough implementation of these systems is their cost. While hospitals can afford expensive IT systems and infrastructure, there are few cost-effective options for small clinics.

Table 1: World Health Organization Guidelines for Primary Prevention

All individuals with total cholesterol ≥8mmol/l (≥320mg/dl) should be advised to follow a lipid-lowering diet and given a statin to lower the risk of cardiovascular disease.
All other individuals need to be managed according to their cardiovascular risk, as follows: 10-year risk of cardiovascular event <10%, 10–<20%, 20–<30% or ≥30%:
• Risk <10% — Should be advised to follow a lipid-lowering diet.
• Risk 10–<20% — Should be advised to follow a lipid-lowering diet.
• Risk 20–<30% — Adults >40 years of age with persistently high serum cholesterol (>5.0mmol/l) and/or LDL cholesterol >3.0mmol/l, despite a lipid-lowering diet, should be given a statin.
• Risk ≥30% — Individuals in this risk category should be advised to follow a lipid-lowering diet and given a statin. Serum cholesterol should be reduced to <5.0mmol/l (LDL cholesterol to <3.0mmol/l) or by 25% (30% for LDL cholesterol), whichever is greater.

LDL = low-density lipoprotein.
Adapted from WHO, 2007.[4]

Table 2: World Health Organization Guidelines for Secondary Prevention

Treatment with statins is recommended for all patients with established CHD.
Treatment should be continued in the long term, and probably lifelong. Patients at high baseline risk are particularly likely to benefit.
Treatment with a statin should be considered for all patients with established CVD, especially if they also have evidence of established CHD.
Monitoring of blood cholesterol levels is not mandatory. Total cholesterol <4.0mmol/l (<152mg/dl) and LDL cholesterol <2.0mmol/l (<77mg/dl), or a reduction of 25% in total cholesterol and 30% in LDL cholesterol, whichever achieves the lower absolute risk level, may be desirable goals.
Other lipid-lowering agents are not recommended, either as an alternative to statins or in addition to them.

CHD = coronary heart disease; CVD = cardiovascular disease; LDL = low-density lipoprotein.
Adapted from WHO, 2007.[4]

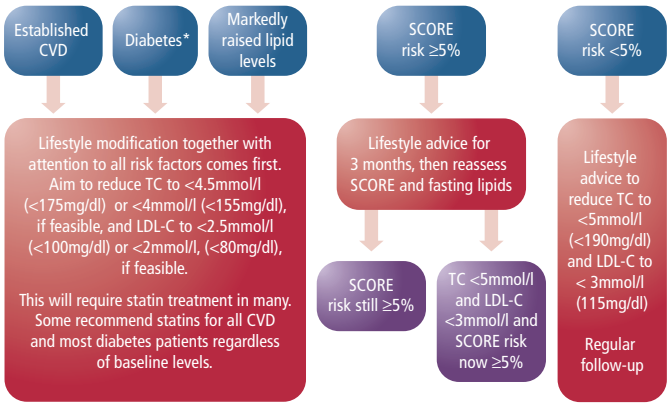
Patient-related Barriers

Patient non-compliance has frequently been reported to be a barrier to goal attainment in cholesterol management.[35,64,74–76] Non-compliance to pharmacotherapy can result in higher LDL-C levels, an increased rate of coronary events and poor quality of life.[75] Poor patient compliance is a contributing factor to failure to reach goal LDL-C levels, even in patients receiving the most effective of the current therapies for lowering LDL-C.[77] It seems that despite the improvement in cholesterol management and risk reduction guidelines, drug non-compliance is still a major barrier to goal attainment.[76]

Non-compliance could itself be due to a variety of barriers, such as adverse drug effects.[35] Overcoming these barriers could help increase patient compliance and, in turn, improve goal attainment. Although the currently available statins are generally safe, discontinuation rates of 30% after six months have been reported.[78] This emphasises the need for even better and safer statins, or modification of existing drugs.[21]

