The Aggressive Low Density Lipoprotein Lowering Controversy
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Recent clinical trials have provided unequivocal evidence of major cardiovascular benefits from low density lipoprotein (LDL) lowering with statins. However, the three critical unresolved questions about aggressive LDL lowering are the shape of the curve relating cardiac events to LDL, the best surrogate measurement for assessing therapeutic efficacy and the best target for LDL therapy. The relation between cardiac events and LDL is curvilinear, both epidemiologically and during therapy. The benefit of lipid lowering diminishes progressively and becomes difficult to detect at lower LDL levels without a very large sample size. Assessment of the benefits of lipid lowering is further confounded by differences in the level of pretreatment LDL and by the non-LDL lowering effects of statins. Both epidemiologic studies and large randomized clinical trials have produced conflicting results concerning the best LDL target. Failure to reduce the event rate in patients with pretreatment LDL <125 mg (Cholesterol And Recurrent Events [CARE] trial) alerts us to the risk of extrapolating epidemiologic data to clinical practice, yet subset analysis of some clinical trials suggests the greatest benefit appears in those patients with the lowest on-treatment LDL levels (Scandinavian Simvastatin Survival Study [4S]). This controversy should be resolved in the next few years by several important on-going trials. In the face of seemingly contradictory data from current clinical trials, we can only speculate that very aggressive LDL lowering to <80 mg/dl could be accompanied by a modest therapeutic benefit beyond the current recommendations of the National Cholesterol Education Program. If any benefit is observed, it will have to be balanced against a small potential for increased adverse events.

Although statins reduce cardiac events by approximately 25% to 35% over five years in a spectrum of patient subsets (1–5), three new fundamental questions about more aggressive low density lipoprotein (LDL) lowering remain unresolved: 1) what is "the shape of the curve" that relates the reduction in coronary heart disease (CHD) events to the magnitude of LDL lowering (6); 2) what is the best surrogate end point for assessing therapeutic efficacy; and 3) what is the best LDL target for lipid lowering? For each question, there is a body of sometimes contradictory information to be considered. In this article, we critically analyze each of these new issues.

Cardiac events and LDL lowering: the issue of a threshold value of LDL. At issue is whether the relation is continuously curvilinear or whether there is a threshold (at which a relation only exists above a given cholesterol level). If there is a threshold relation, then LDL lowering below that level might have no therapeutic benefit. Large epidemiologic studies, such as Multiple Risk Factor Intervention Trial (MRFIT) (7,8), show a curvilinear relation between serum total cholesterol and coronary disease in patients without known CHD. Because LDL cholesterol was not measured in these studies, we must estimate the relation between LDL cholesterol and cardiac events.

These studies, however, have a limitation that has become important with the development of statin therapy. Few individuals in the United States had baseline cholesterol levels <200 mg/dl when the large epidemiologic studies were conducted. Consequently, we must use other populations if we wish to assess the epidemiologic relation between cholesterol and cardiac events at cholesterol levels <200 mg/dl. Here we find a paradox. Even though cholesterol levels <200 mg/dl lie on the relatively flat portion of the Western population's curve, the curvilinear relation between serum cholesterol and CHD clearly persists to the level of 160 mg/dl in the Chinese (9). Thus, the Chinese data provide hope that aggressive lipid lowering might further reduce cardiac events, yet extrapolation from the low cholesterol Chinese population to a high cholesterol Western population may be not be justified.

The curvilinear relation found in epidemiologic studies, however, is far less apparent in data on the effect of therapy on LDL (Table 1). In the Scandinavian Simvastatin Survival Study (4S) post-hoc subgroup analysis, the benefit of the reduction in LDL cholesterol persisted but diminished progressively, creating a curvilinear relation analogous to the epidemiologic data (10). In contrast, subgroup analyses of the West Of Scotland COronary Prevention Study (WOSCOPS) and the Cholesterol And Recurrent Events (CARE) trials showed no further reduction in CHD risk.

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beyond an “inflection point.” The inflection point is roughly defined as a 24% reduction in LDL in WOSCOPS and a LDL level of 125 mg/dl in CARE (11,12). In essence, some trial data can be taken to suggest an inflection point, other data suggest a curvilinear relation. As shown in Figure 1, these apparently contradictory results between trials may be resolved by consideration of the risk of a cardiac event before treatment (13). The shape of the “curve” can be interpreted as curvilinear in high risk patients with coronary artery disease (CAD) (Fig. 1A), but appears to be relatively flat for patients not at high risk (Fig. 1B).

