Counterpoint: Low-Density Lipoprotein Cholesterol Targets Are Not Needed in Lipid Treatment Guidelines

Jennifer G. Robinson, Kausik Ray

Abstract—On the basis of accumulating evidence, low-density lipoprotein cholesterol (LDL-C) treat-to-goal approaches no longer seem to be the best way to optimize lipid-modifying therapy to prevent atherosclerotic cardiovascular disease (ASCVD). The potential for a net ASCVD risk reduction benefit is a more individualized approach to clinical decision making and may better inform patient preferences. However, risk estimation tools will need to be developed to facilitate more personalized CVD risk estimation in statin-treated patients. In the meantime, LDL-C thresholds rather than targets may aid in determining which patients might benefit from additional LDL-C-lowering therapy beyond statins. (Arterioscler Thromb Vasc Biol. 2016;36:586-590. DOI: 10.1161/ATVBAHA.116.306887.)

Key Words: atherosclerosis • cholesterol • goals • LDL cholesterol • patient preference

LDL-C treatment goals were introduced in the first National Cholesterol Education Program Adult Treatment Panel (ATP) Program guideline in 1988.1 On the basis of the epidemiological and clinical trial data available at that time, a minimal LDL-C goal of <130 mg/dL (3.4 mmol/L) was identified for patients with coronary heart disease or 2 other risk factors. Because clinical trials enrolled patients with progressively lower LDL-C levels, subsequent ATP guidelines defined lower LDL-C treatment goals, with an optional LDL-C goal <70 mg/dL (1.8 mmol/L) identified for very high–risk patients with CVD in the ATP III guideline in 2004.2

The National Heart, Lung, and Blood Institute convened ATP IV in 2008 to develop new drug treatment guidelines to reduce cardiovascular risk. This guideline was based on rigorous systematic review of evidence from randomized trials with cardiovascular outcomes. The ATP IV recommendations were transitioned for implementation as the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk.3,4

When recommendations were framed with the requirement that a treatment strategy needed to reduce cardiovascular events, the ATP IV systematic review concluded that there was insufficient evidence from clinical trials to support titrating to specific LDL-C or non–high-density lipoprotein cholesterol goals.3,4 Not only was the ATP IV panel unable to identify an optimal cholesterol treatment goal, they were also unable to identify a CVD risk reduction benefit or rate of adverse events from achieving a particular goal. Moreover, at the time the guideline was developed, there was no clear evidence that any drug added to statin therapy further reduced CVD events. Thus, after >2 years of evidence review and deliberation, the 2013 ACC/AHA guideline panel made the decision to move away from LDL-C goals, and instead focus on the potential for a net ASCVD risk reduction benefit from therapy. This new paradigm integrates a more holistic consideration of the potential for an ASCVD risk reduction benefit for an individual patient based on the absolute risk of the patient, the average relative reduction in risk from the treatment, and the potential for adverse events.

The 2013 ACC/AHA cholesterol guideline identified 4 groups of patients with strong evidence of a net ASCVD risk reduction benefit with statin therapy: those with (1) clinical ASCVD, (2) untreated LDL-C ≥190 mg/dL (4.9 mmol/L), (3) diabetes mellitus aged 40 to 75 years, or (4) ≥7.5% 10-year ASCVD risk who did not fall into the previous 3 categories.3 High-intensity statin therapy was recommended for high-risk patients up to the age of 75 years, and moderate-intensity statin therapy for low-risk patients or high-risk patients >75 years of age or with safety considerations.

The 2013 ACC/AHA guidelines recognized that LDL-C is a causal factor in ASCVD and some high-risk patients might require additional LDL-C lowering to further reduce their ASCVD risk.3 In addition, at least half of the patients receiving a high-intensity statin would have a less than the average of 50% reduction in LDL-C observed with high-intensity statin therapy5 and some patients may not be able to tolerate high-intensity statin therapy. Furthermore, patients with untreated LDL-C ≥190 mg/dL (4.9 mmol/L) would require additional nonstatin therapy to reduce LDL-C to more acceptable levels.3 Nonstatins shown to reduce CVD events were to be preferred. Thus, although firm recommendations were not provided for adding nonstatin therapy because clinical outcome trials were
still underway, there was scope for individual clinical judgment to use nonstatins.

The subsequent completion of the Improved Reduction in Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) provided the first clear randomized trial evidence that a nonstatin added to background statin therapy would further reduce ASCVD risk. IMPROVE-IT found a modest 6% relative reduction in CVD events when ezetimibe was added to background statin therapy, with a mean achieved LDL-C of 54 mg/dL (1.4 mmol/L) compared with a mean of 70 mg/dL (1.8 mmol/L) in the statin monotherapy group. Preliminary data from phase 3a trials of 2 proprotein convertase subtilisin/kexin 9 monoclonal antibodies also suggest these agents may further reduce CVD events when added to background statin therapy. In the 2 proprotein convertase subtilisin/kexin 9 monoclonal antibody trials, the addition of alirocumab or evolocumab to background lipid-lowering therapy reduced CVD events by 50% during a period of 11 to 18 months, with an approximate mean achieved LDL-C of 50 mg/dL (1.3 mmol/L) in the proprotein convertase subtilisin/kexin 9 monoclonal antibody groups compared with ≈120 mg/dL (3.1 mmol/L) in the control groups. Do these new data support returning to the LDL-C treat-to-goal approach?