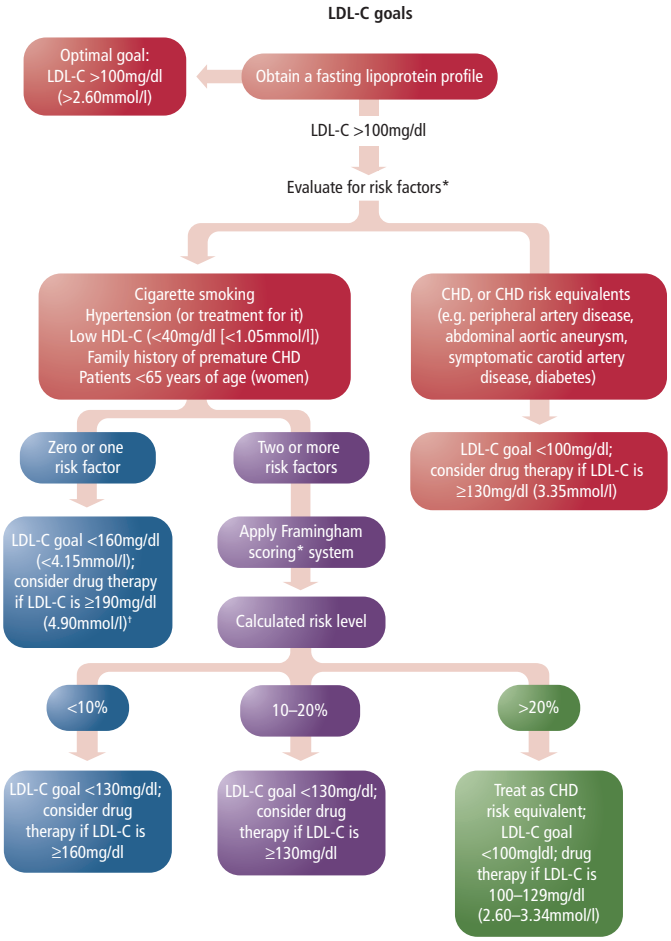
The Global Opinions and Awareness of Cholesterol (GOAL) survey assessed the European public's perception of cardiovascular risk.[65] The majority of participants had only a vague idea about cholesterol's role in

Figure 1: Fourth Joint Task Force Guidelines for Cholesterol Management and Risk Reduction



Treatment goals are not defined for high-density lipoprotein cholesterol (HDL-C) and triglycerides, but HDL-C <1.0mmol/l (<40mg/dl) for men and <1.2mmol/l (<45mg/dl) for women and fasting triglyceride of 1.7mmol/l (150mg/dl) are markers of increased cardiovascular risk. CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.
**Type 2 diabetes or type 1 diabetes with microalbuminuria.*
Source: Graham et al., 2007.[32]

Figure 2: Adult Treatment Panel III Guidelines for Cholesterol Management



Goals for low-density lipoprotein cholesterol (LDL-C) levels based on risk category.
**Other risk factors to consider (although they do not affect target LDL-C goals) include obesity, sedentary lifestyle, atherogenic diet, impaired fasting glucose level and subclinical atherosclerotic disease.*
†Consider drug therapy if LDL-C is 160–189mg/l (4.15–4.89mmol/l) and the patient has a single severe risk factor (e.g. heavy smoking, poorly controlled hypertension), multiple lifestyle risk factors or, if measured, a 10-year risk nearing 10%.
CHD = coronary heart disease; HDL = high-density lipoprotein.
Source: ATPIII, 2001.[33]

CHD, with 40% of the responders being unaware of the link between cholesterol and CHD.[65] These results indicate that the general population has a poor understanding of hypercholesterolaemia and its link to CHD. The survey also indicated that many patients were unaware of their own cholesterol levels, suggesting that physicians may not have adequately discussed therapy with their patients.[65] This lack of knowledge may also be linked to a lack of patient motivation and, consequently, non-compliance.

A stronger physician–patient partnership, with more detailed explanation of the disease and its treatment and more follow-ups for high-risk patients, will improve patient motivation and compliance.[79] However, doctors have little spare time; therefore, more responsibility falls on nurses in terms of thoroughly discussing and monitoring the treatment regimen and the importance of risk factor modification and prevention.[79,80] This would improve patient understanding of the therapy, knowledge of hypercholesterolaemia and its link to CHD and patient motivation, consequently leading to increased patient compliance and better treatment outcome.[80] The need for nurse assistance has been demonstrated by the Randomized Trial of Telephonic Intervention in Chronic Heart Failure (DIAL).[81] This trial investigated whether nurse-assisted treatment reduced the rate of death or admission for worsening heart failure in outpatients with chronic heart failure. This included education, counselling and monitoring by nurses through frequent telephone follow-up in addition to usual care. The results showed that patients in the usual care group were more likely to be admitted for worsening heart failure or to die than those who received the telephone intervention (p=0.026). The intervention group also had a better quality of life than the usual care group (p=0.001). According to the investigators, these results may be partly explained by improved patient compliance with diet and drug treatment regimens in the intervention group.[81]

