Lowering LDL Cholesterol
Questions From Recent Meta-Analyses and Subset Analyses of Clinical Trial Data
Issues From the Interdisciplinary Council on Reducing the Risk for Coronary Heart Disease, Ninth Council Meeting
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Abstract—The benefit of cholesterol-lowering therapy in the prevention of coronary heart disease (CHD) is well established. The secondary prevention Scandinavian Simvastatin Survival Study (4S) and the primary prevention West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated that lipid lowering with a statin can dramatically and cost-effectively reduce CHD morbidity and mortality with no increase in noncardiovascular mortality. The Cholesterol and Recurrent Events (CARE) trial extended benefit to CHD patients without high cholesterol. Post hoc analyses of data from these large trials are contributing to speculation, driven by subset analyses and meta-analyses, about whether cholesterol intervention should be target based, as current guidelines recommend. Whereas CARE data support the importance of baseline LDL cholesterol (LDL-C), with greatest clinical event risk reduction in the upper part of the LDL-C range in the trial, 4S found no difference in outcome according to baseline LDL-C in a quartile analysis, and WOSCOPS found no linear relation between decrease in LDL-C and decrease in relative risk for CHD. Furthermore, WOSCOPS showed no additional clinical benefit with LDL-C lowering beyond 24%. Questions raised by such analyses require answers from prospective, hypothesis-based data, and at present there is no compelling argument for moving away from LDL-C targets. The hypothesis-based findings of 4S, CARE, and WOSCOPS support current clinical guidelines, and lowering LDL-C may reduce risk more substantially than might have been predicted. (Circulation. 1999;99:e4.)

Key Words: cholesterol ■ coronary disease ■ lipoproteins ■ prevention

The Interdisciplinary Council on Reducing the Risk for Coronary Heart Disease (see Appendix) convened September 6 to 7, 1997, in Washington, DC, to examine 2 key topics of current interest in the lipids arena and important to the evolution of clinical guidelines. First, what might the inaugural clinical end-point trials of HMG-CoA reductase inhibitors (statins) tell us about selecting LDL cholesterol (LDL-C) goals in high-risk patients? Second, does statin therapy meet the requirements for cost-effective risk reduction? Discussion of these issues focused on analyses of data from the West of Scotland Coronary Prevention Study (WOSCOPS).

Perspectives on Lowering LDL-C
Evolution of the NCEP Guidelines With Clinical Trial Data
Observational epidemiological findings have long demonstrated a continuous, curvilinear relation between plasma cholesterol concentration and coronary heart disease (CHD) incidence. The association has been shown to apply not only to middle-aged men but also to young men, the elderly, and women.1,2 Likewise, there have been clear answers for many years from clinical trials that lowering moderately high or high total cholesterol (TC) or LDL-C can substantially reduce CHD rates.2,3 These results were achieved even with the less-powerful lipid-lowering agents that antedated the statins, as well as with lifestyle changes alone. The results of the primary prevention Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), published in 1984,4 were key to the initiation of clinical guidelines by the National Cholesterol Education Program (NCEP).5 In the LRC-CPPT, conducted in hypercholesterolemic middle-aged men, there did not appear to be anything but the log-linear relation between cholesterol reduction and CHD risk reduction predicted by observational studies. From its results, the 2:1 rule of thumb evolved: that a 1% lowering of cholesterol would result in about a 2% lowering of risk, or the inverse of the observational ratio of a 2% to 3% increase in risk for each 1%
rise in cholesterol.\(^6\) The LRC-CPTPT results accord well with the 1994 meta-analysis performed by Law et al\(^7\) of 28 trials, nearly all conducted before the advent of the statins, assessing effects of lipid lowering on clinical events or vascular end points.

