

“The Lower the Better” in Hypercholesterolemia Therapy: A Reliable Clinical Guideline?

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Since the publication of the second set of guidelines by the National Cholesterol Education Program, a solid body of data from landmark clinical studies has demonstrated that reduction in low-density lipoprotein (LDL) cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (“statin”) therapy sharply diminishes the risk for coronary artery disease. These trials include the Scandinavian Simvastatin Survival Study, the West of Scotland Coronary Prevention Study, the Air Force/Texas Coronary Atherosclerosis Prevention Study, the Cholesterol and Recurrent Events investigation, and the Long-Term Intervention with Pravastatin in Ischaemic Disease trial. Coronary event rates and, in some cases, all-cause mortality decreased significantly after about 5 years of statin therapy in patients at risk for and those who had coronary artery disease at baseline. In contrast, recent subgroup analyses of these pivotal studies have in the aggregate challenged the premise that lower LDL cholesterol levels necessarily lead to further declines in risk for coronary artery disease, particularly among the patients most likely to be seen by the clinician: those with mod-

erately elevated or normal cholesterol profiles. Indeed, when LDL cholesterol levels are in this range, further lowering with statin therapy elicits diminishing returns in terms of coronary event rates. These findings are readily accommodated by the curvilinear, or log-linear, model between serum cholesterol level and risk for coronary artery disease, which is predicated on data from large epidemiologic studies. In light of the current climate involving competing health care costs, the pursuit of progressively diminishing returns in terms of reductions in coronary artery disease risk through more aggressive lowering of LDL cholesterol levels appears to be unwarranted. Until data are published from ongoing randomized, clinical trials that can more effectively resolve the clinical utility of aggressive lipid-lowering strategies to improve coronary event rates, a prudent, evidence-based strategy seems warranted.

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A welcome advance in contemporary health care decision making is the emerging preponderance of evidence-based medicine over paradigm-based medicine. As the National Cholesterol Education Program (NCEP) Adult Treatment Panel formulates its next set of guidelines for the treatment of hypercholesterolemia, it will consider data from landmark clinical trials (1–4) of the value of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (“statins”) in attenuating the risk for coronary artery disease. Reductions in low-density lipoprotein (LDL) cholesterol levels elicited by these agents (simvastatin, pravastatin, and lovastatin) have steeply decreased coronary event rates in the settings of primary and secondary prevention. These compelling data constitute a sound basis for the widespread use of statins to improve coronary artery disease risk profiles.

However, the robust findings cited above do not necessarily justify targeting LDL cholesterol to its lowest possible level, and the argument expressed by the phrase “the lower the better” is clearly not evidence based. First, a large body of epidemiologic evidence indicates that the relationship between levels of total or LDL cholesterol and risk for coronary artery disease is curvilinear, or log-linear. For most of the U.S. population who exhibit either normal or

mildly elevated serum cholesterol levels, lipid-lowering therapies are likely to produce progressively less benefit in terms of reduction in coronary event rates.

In addition, analyses of findings from recent clinical trials on the use of statins in high-risk persons or patients with baseline coronary artery disease also appear to curb enthusiasm for the argument that lower is better. Rather, results of these analyses suggest a “diminishing-returns” model that is thoroughly consistent with the curvilinear relationship between baseline cholesterol level and risk for coronary artery disease established in epidemiologic trials. No trial of lipid-lowering therapy conducted to date has attempted to establish an optimal target level of LDL cholesterol in patients with or those without baseline coronary artery disease.

EPIDEMIOLOGY

Longitudinal population-based studies, including the Framingham Heart Study (5), the analysis of persons screened in the Multiple Risk Factor Intervention Trial (6), and the Prospective Cardiovascular Munster study (7), established the familiar curvilinear, or log-linear, relationship between levels of total or LDL cholesterol and risk for

Table. Effects of Statin Therapies on Coronary Artery Disease: Results from Clinical Events Trials*

Trial	Baseline LDL Cholesterol Level	Final LDL Cholesterol Level	Reduction in LDL Cholesterol Level	Event Rate in Statin Group†	Event Rate in Placebo Group†	Relative Risk Reduction	Absolute Risk Reduction	Number Needed To Treat for Benefit
	mg/dL (mmol/L)		%					
4S	4.86 (188)	3.15 (122)	35	19.4	28.0	34	8.6	12
LIPID	3.88 (150)	2.90 (112)	25‡	12.3	15.9	24	3.6	28
CARE	3.59 (139)	2.53 (98)	32	10.2	13.2	24	3.0	34
WOSCOPS	4.96 (192)	4.11 (159)	26	5.3	7.5	29	2.2	46
AFCAPS/TextCAPS	3.88 (150)	2.97 (115)	25	3.5	5.5	37	2.0	50