Health-system-related and Other Barriers

Patients at high risk of or with established CHD eventually require statin therapy. Older general population surveys indicated that lipid-lowering therapy was underused, which could account for the barrier to goal attainment for hypercholesterolaemia.[25,55,82] Data from EUROASPIRE II also indicated that inadequate dose titration of the statins may be a barrier.[58,59] This is because most patients who failed to achieve target lipid goals were on low-dose statin therapy, were not at goal and, seemingly, were maintained on that same low dose.[58,59] The lack of variation in therapy, especially with statins, could be easily overcome if conventional pharmacotherapy were correctly implemented.[58,59] This has been shown by Catapano et al., who illustrated that appropriate titration of rosuvastatin and of the new combination drug ezetimibe–simvastatin resulted in many patients achieving ATPIII LDL-C goals.[83] Ezetimibe, a cholesterol-absorption inhibitor, has a different mechanism of action from statins.[84,85] Catapano et al. showed that escalating doses of combination ezetimibe–simvastatin (10/20mg, 10/40mg, 10/80mg) resulted in ATP III LDL-C goal achievement in 94.7, 95.8 and 97.5% of patients, respectively, with 95.9% of patients achieving goal on all doses of ezetimibe–simvastatin.[83] LDL-C goal attainment with escalating doses of rosuvastatin was similar.[83] Thus, a strategy to overcome the barrier of statin underuse might be to use more aggressive statin therapy at initial dosing to get patients to goal.[86] A combination of ezetimibe and simvastatin is currently being evaluated in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study to determine whether large LDL-C lowering effect has any clinical benefit.[87]

The insufficient LDL-C lowering effect of some existing statins, even at their most commonly prescribed doses, has been indicated to be a barrier to LDL-C goal attainment.[43,88–90] Several studies suggest that more aggressive LDL-C reduction to levels below those recommended in treatment guidelines might provide additional benefit in treatment of CVD.[91–93] The Heart Protection Study, involving more than 20,000 high-risk patients, demonstrated clinical benefit from treatment with simvastatin at a dose of 40mg/dl irrespective of baseline cholesterol level, even in patients whose LDL-C was below 100mg/dl.[21,94] Gaw suggests that drugs that could achieve greater LDL-C reduction would most likely prove to be of considerable usefulness in the primary care setting.[88]

Inadequate screening of patients for cardiovascular risk may be yet another barrier.[35] The implementation of screening strategies for hypercholesterolaemia is suboptimal, and improvements are particularly needed for patients at the greatest risk of CHD events.[35] To overcome such obstacles, the guidelines should focus even more on screening strategies, and health services should draw up policies to ensure the implementation of these strategies.

To overcome the numerous barriers to cholesterol goal attainment, policy-makers, healthcare provides and patients all have roles to play in maximising adherence to preventative interventions and reducing the burden of CVD.[95] Robust research is needed to examine the reasons for the poor adherence to cholesterol management and risk reduction guidelines and, hence, the measures that should be taken to address the situation.[96]

Conclusions

Hypercholesterolaemia, particularly elevated LDL-C, is well-established as a major, modifiable risk factor for CHD. Current cholesterol management and CHD risk reduction guidelines target elevated LDL-C levels. The treatment regime is dictated by the severity of disease and usually involves lifestyle modifications, with lipid-lowering drugs eventually required by most patients. The lipid-lowering statins are the mainstay of treatment and can significantly lower LDL-C levels. However, statin monotherapy may be insufficient in some high-risk patients. A number of new agents acting on targets other than LDL-C are currently under investigation. Such targets include non-high-density lipoprotein cholesterol, high-sensitivity C-reactive protein and apolipoprotein B. Combination therapy with these other agents may provide an alternative to achieve optimal therapeutic approach.

Policy-makers, healthcare providers and patients all have roles to play in maximising adherence to preventative interventions and reducing the burden of cardiovascular disease.

