IMPLICATIONS OF RECENT CLINICAL TRIALS ON THE MANAGEMENT OF PATIENTS WITH HYPERLIPIDEMIA

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EPIDEMIOLOGICAL SURVEYS HAVE SHOWN that serum total cholesterol levels are continuously correlated with CHD risk over abroad range of cholesterol values. This relationship has been observed in many populations throughout the world.[1-3] Because serum LDL-C levels correlate highly with total cholesterol in populations, the same relation must exist between LDL-C concentrations and CHD risk. Although the association between LDL-C levels and CHD risk is continuous, it is not linear; risk rises more steeply with increasing LDL-C concentrations. This results in a curvilinear, or log-linear, relationship.

Since the publication of ATP III [4,5] major clinical trials with statin therapy and clinical end points have been published. These include the Heart Protection Study (HPS),[5] the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[6] Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT),[7] Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA),[8] and the Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial.[9]. These trials addressed issues that had not been adequately addressed in previous statin trials. The results appear to have important implications for the management of patients with lipid disorders, particularly for high-risk patients. They further may require some rethinking of the treatment thresholds of ATP III recommendations. In addition, findings of other smaller trials or subgroup analyses of major trials have been published. The purpose of the present review is to examine the results of all of these studies and to assess their implications in relation to patient management. First, we will summarize the principal findings of these trials and then the implications on practice.

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Review of Recent Clinical Trials With MajorCardiovascular End Points

Heart Protection Study

This clinical trial was carried out in 20 536 adults living in the United Kingdom (aged 40 to 80 years) who were at high risk for a CVD event.5 Entrance criteria included coronary disease, other occlusive arterial disease, or diabetes. Patients were randomly allocated to 40 mg simvastatin daily or placebo. Primary outcomes included total mortality for overall analysis and fatal or nonfatal vascular events for subcategory analyses. The incidence of cancer and other major morbidity also was determined.

Serum lipids at baseline were determined on nonfasting samples. Levels of LDL-C were measured by the direct LDL method.10 Average lipid values at baseline were total cholesterol 228 mg/dL, triglycerides 186 mg/dL (nonfasting), HDL-C 41 mg/dL, non-HDL-C 187 mg/dL, and direct LDL-C 131 mg/dL. In most other clinical trials of cholesterol- lowering therapy, serum lipid levels have been determined on fasting samples, and LDL-C has been calculated by the Friedewald equation [LDL-C - total cholesterol - HDL-C- VLDL-C (triglycerides/5)], where VLDL indicates very low-density lipoprotein.[11] This calculation includes intermediate-density lipoprotein in the LDL fraction. If this equation were applied to the HPS values cited above, the average calculated LDL-C

would be approximately 150mg/dL [(228-41-(186/5)]. In patients allocated to simvastatin, all-cause mortality was significantly reduced by 13% (P=0.0003). Major vascular events were reduced by 24%, coronary death rate by 18%, nonfatal myocardial infarction - coronary death by 27%, nonfatal or fatal stroke by 25%, and cardiovascular revascularization by 24%. The reduction in the event rate was similar in each subcategory, including patients without diagnosed coronary disease who had cerebrovascular disease, or peripheral artery disease, or diabetes. Similar event reductions on simvastatin therapy occurred for men and women and for participants either under or over 70 years of age at entry. No significant adverse effects of simvastatin therapy were reported, including no significant increase in myopathy, cancer incidence, or hospitalization for any other nonvascular cause.

Subgroup analysis of HPS suggests that simvastatin therapy produced similar reductions in relative risk regardless of the baseline levels of LDL-C, including subgroups with initial (or baseline) LDL-C levels - 135 mg/dL, -116 mg/dL, or 100 mg/dL. At least 2 issues, however, can be noted with regard to the reported subgroup analysis of HPS at low (or very low) LDL-C levels. First, LDL-C cutpoints to define these subgroups would have been higher if LDL-C had been calculated by the Friedewald equation, the method employed by ATP III for routine clinical practice. Second, the characteristics of low-LDL subgroups, ie, what portions had hypertriglyceridemia, elevated non-HDL-C, or diabetes, or were free of CVD, have not been made available. These qualifying issues must be kept in mind when generalizing HPS findings to all high-risk patients with low baseline LDL-C levels. HPS investigators further examined their results more closely for persons with diabetes.[12] The study included 5963 individuals with diabetes (ages 40 to 80 years). Those subjects receiving simvastatin 40 mg/d had significant reductions of approximately one quarter in first-event rates for major coronary events, strokes, and revascularizations. Event reductions were similar to those for nondiabetic patients.