* 4S = Scandinavian Simvastatin Survival Study; AFCAPS/TextCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol and Recurrent Events; LDL = low-density lipoprotein; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS = West of Scotland Coronary Prevention Study. Adapted from reference 8.
 † Nonfatal myocardial infarction or coronary artery disease death in WOSCOPS, CARE, and LIPID; nonfatal or fatal myocardial infarction, unstable angina, or sudden cardiac death as first event in AFCAPS/TextCAPS; nonfatal myocardial infarction, coronary death, or resuscitated cardiac arrest in 4S.
 ‡ Compared with placebo.

coronary artery disease. This curvilinear relationship predicts that reductions in LDL cholesterol level will confer more pronounced cardioprotective benefits in persons with higher serum concentrations of LDL cholesterol, for whom the curve is relatively steep, than in patients who have lower levels, for whom the curve is relatively flat.

ABSOLUTE RISK AND NUMBER NEEDED TO TREAT FOR BENEFIT

To clarify the relationship between declines in serum LDL cholesterol levels and coronary event rates associated with HMG-CoA reductase inhibitor therapy, it is useful to consider the concept of the number needed to treat for benefit (NNT_B): that is, the number of patients who must be treated to prevent one coronary artery disease event over a 5-year period. This value, which represents the reciprocal of the absolute risk reduction, enables clinicians and policy-makers to assess the advisability of undertaking statin treatment for patients at various degrees of baseline risk.

In this paper, the NNT_B associated with treatment of patient populations with distinct baseline risk profiles for coronary artery disease will be cited to substantiate the argument that targeting LDL cholesterol to progressively lower levels is associated with diminishing cardioprotective benefits. This diminishing-returns argument is particularly relevant when statin therapy is being contemplated for patients with modest absolute risk for coronary artery disease at baseline, such as in primary prevention.

When NNT_B values are used, a stronger case can be made for using HMG-CoA reductase inhibitors in secondary prevention than in primary prevention. In addition, a stronger case can be made for targeting patients with higher levels of LDL cholesterol or greater risk for coronary

artery disease at baseline, because diminishing returns set in at progressively lower baseline levels of LDL cholesterol. Data on changes in LDL cholesterol levels and coronary event rates and the corresponding NNT_B values from landmark clinical trials involving statins are summarized in the Table.

CLINICAL TRIALS

Treatment of Hypercholesterolemia in Patients with Coronary Artery Disease

The log-linear diminishing-returns model predicted by epidemiologic data appears to accommodate the findings from three landmark trials of secondary prevention reported since the publication of the NCEP Adult Treatment Panel II guidelines (9): the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE) trial, and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (1–3). These clinical studies, which tested statins in patients with previous myocardial infarction, laid a stable foundation for institution of therapy with these agents even when LDL cholesterol levels are not markedly elevated (2, 3). Because coronary artery disease is multifactorial, most patients with coronary artery disease have serum LDL cholesterol values that are not even markedly elevated, on the order of 3.10 to 3.62 mmol/L (120 to 140 mg/dL) (10, 11).

In this regard, analyses of major secondary prevention trials have imposed clear constraints on the premise that “lower is better,” and their conclusions are more consistent with a diminishing-returns model. First, post hoc subgroup analysis of the CARE study (12) demonstrated that coronary event rates decreased as LDL cholesterol levels declined from 4.50 mmol/L (174 mg/dL) to approximately

3.23 mmol/L (125 mg/dL) among 4159 patients with coronary artery disease and “average” cholesterol levels who were treated with pravastatin (40 mg/d) or placebo. On the other hand, no significant further cardioprotective benefits were conferred when LDL cholesterol levels were decreased from 3.21 mmol/L (124 mg/dL) to 1.84 mmol/L (71 mg/dL). The NNT_B for all CARE trial participants was 34.

The LIPID trial (3) also supported the contention that progressive reductions in LDL cholesterol level yield diminishing clinical benefits. As the largest double-blind, randomized, placebo-controlled trial to date of use of an HMG-CoA reductase inhibitor in the setting of secondary prevention (9014 patients), the LIPID study had more statistical power than the CARE trial to determine whether patients who reached progressively lower LDL cholesterol levels while receiving a fixed dose of pravastatin (40 mg/d) exhibited significant improvements in death from coronary artery disease and all-cause mortality, among other clinical outcomes.

