Targeting Targets for LDL-Lowering Therapy: Lessons from the Collaborative Atorvastatin Diabetes Study (CARDS)

The results from the clinical trials of LDL lowering with statins could not be clearer or more compelling, and yet the treatment recommendations they have produced could not be more complex or recondite. On the one hand, the densely interwoven skein of pathophysiological, epidemiological, and clinical trial evidence tying LDL to arterial disease and arterial disease to clinical events makes the conclusion that decreasing LDL is the principal mechanism of benefit of statins as secure as any scientific hypothesis can be. But on the other hand, what should the therapeutic target be and, even more to the point, how should it be chosen? The straightforward—and the logically correct—answer is to reject the question and simply use the same dose of the same LDL-lowering agent successfully used in the clinical trial (1). The more ambitious—and the necessarily more imaginative and less secure—approach is to try to reason through the puzzle as to which is the best parameter to target LDL for maximal benefit from statins and, after that, settle on the concentration of that parameter that should be achieved and set out why.

The article by Charlton-Menys et al. that appears in this issue represents a major step forward to meeting that challenge (2). The Collaborative Atorvastatin Diabetes Study (CARDS)1 was a stunningly positive demonstration of the clinical benefit of statin therapy in patients with type 2 diabetes (3). In their analysis of the outcomes from CARDS, based on linear analysis, they determine the value of apolipoprotein B (apoB) that corresponds to target values of LDL cholesterol (LDL-C) and non-HDL cholesterol (non-HDL-C) in the treated and untreated groups. Notwithstanding that >25 major studies of all types, clinical trials of primary and secondary prevention and epidemiological studies that are worldwide in scope, have shown that apoB is superior to LDL-C as a marker of atherogenic risk, and notwithstanding the substantial and uncorrectable errors in the individual calculation or measurement of LDL-C (4, 5), its hold on the core of the cholesterol community is remarkable. Both the Canadian Diabetes Association (6) and the Endocrine Society (7) continue to rate LDL-C as the primary target of therapy and continue to downgrade the usefulness of apoB. Change is never easy, particularly when it requires those in power to change long-held views. In science, as elsewhere, change may require new players at the table: new conclusions require new minds as much as new evidence. The American Diabetes Association and the American College of Cardiology have taken on the issue for the first time, and their joint report states that apoB is superior to LDL-C as a target of LDL therapy (8, 9).

If evidence is the standard, LDL-C is irrevocably in third place, and the issue now is non-HDL-C vs apoB. Neither requires fasting samples and both can be accurately measured. It is worth noting that apoB, along with total cholesterol and triglyceride, allows accurate diagnosis of all the atherogenic dyslipoproteinemias, whereas non-HDL-C adds no more than total cholesterol (5). Nevertheless, if lipids are to be done as well (although this should not be necessary on follow-up), apoB is an additional expense, and non-HDL-C certainly correlates more closely with apoB than LDL-C.

But is non-HDL-C an adequate clinical surrogate for apoB? In studies with fewer events, such as the Framingham Offspring Study (10), they do tend to be equivalent in predictive power, whereas in larger studies with more events, such as Apolipoprotein-Related Mortality Risk (AMORIS) (11) and INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) (12), apoB is clearly superior. The present study expands our knowledge on these critical points and indeed allows us to expand our concepts as to how to compare parameters. First, CARDS confirms a key therapeutic point too many remain unaware of: statins lower cholesterol substantially more than they decrease apoB. In CARDS, compared with placebo, atorvastatin decreased LDL-C 40.9%, non-HDL-C 38.1%, and apoB only 24.3%. Put differently, apoB was decreased 36% less than non-HDL-C. Because risk relates to plasma concentration, the posttreatment concentration of apoB is substantially higher than the posttreatment concentration of non-HDL-C. This means that a major treatment gap will necessarily often be present if non-HDL-C is the preferred marker of the adequacy of statin treatment (13). On these grounds alone, apoB is

1 Nonstandard abbreviations: CARDS, Collaborative Atorvastatin Diabetes Study; apoB, apolipoprotein B; LDL-C, non-HDL-C, non-HDL cholesterol; AMORIS, Apolipoprotein-Related Mortality Risk.
superior to non-HDL-C as a marker of the residual risk and of the need for further treatment.