Despite the availability of these guidelines, there exists a wide treatment gap between what the guidelines recommend and what is seen in clinical practice because of barriers to goal attainment. The barriers can be classified as physician-, patient- and health-service-related. Physician-related barriers include lack of time, motivation and awareness of guidelines, while patient-related barriers include lack of compliance, motivation and knowledge. Health-service-related barriers include inadequate screening and dose titration of statins. To overcome these barriers, policy-makers, healthcare providers and patients all have roles to play in maximising adherence to preventative interventions and reducing the burden of CVD. ■

1. World Health Organization, Cardiovascular diseases, Updated February 2007. Available at: www.who.int/mediacentre/factsheets/fs317/en/index.html (accessed January 2009).
2. Rosamund WD, Chambless LE, Folsom AR, et al., Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994, *N Engl J Med*, 1998;339:861–7.
3. Murray CJL, Lopez AD, Mortality by cause for eight regions of the world: Global Burden of Disease Study, *Lancet*, 1997;349:1269–76.
4. World Health Organization, *Prevention of cardiovascular disease: pocket guidelines for assessment and management of cardiovascular risk*, Geneva, 2007.
5. Heart and Stroke Foundation of Canada, The changing face of heart disease and stroke in Canada 2000. Available at: www.hc-sc.gc.ca/main/lcdc/web/bcrdd/hdsc2000/pdf/card2ke.pdf (accessed January 2009).
6. American Heart Association, 2001 Heart and Stroke Statistical Update, American Heart Association, Dallas, 2000. Available at: www.americanheart.org/statistics/pdf/HSSTATS2001_1.0.pdf (accessed January 2009).
7. Anderson KM, Castelli W, Levy D, Cholesterol and mortality, *JAMA*, 1987;257:2176–80.
8. Stamler J, Wentworth D, Neaton JD, Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?, *JAMA*, 1986;256:2823–8.
9. Kastelein JJ, The future of best practice, *Atherosclerosis*, 1999;143:S17–S21.
10. Baigent C, Keech A, Kearney PM, et al., Efficacy and safety of cholesterollowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, *Lancet*, 2005;366:1267–78.
11. Cannon CP, Steinberg BA, Murphy SA, et al., Metaanalysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy, *JACC*, 2006;48:438–45.
12. .Safeer RS, Ugalat PS, Cholesterol treatment guidelines update, *Am Fam Physician*, 2002;65(5):871–80.
13. Levine GN, Keaney JF Jr., Vita JA, Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms, *N Engl J Med*, 1995;332:512–21.
14. Levy RI, Brensike JF, Epstein SE, et al., The influence of changes in lipid values induced by cholestyramine and diet on progression of coronary artery disease: results of the NHLBI Type II Coronary Intervention Study, *Circulation*, 1984;69:325–37.
15. Kane JP, Malloy MJ, Ports TA, et al., Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens, *JAMA*, 1990;264:3007–12.
16. Watts GF, Lewis B, Brunt JNH, et al., Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' Atherosclerosis Regression Study (STARS), *Lancet*, 1992;339:563–9.
17. Keys A, Coronary heart disease in seven countries: American Heart Association monograph 29, *Circulation*, 1970;41 (Suppl. 1):1–211.
18. Dayton S, Pearce ML, Hashimoto S, et al., A controlled clinical trial of a diet high in unsaturated fat preventing complications of atherosclerosis, *Circulation*, 1969;40 (Suppl. II):II1–63.
19. Woodhill JM, Palmer AJ, Leelarthaepin B, et al., Low fat, low cholesterol diet in secondary prevention of coronary heart disease, *Adv Exp Med Biol*, 1978;109:317–30.
20. Hjerman I, Byre KV, Holme I, et al., Effect of diet and smoking on the incidence of coronary heart disease. Report from the Oslo Study group of a randomised trial of healthy men, *Lancet*, 1981;2:1303–10.
21. Clearfield M, Evolution of cholesterol management therapies: exploiting potential for further improvement, *Am J Ther*, 2003;10(4):275–81.
22. Steinberg D, Gotto AM Jr, Preventing coronary artery disease by lowering cholesterol levels: fifty years from bench to bedside, *JAMA*, 1999;282:2043–50.
23. Maron DJ, Fazio S, Linton MF, Current perspectives on statins, *Circulation*, 2000;101:207–13.
24. Siperstein MD, Fagan VM, Feedback control of mevalonate synthesis by dietary cholesterol, *J Biol Chem*, 1966;241:602–9.
25. Scandinavian Simvastatin Survival Study Group, Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study, *Lancet*, 1994;344:1383–9.
26. Shepherd J, Cobbe SM, Ford I, et al., Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group, *N Engl J Med*, 1995;333:1301–7.
27. Downs JR, Clearfield M, Weis S, et al., Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study, *JAMA*, 1998;279:1615–22.
28. Serruys PW, de Feyter P, Macaya C, et al.; Lescol Intervention Prevention Study (LIPS) Investigators, Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial, *JAMA*, 2002;287:3215–22.
29. Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, *Lancet*, 2002;360:7–22.

