

Cost Efficiency and Formulary Considerations for Statin Therapy

Terrance Killilea, PharmD; and Lori Funk, PharmD

Abstract

Extensive epidemiologic evidence and reports issued by the National Cholesterol Education Program have repeatedly identified low-density lipoprotein cholesterol (LDL-C) as the primary target in reducing the primary and secondary risk of coronary events.

With recent evidence supporting a more aggressive approach using higher potency statins, and a lower threshold for initiating drug therapy for high-risk patients, providers and administrators in managed care are charged with finding the most effective and cost-effective means of attaining these goals. Changes in the market, such as newer high-potency statins and statin combinations available at lower cost and expiration of patents on widely accepted brand drugs, have provided practitioners with the ability to reduce LDL-C at lower costs than ever. The cost-efficiency analysis presented here finds that, for low-to-moderate reduction (<40%), generic lovastatin and simvastatin provide the lowest cost per 1% LDL-C reduction. Similarly, for reduction greater than 40%, branded rosuvastatin and ezetimibe/simvastatin have the lowest cost per 1% reduction.

(*Am J Manag Care. 2006;12:S325-S331*)

LDL-C Reduction Is the Basis for Cardioprotection

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. According to the American Heart Association, it accounted for or contributed to approximately 58% of the total mortality of the general population in 2003, with estimated direct and indirect cost of CVD for 2006 at \$403.1 billion.¹ Along with several other factors, increased low-density lipoprotein cholesterol (LDL-C) levels are associated with increased risk of CVD. A large body of epidemiologic evidence supports a direct relationship

between the level of serum LDL-C and the risk of CVD. It has been documented that lower levels of LDL-C reduce risk of coronary heart disease (**Figure 1**).²

Along with diet and lifestyle improvement, lipid-lowering drug therapy is a primary intervention in the prevention and treatment of CVD. The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program issued an evidence-based set of guidelines on cholesterol management in 2001.³ ATP reports have repeatedly identified LDL-C as the primary target of cholesterol-lowering therapy.²

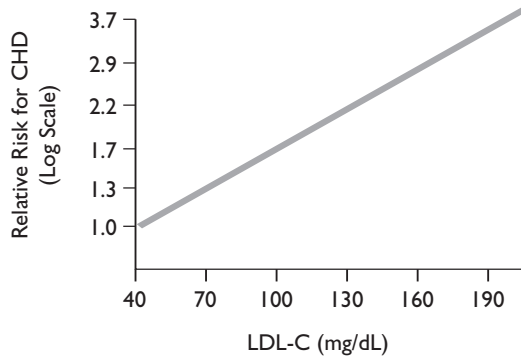
Primary Prevention of Coronary Artery Disease

The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated the benefit and safety of lipid-lowering therapy with a statin for primary prevention of CVD in patients with hypercholesterolemia. Treatment with statin therapy reduced the risk of key end points, including death from all CVDs.⁴ Additional studies that have documented benefit from LDL-C reduction in primary prevention include the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)⁵ and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).⁶ These studies consistently demonstrated reduction of CVD risk from statin treatment in a primary setting, including in patients without CVD (**Table 1**).

Dr Killilea wishes to state that he does not receive any funding in any manner from pharmaceutical companies.

Address correspondence to: Terrance Killilea, PharmD, Director, Pharmacy Services, The Regence Group, 1211 West Myrtle, #110, Boise, ID 83701. E-mail: tkillilea.id@regence.com.

Figure 1. Log-linear Relationship between LDL-C and Relative Risk for CHD



This relationship is consistent with a large body of epidemiologic data and with data available from clinical trials of LDL-C-lowering therapy. These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%. The relative risk is set at 1.0 for LDL-C = 40 mg/dL. LDL-C indicates low-density lipoprotein cholesterol; CHD, coronary heart disease.
 Source: Reprinted with permission from Reference 2.