In 2912 patients with diabetes and without diagnosed coronary or other occlusive arterial disease at entry, simvastatin therapy reduced risk by about one third. In 2426 participants with diabetes whose pretreatment LDL-C was -116 mg/dL, event rates were 27% lower on simvastatin therapy. In the subgroup of patients with diabetes who were without vascular disease and whose LDL-C levels were-116 mg/dL at baseline, a marginally significant 30% reduction in risk was observed. Efficacy of simvastatin therapy in the subgroup of patients with LDL-C-100 mg/dL was not reported. HPS investigators concluded that, in general, cholesterol lowering with statin therapy is efficacious in patients with diabetes, including those without manifest CHD and those with relatively low LDL-C levels.

Prospective Study of Pravastatin in the Elderly at Risk

This trial examined the efficacy of pravastatin treatment in older men and women with or at high risk of developing CVD and stroke.[6] Subjects (n=5804; 2804 men and 3000 women), ages 70 to 82 years, who had a history of vascular disease or CVD risk factors were randomized to pravastatin (40 mg/d) or placebo. The primary end point was a composite of coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Baseline total cholesterol varied widely from 150 mg/dL to 350 mg/dL. Follow-up averaged 32 years. Pravastatin reduced LDL-C levels by 34%. The composite end point was reduced on pravastatin therapy by 15% (P=0.014). Major coronary events, defined as nonfatal myocardial infarction and CHD death, fell on therapy by 19% (P=0.006), and CHD mortality by 24% (P=0.043). No reduction in stroke was observed, but transient ischemic attacks fell by 25% on therapy (P=0.051). The stroke rate in the trial, however, was about half of that predicted, so the effects of statin therapy on stroke must be viewed in this light. New cancer unexpectedly was found 25% more often on pravastatin treatment (P=0.020). This finding, however, contrasts with meta-analysis of all pravastatin and all statin trials, in which overall cancer incidence was not increased.[6]. Pravastatin therapy neither improved cognitive function nor retarded progression of disability. According to the authors, PROSPER results allow statin therapy to be extended to older persons.

Antihypertensive and Lipid-LoweringTreatment to Prevent Heart Attack Trial—Lipid-Lowering Trial

The primary goal of ALLHAT was to evaluate current modalities of hypertension treatment. The lipid-lowering component, which was a subset of this trial, was designed to assess whether pravastatin therapy compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least one additional CHD risk factor.[7] The study used 513 primarily community-based North American clinical centers. The lipidlowering component of ALLHAT randomized 10 355 persons. Participants were over 55 years of age and had LDL-C levels ranging from 120 to 189 mg/dL and triglycerides below 350 mg/dL. Those patients with LDL-C levels ≥120 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL were randomized to nonblinded arms of pravastatin (n-5170) or usual care (n-5185). Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; HDL-C, 48 mg/dL; and triglycerides, 152 mg/dL. Mean age was 66 years; 49% were women; 38% were black and 23% Hispanic; 14% had a history of CHD; and 35% had type 2 diabetes. The primary outcome was all-cause mortality, and secondary outcomes were nonfatal myocardial infarction or fatal CHD (CHD events) combined, cause-specific mortality, and cancer.

Mean follow-up duration of participants was 4.8 years. Crossover of usual-care participants to lipid-lowering drugs was high (32% of usual-care participants with CHD and 29% without CHD). Follow-up of patients for lipid results was not complete. Among a nonrandom subset of participants tested, total cholesterol levels were reduced by 17% with pravastatin versus 8% with usual care at 4 years. In ALLHAT-LLT, all-cause mortality was similar for the 2 groups, with 6-year mortality rates of 14.9% for pravastatin versus 15.3% with usual care. For all participants, CHD event rates were not significantly different between the groups, with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care. In the African-American subgroup, however, CHD events were significantly reduced in the pravastatin arm compared with usual care. The authors speculated that the failure to detect a significant reduction in risk in hypertensive patients treated with pravastatin may be due to the modest differential in total cholesterol (9.6%) between pravastatin and usual care. Other possible explanations for the failure to observe a treatment benefit could be the unblinded nature of the study without a placebo arm and a large crossover of higher-risk subjects in the usual-care arm to active lipid-lowering therapy.

Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm

In contrast to the ALLHAT lipid-lowering component, a markedly different result was obtained in hypertensive patients in ASCOT-LLA.[8] In this study, 19 342 hypertensive patients, 40 to 79 years old and having at least 3 other cardiovascular risk factors, were randomized to 1 of 2 antihypertensive regimens. Among these subjects, 10 305 were in addition randomly assigned atorvastatin 10 mg or placebo. Selection was made on the basis of nonfasting total cholesterol of - 251 mg/dL (6.5 mmol/L). LDL-C levels averaged 132 mg/dL and were reduced by an average of 42 mg/dL (29%) in the atorvastatin-treated group at the end of the study. The primary end point was nonfatal myocardial infarction and fatal CHD. The study was planned for a follow-up of an average of 5 years but was stopped after a median follow-up of 3.3 years. At that time, 100 primary events had occurred in the atorvastatin group, compared with 154 events in the placebo group (hazard ratio 0.64, *P*-0.0005). In the atorvastatin group, incidence of fatal and nonfatal stroke was reduced by 27% (P=0.024), total cardiovascular events by 21% (P=0.0005), and total coronary events by 29% (P=0.0005). There was a nonsignificant trend toward a reduction in total mortality in the atorvastatin group (13%; P=0.16). Because of these markedly positive findings with atorvastatin therapy, the study was terminated prematurely.