30. Nissen SE, Tuzcu EM, Schoenhagen P, et al.; REVERSAL Investigators, Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial, *JAMA*, 2004;291:1071–80.
31. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), *JAMA*, 1993;269:3015–23.
32. Graham I, Atar D, Borch-Johnsen K, et al., European guidelines on cardiovascular disease prevention in clinical practice: executive summary Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts), *Eur J Cardiovasc Prev Rehabil*, 2007;14(Suppl. 2):1741–8267.
33. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), *JAMA*, 2001;285:2486–97.
34. Mosca LJ, Optimal management of cholesterol levels and the prevention of coronary heart disease in women, *Am Fam Physician,* 2002;65(2):217–26.
35. Olson KL, Bungard TJ, Tsuyuki RT, Cholesterol risk management: a systematic examination of the gap from evidence to practice, *Pharmacotherapy*, 2001;21(7):807–17.
36. Pygove MP, Phillips CT, Atkins D, et al., Screening and treating adults for lipid disorders, *Am J Prev Med*, 2001;20:77–89.
37. Yarnell KSH, Pollack KI, Ostbye T, et al., Primary care: is there enough time for prevention?, *Am J Public Health*, 2003;93: 635–41.
38. Smith RA, Wender RC, Cancer screening and the periodic health examination, *Cancer*, 2004;100:1553–7.
39. Bhatt DL, Steg PG, Ohman EM, et al., International prevalence, recognition, and treatment for cardiovascular risk factor in outpatients with atherothrombosis, *JAMA*, 2006;295:180–89.
40. Saaddine JB, Cadwell B, Gregg EW, et al., Improvements in diabetes processes of care and intermediate outcomes: United States, 1988–2002, *Ann Intern Med*, 2006;144:465–74.
41. Pearson TA, McBride PE, Houston-Miller N, et al., 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 8. Organization of preventive cardiology service, *J Am Coll Cardiol*, 1996;27:1039–47.
42. Burke LE, Ockene IS (eds), *Compliance in Healthcare and Research*, Armonk, NY: Futura Publishing Co., 2001.
43. Pearson TA, Laurora I, Chu H, et al., The lipid treatment assessment project (L-TAP). A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals, *Arch Intern Med*, 2000;160:459–67.
44. Qureshi AI, Suri MF, Guterman LR, et al., Ineffective secondary prevention in survivors of cardiovascular events in the US population: report from the Third National Health and Nutrition Examination Survey, *Arch Intern Med*, 2001;161:1621–8.
45. Northridge DB, Shandall A, Rees A, et al., Inadequate management of hyperlipidaemia after coronary bypass surgery shown by medical audit, *Br Heart J*, 1994;72:466–7.
46. The Clinical Quality Improvement Network (CQIN) Investigators, Low incidence of assessment and modification of risk factors in acute care patients at high-risk for cardiovascular events, particularly among females and the elderly, *Am J Cardiol*, 1995;76:570–73.
47. ASPIRE Steering Group, A British cardiac society survey of the potential for the secondary prevention of coronary disease: ASPIRE (action on secondary prevention through intervention to reduce events), *Heart*, 1996;75:334–42.
48. Bramlet DA, King H, Young L, et al., Management of hypercholesterolemia: practice patterns for primary care providers and cardiologists, *Am J Cardiol*, 1997;80:39H–44.
49. McBride P, Schrott HG, Plane MB, et al., Primary care practice adherence to national cholesterol education program guidelines for patients with coronary heart disease, *Arch Intern Med*, 1998;158:1238–44.
50. Frolkis JP, Zyzanski SJ, Schwartz JM, et al., Physician noncompliance with the 1993 National Cholesterol Education Program (NCEP-ATPII) guidelines, *Circulation*, 1998;98:851–5.
51. Sueta C, Chowdhury M, Boccuzzi SJ, et al., Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease, *Am J Cardiol*, 1999;83:1303–7.
52. Watt P, Gecker DM, Salaita K, et al., Hypercholesterolemia in patients undergoing coronary bypass surgery: are they aware, under treatment, and under control, *Heart Lung*, 1988;17:205–8.
