Statin Trials and Goals of Cholesterol-Lowering Therapy

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Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are a breakthrough in the treatment of high serum cholesterol. Several recent clinical trials demonstrate that statins can substantially reduce both morbidity and mortality from CHD. They are becoming a mainstay in management of patients with established CHD (secondary prevention), and they hold promise for high-risk patients without evident CHD (primary prevention). The introduction of statins occurred about the same time as the initiation of the NCEP; this program is a national effort to increase public and professional awareness of the dangers of high serum cholesterol and to emphasize the benefits of reducing serum cholesterol concentrations. Besides the NCEP’s public health effort to lower serum cholesterol levels in the general public through modification of life habits, the NCEP has established guidelines for cholesterol management in both secondary prevention and high-risk primary prevention. These guidelines identify LDL cholesterol as the primary target of therapy, and they specify goals for LDL cholesterol-lowering therapy. For example, the NCEP recommended that high-risk patients who have elevated LDL cholesterol levels but not clinical CHD or other atherosclerotic disease should have their LDL cholesterol concentration reduced to <130 mg/dL. For patients with CHD or other atherosclerotic diseases, the goal of the NCEP is an LDL cholesterol of ≤100 mg/dL. These therapeutic goals derive from judgments based on epidemiological data and clinical trial results available at the time of reporting.

Recent statin trials provide a wealth of data documenting the benefit of cholesterol-lowering therapy in both primary and secondary prevention. A major fact has been established: cholesterol lowering with statins is both safe and effective in high-risk patients. Recent statin trials amply underpin the NCEP’s promotion of efforts for decreasing coronary morbidity or mortality. Of some importance, however, is whether these trials also justify the NCEP’s criteria for selection of patients for therapy and its goals for LDL cholesterol in secondary and primary prevention. Of note, none of the reported trials specifically addressed optimal goals for LDL-lowering therapy. Future trials may address this issue, but several years will be required to produce an answer. In the meantime, more detailed analysis of data from recent statin trials may shed some light on optimal goals for LDL cholesterol.

New analyses of statin trial data are published in this issue of Circulation. The approach taken is called subgroup analysis. The reader must recognize that subgroup analysis is a thorny area. A large set of data can be dissected in many ways, and a variety of questions posed. If the answers are not appealing, the questions can be changed and the data reanalyzed. According to an old adage, “the data can be tortured until they confess.” Nonetheless, despite limitations, subgroup analysis sometimes provides useful information. It may suggest new questions for future clinical trials, ie, it is a hypothesis-generating exercise. With these points in mind, let us examine and compare these three subgroup analyses. Particular attention should be given to whether they support or dispute current guidelines for cholesterol-lowering therapy.

The quantitative relation between serum cholesterol levels and coronary events has long been a topic of interest. Earlier prospective studies suggested that risk for new-onset CHD changed little up to a level of total cholesterol of 200 mg/dL; above this threshold level, risk apparently began to rise (Fig 1). A total cholesterol level of 200 mg/dL corresponds to an LDL cholesterol level of ~130 mg/dL. A different relationship was obtained in follow-up of screenees of MRFIT. By greatly expanding the population base compared with earlier studies, a curvilinear relation was uncovered between serum cholesterol levels and CHD risk; in the MRFIT follow-up, no evidence for threshold level was observed (Fig 1B). The prospective association between serum cholesterol levels and recurrent coronary events in patients with existing CHD is less well established than for populations without CHD, although some investigations indicate a positive relationship. More importantly, the quantitative correlation between magnitude of cholesterol lowering and CHD reduction in secondary prevention has not been precisely defined. It may therefore be useful to examine theoretical relationships in the light of recent subgroup analysis. Three possible models are shown in Fig 2. According to the linear model (Fig 2A), progressive lowering of LDL cholesterol would reduce CHD risk linearly. If this model pertains for secondary prevention, the lower the LDL level the better; consequently, reducing LDL cholesterol levels even to <100 mg/dL could be advantageous. In contrast, if a threshold model holds (Fig 2B), no incremental benefit would be achieved by reducing LDL cholesterol concentrations to below the threshold value. This model is analogous to that suggested by earlier prospective studies (Fig 1A). A third possibility, the curvilinear model (Fig 2C),
is analogous to the relationship reported in the large MRFIT follow-up\textsuperscript{13} (Fig 1B); accordingly, progressive lowering of LDL to very low values should yield increasing benefit, but with diminishing returns at lower levels. Let us consider which model best fits the subgroup analysis for secondary prevention.