The Atherosclerosis Risk in Communities (ARIC) study, in which more than 12 000 middle-aged subjects with no evidence of CVD were followed prospectively for 10 years, showed that the incidence of coronary heart disease (CHD)-related death, myocardial infarction (MI), silent infarction, coronary artery bypass graft, and angioplasty was lower in subjects with baseline serum LDL-C levels of less than 88 mg/dL for women and less than 95 mg/dL for men.⁷ The ARIC study, which can be thought of as “the Framingham of the future,” confirms the wisdom of the ATP III guidelines, which identify LDL-C levels of less than 100 mg/dL as optimal and emphasize the value of aggressive, multifactorial risk reduction for primary CVD prevention.⁸

Secondary Prevention

Regardless of baseline, patients with a history of a cardiovascular (CV) event benefit from LDL-C reduction (Table 2). The landmark Scandinavian Simvastatin Survival Study (4S) demonstrated, in a large popula-

Table 1. Summary of LDL-C-Lowering Trials*: Primary Prevention

Trial	n	Population	Design	Results
WOSCOPS ⁴ 1995	6595	Men with high TC and no prior CVD Ages: 45-64 y	Pravastatin 40 mg vs placebo Mean follow-up: 4.9 y	LDL-C reduction: 26% RR reduction in CVD: 31% (P < .001)
AFCAPS/TexCAPS ⁵ 1998	5608 ♂/997 ♀	Men and women with no CVD and average TC Ages: 45-73 y	Lovastatin 20-40 mg vs placebo Mean follow-up: 5.2 y	LDL-C reduction: 25% RR reduction in first major coronary events: 37% (P < .001)
ASCOT-LLA ⁶ 2003	10 305	Hypertensive patients with normal LDL-C Ages: 40-79 y (mean: 63 y)	Atorvastatin 10 mg vs placebo Mean follow-up: 5 y	LDL-C reduction: 29% RR reduction of primary CV events (nonfatal MI and total CHD): 21% (P < .0005)
ARIC ⁷ 2001	12 339	No CHD at baseline	Prospective study followed subjects Follow-up: 10 y	Findings: CHD risk elevated by ~40% for every 39 mg/dL increase in LDL-C

*Unless otherwise noted, trials are randomized, double-blind, placebo-controlled studies. LDL-C indicates low-density lipoprotein cholesterol; TC, total cholesterol; CVD, cardiovascular disease; RR, relative risk; CV, cardiovascular; MI, myocardial infarction; CHD, coronary heart disease; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; ARIC, Atherosclerosis Risk in Communities.
 Sources: References 4 to 7.