53. Cohen MV, Byrne M, Levine B, et al., Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease, *Circulation*, 1991;83: 1294–1304.
54. Schrott HG, Bittner V, Vittinghoff E, et al., Adherence to national cholesterol education program treatment goals in postmenopausal women with heart disease: the heart and estrogen/progestin replacement study (HERS), *JAMA*, 1997;277:1281–6.
55. Hoerger TJ, Bala MV, Bray JW, et al., Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults, *Am J Cardiol*, 1998;82:61–5.
56. McCormick D, Gurwitz JH, Lessard D, et al., Use of aspirin, β-blockers, and lipid-lowering medications before recurrent acute myocardial infarction: missed opportunities for prevention?, *Arch Intern Med*, 1999;159:561–7.
57. EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) Study Group, EUROASPIRE: a European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results, *Eur Heart J*, 1997;18:1569–82.
58. EUROASPIRE (European Action on Secondary Prevention by Intervention to Reduce Events) I and II Group, Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries, *Lancet*, 2001;357:995–1001.
59. Alsheikh-Ali AA, Lin JL, Abourjaily P, et al., Extent to which accepted serum lipid goals are achieved in a contemporary general medical population with coronary heart disease risk equivalents, *Am J Cardiol*, 2006;98:1231–3.
60. O'Riordan M, EUROASPIRE III: Not Enough Being Done in the Treatment of High-Risk Primary-Prevention Patients, heartwire, 2008. Available at: www.medscape.com/viewarticle/580010_print (accessed January 2009).
61. Wood DA, Ryden L, EUROASPIRE III: Lifestyle, risk factor and therapeutic menagement in people at high risk of developing cardiovascular disease from 12 European regions, 2008. Clinical Trial Update III, European Society of Cardiology. Available at: www.escardio.org/congresses/esc2008/congress-reports/Pages/4480-4481-wood-ryden.aspx (accessed January 2009).
62. Rapezzi C, Biagini E, Bellis P, et al., Exploring the gap between National Cholesterol Education Program guidelines and clinical practice in secondary care: results of a cross-sectional study involving over 10 000 patients followed in different specialty settings across Italy, *J Cardiovasc Med (Hagerstown)*, 2008;9(9): 878–87.
63. Zachariadou T, Stoffers HE, Christophi CA, et al., Implementing the European guidelines for cardiovascular disease prevention in the primary care setting in Cyprus: lessons learned from a health care services study, *BMC Health Serv Res*, 2008;8:148.
64. Hobbs FD, Erhardt L, Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey, *Fam Pract*, 2002;19:596–604.
65. Erhardt L, Barriers to effective implementation of guideline recommendations, *Am J Med*, 2005;118(12A):36S–41S.
66. Andrade SE, Walker AM, Gottlieb LK, et al., Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings?, *N Engl J Med*, 1995;332:1125–31.
67. Col N, Fanale JE, Kronholm P, The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly, *Arch Intern Med*, 1990;150:841–5.
68. González-González AI, Dawes M, Sánchez-Mateos J, et al., Information Needs and Information-Seeking Behavior of Primary Care Physicians, *Ann Fam Med*, 2007;5(4):345–52.
69. Davenport TH, Glaser J, Just-in-time delivery comes to knowledge management, *Harv Bus Rev*, 2002;80(7):107–11, 126.
70. Ketchum B, IT equals better patient care?, *Nurs Manage*, 2008;39(6):21–3.
71. Shekelle PG, Morton SC, Keeler EB, Costs and Benefits of Health Information Technology. Evidence Report/Technology Assessment No. 132. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-02-0003.) AHRQ Publication No. 06-E006. Rockville, MD: Agency for Healthcare Research and Quality, 2006.
72. Walsh KE, Landrigan CP, Adams WG, et al., Effect of computer order entry on prevention of serious medication errors in hospitalized children, *Pediatrics*, 2008;121(3):e421–7.