When divided into tertiles, data from the LIPID trial clearly suggested otherwise (3). This subgroup analysis demonstrated that reductions in the risk for coronary artery disease death or myocardial infarction were 30% in patients who had LDL cholesterol levels greater than 4.5 mmol/L (174 mg/dL) after 6.1 years of treatment with fixed-dose pravastatin and 26% in those with LDL cholesterol levels from 3.49 to 4.5 mmol/L (135 to 173 mg/dL) but only 16% in the group with levels below 3.49 mmol/L (135 mg/dL) (3). The NNT_B also demonstrated diminishing absolute risk reductions, ranging from 22 for the highest LDL cholesterol tertile (>4.5 mmol/L [174 mg/dL]) to 52 for the lowest tertile (<3.49 mmol/L [135 mg/dL]). Therefore, the findings of the LIPID study, together with evidence from the CARE trial (2, 12), are most compatible with the diminishing-returns model.

The angiographic Post Coronary Artery Bypass Graft Trial (13), the only randomized, controlled clinical trial to compare directly the effects of aggressive lipid-lowering therapy with those of usual care on risk for coronary artery disease, detected no significant decline in 4-year rates of death, myocardial infarction, stroke, or a composite end point among aggressively treated patients. In this trial, patients with coronary artery disease were randomly allocated to receive high-dose therapy with lovastatin (40 or 80 mg/d), which reduced their LDL cholesterol levels to 2.40 to 2.51 mmol/L (93 to 97 mg/dL), or moderate, lower-dose

lovastatin, which produced values of 3.41 to 3.52 mmol/L (132 to 136 mg/dL).

Statistically significant decreases in the proportion of grafts with atherosclerotic progression, occurrence of new occlusions, and mean lumen diameters and a nonsignificant decline in the revascularization rate were seen in the aggressive treatment group of the Post Coronary Artery Bypass Graft Trial (13). However, the more aggressive lipid-lowering treatment failed to improve coronary event rates. Although the Post Coronary Artery Bypass Graft Trial study was not statistically powered to examine coronary events, it was the first trial to compare aggressive with moderate lipid-lowering therapy. A recent follow-up study of the same cohort over a longer time (7.5 years) also failed to show a statistically significant difference in coronary events (cardiovascular death or nonfatal myocardial infarction) between these two lipid-lowering strategies (14).

The Atorvastatin versus Revascularization Treatment (AVERT) study (15) demonstrated a significant difference between rates of ischemic events (such as worsening angina and need for revascularization) among 164 patients aggressively treated with the statin to a mean LDL cholesterol level of 1.99 mmol/L (77 mg/dL) compared with 177 patients in the angioplasty (usual care) group, whose mean LDL cholesterol level was lowered to 3.08 mmol/L (119 mg/dL). However, the incidence rates of major coronary events (cardiac death and nonfatal myocardial infarction)—which are considered the gold standard for outcomes in clinical trials—were 3.0% and 3.4% in the aggressive and usual-care groups, respectively, and the attendant absolute risk reductions were unimpressive.

Subgroup analysis (16) of data from the 4S also challenged the premise that lower is better. This tertile analysis demonstrated a decline in 4-year coronary event rates to 18.9% among patients who achieved LDL cholesterol levels of 3.28 to 6.88 mmol/L (127 to 266 mg/dL), 13.3% in those with levels of 2.71 to 3.26 mmol/L (105 to 126 mg/dL), and 11.0% among those with levels of 1.50 to 2.69 mmol/L (58 to 104 mg/dL) after treatment with simvastatin (20 to 40 mg/d). The 4S investigators did not provide confidence intervals or *P* values to suggest whether the small difference in the lower two tertiles was statistically significant. Thus, the 4S data appear to be fundamentally consistent with findings from the LIPID and CARE subgroup analyses and the diminishing-returns model (3, 12).