The concept of the NCEP’s first Adult Treatment Panel (ATP I) guidelines\(^5\) was diet-driven intervention; there was no special focus on secondary prevention. Although the guidelines emphasized evaluation of an individual’s overall risk for CHD (including lipid and nonlipid factors) as well as reliance on the physician’s clinical judgment, the need for an acceptable definition of desirable cholesterol ranges and action limits was answered. Cutoffs were based on estimates of lipid risk requiring intervention from US adult population percentiles for TC (where \(\approx 200\) and \(240\) mg/dL defined the 50th and 75th percentiles, respectively) and for LDL-C (where \(\approx 130\) and \(160\) mg/dL defined those percentiles). The LDL-C goal for patients at high risk (whether from multiple risk factors or the presence of CHD) was \(< 130\) mg/dL; for others with elevated cholesterol, it was \(< 160\) mg/dL.

Between the first NCEP guidelines and the convening of the ATP II, useful evidence became available from secondary prevention trials indicating the value of aggressive lipid lowering in patients with CHD. The meta-analysis by Rossouw et al\(^a\) of 8 secondary prevention trials, indicating clear-cut benefit, was very influential. In the trials analyzed (in which baseline cholesterol ranged from 240 to 300 mg/dL), a 10% to 15% reduction in cholesterol concentration gave an \(\approx 25\)% reduction in recurrent myocardial infarction (MI), with no evidence for an increase in the noncardiovascular mortality rate and a strong trend toward a reduction in total mortality. Hence, the ATP II algorithm was stratified according to whether atherosclerotic disease was or was not present, and the emphasis shifted to identifying the highest-risk patients for aggressive therapy: the higher the risk, the more aggressive the therapy.\(^3\) Among the lipid experts on the ATP II panel, there was almost universal agreement on \(100\) mg/dL as the more stringent target for secondary prevention patients, based in part on findings from regression trials such as the Familial Atherosclerosis Treatment Study (FATS).

Mean on-trial LDL-C was \(98\) mg/dL in the FATS subgroup (40 patients) with the least coronary lesion progression.\(^9\) Certainly, the results of WOSCOPS,\(^10,11\) the Scandinavian Simvastatin Survival Study (4S),\(^12-14\) and the Cholesterol and Recurrent Events trial (CARE)\(^15\) appear to support the recommendations of the ATP II; the feeling is that the recommendations and goals work as they were predicted to work.

In the men and women of 4S, aged 35 to 70 years with a history of angina pectoris or MI (TC enrollment criterion of \(212\) to \(310\) mg/dL; mean TC and LDL-C of \(261\) and \(188\) mg/dL, respectively), simvastatin (20 or \(40\) mg/d) lowered LDL-C \(35\)% (mean on-trial value of \(\approx 120\) mg/dL), lowered triglyceride \(10\)% , and raised HDL cholesterol (HDL-C) \(8\)% from baseline and reduced all-cause mortality \(30\)% \((P=0.0003)\), for the first unequivocal demonstration of mortality benefit.\(^12\) Also, therapy significantly reduced rates of major coronary events, coronary death, and need for revascularization. Benefit was evident after \(\approx 1\) year of treatment.\(^12\)

The results from the CARE trial, which started at a lower cholesterol range (TC \(< 240\) mg/dL and LDL-C of \(115\) to \(174\) mg/dL; means of \(209\) and \(139\) mg/dL) in patients aged 21 to 75 years (mean, \(59\) years), support aggressive cholesterol reduction in MI survivors even without high LDL-C. Therapy with pravastatin prescribed at \(40\) mg/d (with or without cholestyramine) lowered LDL-C \(28\)% and triglyceride \(14\)% and increased HDL-C \(5\)% compared with placebo. Mean on-trial LDL-C in the pravastatin group throughout the 5 years of the study was \(97\) to \(98\) mg/dL, \(28\)% lower than in the placebo group. Nonfatal MI or CHD death was reduced \(24\)% \((P=0.003)\), with no increase in noncardiovascular deaths; divergence between the drug and placebo arms began at \(\approx 2\) years. The rate of revascularization procedures was \(27\)% lower \((P<0.001)\) with statin treatment, and the rate of stroke was \(31\)% lower \((P=0.03)\).\(^15\)