Table 2. Summary of LDL-C–Lowering Trials*: Secondary Prevention

Trial	n	Population	Design	Results
4S ⁹ 2001	4444	Patients with angina or history of MI and high TC Ages: 35-70 y	Simvastatin 10-40 mg vs placebo Median follow-up: 5.4 y	LDL-C reduction: 35% RR reduction in mortality: 30% ($P = .0003$); major coronary events: 34% ($P < .00001$)
HPS ¹⁰ 2002	20 536	Patients with CHD or other occlusive disease, or diabetes Ages: 40-80 y	Simvastatin 40 mg vs placebo Follow-up: 5 y	LDL-C reduction (from <116 mg/dL to <77 mg/dL): 33% RR reduction in first event: ~25%
PROVE IT ^{11†} 2004	4162	Patients with recent ACS Ages: ≥18 y (mean: 58 y)	Pravastatin 40 mg (standard therapy) vs atorvastatin 80 mg (aggressive therapy) Mean follow-up: 2 y (1.5-3 y)	LDL-C reduction: 35% ($P = .005$) RR reduction of all-cause mortality: 16%
CARE ¹² 1996	4159	Patients with prior MI Mean age: 59 y	Pravastatin 40 mg vs placebo Median follow-up: 5.0 y	LDL-C reduction: 28% RR reduction (fatal coronary or nonfatal MI): 24% ($P = .003$)
LIPID ¹³ 1998	9014	Patients with history of MI or UA Ages: 31-75 y (median: 62 y)	Pravastatin 40 mg vs placebo Mean follow-up: 6.1 y ($P < .001$)	LDL-C reduction: 25% RR reduction of CHD mortality: 24%
LIPS ¹⁴ 2002	1677	Post-PCI patients with angina or silent ischemia Ages: 18-80 y (mean: 60 y)	Fluvastatin 80 mg vs placebo Median follow-up: 3.9 y	LDL-C reduction: 27% (median) RR reduction of major cardiac events: 22% (median; $P = .01$)
GREACE ^{15†} 2004	—	Patients with CHD and <75 y Mean age: 58 y	Atorvastatin 10 mg titrated to 80 mg vs “usual care” Mean follow-up: 3 y	LDL-C reduction: 52% (upper quartiles); 35% (lower quartiles) RR reduction (coronary death and nonfatal MI): 61% (upper quartiles; $P < .0001$ vs usual care); 35% (lower quartiles; $P < .0001$ vs usual care)
A to Z ¹⁶ 2004	4497	ACS patients Ages: 21-80 y (median: 61 y)	Simvastatin 40 mg/80 mg vs placebo/simvastatin 20 mg Follow-up: 6-24 m	LDL-C reduction (median): 18% RR reduction of primary end point (CV death, nonfatal MI, ACS event, stroke): 11% ($P = .14$), RR reduction of CV mortality: 25% ($P = .05$) and CHF: 28% ($P = .04$)
TNT ^{17†} 2005	10 001	Patients with clinical CHD and LDL-C <130 mg/dL Mean age: 61 y	Atorvastatin 10 mg vs 80 mg Median follow-up: 4.9 y	LDL-C reduction: 24% (101 vs 77 mg/dL) RR reduction (first major CV event): 22% ($P < .001$)

*Unless otherwise noted, trials are randomized, double-blind, placebo-controlled studies.

†PROVE IT, GREACE, and TNT are not placebo-controlled trials.

LDL-C indicates low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; RR, relative risk; CHD, coronary heart disease; ACS, acute coronary syndromes; UA, unstable angina; PCI, percutaneous coronary intervention; CV, cardiovascular; 4S, Scandinavian Simvastatin Survival Study; HPS, Heart Protection Study; PROVE IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; CARE, Cholesterol and Recurrent Events; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; GREACE, Greek Atorvastatin and Coronary-Heart-Disease Evaluation; TNT, Treating to New Targets.

Sources: References 9 to 17.

tion, a reduction in mortality secondary to LDL-C reduction. Benefit from LDL-C reduction, in terms of total risk reduction for both overall mortality and major coronary events, was documented.⁹

The Heart Protection Study (HPS) was noteworthy because of the large, heterogeneous patient population with a variety of comorbidities, as well as those with below-average cholesterol levels. Over 20 000 peo-

ple, up to 80 years of age, were enrolled. After an average of approximately 5 years, the reduction in major vascular events from baseline was significant in patients treated with simvastatin compared with placebo, and the reduction in events was similar regardless of the baseline LDL-C concentration. Thus, all patient groups studied in the trial benefited from further reduction of their LDL-C levels.¹⁰

Intensive Therapy for Secondary Prevention

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT) trial,¹¹ a randomized, double-blind study of 4162 patients with acute coronary syndromes (ACS; manifested as either acute MI or high-risk unstable angina), provides further support to the “lower is better” theory. The primary end point was a composite of death from any cause, MI, documented unstable angina requiring rehospitalization, stroke, and revascularization (performed at least 30 days after randomization). After an average follow-up time of 2 years, event reduction was compared between standard and intensive LDL-C reduction.