The 4S,\textsuperscript{7} a secondary prevention trial, used simvastatin to treat hypercholesterolemic patients. Simvastatin therapy, on average, reduced LDL cholesterol levels by 35%, from a mean of 188 to 122 mg/dL; this change decreased major coronary events by 34%. Although the goal of therapy in 4S was to lower total cholesterol to at least <200 mg/dL (LDL cholesterol <130 mg/dL), many patients experienced even greater reductions in serum cholesterol levels. Thus, in 4S subgroup analysis,\textsuperscript{7} the decline in cholesterol levels was compared with the decrease in risk for recurrent major coronary events. The data best fit the curvilinear model (Fig 1C), ie, greater cholesterol reductions gave continuous but progressively smaller decrements in CHD risk. Although the analysis did not specify an LDL cholesterol goal, the authors concluded that the goal for secondary prevention proposed by current guidelines\textsuperscript{5,6} is appropriate; even so, it was speculated that little would be gained by driving LDL to very low concentrations. These 4S results, in general, are consistent with the relationship observed with the large data set from MRFIT screenees\textsuperscript{13} (Fig 1B).

A different result is reported from subgroup analysis of the CARE trial. CARE\textsuperscript{2} was a secondary prevention trial using pravastatin to treat coronary patients with relatively normal cholesterol levels. In the full CARE trial,\textsuperscript{2} the mean LDL cholesterol at baseline was 139 mg/dL. Pravastatin therapy lowered LDL cholesterol to an average level of 98 mg/dL; with this response, major coronary events were decreased by 24%. The positive clinical outcome of CARE and the average level of LDL reached on therapy might be taken to mean that the overall results support current NCEP goals for secondary prevention, ie, an LDL cholesterol level of ≤100 mg/dL.\textsuperscript{5,6}

On the other hand, subgroup analysis\textsuperscript{8} revealed that CHD event rates decreased progressively as LDL cholesterol levels fell from 174 to 125 mg/dL, but from 125 to 71 mg/dL, CHD events did not decline further. This finding supports the threshold model (Fig 2B) and speaks against the linear model (Fig 2A). A question of some importance is whether the analysis had the power to distinguish between the threshold model (Fig 2B) and the curvilinear model (Fig 2C). Certainly, the more a set of data is dissected into its components, the less will be the statistical power to precisely define a relationship. On the one hand, 4S analysis\textsuperscript{7} favors the curvilinear model, whereas CARE analysis\textsuperscript{8} tilts toward a threshold response. If an analogy can be drawn between smaller prospective studies\textsuperscript{10-12} (Fig 1A) and the larger MRFIT experience\textsuperscript{13} (Fig 1B), the curvilinear model most likely will prevail when the data set for secondary prevention is expanded; but in the meantime, the exact shape of the curve within the LDL cholesterol range from 125 to 70 mg/dL will remain uncertain.

The third trial, WOSCOPS,\textsuperscript{9} was a primary prevention trial in high-risk patients. According to NCEP guidelines,\textsuperscript{5,6} the LDL cholesterol goal in high-risk primary prevention is a serum concentration of <130 mg/dL. WOSCOPS patients generally had hypercholesterolemia, and on the basis of risk factor status, most enrollees fell into the high-risk category. Baseline LDL cholesterol levels for all patients averaged 197 mg/dL, and on pravastatin therapy, an average concentration of 142 mg/dL was achieved. This LDL reduction was accompanied by a 31% decrease in major coronary events. For subgroup analysis,\textsuperscript{8} WOSCOPS investigators did not directly address whether a reduction of LDL cholesterol levels to <130 mg/dL is an appropriate goal in primary prevention. Instead, they inquired whether the reduction of CHD risk is proportional to the percentage reduction in LDL cholesterol levels.