Finally, a quartile analysis (17) of the relationship

between baseline LDL cholesterol level and frequencies of major coronary events in the 4S also challenges the assertion that progressively lower levels of LDL cholesterol are associated with improved event rates in secondary prevention. Although the study protocol (1) specified titration of simvastatin dosages from 20 to 40 mg/d in patients who did not reach the target total cholesterol level of less than 5.17 mmol/L (200 mg/dL) after 6 or 18 weeks, the quartile analysis demonstrated that reductions in relative risk were independent of baseline LDL cholesterol levels. These risk reductions ranged from 35% in patients with entry LDL cholesterol levels less than 4.37 mmol/L (169 mg/dL) to 36% among those with levels greater than 5.33 mmol/L (206 mg/dL). Clearly, patients with the higher levels of LDL cholesterol at baseline needed to lower them to a greater extent in order to achieve target values, but these larger reductions were not associated with sharper declines in the risk for major coronary events.

Treatment of Hypercholesterolemia in Patients without Coronary Artery Disease

The premise that greater reductions in LDL cholesterol level are desirable was also challenged in the setting of primary prevention. First, follow-up multivariate regression analysis (18) of the West of Scotland Coronary Prevention Study (WOSCOPS) (4) demonstrated that the optimal relative risk reduction in coronary artery disease was attained when pravastatin (40 mg/d) therapy decreased LDL cholesterol levels in moderately hypercholesterolemic men by a mean of 24% (the middle quintile); progressively greater declines in LDL cholesterol level did not further enhance risk profiles. In WOSCOPS (4), all patients received a fixed dosage of pravastatin (40 mg/d), including patients with a greater degree of baseline hypercholesterolemia. Even in these men, the relative risk reduction of 31% in coronary events was similar among patients in all quintiles of baseline LDL cholesterol values. The NNT_B for the entire WOSCOPS cohort was 46.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (19), which involved 6605 patients without previous myocardial infarction, also disputed the desirability of attaining progressively lower LDL cholesterol levels in the setting of primary prevention. In relatively low-risk persons with a mean baseline LDL cholesterol level of 3.88 mmol/L (150 mg/dL), reductions in coronary events were independent of baseline LDL cho-

lesterol levels, as demonstrated by tertile analysis. In addition, this titration-to-goal study demonstrated that patients randomly allocated to treatment with lovastatin, whether 20 or 40 mg/d, exhibited the same 37% relative risk reduction for the incidence of first acute major coronary events. In this population with low baseline LDL cholesterol levels and low baseline risk for coronary artery disease, the NNT_B was 50, a value even higher than the NNT_B in WOSCOPS. These results support the interpretation that higher lovastatin doses and lower attendant LDL cholesterol levels in these patients conferred no additional cardioprotective benefit. A recent regression analysis of AFCAPS/TexCAPS confirmed that baseline LDL cholesterol level, not the LDL cholesterol level achieved with treatment, was predictive of coronary events at 1 year (20).

Thus, in patients with varying degrees of baseline risk who had not previously experienced coronary events, reducing LDL cholesterol levels by more than 24% in WOSCOPS or doubling the statin dose in AFCAPS/TexCAPS did not further diminish risk for coronary artery disease. As with the evidence cited above for secondary prevention statin trials (4S, CARE, and LIPID), these data are compatible with the curvilinear relationship between LDL cholesterol level and coronary artery disease risk predicted by epidemiologic data.

SOCIETAL IMPLICATIONS OF “LOWER IS BETTER”

The favorable findings reported by the AFCAPS/TexCAPS investigators could add a substantial financial onus to an already overburdened health care delivery system (8). By one estimate (21), the conclusions of this study in low-risk patients could bring the number of U.S. residents who could conceivably benefit from LDL cholesterol-lowering therapy to 28.4 million. At an annual cost of \$1075 for low-dose lovastatin treatment (20 mg/d) and \$1766 for therapy with 40 mg/d (19), treatment of low-risk patients could cost the U.S. health care system \$22 to \$36 billion annually. Even more concerning is the fact that approximately 83% of patients in the AFCAPS/TexCAPS study (19) would not have been eligible for pharmacotherapeutic lipid lowering according to NCEP guidelines (9).

Ultimately, to establish the advisability of instituting treatment with HMG-CoA reductase inhibitors, health care policymakers in the United States must forge consensus on a threshold of absolute risk for coronary artery disease at which such therapy should be undertaken. The

Second Joint Task Force of European and other Societies on Coronary Prevention (22) addressed this matter by discussing cholesterol level elevations in the context of an annual coronary artery disease risk of more than 2% or a 10-year risk of more than 20% if projected to 60 years of age. For both primary and secondary prevention, one target level of LDL cholesterol was established: 2.97 mmol/L (115 mg/dL). This value is consistent with the conclusion of a meta-analysis (23) of primary and secondary prevention studies that scant additional clinical benefit accrues by reducing LDL cholesterol levels to below 2.84 mmol/L (110 mg/dL). Recently, Grundy and colleagues (24) advocated use of a 10-year absolute coronary-risk threshold of 20% as a “coronary artery disease equivalent.”