The WOSCOPS results in men aged \(45\) to \(64\) years (mean, \(55\) years) who had hypercholesterolemia (mean TC, \(272\) mg/dL; mean LDL-C, \(192\) mg/dL) reiterated the value of cholesterol lowering in high-risk primary prevention.\(^10,11\) Treatment with pravastatin prescribed at \(40\) mg/d reduced LDL-C \(26\)% (mean on-trial value of \(\approx 140\) mg/dL), reduced triglyceride \(12\)% , and raised HDL-C \(5\)% from baseline, for reductions in rates of nonfatal MI plus CHD death (\(-31\%\); \(P<0.001)\), nonfatal MI (\(-31\%\); \(P<0.001)\), all-cause death (\(-22\%\); \(P=0.051)\), and need for revascularization procedures (\(-37\%\); \(P=0.009)\). A divergence in CHD effect between the drug and placebo groups began to emerge as soon as \(6\) months after the beginning of the trial.

**Action Limits**

Now that LDL-C concentrations can routinely be substantially reduced safely and with excellent agent tolerability, how low should they go? Is benefit best predicted by baseline LDL-C concentration, percentage LDL-C reduction, or LDL-C concentration achieved?

**Predictivity of Baseline and On-Treatment LDL-C Concentrations**

In the curvilinear relation between cholesterol concentration and CHD risk, risk is stronger at higher concentrations,\(^1-6\) and several analyses have indicated greater benefit of cholesterol lowering for those with higher concentrations. In the Cholesterol Lowering Atherosclerosis Study (CLAS), for example, angiographic benefit was more striking in patients with baseline TC of \(240\) to \(350\) mg/dL than in those with beginning values of \(185\) to \(240\) mg/dL.\(^7\) A meta-analysis of 13 angiographic trials by Sacks et al\(^18\) showed atherosclerotic lesion regression to be more common when mean baseline LDL-C was \(> 170\) mg/dL, whereas progression occurred with baseline LDL-C \(< 170\) mg/dL. Baseline LDL-C was significantly correlated with the difference between the changes in percent diameter stenosis in the treatment and control groups. Neither change in LDL-C with treatment nor LDL-C concentration during treatment was associated with angiographic outcome; in fact, the greatest percentage reductions in LDL-C tended to predict the smallest changes in coronary stenosis, reflecting, in the authors’ view, the predominant influence of baseline LDL-C. In a regression trial conducted by Sacks et
Importance of Percentage Change in LDL-C

Other analysts argue that baseline or on-treatment LDL-C concentration is not an important determinant of the outcome of lipid lowering, and thus, that the concept of LDL-C action limits in clinical guidelines is flawed. Thompson et al performed a meta-analysis of data from 8 statin regression trials plus 3 trials using other forms of therapy, with enrollments ranging from 39 to 331 patients. They found a significant association of change in percent diameter stenosis with percentage change in LDL-C ($P<0.0005$) but not with the LDL-C concentration during the trial. Thompson also examined the results from 4S, CARE, and WOSCOPS, as well as 2 large statin angiographic trials (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries [PLAC I, n=408] and the Regression Growth Evaluation Statin Study [REGRESS, n=885]), and concluded that percentage decrease in LDL-C predicted clinical benefit better than LDL-C on treatment.

Similarly, Holme, in a “metaregression analysis” of 42 randomized cholesterol-lowering trials that antedated 4S, CARE, and WOSCOPS, among them a number of diet trials and several statin angiographic trials, found a significant dose-response relation between percentage reduction in cholesterol and reductions in total mortality and CHD rates. This agrees with results of some individual trials. In the LRC-CPT, for example, a 64% reduction in CHD risk was observed in the group with decreases of >25% in LDL-C compared with the 19% CHD reduction that occurred with 13% LDL-C reduction (versus placebo) for the group as a whole; that is, reduction in CHD appeared to have been mediated chiefly by cholesterol reduction. The Holme analysis indicated that substantial reduction in total mortality rate should be expected with aggressive cholesterol reduction, at least in populations at moderate or higher risk for CHD. Interestingly, its regression lines for both total mortality and CHD incidence accurately predicted the 4S results.