A finding of considerable interest in the subgroup analysis of WOSCOPS\textsuperscript{9} was that differences in baseline LDL cholesterol concentrations before therapy did not alter relative risk reduction accompanying pravastatin therapy. In other words, when subjects receiving pravastatin were grouped according to baseline LDL levels, all subgroups experienced a similar

**Figure 1.** Relationship between serum cholesterol levels and CHD in male subjects without established CHD at entrance into prospective study. Fig 1A relates serum cholesterol levels to relative risk (risk ratio) for developing clinical CHD in earlier prospective studies: Framingham Heart Study\textsuperscript{10} ( ), Pooling Project\textsuperscript{11} ( ), and Israeli Prospective Study\textsuperscript{12} ( ). These surveys suggest a threshold relationship. Fig 1B plots association between serum cholesterol levels and CHD mortality for 356,222 male screenees of MRFIT.\textsuperscript{13} A curvilinear relationship was observed. Figure modified from Reference 17.

**Figure 2.** Theoretical models for effects of reducing serum LDL cholesterol concentrations on relative risk for recurrent coronary heart disease. Model A shows linear relationship; model B, threshold relationship; and model C, curvilinear relationship.
risk reduction, regardless of initial levels. In WOSCOPS, comparing the percentage decrease in LDL cholesterol level versus risk reduction on pravastatin therapy revealed the relationship shown in Fig 3. According to the data, maximal risk reduction occurred when LDL cholesterol concentrations fell by 24%; greater lowering of LDL apparently gave no additional reduction in risk. The authors nonetheless recognize the possibility that the true response may have been curvilinear, although the data seemed to fit the threshold model better.

On the basis of these analyses, a few solid conclusions can be drawn, and other tentative conclusions are suggested. First, statin therapy is highly effective for reducing CHD risk in secondary prevention. Clear evidence of benefit is seen when baseline LDL cholesterol levels are >130 mg/dL at baseline. Therefore, most CHD patients whose LDL cholesterol concentrations exceed 130 mg/dL should receive cholesterol-lowering drugs. A delay in drug treatment for a trial of dietary therapy in such patients is not necessary or warranted. Unfortunately, a great many CHD patients are not receiving the life-saving benefits of statin therapy, and extension of this therapy to untreated patients is urgently needed.

Subgroup analyses of 4S and CARE do not actually reveal the optimal goal for LDL cholesterol in secondary prevention. However, both trials suggest some attenuation of benefit when LDL cholesterol levels are lowered to well below 130 mg/dL. CARE results reveal no further risk reduction when LDL cholesterol falls below 125 mg/dL. Conversely, 4S results suggested continuing benefit below this level, but with diminishing returns. By analogy, the large MRFIT data set (Fig 1B) also speaks in favor of a curvilinear relationship similar to that suggested by 4S analysis. Consequently, for secondary prevention it seems reasonable to lower LDL cholesterol levels to ≤100 mg/dL if this goal can be achieved with moderate doses of statins. On the other hand, if high doses of statins or combined drug therapy are required to reduce LDL cholesterol levels from <130 mg/dL to ≤100 mg/dL, clinical judgment is required as to whether to intensify therapy. Lower LDL cholesterol levels (≤100 mg/dL) seem warranted if they can be achieved without excessive cost, undue nuisance of therapy, or substantial risk of side effects, but not otherwise. This judgmental approach to intensification of therapy indeed accords with NCEP guidelines.

Subgroup analyses of 4S and CARE do not reveal unequivocally whether institution of cholesterol-lowering drugs is beneficial when baseline LDL cholesterol levels range from 100 to 129 mg/dL. CARE data call this benefit into question, but some authorities favor use of drugs to reach an LDL cholesterol ≤100 mg/dL, even when baseline LDL cholesterol levels are in this range. If the decision is made to use drugs, an LDL cholesterol level of ≤100 mg/dL can easily be obtained with a relatively low dose of statin. Because a sizable portion of CHD patients have baseline LDL cholesterol levels from 100 to 129 mg/dL, a new clinical trial is needed that directly tests benefit of further LDL reduction in these patients. In the meantime, an evidence-based recommendation cannot be made, and the decision must be left to physician judgment. Moreover, the physician should not overlook the fact that NCEP goals can be achieved in some patients of this type by dietary therapy alone.