Charlton-Menys et al. stratify their subjects based on LDL-C and demonstrate that, for the same LDL-C, apoB is lower in the treated group than in the placebo group, demonstrating, yet again, that apoB cannot be inferred from LDL-C. As well, assuming a linear relation, the authors calculate values of apoB with and without treatment that are equivalent to therapeutic targets of LDL-C and non-HDL-C and compare these to therapeutic targets recently selected by the American Diabetes Association and the American College of Cardiology (8, 9).

That raises the core issue: just how should targets be selected? All the clinical statin trials tested therapeutic regimens, not targets, and therefore they do not establish target concentrations as such. They only prove that reduction to a particular concentration is associated with that much benefit. CARDS demonstrates that there was clinical benefit with average reductions in the treated group to an LDL-C of 70 mg/dL (1.81 mmol/L) and an apoB of 80 mg/dL (800 mg/L) (3). For this specific population, with this specific treatment, these outcome concentrations are indeed arithmetic equivalents.

They are not, however, equivalent from a cost-benefit perspective. If the LDL-C concentration achieved in this trial is adopted for more general care, everyone must be treated to a value equivalent to the 5th percentile of the North American population. By contrast, if apoB is the target, subjects only have to be treated to a value equivalent to the 20th percentile of the population. Therefore, from the cost side of the equation, apoB is the more efficient target since the total cost and effort of therapy will be less.

Apo B is also the more effective target because it establishes more precisely than LDL-C or non-HDL-C how much further benefit there will be with further therapy. As the authors note: “The scatter in the graphs relating apoB to LDL-C and to non-HDL-C reveals that there are many patients achieving their LDL-C or non-HDL-C target, who remain above the recommended apoB therapeutic target.” Thus, any patient with an apoB above the 20th percentile of the population would benefit from further therapy, no matter the values of LDL-C or non-HDL-C. On the other hand, once the apoB target has been achieved, further effort to decrease LDL-C or non-HDL-C is wasteful.

The discordant performance of the markers in CARDS is based on the documented compositional heterogeneity of LDL particles. In patients with large cholesterol-enriched LDL particles, LDL-C and non-HDL-C overestimate risk and will result in overtreatment, whereas in subjects with small cholesterol-depleted LDL, they underestimate risk and will result in undertreatment. Only apoB gets it right no matter the composition of the LDL particle.

We believe the evidence in toto supports apoB as the target of choice for LDL-lowering therapy. Moreover, the evidence indicates there should be a single target value for apoB. We do not accept the argument that patients at low or moderate risk should have their therapy tailored to higher targets, an approach that was adopted before the clinical efficacy and safety of statins were well established. If a patient is to be treated, then the treatment should nullify (or, perhaps more realistically, largely nullify) the risk due to apoB.

Based on this reasoning, in our view, the preferred target of apoB should be 80 mg/dL (800 mg/L). That concentration has been validated by clinical trials including CARDS and is therefore evidence-established. This value should be very close to the point at which further substantial reductions in absolute risk by decreasing apoB are no longer achievable. In other words, we advocate an as-low-as-you-should-go, not as-low-as-you-can-go, policy.

By choosing a single target for apoB, we are choosing simplicity for clinical practice. We are also conserving scarce resources. The very low risk target of an LDL-C at 70 mg/dL (1.81 mmol/L) is at the 5th percentile of the population, and the equivalent concentration of apoB would be 60 mg/dL (600 mg/L). Until there is definite evidence of significant clinical benefit by achieving this value of apoB, we believe that the additional costs do not justify this objective. For those who differ, however—for those who argue that lowest possible concentration is the best possible concentration—an apoB of 60 mg/dL (600 mg/L) would be the very-high-risk target.

Finally, lipidology cannot be reduced to simply apoB. Large numbers of remnant particles, such as familial dysbetalipoproteinemia, do increase risk; in this specific circumstance, total cholesterol or non-HDL-C, not apoB, should be the therapeutic target (14).

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References


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