The key finding of this study was that patients with recent ACS benefited from LDL-C reduction that resulted in values less than 100 mg/dL. PROVE IT provided evidence that more intensive LDL-C-lowering therapy reduces major CV events in patients with ACS compared with less intensive therapy over a period of 2 years.

Based on the results of 5 major recent clinical trials, in 2004 the ATP III authors issued an interim report that updated recommendations to the 2001 guidelines on cholesterol management, the second time the guidelines have been updated since their inception in 1993.² Therapeutic lifestyle changes (eating a diet low in saturated fat and cholesterol, getting regular physical exercise, achieving overall weight management, and smoking cessation) remain essential modalities in clinical management. However, a more aggressive approach with a lower threshold for initiating drug therapy (from <130 mg/dL to <100 mg/dL) is now recommended for high-risk patients. An

LDL-C goal of less than 70 mg/dL is an optional target for consideration based on recommendations from 2004 in patients at very high risk; established atherosclerotic CVD combined with either: (1) diabetes mellitus, (2) cigarette smoking, (3) metabolic syndrome, or (4) ACS.²

Since the 2004 interim report on ATP III, several trials have set out to strengthen the direct relationship between LDL-C levels and relative risk of CVD. Included in these trials are the Cholesterol and Recurrent Events (CARE) trial¹² and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study.¹³ These clinical studies, along with the findings of the Lescol Intervention Prevention Study (LIPS) published in 2002,¹⁴ laid a stable foundation for institution of therapy with these agents even when LDL-C levels are not markedly elevated.

Treating to Target

Although reduction of LDL-C contributing to lower incidence of CVD had been documented, the actual relationship between incidence of CVD and lower LDL-C attributed to statin therapy remained unexamined until publication of the results of the Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) study in 2004. This study demonstrated a linear relationship between lower LDL-C levels obtained with statin therapy and lower incidence of adverse cardiology outcomes. It also showed that patients with the highest baseline LDL-C levels benefited the most from reduction to less than 100 mg/dL.¹⁵

Two additional studies have validated that aggressive LDL-C reduction provides enhanced avoidance of CVD events in patients with CHD. Both the A to Z trial and the Treating to New Targets (TNT) trial support a dosing strategy tailored to achieve lower LDL-C levels. When early initiation of aggressive statin therapy was compared with delayed, less intensive therapy in the A to Z trial in patients with recent ACS events, there was a favorable trend toward reduced CV events (hazard ratio at study's end, 0.75; $P = .02$).¹⁶ In TNT, reduction of LDL-C to a level below 80 mg/dL reduced the occurrence of events significantly greater than reduction to approximately 100 mg/dL.¹⁷

With the widely accepted idea that aggressive LDL-C reduction reduces risk of CVD in both a primary and a secondary setting, the challenge arises for practitioners to achieve the desired reduction, with safety, at the lowest possible cost. Current guidelines promote the concept of a target-based strategy as opposed to a specific initial dosing strategy. Recent changes in the statin marketplace reduce the cost of achieving these goals.

Maximizing Outcomes

Extent of LDL-C reduction appears to be a critical factor in the success of statin treatment. The extent of reduction required is determined by the LDL-C level existing in the patient and the LDL-C level that is desired (target LDL-C). The percent reduction required for the treatment of a specific patient is a critical assessment in each situation where a statin is to be used. Selection of a statin that offers maximum cost-efficiency (in terms of greatest reduction per dollar cost) while providing the desired LDL-C reduction needed to reach a particular treatment goal will minimize unnecessary treatment costs.