Subgroup analysis of the 4S results has been interpreted as supportive of the precedence of percentage lowering over baseline LDL-C in prediction of outcome. In all quartiles of baseline LDL-C in 4S ($\geq 100$ patients) and intervention (a statin with or without a resin) and concluded that on-treatment LDL-C appeared to be as good a predictor of angiographic improvement as percentage reduction in LDL-C. In that analysis, weighted by sample size, the relation between change in minimum lumen diameter and either on-treatment LDL-C or percentage change in LDL-C was identical.

Recent Analyses From WOSCOPS
The WOSCOPS investigators used the Cox proportional hazards model to assess the influence of baseline risk factors on clinical events in the trial as well as their interaction with therapy. They found that the drug-induced reductions in...
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CHD morbidity, CHD mortality, and all-cause mortality rates were independent of baseline predictors of outcome; that is, pravastatin intervention yielded the same proportional benefit regardless of the baseline risk characteristics, including, as in 4S, lipoprotein phenotype. In other words, benefit was seen essentially regardless of to whom the drug was given in the WOSCOPS population. Besides treatment allocation (pravastatin or placebo), independent predictors of nonfatal or fatal coronary events were current smoking, diabetes mellitus, diastolic blood pressure (difference of 10 mm Hg), and the TC:HDL-C ratio (difference of 0.5), as well as angina pectoris, nitrate consumption, minor ECG abnormalities, widowhood, and family history of early CHD death. Neither TC nor LDL-C was an independent predictor of outcome in WOSCOPS, which was attributed to the narrow entry range: LDL-C of $\geq 155$ mg/dL during 2 screening visits, with at least 1 value $\geq 174$ mg/dL and 1 value $\leq 232$ mg/dL.$^{10}$ The investigators believed the narrow range may have been a limitation in attempting to determine the influence on a wider population. However, relative risk reduction was not significantly different whether baseline LDL-C concentration was above or below the median of 193 mg/dL,$^{11}$ which is consonant with the consistent results across baseline LDL-C concentrations in 4S,$^{13}$ which had a wider range of values.

Calculating risk scores by use of the multivariate predictors in this analysis showed that the highest quartile of risk distribution for nonfatal MI or CHD death encompassed 45% of coronary events. Because relative risk reduction was uniform in all WOSCOPS subgroups, therapy could be offered throughout such a risk range, including the lower 3 quartiles that accounted for the other 55% of events, with the knowledge that coronary events would be prevented without any increase in noncardiovascular death.$^{11}$

The WOSCOPS investigators have now extended the Cox proportional hazards analysis to focus on how changes in LDL-C related to decreased CHD risk in the patients who received pravastatin in this primary prevention trial (findings presented to the Interdisciplinary Council on September 6, 1997 by Dr Christopher J. Packard; now published$^{13}$). Baseline and on-trial LDL-C values represented means of multiple determinations in a single laboratory certified by the Lipid Standardization Program of the Centers for Disease Control and Prevention. LDL-C response in the pravastatin group was variable, ranging from increases (in noncompliant patients) to reductions $>40\%$, for an average decrease of 26%, as noted above. Regardless of how LDL-C response was divided, the way in which on-treatment LDL-C was assessed, and whether the clinical end point assessed was the primary end point (coronary death and nonfatal MI) alone or expanded with revascularization procedures, no linear relation was found between decrease in LDL-C and decrease in relative risk for CHD. In a quintile analysis, for example, reductions of LDL-C by 0%, 12%, 24%, 31%, and 39% translated to relative risks (versus placebo) of 1.09, 0.72, 0.53, 0.69, and 0.51 for the primary end point; within the quintiles, other risk factors were fairly evenly distributed. Analyses demonstrated that CHD risk reduction was maximized (at $\approx 45\%$) with LDL-C lowering of $\approx 24\%$; there was no further benefit with additional LDL-C lowering (up to 39% lowering achieved), although a fall in LDL-C was required for any risk reduction. The same on-trial LDL-C value translated into different outcomes according to whether patients were assigned drug or placebo; in the LDL-C range of 140 to 180 mg/dL, for example, in which substantial numbers of patients had similar LDL-C values, there were 180 coronary events per 1000 patients in the placebo group compared with 67 events per 1000 patients in the drug group. Absolute change in LDL-C, like percentage change, did not define risk reduction.