The WOSCOPS trial provides strong confirmation of efficacy of cholesterol lowering in primary prevention. WOSCOPS patients who were at high risk on the basis of LDL cholesterol >160 mg/dL plus multiple risk factors experienced a significant decrease in coronary morbidity and mortality on pravastatin therapy. Consequently, statin therapy is justified in high-risk patients with elevated LDL cholesterol concentrations. This trial, however, does not fully define the appropriate candidate for statin therapy among patients who are without CHD or other forms of atherosclerotic disease. A general consensus holds that statins should be used only when absolute risk for developing new-onset CHD over the short term (1 to 10 years) is high. Projected long-term use of statins in primary prevention is problematic because of the high cost of these drugs and lack of 10- to 20-year safety data. The WOSCOP trial provides the impetus to develop and evaluate improved tools for risk assessment to better estimate absolute risk as a guide to use of statin therapy. NCEP guidelines currently stratify risk by simply counting risk factors. It is possible that continuous risk models and/or noninvasive techniques for detection of subclinical atherosclerotic disease will give more precise estimates of absolute risk. There is a growing interest in the investment of resources into development of improved techniques of risk assessment to provide better guidance for cholesterol-lowering therapy.

The WOSCOPS trial gives sparse information about the optimal LDL cholesterol goal for high-risk primary prevention. According to NCEP guidelines, hypercholesterolemic patients have a minimal LDL cholesterol goal of <160 mg/dL, and when multiple risk factors are present, a desirable goal is <130 mg/dL. In WOSCOPS, the average LDL cholesterol level achieved on pravastatin therapy was 142 mg/dL, and this response was accompanied by substantial clinical benefit. WOSCOPS results suggest that the principle...
of graded intensity of therapy proposed for secondary prevention extends to primary prevention. Thus, for high-risk patients with hypercholesterolemia, if the NCEP goal for LDL cholesterol of <130 mg/dL can be achieved with moderate doses of cholesterol-lowering drugs, such levels seem desirable. Conversely, if a high dose of statin or combined drug therapy is required to reduce LDL cholesterol from <160 to <130 mg/dL, clinical judgment must come into play. A general rule might be followed: the higher the estimated absolute risk, the more aggressive the therapy should be. Moreover, for patients with severe hypercholesterolemia, such as those with heterozygous familial hypercholesterolemia, combined drug therapy (ie, statin plus bile acid sequestrant) usually is indicated to achieve acceptable cholesterol levels.6

Another important question about primary prevention is whether some high-risk patients who have borderline high-risk levels of LDL cholesterol (130 to 159 mg/dL) are candidates for statin therapy. The findings of CARE7 and the recent Air Force/Texas Coronary Atherosclerosis Prevention trial8 reveal the potential for risk reduction in patients whose baseline LDL cholesterol levels are in this range. Examples of very-high-risk patients who may not yet manifest clinical CHD include those with diabetes mellitus, heavy smokers, and patients with the metabolic syndrome, ie, clustering of multiple metabolic risk factors in a single patient. Although current NCEP guidelines9,10 do not call for cholesterol-lowering drugs for primary prevention in such very-high-risk patients having LDL cholesterol concentrations in the range of 130 to 159 mg/dL, a strong argument for using statin therapy in selected patients can be made on the basis of recent trials.

In summary, recent statin trials strongly support the NCEP approach of adjusting intensity of cholesterol-lowering therapy to absolute risk. They also confirm the NCEP concept that cholesterol-reducing drugs are indicated for many high-risk patients in both primary and secondary prevention. These trials were not specifically designed to define optimal goals for LDL cholesterol in primary and secondary prevention. Even so, findings of subgroup analysis do not negate current NCEP goals of therapy; on the whole, they provide support for their validity. They do, however, emphasize the need to use clinical judgment as to whether to intensify therapy in patients whose LDL cholesterol levels are already nearing these goals.

References

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