In a recent pooled data study of 3 active-comparator trials, 76% of patients receiving rosuvastatin 10 mg for 12 weeks achieved ATP III LDL-C targets, whereas 53% of those receiving atorvastatin 10 mg achieved goal ($P < .001$).¹⁸ The highest CHD risk category goal of LDL-C less than 100 mg/dL was attained by 60% of rosuvastatin patients compared with only 19% of those receiving atorvastatin ($P < .001$). Pooled data from 2 trials comparing rosuvastatin with simvastatin and pravastatin also showed that 86% of patients who received rosuvastatin 10 mg for 12 weeks met their ATP III LDL-C goals, but only 64% of patients receiving simvastatin 20 mg and 49% of those receiving pravastatin 20 mg met their lipoprotein targets ($P < .001$).¹⁸ These analyses provide further credence to the recommendations derived from the comparison presented in Figure 2.

Cost per LDL-C Reduction

Cost-effective care can be defined as the point at which the minimum amount of input (of which cost is one measurement) is

used to achieve a given output or result. Thus, in the search for cost-effective statin therapy, achieving a given level of LDL-C reduction at the lowest pharmacy and medical cost (attained via efficacy and safety) achieves high cost efficiency. Therefore, one would seek to achieve optimal utilization of resources by minimizing the cost to achieve the defined goal (LDL-C reduction). In the area of statin therapy, this analysis would be performed if it can be stated that the adverse event occurrence rates for the various statins were similar. In spite of some concerns on the introduction of some new products, postmarketing analysis has determined that the occurrence of serious side effects from various statins is similar.¹⁹

Concomitant with the introduction of new high-potency LDL-C-reduction drugs (with lower wholesale cost than previous high-potency drugs) in 2004 and 2005, widely accepted brand drugs were nearing patent expiration. Newly available generic medications, previously only available as a brand, have been introduced in mid-2006. These changes have provided practitioners the ability to reduce LDL-C at costs lower than ever.

In pursuing treatment strategies that achieve the desired therapeutic effect (with allowable side-effect risk) at the lowest cost, methods to assess cost-effectiveness are valuable. A primary measure in analyzing cost-effectiveness is the cost-effectiveness ratio, or dollar cost per unit of improvement for a given expenditure.

Figure 2 depicts the annual cost of various lipid-lowering therapies for each 1% reduction in LDL-C. Costs were derived from average wholesale price (AWP from First DataBank; August 2006) for branded drugs and the maximum allowable cost for generics from a large health plan.

This analysis depicts that, for low-to-moderate reduction (30%-40%), both lovastatin (at 34% LDL-C reduction) and simvastatin (at 39%-41% LDL-C reduction) provide the lowest cost per 1% reduction (\$12-\$19 per % reduction). The net dollar per percent reduction of simvastatin is likely to decrease in early 2007, when multiple generic manufacturers will lower wholesale price. Similarly, for reduction greater than 40%, Crestor (rosuvastatin)

and Vytorin (ezetimibe/simvastatin) have the lowest cost per 1% reduction, ranging from \$19 to \$26 per 1% reduction in LDL-C. Because reduction of LDL-C is the primary goal of statin therapy, selection of agents other than these is likely to cost more per 1% LDL-C reduction and be an unnecessary use of fiscal resources. In addition, in the era of percent coinsurance of brand drugs, the drugs with the lowest cost per 1% reduction in LDL-C will cost the patient less and possibly lead to higher adherence.

A Simple Strategy for Step Therapy

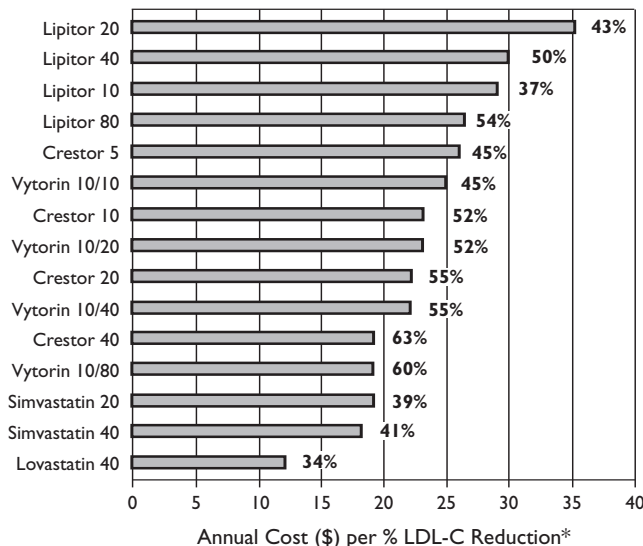
For patients who are considered to be at moderate-to-high risk or who have inherently