These findings suggest several possible mechanisms of benefit. Simply lowering LDL-C may reduce risk more substantially and dramatically than might have been predicted. The drug therapy may have lowered concentrations of other atherogenic lipoproteins, such as chylomicron remnants and VLDL remnants,$^{34}$ which are not recorded simply by the change in LDL-C. Statins have been demonstrated to enhance removal of chylomicron remnants$^{35}$ and to significantly reduce concentrations of LDL cholesterol.$^{36,37}$

Furthermore, it has been suggested on the basis of recent findings in human and animal studies, as well as the apparent discrepancy between small reductions in stenosis and large improvements in coronary event rates,$^{2,38}$ that lipid-lowering therapy may achieve its clinical benefit through ancillary effects, as has been reviewed elsewhere.$^{39–42}$ Stabilization of lipid-rich, rupture-prone lesions may be more important than lesion regression. Effects on vascular reactivity, rheological/thrombotic effects, local cellular actions, and reduced oxidation potential are among mechanisms for which evidence is available for the HMG-CoA reductase inhibitors. Such effects may be specific or modified through LDL-C reduction. The possibility of nonlipid effects in WOSCOPS has been raised by its investigators on the basis of the results of applying a Framingham risk prediction model$^{43}$ to the data: whereas risk for CHD was accurately predicted in the placebo group, risk reduction in the pravastatin group was underestimated by 35%.$^{33,44}$

Effects on endothelial and vascular wall dysfunctions have occurred rapidly in lipid-lowering studies, within 2 to 6 months in many studies, which may help explain the beginning of divergence in clinical outcome curves at about 6 months in WOSCOPS. However, available data are insufficient to support or reject the hypothesis that there are class differences among the statins, and improvements in atherosclerosis parameters other than stenosis have not been related to reductions in coronary events. The statins most certainly are individual chemical entities, and in general, the differences in chemical structure have not been linked to in vivo effects on clinical events or disease progression apart from LDL-C lowering. This is not to say that the statins are the same and that “a statin is a statin is a statin.”

Interestingly, with regard to reductions in plaque size rather than plaque stabilization, Rossouw$^{36}$ hypothesized, on the basis of his meta-analysis of angiographic trials, that a decrease of $\approx 20\%$, or 30 mg/dL, in LDL-C is sufficient to modify the angiographic course of coronary atherosclerosis (for follow-up of $\approx 2$ to 3 years), with only modest gains to be expected from additional reductions in LDL-C.
Interpretations
Many types of data over many years have clearly demonstrated that elevated cholesterol is one of the most important determinants, if not the single most important determinant, of the atherogenic process and that its reduction significantly reduces risk for CHD.2,3,4–45 When concentrations are low enough, atherosclerosis does not develop.45 Post hoc assessments and meta-analyses of clinical trial data that call into question whether the degree of LDL-C lowering or baseline or on-trial LDL-C concentrations relate to relative risk reduction suggest that clinical guidelines might best focus on patient selection or additional markers of dyslipidemia (eg, triglyceride-rich lipoproteins or apolipoprotein-defined particle families) rather than LDL-C action limits. No unified view, however, has yet emerged; whether to move away from LDL-C targets is not clear from data thus far, and there seems to be no compelling argument for doing so. The clinical end-point statin trials support the NCEP approach of adjusting the intensity of lipid-lowering intervention to the patient’s absolute risk. Questions raised by subset analyses and meta-analyses require answers from prospective, hypothesis-based data (just as clinical end-point findings in 4S and WOSCOPS rebut claims of increased noncardiovascular mortality with lipid lowering per se). Whether greater reduction of LDL-C may yield greater clinical benefit will be tested in the secondary prevention Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH trial) in the United Kingdom (20 versus 80 mg of simvastatin daily) (www.admin.ox.ac.uk/science/projects/collins.htm). Also, it must be borne in mind that although the NCEP management guidelines include an algorithmic approach to facilitate implementation, their core has always been the primacy of clinical judgment in assessing overall risk from multiple risk factors in any given patient.