Although the appropriateness of an annual coronary artery disease risk threshold of 2% for lipid-lowering therapy must be debated in the United States, the Task Force’s overall recommendations underscore the value of using estimates of absolute risk for coronary artery disease that are based on multiple variables, including age, smoking status, levels of cholesterol and triglycerides, diabetes, and systolic blood pressure. These risk estimates may assist the clinician in a manner similar to the valuable nomograms developed from the Framingham Heart Study (25).

Apart from using a threshold value for coronary artery disease risk for initiating lipid-lowering therapy, pivotal measures to contain the cost of such treatment should include targeting patients at highest absolute risk for coronary artery disease, improving patient adherence, maximizing the benefits of improvements in nonlipid risk factors (such as hypertension, diabetes, and smoking), and using the most cost-effective lipid-lowering medications wherever suitable. Effective treatment with HMG-CoA reductase inhibitors can not only prevent coronary artery disease but also reduce its economic and human costs. Five-year estimated costs (in 1986 dollars) are \$51 211 for acute myocardial infarction, \$40 581 for unstable angina, \$32 465 for coronary artery bypass graft surgery, and \$26 916 for percutaneous transluminal angioplasty (26). The reductions in coronary artery disease end points, expensive hospitalizations, and revascularization procedures demonstrate the true value of statin therapy.

On the other hand, the cost-effectiveness literature (27, 28) demonstrates that doubling the dose of a given HMG-CoA reductase inhibitor will lead to a further decline in LDL cholesterol level of only about 6% while sharply increasing the cost of the more aggressive statin

regimen. Perreault and coworkers (28) showed that therapy with lovastatin, 80 mg/d, was not cost-effective for primary prevention of coronary artery disease and that 40 mg/d (compared with 20 mg/d) was cost-effective only if the total cholesterol level at baseline was greater than 7.74 mmol/L (300 mg/dL). Thus, the diminishing-returns model appears to hold true from the pharmacologic as well as the epidemiologic and clinical standpoints.

In conclusion, enthusiasm for the argument that “lower is better” for LDL cholesterol levels seems to be tempered, if not contradicted, by convergent epidemiologic, clinical, and pharmacologic data consistent with a diminishing-returns model. However, the argument advanced in this paper has limitations. First, because the incidence of coronary artery disease in persons with type 2 diabetes mellitus is elevated twofold to fourfold at any given level of LDL cholesterol (29), aggressive lipid-lowering therapy may be warranted for patients with diabetes. According to the new American Diabetes Association guidelines (30), the target LDL cholesterol level for patients with diabetes is 3.59 mmol/L or less (≤ 100 mg/dL)—the same target as the NCEP’s guideline for patients with coronary artery disease—irrespective of whether the patient has evidence of coronary artery disease or other cardiovascular diseases.

Second, this argument does not take into account other possible cardioprotective effects conferred by statin therapy, such as increases in HDL cholesterol levels. In the major landmark clinical trials (1–4, 19), statin therapy increased HDL cholesterol levels by 5% to 8%. Evidence from both clinical trials and epidemiologic studies suggest that every 0.02-mmol/L (1-mg/dL) increase in HDL cholesterol level may produce a 2% to 3% decrease in risk for coronary artery disease (31). Third, HMG-CoA reductase inhibitor therapy confers other potential benefits not related to lipid levels, including improvements in endothelial function, plaque stabilization, fibrinolysis, and C-reactive protein levels.

Finally, although the conclusions of subgroup analyses were derived from post hoc data, which are inherently “hypothesis generating” rather than “hypothesis proving,” they are compatible with the curvilinear relationship between LDL cholesterol level and coronary artery disease risk demonstrated in previous epidemiologic studies. Only well-designed clinical trials of aggressive lipid-lowering strategies can reliably determine the validity of the premise that “lower is better.” Two such trials now in progress are the Treat to New Targets study of atorvastatin and the Study

to Evaluate Additional Reductions of Cholesterol and Homocysteine of simvastatin. Until the results of these trials are published, a prudent, proportionate approach to the treatment of hypercholesterolemia is warranted.

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