Taking the data from the epidemiologic data in healthy patients, the post-hoc subgroup analyses of the statin trials, data from the placebo arms of randomized trials, as well as smaller prospective data bases (14,15), we can make two reasonable inferences. First, we may speculate that the relation between coronary events and LDL is curvilinear for both patients with and without CHD. Second, although a true inflection point is probably impossible to identify, the slope of this relation is substantially steeper in the region above a LDL level of 100 mg/dl than in the region of a LDL level <100 mg/dl.

**Identification of the best surrogate measurement for therapeutic efficacy.** For assessment of drug efficacy, a surrogate lipid measurement that can predict long-term outcomes would have substantial clinical value. Potential surrogate measures independent of lipids include systemic markers of inflammation (16), endothelial dysfunction (17,18) and vessel wall imaging (19). Use of LDL as a surrogate allows comparison of different LDL lowering strategies and serves as a guideline for initiation and maintenance of therapy. Three LDL measurements have been related to therapeutic efficacy. At issue is which one best predicts a reduction in the cardiac event rate. The three leading candidates are baseline LDL, percent LDL reduction and on-treatment LDL.

**Table 1. Major Clinical Trials of Statin Therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>LDL Before</th>
<th>LDL After</th>
<th>%Change</th>
<th>Placebo (%)</th>
<th>Coronary Events*</th>
<th>%RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S (n = 4,444)</td>
<td>5.4</td>
<td>188</td>
<td>120</td>
<td>−35</td>
<td>28.0</td>
<td>19.4</td>
<td>−34</td>
</tr>
<tr>
<td>CARE (n = 4,159)</td>
<td>5.0</td>
<td>139</td>
<td>98</td>
<td>−28</td>
<td>12.9</td>
<td>9.9</td>
<td>−24</td>
</tr>
<tr>
<td>LIPID (n = 9,014)</td>
<td>6.1</td>
<td>150</td>
<td>112</td>
<td>−25</td>
<td>15.9</td>
<td>12.3</td>
<td>−24</td>
</tr>
<tr>
<td>WOSCOPS (6,595)</td>
<td>4.9</td>
<td>192</td>
<td>140</td>
<td>−26</td>
<td>7.5</td>
<td>5.3</td>
<td>−31</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS (n = 6,605)</td>
<td>5.2</td>
<td>150</td>
<td>115</td>
<td>−26</td>
<td>6.5</td>
<td>4.9</td>
<td>−25</td>
</tr>
</tbody>
</table>

*Coronary events = death due to myocardial infarction or coronary heart disease.

4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force Coronary/Texas Atherosclerosis Prevention Study; CARE = Cholesterol And Recurrent Events trial; LDL = low density lipoprotein; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease Study; WOSCOPS = West Of Scotland COronary Prevention Study.

**Figure 1.** The relation between risk of CHD events and LDL levels achieved with statin therapy in secondary and primary prevention trials. In the secondary prevention trials (A), patients are at higher antecedent risk of a coronary event, and there appears to be a curvilinear relation, similar to the epidemiologic relation. In the primary prevention trials (B), with lower risk patients, the relation is much less steep. 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events trial; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease Study; WOSCOPS = West Of Scotland COronary Prevention Study; P = placebo; T = treatment.
tage is that the end point focuses on stenoses, whereas adverse outcomes are due to plaque instability. Stenoses are not necessarily unstable, and unstable lesions are not necessarily stenotic (20). Meta-analyses of angiographic trials have produced conflicting conclusions. Two meta-analyses of angiographic trials (21,22) concluded that the pretreatment LDL level best predicts angiographic outcome, and that both percent LDL reduction and on-treatment LDL are of little predictive value. In contrast, Thompson et al. (23) found that percent reduction in LDL correlated best with angiographic outcome, whereas on-treatment LDL was of little value. Finally, two other meta-analyses (24,25) found that on-treatment LDL cholesterol was as strongly correlated with angiographic improvement as percent reduction in LDL. In summary, for each of the three potential surrogate measurements, there is both an individual angiographic trial and an angiographic meta-analysis to suggest that one of the three is the most predictive, and another to suggest that it is of little value.

Statin trials that used a clinical end point provide somewhat more insight (Table 1). Among the three potential surrogate measurements, the best correlation with cardiac event reduction has been with pretreatment LDL (Fig. 2A). Pretreatment LDL level predicts a reduction in events during treatment in the trials with pretreatment LDL >160 mg/dl. The correlation is less good in trials that began with lower pretreatment LDL levels. In the CARE trial, for instance, patients with pretreatment LDL of 150 to 174 mg/dl had reduced coronary events by 35%, and in those with pretreatment LDL of 127 to 149 mg/dl, events fell by 26%. But in patients with pretreatment LDL levels <126 mg/dl, there was no reduction in cardiac events (12). Similar data have been reported from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, in which the treatment benefits in those with a baseline LDL <135 mg/dl was approximately one-half of those with LDL >135 mg/dl (3). Taken together, the statin trial data allow us to conclude that the pretreatment LDL level is an excellent predictor of therapeutic efficacy (i.e., the higher the pretreatment LDL level, the greater the benefit of therapy).