high LDL-C levels, more aggressive lipid lowering with rosuvastatin or simvastatin/ezetimibe are cost-effective options. This is based on the information displayed in Figure 2. For those at lower risk requiring lower LDL-C reduction, use of a generic agent will provide adequate LDL-C reduction. An additional benefit of selection of a generic for therapy in these situations is that the patient will only be responsible for a generic copay in most situations.

Conclusions

It is a rare occasion when new agents within a therapeutic class provide equal or greater efficacy for decreased cost. With the availability of both new brand and recent generic statin alternatives, LDL-C reduction can be achieved more economically than ever. For patients who need less than 40% LDL-C reduction, generic medications provide the most cost-effective choice. Crestor and Vytorin reduce LDL-C cost effectively (relative to other brands) for patients requiring LDL-C reduction greater than 40%. It should be noted that the LDL-C reduction percentages presented in this article are based on clinical trial data; in the clinical setting, factors such as population differences, comorbidity, adherence, and differences in baseline lipid profiles may result in LDL-C reductions different than expected.

Figure 2. Annual Cost per % LDL-C Reduction: Comparison of Lipid-lowering Therapies



*Costs per % LDL-C reduction are shown for the most commonly used statins and statin combinations. Total expected LDL-C reduction for each statin therapy, based on clinical data from package inserts, is listed next to each bar. Costs for branded drugs are derived from August 2006 AWP from First DataBank. Costs for generic drugs are derived from WAC of multiple manufacturers of generics.

LDL-C indicates low-density lipoprotein cholesterol; AWP, average wholesale price; WAC, wholesale acquisition cost.

Sources: Lipitor (atorvastatin) [package insert]. New York, NY: Pfizer, Inc; September 2005; Crestor (rosuvastatin) [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals LP; 2005; Vytorin (ezetimibe/simvastatin) [package insert]. North Wales, Pa: Merck/Schering-Plough Pharmaceuticals; November 2005; Mevacor (lovastatin) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; November 2005; Zocor (simvastatin) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; August 2005.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics—2006 Update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006; 113:e85-e151.
2. Grundy SM, Cleeman JI, Bairey Merz CN, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004; 110:227-239.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
4. Shepherd J, Cobbe SM, Ford I, 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;333:1301-1307.

5. Downs JR, Clearfield M, Weis S, 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;270:1615-1622.

6. Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. 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 multi-centre randomised controlled trial. *Lancet.* 2003;361:1149-1158.

7. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-1 and B, and HDL density sub-fractions: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2001;104:1108-1113.

8. Chilton RJ. The new “lower is better” lipid goals: are they achievable with today’s drugs? *JAHA.* 2002;102(suppl 1):S1-S5.

9. 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;344:1383-1389.

10. 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.

11. Cannon CP, Braunwald E, McCabe CH, et al, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495-1504.

12. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on

coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-1009.

13. The Long-Term Intervention with Pravastatin in Ischaemic 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. *N Engl J Med.* 1998;339:1349-1357.

14. 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;287:3215-3222.

15. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al, for the GREACE Study Collaborative Group. Relationship between LDL-C and non-HDL-C levels and clinical outcome in the Greek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin.* 2004;20:1385-1392.

16. de Lemos JA, Blazing MA, Wiviott SD, et al, for the A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA.* 2004;292:1307-1316.

17. LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Invasive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425-1435.

18. Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003;91(suppl):11C-19C.

19. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol.* 2006;97(suppl):88C-94C.