The authors indicated that LDL lowering with atorvastatin therapy has considerable potential to reduce risk for CVD in primary prevention in patients with multiple CVD risk factors.

Pravastatin or Atorvastatin Evaluation and Infection—Thrombolysis in Myocardial Infarction 22

This study, designated PROVE IT,9 was designed to determine whether intensive LDL-C

lowering will reduce major coronary events, including mortality, more than "standard" LDL-C lowering with statin therapy in high-risk patients. Two statins at different doses were compared: follow-up time was 24 months. At the end of 2 years of therapy, the composite cardiovascular end point was reduced by 16% with atorvastatin compared with pravastatin (P=0.005).

Table 1. *ATP III LDL-C Goals and cutpoints for TLC and Drug Therapy in different risk categories and proposed modifications based on recent clinical trial evidence.*

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD* or CHD risk equivalents† (10-year risk > 20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥ 100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100-129 mg/dL; consider drug options) ‡‡
Moderate risk: 2+ risk factors‡ (10-year risk < 10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor§	<160 mg/dL	≥160 mg/dL	≥ 190mg/dL (160-189 mg/dL; LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease _transient ischemic attacks or stroke of carotid origin or _50% obstruction of a carotid artery_), diabetes, and 2_ risk factors with 10-year risk for hard CHD _20%.

‡Risk factors include cigarette smoking, hypertension (BP _140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (_40 mg/dL), family history of premature CHD (CHD in male first-degree relative _55 years of age; CHD in female first-degree relative _65 years of age), and age (men _45 years; women _55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol. §Almost all people with zero or 1 risk factor have a 10-year risk _10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

_Very high risk favors the optional LDL-C goal of _70 mg/dL, and in patients with high triglycerides, non-HDL-C _100 mg/dL.

¶Optional LDL-C goal _100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is _100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level _100 mg/dL is a therapeutic option on the basis of available clinical trial results.

atorvastatin 80mg versus pravastatin 40 mg. Previous studies have shown that pravastatin 40 mg produces a reduction of LDL-C equivalent to approximately 10 mg of atorvastatin. Prior clinical trials have demonstrated that treatment of patients with established CHD with pravastatin 40 mg will reduce LDL-C levels to near 100 mg/dL and will reduce risk for major coronary events by approximately 27%.[12] In PROVE IT, 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days were enrolled and randomized to the 2 therapies. The primary end point of the trial was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean Nonsignificant trends were observed on atorvastatin therapy for total mortality (P-0.07) and for death or myocardial infarction (P-0.06). The high dose of atorvastatin was well tolerated, and no case of severe myopathy (rhabdomyolysis) was observed in either treatment group. Greater than 3-fold elevations of alanine aminotransferase were observed in 3.3% of patients treated with atorvastatin versus 1.1% on pravastatin (P=0.003).

The LDL-C level attained on pravastatin 40 mg was 95 mg/dL, whereas the level attained on atorvastatin 80 mg was 62 mg/dL. The difference in LDL-C thus was 33 mg/dL (35%). The results of PROVE IT suggest that more intensive LDL-C–lowering therapy reduces major cardiovascular events in patients with acute coronary syndrome compared with less intensive therapy over a period

of 2 years. It must be noted, however, that 72% of the patients had LDL-C levels-125 mg/dL, and in this large subgroup, the modest trend toward benefit of atorvastatin over pravastatin was not statistically significant in terms of clinical implications. From the evidence of previous statin trials , the ATP III recommendations have been recently modified.[13] Table 1 is shows the latest modification .

Clinical Implications

Therefore our targets for management of patient with hyperlipidemia have been changed accordingly. Patient with high risk should be treated with the aim to reduce the LDL level to < 100 mg dL 2-6 mmol L) The level of <70 mg/dL for LDL has been so far considered optimal awaiting for more supporting trials