Cost-Effectiveness Findings From WOSCOPS
Decision making in medicine increasingly must take into account issues of cost-effectiveness. In the prevention of CHD, the use of lipid-lowering drugs is not only efficacious but also nearly always cost-effective in secondary prevention.40,46–48 It has been estimated that $1 billion could be saved annually in the United States with appropriate lipid-lowering drug therapy in patients with CHD.49 In preventing new-onset CHD altogether, however, the drugs, although effective, are generally viewed as too expensive at present for use as a mass strategy; for such therapy to be cost-effective, only those patients in the higher range of risk (from hypercholesterolemia plus other risk5) can be selected for treatment.66–48 For those at moderately high risk, careful attention must be given to nondrug approaches, including a low-fat diet, weight control, and increased physical activity.3 For the general population, nondrug approaches to reduce the overall incidence of CHD need to be more broadly applied; because the relation of plasma cholesterol to CHD risk is graded across a broad range, shifting the distribution of the entire curve by even a modest amount will yield substantial benefits.3,22,50

Although WOSCOPS was initiated before development of the ATP II guidelines, 77% of its patients in fact fell within ATP II categories for consideration of lipid-lowering pharmacotherapy, given that all had received diet therapy.11 As reviewed above, subjects were middle-aged men (a category that is itself a risk factor5) with hypercholesterolemia (mean TC of 272 mg/dL) and no history of MI. Their cholesterol values were in the highest quartile of the range found in the British population; prevalence was 1% for self-reported diabetes mellitus, 16% for history of hypertension, and 44% for current smoking.10 Extension of the WOSCOPS findings from Scotland to the United States (by use of US vital statistics, Framingham Heart Study data, and a health-insurer database, with societal and managed care perspectives) indicated that pravastatin therapy is cost-effective for Americans in primary prevention (findings presented to the Interdisciplinary Council on September 6, 1997, by Dr Joel W. Hay, and presented at the 70th Scientific Sessions of the American Heart Association51). By intent-to-treat analysis, treatment of 1000 patients for 5 years resulted in the prevention of 31 initial cardiovascular events (13 MIs, 5 strokes, 10 angina presentations, and 3 cardiovascular deaths); avoiding these events would save 129 years of life and $2.2 million in subsequent healthcare costs. Base-case cost-effectiveness was estimated at $17 000 per year of life saved, and cost per life-year saved compared favorably with antihypertension medications, smoking cessation programs, exercise programs, CABG, PTCA, and other interventions widely used in CHD prevention.51 The cost-effectiveness was applicable under a wide range of risk factors and model assumptions,51 consonant with the uniform relative risk reduction in all WOSCOPS subgroups.11 Because pravastatin is the only statin for which long-term longitudinal data are available in both primary prevention (WOSCOPS) and secondary prevention (CARE and LIPID), economic analyses were awaited with interest. Analysis of pooled data from angiographic trials has previously shown the cost-effectiveness of pravastatin therapy in secondary prevention in the United States: depending on the patient risk profile, cost per life-year saved ranged from $7124 to $12 665, which is favorable compared with other widely accepted medical interventions.52

Appendix
Drs Gotto and Grundy cochaired the ninth meeting of the Interdisciplinary Council on Reducing the Risk for Coronary Heart Disease. The council, a multidisciplinary outgrowth of task groups initially brought together by the American Heart Association and the National Heart, Lung, and Blood Institute, comprises opinion leaders in fields related to the prevention and treatment of atherosclerotic disease. Other council members participating in the ninth meeting were Jerome Cohen, MD, FACC, of the St. Louis University School of Medicine; James M. McKenney, PharmD, of Virginia Commonwealth University; Thomas A. Pearson, MD, PhD, of the University of Rochester School of Medicine; Charles E. Rackley, MD, of Georgetown University Medical Center; and Elliot Rapoport, MD, of the University of California, San Francisco, School of Medicine.
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Guest speakers were Joel W. Hay, PhD, of the University of Southern California School of Pharmacy; James D. Otvos, PhD, of North Carolina State University; and Christopher J. Packard, PhD, FRCPath, DSc, of the University of Glasgow Royal Infirmary.

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