73. Sandrick K, Be all that you can be. Information technology and quality care go hand in hand, *Trustee*, 2000;53(5):6–10, 1.
74. Marcelino JJ, Feingold KR, Inadequate treatment with HMG-CoA reductase inhibitors by health care providers, *Am J Med*, 1996;100:605–10.
75. Ansell, Not Getting to Goal: The Clinical Costs of Noncompliance, *J Manag Care Pharm*, 2008;14(6 Suppl. S-b):S9–S15.
76. Steinberg BA, Bhatt DL, Mehta S, et al., Nine-year trends in achievement of risk factor goals in the US and European outpatients with cardiovascular disease, *Am Heart J*, 2008;156(4):719–27.
77. Davidson M, McKenney J, Stein E, et al., Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia, Atorvastatin Study Group I, *Am J Cardiol*, 1997;79:1475–81.
78. Simons LA, Simons J, McManus P, et al., Discontinuation rates for use of statins are high [letter], *BMJ*, 2000;321:1084.
79. Peterson AM, Takiya L, Finley R, Meta-analysis of trials of interventions to improve medication adherence, *Am J Health Syst Pharm*, 2003;60:657–65.
80. Erhardt LR, Barriers to effective implementation of guideline recommendations, *Am J Med*, 2005;118(12A):36S–41S.
81. GESICA Investigators, Randomised trial of telephone intervention in chronic heart failure: DIAL trial, *BMJ*, 2005;331(7514):425.
82. Giles WH, Anda RF, Jones DH, et al., Recent trends in the identification and treatment of high blood cholesterol by physicians: progress and missed opportunities, *JAMA*, 1993;269:1133–8.
83. Catapano AL, Davidson MH, Ballantyne CM et al., Lipidaltering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients, *Curr Med Res Opin*, 2006;22:2041–53.
84. Fleg, JL, Mete M, Howard, BV, et al., Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes: The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial, *J Am Coll Cardiol*, 2008;52:2198–2205.
85. Kimberlin CL, Winterstein AG, Validity and reliability of measurement instruments used in research, *Am J Health Syst Pharm*, 2008;65:2276–84.
86. Kotseva K, Stagmo M, De Bacquer D, et al., Treatment potential for cholesterol management in patients with coronary heart disease in 15 European countries: findings from the EUROASPIRE II survey, *Atherosclerosis*, 2008;197:710–17.
87. IMPROVE-IT: examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (study P04103). Available at: clinicaltrials.gov/ct2/show/NCT00202878 (accessed January 2009).
88. Gaw A, A new reality: achieving cholesterol-lowering goals in clinical practice, *Atherosclerosis*, 2002;(Suppl. 2):5–11.
89. Majumdar SR, Gurwitz JH, Soumerai SB, Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease, *J Gen Intern Med*, 1999;14:711–17.
90. ASPIRE Steering Group, A British Cardiac Society survey of the potential for secondary prevention of coronary disease: ASPIRE (Action on Secondary Prevention through Intervention to Reduce Events): principal results, *Heart*, 1996;75:334–42.
91. Pitt B, Waters D, Brown WV, et al., Aggressive lipidlowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin Versus Revascularization Treatment Investigators, *N Engl J Med*, 1999;341:70–76.
92. The Post Coronary Artery Bypass Graft Trial Investigators, The effect of aggressive lipid-lowering of lowdensity 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.
93. Ginsberg HN, The Prove It Study: Is It Really a Landmark Study or Another Piece of a Very Important Puzzle?, *N Engl J Med*, 2004;350:1495–1504.
94. Kmietowicz Z, Statins are the new aspirin, Oxford researchers say [news], *BMJ*, 2001;323:1145.
95. Mosca L, Banka CL, Benjamin EJ, et al., Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update, *Circulation*, 2007;115:1481–1501.
96. Hobbs FDR, Guidelines and management of global risk: the European perspective, *Eur Heart J Suppl*, 2004;6(Suppl. C): C5–C14.