The Role of C-reactive Protein

Previous studies have shown that C-reactive protein (CRP) is a strong predictor of future cardiac events, regardless of baseline LDL-cholesterol (LDL-C) or Framingham Risk Score, and at all levels of the metabolic syndrome. Furthermore, studies have shown that statin therapy lowers CRP levels independently of LDL-C, and also provides a greater benefit in patients with increased CRP levels. These studies have led to the hypothesis that statins might have anti-inflammatory properties that are important for prognosis and treatment. Therefore, the level of CRP achieved with statin therapy might have clinical relevance in a manner similar to that of achieved LDL-C levels.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy -- Thrombolysis in Myocardial Infarction 22 (PROVE-IT – TIMI 22)[9] trial was a multicenter randomized study designed to compare the clinical event reduction rates achieved with a standard degree of LDL-C lowering (to 100 mg/dL) using moderate lipid-lowering therapy (pravastatin 40 mg) vs those achieved with the use of more intensive therapy (atorvastatin 80 mg) to lower LDL-C to 70 mg/dL in patients with an acute coronary syndrome (ACS). Specifically, the effects of the 2 drugs on rates of death and major cardiovascular events were compared. Patients were followed for 2 years.

The details of PROVE-IT - TIMI 22 have previously been presented and published in detail. In brief, the overall results of the trial found that intensive lipid-lowering therapy using atorvastatin was associated with a 16% reduction in all-cause mortality or major cardiovascular events vs patients treated with moderate therapy (P = .005). In addition, investigators reported that the 30-day event rate in patients who had achieved an LDL-C level <70 mg/dL was significantly lower when compared with patients with an LDL-C > 70 mg/dL.

These findings suggest that individuals with ACS derive a clinically significant benefit from intensive lipid-lowering therapy using atorvastatin 80 mg compared with the well-proven efficacy against placebo associated with use of pravastatin 40 mg. In addition, these findings demonstrate that additional benefit is observed when achieved LDL-C levels are well below current targets.

Among others, CRP analyses were prespecified in the study protocol, in which CRP levels were measured at enrollment, at 30 and 120 days, and at study end. The current analysis[14] reflects the following hypotheses:

1. Patients who achieve lower CRP levels with statin treatment will have a better clinical outcome compared with those patients who do not, even after controlling for LDL-C levels.
2. The difference between aggressive and moderate statin regimens in terms of clinical event reduction can be explained at least in part on the basis of achieved CRP levels.

Results

CRP Analyses

PROVE-IT – TIMI 22 randomized 4162 patients, 3745 of whom underwent evaluation for achieved LDL-C and achieved CRP.

As with the primary results of the study associating lower LDL-C levels with significant reductions in the relative risk of recurrent coronary events, similar findings were also noted among patients who achieved the lowest CRP level (< 0.9 mg/L) . Specifically, the event rate was significantly lower in patients who achieved a CRP level of < 2 mg/L compared with those patients with a CRP level > 2 mg/L

Noting that reductions in LDL do not necessarily correlate with reductions in CRP, investigators analyzed the interactions between achieved LDL-C levels and CRP levels. At 2-year

follow-up, when both parameters were analyzed together, patients were stratified according to the following levels achieved:

1. LDL-C >/= 70 mg/dL and CRP >/= 2 mg/L
2. LDL-C >/= 70 mg/dL and CRP < 2 mg/L
3. LDL-C < 70 mg/dL and CRP >/= 2 mg/L
4. LDL-C < 70 mg/dL and CRP < 2 mg/L

Investigators found that patients with elevated LDL-C and an elevated CRP level had a significantly higher recurrence of MI or coronary death compared with the other groups.

Interestingly, similar favorable risk reductions were noted in patients who achieved lower CRP levels, but not lower LDL-C levels, and in those patients who did achieve low LDL-C levels but did not reduce their CRP levels, which suggests that both LDL-C levels and CRP levels act independently of each other. Most notable is the suggestion that lowering CRP levels is associated with a reduction in event rates. As expected from these results, the lowest relative risk of events was observed in patients who achieved both low levels of LDL-C and low levels of CRP.

Compared with baseline, the use of atorvastatin was, on average, associated with significantly lower levels of CRP at 30- and 120-day follow-up and at study end than those recorded among patients treated with pravastatin ($P < .001$ at all intervals).

The majority of patients who achieved the optimal levels of LDL and CRP lowering were those treated with intensive lipid-lowering therapy (44% vs 11%) . The investigators noted, however, that neither regimen was effective in getting the majority of patients into the lowest levels of both parameters; only 11% of pravastatin patients and 44% of the atorvastatin group achieved those levels. In addition, there was no difference in clinical outcomes between the 2 drugs in any given strata, suggesting that reaching the dual goal is more important than the drug used to achieve it.

These results, if confirmed in further studies, will have a profound impact on the way we look at LDL-C, CRP, and the use of statin therapy. It is likely that the concept of lowering LDL-C levels with statin therapy will introduce a completely new perspective and emphasize the fact that CRP is a strong predictor of cardiovascular events.

We believe that very soon we will not be monitoring only LDL-C levels in our cardiovascular disease patients, but we will also be monitoring CRP levels and will strive for to achieve the "dual goal" of both parameters.

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