**PERCENT LDL LOWERING.** The value of percent LDL lowering for predicting CHD reduction is best seen in the post-hoc analysis of the 4S trial. The percent LDL reduction correlated well with the difference in risk for a cardiac event. The risk of an event was 18% in the group with 34% reduction in LDL, which fell to 11% in those with 44% to 70% reduction in LDL (10). On the basis of these and other similar results, some meta-analyses have concluded that percent LDL lowering may be a more logical surrogate for therapeutic efficacy than a specific LDL target (23). Accepting the meta-analyses as valid, however, percent LDL lowering has a major intrinsic limitation, if the relation between LDL and cardiac events is indeed curvilinear. When the baseline LDL is higher, then any given level of percent LDL lowering must result in a greater reduction of cardiac events. Thus, the benefit a patient derives from treatment is a function of not only the percent LDL lowering, but also its level before treatment. The relevance of the interaction between pretreatment LDL and percent LDL lowering is that the most widely quoted
The argument in favor of on-treatment LDL or to use it as a criterion for individual patient therapy. Potentially misleading when one wishes to compare studies outcome, its use as a surrogate for therapeutic efficacy is a useful measure of drug potency and predicts therapeutic conclusion is that even though percent LDL lowering is greater than is found for pretreatment LDL. Thus, a reasonable LDL reduction and cardiac events across studies (Fig. 2B) explains the somewhat weaker correlation between percent LDL reduction and cardiac events across studies (Fig. 2B) than is found for pretreatment LDL. Thus, a reasonable conclusion is that even though percent LDL lowering is a useful measure of drug potency and predicts therapeutic outcome, its use as a surrogate for therapeutic efficacy is potentially misleading when one wishes to compare studies or to use it as a criterion for individual patient therapy.

ON-TREATMENT LDL. The argument in favor of on-treatment LDL derives from the results of angiographic and vasomotor reactivity trials and from the post-hoc analysis of the 4S trial. In vasomotor reactivity trials, the correlation between improvement in endothelial function and on-treatment LDL levels is modest but statistically significant (17,18). In the tertiles of on-treatment LDL established by cut-points of 126 and 105 mg/dl in the 4S trial, major coronary event rates at four-year follow-up were 18.9%, 13.3% and 11.0%. The lowest LDL tertile is similar to that recommended by the National Cholesterol Education Program (NCEP) for patients with established CHD. Nonetheless, on-treatment LDL does not correlate better with cardiac events than the other two surrogate measurements (Fig. 2C).

Failure of on-treatment LDL to more clearly predict the cardiac event rate highlights three limitations in extrapolating therapeutic implications from the epidemiologic relation of LDL to cardiac events. First, other risk factors for CHD, including cigarette smoking, hypertension, diet) shift the curve upward and to the left (26). This is best illustrated by the striking differences in cardiac event rates at the same levels of serum total cholesterol that are found in different Western countries, despite the persistence of the curvilinear relation in individual populations (27). For instance, Figure 3 shows a fourfold difference in CAD risk between Australia and France, although the average level of cholesterol in the two populations is similar. Second, populations with different genetics also exhibit major differences in the relation of LDL to cardiac events. Unlike Western populations, in the Chinese, a steep slope persists into the range of total cholesterol 160 mg/dl and LDL cholesterol 60 mg/dl (9), but in the Japanese, the relation is flat across a wide range of cholesterol levels (26). Third, statins and other LDL lowering therapies alter other lipid fractions that modify CAD risk, independent of the LDL effect. Statins decrease triglycerides by 11% to 17% and increase high density lipoprotein cholesterol by 5% to 7% in clinical trials. A significant reduction of chylomicrons, very low density lipoprotein remnants and LDL cholesterol has also been reported (28). Finally, a direct nonlipid effect of statins may also preclude epidemiologic data from being used to predict results of LDL lowering therapy with statins (29). This was first suggested by WOSCOPS, in which the Framingham risk prediction model accurately predicted risk in the placebo arm but underestimated risk reduction in the treatment arm by 35% (4,30) (Fig. 4). The large number of potential lipid-independent statin actions include antiplatelet (31,32), fibrinolytic (32), anti-inflammatory (16), antiproliferative (29), antioxidant (33) and immunosuppressive effects (34), inhibition of cholesterol esterification and upregulation of nitric oxide (35,36). It is possible, given the pharmacologic differences amongst statins (37), that the magnitude of these nonlipid-lowering effects may differ between statins.

