Editor’s Perspective

Three Reasons to Abandon Low-Density Lipoprotein Targets
An Open Letter to the Adult Treatment Panel IV of the National Institutes of Health

Rodney A. Hayward, MD; Harlan M. Krumholz, MD, SM

The updated clinical guidelines for cholesterol testing and management (Adult Treatment Panel (ATP) IV) from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults are under development and due to be published in 2012. These influential guidelines are organized and funded by the National Heart, Lung, and Blood Institute (NHLBI) and carry the imprimatur of the federal government. In this iteration, the NHLBI has a stated goal of integrating its set of Cardiovascular Risk Reduction guidelines.

A primary focus of the previous version of the guidelines, ATP III, was a strategy of treating patients to target low-density lipoprotein (LDL) cholesterol levels. ATP III stated that “recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD.” For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.” This reasoning, however, diverged from the clinical evidence, recommending an approach that was not tested in any clinical trial.

Outcomes research promotes the need to demonstrate benefit before making recommendations for medical intervention. In that spirit, we present an open letter to the ATP IV Committee that provides the rationale for why the new guidelines should abandon the treat-to-target paradigm.

Dear ATP IV Committee,

We are writing to encourage you to abandon the paradigm of treating patients to LDL targets, a change that will better align ATP IV with current clinical evidence. Changing long-held beliefs is never easy, even when the need for change is based on strong evidence. Change is especially difficult when prior beliefs are firmly embedded in culture, accepted as dogma, and codified in books, articles, guidelines, public service announcements, and performance measures. Still, what is most important is that guideline committees follow a process that adheres closely to the scientific evidence, particularly the details of the clinical trials—which are abundant for lipid treatment.

The evidence supports moving away from a target-based approach, a step that could launch a new era of guidelines in which treatment targets are replaced by a more tailored treatment approach (sometimes referred to as “individualized” or “personalized” care), which can improve patient outcomes while reducing harms and costs caused by over-treating low-risk/low-benefit individuals.

Below, we present briefly the primary reasons that justify a major change in the next generation of ATP guidelines.

There Is No Scientific Basis to Support Treating to LDL Targets

First, no major randomized clinical trial (RCT) has tested the benefits of treating patients according to LDL targets. The clinical trials tested fixed doses of drugs that lower lipid levels in specific patient populations. In some of these trials, drugs were shown to reduce risk (eg, statins), but in others, this reduction in risk was not demonstrated (eg, clofibrate and torcetrapib). Other drugs, such as ezetimibe, remain to be tested. The trials do not demonstrate that all drugs that reduce lipid levels reduce patient risk. Thus, the dogma that treating to target is based on clinical trial evidence belies the fact that no clinical trial has yet tested this strategy.

As noted above, trials show that not all drugs that improve lipid profiles reduce patient risk. In fact, almost all the trial evidence for patient benefit is for a single medication class—statins—that is known to have multiple biological activities that are often referred to as “pleiotropic” effects. Standard doses of the first generation of statins, such as simvastatin, dramatically reduce cardiovascular events and mortality. High-potency statins, such as atorvastatin, reduce nonfatal events by an additional 15–20%. Thus, the trial evidence indicates that the use of statins, and not treatment to target, can reduce risk. Although the mechanism(s) by which statins exert their benefit is controversial, one does not need to impugn the cholesterol hypothesis to recognize that different lipid-lowering drugs could possibly have deleterious effects.

The opinions expressed in this article are those of the authors and do not necessarily represent the opinions of the American Heart Association, Department of Veterans Affairs, University of Michigan, or Yale University.

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that offset their potential benefit. Further, it is quite possible that a surrogate measure, such as LDL, may appear to be a single entity even though clinically important subcomponents (such as heterogeneity in particle size) or interactions (such as total cholesterol/high-density lipoprotein [HDL] ratio) may exist. Thus, we cannot assume that lowering LDL, by any means, will improve patient outcomes.