In summary, all three surrogate LDL measurements have both value and limitations for predicting therapeutic efficacy. Consequently, all three statin effects need to be analyzed and reported. Baseline LDL is an excellent predictor of risk reduction. Percent LDL lowering is also excellent, but interacts with baseline LDL, confounding cross-trial comparisons. From a practical standpoint, however, the clear relation of LDL to clinical events and the widespread use of LDL targets suggest that on-treatment LDL has the greatest relevance to the clinical practice of preventive cardiology.
What is the best LDL target? There are two components to this issue: first, is the NCEP LDL target level of 100 mg/dl for secondary prevention still a reasonable target, given randomized trial results, and second, will therapeutic efficacy be increased by much more aggressive LDL lowering?

The first issue concerns the value of lowering LDL below 125 mg/dl. There are two schools of thought. One holds that a reduction in LDL below the range of 100 to 125 mg/dl provides little additional beneficial effect for reducing cardiac events (2,12); the alternative position is that a substantial further reduction in cardiac events can be obtained with more dramatic LDL lowering (38–40). The strongest support for the view that the relation between on-treatment LDL and coronary events has an inflection point at \( \leq 125 \) mg/dl is provided by the CARE trial. The CHD events declined progressively as LDL levels fell from 174 to 125 mg/dl; however, from 125 to 71 mg/dl, CHD events did not decline further (2,12). An important limitation of the CARE analysis is that only 20% of the patients in the trial had on-treatment levels \(<125\) mg/dl. Further, arbitrary post-hoc selection of end points carries the intrinsic risk of leading to conclusions that cannot be supported by prospective studies. Other studies, however, provide partial support to the idea that LDL lowering below 125 mg/dl has limited value. In WOSCOPS, for instance, there was no further decrease in cardiac events beyond a reduction of LDL of 24% (3,11).

The randomized trial that most directly challenges the conclusions of CARE is the Post Coronary Artery Bypass Graft (Post CABG) clinical trial, which used an angiographic end point. The trial demonstrated a significant angiographic and revascularization benefit and 18% lower clinical events with aggressive LDL lowering to slightly below the NCEP target level of \(<100\) mg/dl (38). Because the on-treatment level of LDL in the moderate treatment group was only slightly higher than the cut-point chosen for CARE (135 vs. 125 mg/dl), the data suggest that there may be substantial benefit from aggressive LDL lowering toward the NCEP target level of 100 mg/dl. In contrast, a purist might legitimately question whether vein graft disease, a model of accelerated atherosclerosis, is directly relevant to targets for CAD. Clearly, no definitive conclusion can be drawn from these competing results. The curvilinear epidemiologic relation between events and cholesterol and the Post CABG trial results, however, suggest that benefit is more likely to be spread over the range of LDL between 95 and 135 mg/dl, and probably does not terminate at an LDL level of 125 mg/dl.

The second question, whether substantially greater LDL lowering will increase therapeutic efficacy, is arguably the central issue in lipid-lowering therapy today. There is little information to guide our reasoning. In summary, epidemiologic data suggest the potential for further benefit, albeit with a lesser slope. Randomized clinical trial data, exemplified by the differences between CARE and Post CABG, provide conflicting insights. Very large reductions in LDL substantially improve endothelial function, however (41); and endothelial dysfunction probably plays a role in atherogenesis (42). Thus, Baller et al. (43) found that after six months of cholesterol lowering with simvastatin, from LDL level of 165 to 95 mg/dl, coronary flow reserve as measured by positron emission tomography increased by 20%, with concomitant regression of angina in most patients. Shechter et al. (44) found that flow-mediated endothelial relaxation was significantly better in a group of 28 patients with stable angina when the mean LDL level was 77 mg/dl than in a similar group with a mean LDL level of 106 mg/dl. Few trials have examined the effects of LDL lowering to levels below the NCEP target. The Harvard Atherosclerosis Reversibility Project (HARP), the smallest of the angiographic trials, reported no benefit of lowering LDL from 140 to 86 mg/dl (38% reduction) with pravastatin (45). A larger and more recent angiographic trial—Lipoprotein and Coronary Atherosclerosis Study (LCAS)—however, reported slowed progression associated with a 24% reduction in LDL (from 146 to 111 mg/dl) with fluvasstatin (46). The Atorvastatin Versus Revascularization Treatment (AVERT) trial of 341 stable patients with mild to moderate CAD suggests that aggressive LDL lowering to 77 mg/dl with atorvastatin is at least as safe and effective as a strategy of angioplasty plus a modest reduction in LDL to 119 mg/dl (47). The sample size and duration of follow-up in all of these trials was too small to allow detection of any significant difference in the hard end points of death or myocardial infarction. Taken together, the vascular reactivity studies and limited trial data support the speculation that even more aggressive lipid lowering will result in a further increment of reduction in cardiac events. If so, the reduction in events between LDL target levels of 100 and 70 mg/dl is likely to be less dramatic than that in higher LDL ranges.

It is also possible that aggressive LDL lowering could increase the risk of hemorrhagic stroke or malignancy. There is an established relation between malignancy and very low cholesterol levels, but the low cholesterol levels are widely thought to be secondary rather than causal. In the MRFT screening study, six-year follow-up data revealed risk of hemorrhagic stroke to be threefold higher in men whose total cholesterol was \(<160\) mg/dl (48). Similarly, the Honolulu Heart Program, an 18-year follow-up study of 7,850 Japanese men, revealed that the highest incidence of hemorrhagic stroke occurred in those with total cholesterol \(<160\) mg/dl (49). Clearly, these epidemiologic results that relate hemorrhagic stroke risk to nontreatment cholesterol levels may reflect the presence of concomitant disease and have no relation to statin therapy. Neither randomized clinical trial data nor widespread clinical experience has suggested an increased risk at lower LDL levels, although the published data are thus far insufficient to allow any definite conclusion. Consequently, the possibility of finding an adverse effect of more aggressive cholesterol lowering cannot be completely ruled out. We may conclude that both
the benefit and the risk of aggressive LDL lowering to <80 mg/dl can only be known through randomized clinical trials with long-term follow-up.

This issue is now being tested in randomized trials. The Treat to New Targets (TNT) trial compares 10 and 80 mg of atorvastatin with the predicted outcome LDL levels of 70 and 90 mg/dl, respectively. Patient recruitment was completed in July 1999. The Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH trial) in the United Kingdom compares 20 to 80 mg of simvastatin. A fascinating aspect of the debate regarding the best LDL target is illustrated by two trials sponsored by competing pharmaceutical companies. Both trials compare 40 mg of pravastatin with 80 mg of atorvastatin. Depending on the mean entry level of LDL, we might estimate that the pravastatin dose will reduce LDL to ~100 to 115 mg/dl, whereas the atorvastatin dose will reduce LDL to ~70 to 80 mg/dl. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial, sponsored by the makers of pravastatin, aims to demonstrate that there is no difference in clinical outcomes beyond an LDL level close to the current NCEP guideline. The REVERSAL trial, sponsored by the makers of atorvastatin, aims to demonstrate plaque regression and stabilization by intravascular ultrasound with aggressive lipid lowering. The results of these trials should finally resolve what may reasonably be described as the most important issue in preventive cardiology today.

Conclusions. There are three critical unresolved questions relating to statin therapy. Each is a part of the broader issue of how best to manage elevated LDL cholesterol in patients at risk for a coronary event. These questions are about the shape of the curve relating cardiac events to LDL, the best surrogate measurement for assessing therapeutic efficacy and the best target for LDL therapy. The current information allows us to offer a number of speculations. The relation between cardiac events and LDL is curvilinear, both epidemiologically and during therapy. The relation is confounded by large quantitative differences between populations and by coexisting risk factors. The benefit of lipid lowering is heavily influenced by the level of pretreatment LDL and by the non-LDL–lowering effects of statins. The benefit of lipid lowering is greatest at high levels of pretreatment LDL and least at low levels. The benefit of lipid lowering diminishes progressively and becomes difficult to detect at lower LDL levels.

In the absence of data to guide us, however, we can only speculate about the best LDL target. Epidemiologic data suggest that there may be some benefit to greater LDL lowering. Failure to reduce the event rate in patients with pretreatment LDL <125 mg (CARE study) alerts us to the risk of extrapolating epidemiology to clinical practice, yet subset analysis of some clinical trials suggests the greatest benefit appears in those patients with the lowest on-treatment LDL levels. In the face of this seemingly contradictory data, we can only speculate that given a sufficient sample size, very aggressive LDL lowering to <80 mg/dl could be accompanied by a modest therapeutic benefit beyond the current NCEP recommendations. In contrast, if benefit is observed, it will have to be balanced against the as yet unknown risk of an increase in adverse events.

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