A closer look at the evidence demonstrates further reasons against basing treatment decisions on LDL levels. In considering recommendations, it is useful to recognize that there are only 2 factors that determine the benefit of a treatment for an individual patient: (1) the risks of morbidity or mortality in the absence of treatment and (2) the degree to which the treatment reduces or increases these risks. LDL levels are not useful in either of these areas. The LDL level contributes little to estimating cardiovascular risk overall and especially compared with non-HDL or total cholesterol/HDL ratio. Moreover, clinical trials demonstrate that the relative effects of statin therapy are not substantially related to a patient’s pretreatment LDL,13,14. It should be noted that although C-reactive protein has been demonstrated to be an independent predictor of cardiovascular risk, it is not strongly related to the relative risk reduction of statins, although the evidence is not entirely consistent.13,15,16 Thus, there is strong scientific evidence that LDL is not a very useful factor in determining who is at risk for cardiovascular disease or how much that risk will be reduced by a statin (Table).

The conclusion that the evidence does not support a target-based approach may seem counterintuitive to those whose work has been focused on the biology of cardiovascular disease mechanisms, but the science of clinical decision-making requires a different approach. The critical component of good clinical decision-making is not the scientific evidence regarding disease pathogenesis or treatment mechanisms but rather the best empirical predictors of patient risk and factors that reduce risk, the 2 elements that help determine the risks and benefits of a treatment in individual patients. As has been demonstrated conclusively, it does not matter whether LDL is the sole biological mechanism mediating the treatment benefits of statins. What matters is that LDL does not appreciably help predict a patient’s cardiovascular risk or a statin’s relative risk reduction and therefore provides a poor premise on which to base treatment recommendations. Beyond statins, we must extend our concern to the question of whether treatments might be harmful and not just whether they may or may not be effective.

The Safety of Treating to LDL Targets Has Never Been Proven

The LDL target-based guidelines are commonly used to indirectly promote treatments that have not been shown to be safe. The target-based approach can lead to recommendations to treat patients with a low risk of cardiovascular outcomes. If there is a benefit for these patients, it is likely to accrue only after decades of treatment. In this setting, even minor risks can outweigh benefits. Although statins can have appreciable side effects and there are potentially serious drug-drug interactions, they have been shown to be a relatively safe class of medications over a 5- to 7-year treatment period. Longer-term safety is not yet known and other lipid-lowering agents have less safety data.

Table. Why Focusing on an LDL Targets Leads to Poor Identification of Which Patients Benefit From Statin Therapy*

<table>
<thead>
<tr>
<th></th>
<th>Baseline 5-Year CV Risk</th>
<th>Absolute CV Risk Reduction for 5 Years</th>
<th>Net Benefit If Treated for 5 Years With 40 mg Simvastatin (NNT to Prevent 1 CV Event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Do Those Without Other CV Risk Factors Benefit Considerably From Statin Treatment Just Because Their LDL Is High?†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, Age 55 Years, Nonsmoker, SBP=120, HDL=55, CRP=5, No Family History</td>
<td>LDL=90 mg/dL</td>
<td>−2%</td>
<td>8 in 1000</td>
</tr>
<tr>
<td></td>
<td>LDL=145 mg/dL</td>
<td>−2.5%</td>
<td>10 in 1000</td>
</tr>
<tr>
<td></td>
<td>LDL=190 mg/dL</td>
<td>−3%</td>
<td>12 in 1000</td>
</tr>
<tr>
<td>B. Do Those With Many CV Risk Factors Get Much Less Benefit From Statin Treatment Just Because Their LDL Is Naturally Low?†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, Age 55 Years, Smoker, SBP=140, HDL=25, CRP=5, Positive Family History</td>
<td>LDL=190 mg/dL</td>
<td>−13%</td>
<td>52 in 1000</td>
</tr>
<tr>
<td></td>
<td>LDL=145 mg/dL</td>
<td>−11%</td>
<td>44 in 1000</td>
</tr>
<tr>
<td></td>
<td>LDL=90 mg/dL</td>
<td>−8%</td>
<td>32 in 1000</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; SBP, systolic blood pressure; HDL, high-density lipoprotein; CRP, C-reactive protein; CV, cardiovascular (heart attack, stroke, coronary angioplasty, coronary artery bypass surgery, or death related to heart disease); and NNT, number needed to treat.

*Based on clinical trial meta-analysis results in which 40 mg simvastatin decreased CV events by −40% and the relative effect was not associated with pretreatment LDL level or overall CV risk.

†Because LDL is a single risk factor, varying it from an unusually low to an unusually high level only has a modest impact on CV risk and the expected benefit of a statin. Because risk factors are multiplicative, not additive, their combined effects have major and often complex effects on a patient’s overall CV risk and the expected benefit of a statin.
Some advocates\(^{18,19}\) justify treating LDL in individuals with low 10-year cardiovascular risk by noting that although there might not be appreciable benefit over a 10-year period, individuals with elevated LDL generally have a high “lifetime” cardiovascular risk; incidentally, this is also true of those with low LDL. Recently published guidelines promote screening all children for elevated LDL levels and possible use of statins at early ages.\(^{20}\) Recommending that patients take this potential risk would only be justified if early treatment is shown to have substantial benefit beyond that achieved by delaying treatment until a person’s overall 5- to 10-year cardiovascular risk is at least moderately elevated. However, this beneficial effect of early treatment has not yet been demonstrated. If long-term benefits in populations with lower short-term risks were secure and substantial, then uncertainty about treatment might be less troublesome, but that is not the case.

In addition, LDL targets are commonly used to promote the use of newer lipid-lowering treatments, often in combination with a statin. These treatments are often more expensive than statin treatment, and evidence that they reduce cardiovascular events is lacking, as are adequate safety data.\(^{19}\) The suggestion that RCTs have shown these treatments to be safe and that they have just not yet been shown to substantially decrease cardiovascular events neglects the symmetry of statistical power. If the RCT evidence is insufficient to demonstrate a substantial reduction in morbidity and mortality, there is also not enough evidence to determine whether the treatment seriously harms patients, including substantially increasing morbidity and mortality. Further, arguing that evidence of significant LDL-lowering should be a sufficient rationale for promoting use of a lipid medication ignores recent examples of the dangers of trusting surrogates. In recent years, RCTs have demonstrated that intensive therapy in pursuit of recommended blood pressure goals can result in substantial patient harm,\(^{21}\) that striving for recommended glycemic goals can increase mortality,\(^ {21}\) and that torcetrapib and hormone replacement therapy can both “improve lipids” and elevate risk.\(^ {22,23}\) New classes of medications must be adequately evaluated for their effects, both positive and negative, on patient outcomes before being recommended in guidelines, especially when these recommendations often become mandated in quality measures.\(^ {24}\) Their effect on LDL levels is not sufficient justification for a strong recommendation, but an emphasis on targets can tend to encourage their use.

**Tailored Treatment Is a Simpler, Safer, More Effective, More Evidence-Based Approach**

As mentioned above, the ATP III LDL targets were based on extrapolations of the RCT evidence, a model that had not been directly tested. Recently, formal simulations found the LDL-target model to be deficient even under assumptions that favor the approach, such as LDL being the sole mechanism of statin therapy and LDL being reliably measured (which it is not in current practice).\(^ {25}\) This research demonstrated that LDL-based guidelines will either recommend undertreating (by not recommending adequate statin therapy in high cardiovascular risk/low LDL patients) or overtreating (by recommending statin treatment in low cardiovascular risk/high LDL patients).

In contrast, the model for a simple tailored treatment approach, in which statin treatment intensity is based on a person’s overall 5- to 10-year cardiovascular risk regardless of LDL level, was estimated to save about 100,000 more quality-adjusted life years annually while having fewer people on high doses of statins than a treat-to-target approach. Further, the tailored treatment model is based more directly on the clinical trial evidence. However, it was not possible to demonstrate a situation in which treat-to-target could approximate the effectiveness or efficiency of a more tailored approach, even using assumptions that strongly favor LDL targets. In fact, when 10 international lipid experts, most of whom had previously advocated for an LDL-based approach, were asked to provide any reasonable scientific arguments that would result in a treat-to-target approach being as good as a tailored treatment approach, none were able to do so.\(^ {6}\) This was not surprising, given that the RCT evidence clearly suggests that LDL does not help identify patients who are more likely to benefit from a statin.

In conclusion, the treat-to-target paradigm had many attractive aspects. It seemed to emerge from an understanding of mechanism and had great intuitive appeal. Unfortunately, the recommendation was not based on the strongest clinical evidence. ATP IV presents the opportunity to align recommendations with strong clinical evidence regarding patient risk and risk reduction with lipid-lowering agents. Such a change has the potential to ensure the reduction of undertreatment and overtreatment—and promote appropriate treatment with statins. For interventions with less evidence, we must make clear the uncertainty, outline how best to make decisions given that adequate evidence does not exist, and resist the temptation to make strong recommendations that are not supported by the evidence. With such an approach, the Committee will set a high standard for all future groups to follow and will provide an immense service to the public.

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