The answer is no, for several reasons. None of these trials tested a treat-to-target approach, but rather tested the addition of treatments that further reduced LDL on top of statin therapy. Although fixed LDL-C goals have some advantages, they have even more serious disadvantages. LDL-C goals do provide a relatively simple treatment algorithm for clinicians and may engage patients about their treatment. However, a serious limitation is that a high-risk patient may be at goal and, therefore, not receive appropriate risk reduction therapy. For example, a very high-risk patient with CVD and diabetes mellitus with an LDL-C of 69 mg/dL (1.79 mmol/L; at goal) has an ASCVD risk indistinguishable from that of patient whose LDL-C is 71 mg (1.84 mmol/L; not at goal). It seems arbitrary, and needless to say inappropriate, not to treat the first patient, but treat the second patient based on a 2 mg/dL (0.05 mmol/L) difference in LDL-C. Furthermore, in the second case, if the patient were not receiving a statin, the LDL-C goal could be achieved using a low-intensity statin that lowered LDL-C by 10%, whereas the randomized trial evidence supports using a high-intensity statin to lower LDL-C by at least 50%.

**Net Benefit Approach**

Is there a better way? We think there is. Although lower LDL-C seems to be better, it matters which LDL-C therapy is used to lower LDL-C, and in whom such therapy is used. In intravascular ultrasound trials, the greatest regression of atherosclerosis occurs when LDL-C levels are <15 mg/dL (0.4 mmol/L). This corresponds to the greatest relative reduction in cardiovascular events occurring when LDL-C levels are <50 mg/dL (1.3 mmol/L) in the statin trials (lower LDL-C cutpoints were not evaluated). Thus, there seems to be no particular reason to stop lowering LDL-C at a level of 70 or 100 mg/dL (1.8 or 2.6 mmol/L).

The most critical information needed for clinical decision making for an individual patient is the potential for net benefit from additional therapy. The net benefit concept introduced in the 2013 ACC/AHA cholesterol guideline for statin therapy can be used to guide consideration of nonstatin therapy as well. The potential for net benefit is a function of the absolute risk of the individual and the potential for a reduction in ASCVD as well as adverse effects from additional therapy. The starting LDL-C determines the likely benefit a patient can expect for a given LDL-C–lowering regimen.

A straightforward approach to operationalizing net benefit could be based on the number needed to treat (NNT) to prevent one event and number needed to harm to cause 1 adverse event (NNH). These are easily interpreted, well-accepted methods of estimating benefit and risk. NNT is derived from the predicted absolute risk of the patient (based on personal levels of risk factors and LDL-C), multiplied by the relative risk reduction from the added therapy (which may be a function of the magnitude of LDL-C reduction). Recent work suggests NNT may be useful for guiding the addition of ezetimibe in secondary prevention patients and primary prevention statin use in patients at low risk by conventional risk calculators.

Number of patients needed to treat for a net benefit (NNT minus NNH) is a concept easily communicated to patients. Interestingly, work in the hypertension field has revealed that clinicians, on average, consider an NNT ≤50 acceptable when
considering adding a new treatment, while on average, patients consider an NNT $\leq 30$ acceptable. Thus, net benefit derived from NNT and NNH can inform shared decision making for adding a nonstatin, an approach recommended for primary prevention in the 2013 ACC/AHA cholesterol guideline. Of note, the concept of NNT minus NNH estimating net benefit could be extended to future CVD prevention drugs that act through mechanisms other than LDL-C lowering once they have been shown to reduce CVD events in randomized trials.

## Net Benefit Examples

### On the basis of the Cholesterol Treatment Trials meta-analysis, each 39 mg/dL (1 mmol/L) reduction in LDL-C reduces CVD events by $\approx 20\%$. IMPROVE-IT and the PCKS9 monoclonal antibody trials also plot along this line (Figure). Using the examples below, we demonstrate scenarios where a treatment that offers modest LDL-C reduction in high-risk patients could achieve a similar NNT as treatment offering a greater LDL-C reduction in low-risk patients (Table 1).

In IMPROVE-IT, the relative risk reduction for hard events with ezetimibe was $10\%$, without adverse events to counteract the benefit. So for the average IMPROVE-IT very high-risk patient with $15\%$ 5-year hard ASCVD risk, the NNT to prevent 1 hard ASCVD with ezetimibe treatment to lower LDL-C from 70 to 54 mg/dL (1.8–1.4 mmol/L) is 67 for 5 years, and 33 for 10 years (Table 1). Similar NNTs would occur in a low-risk patient with $10\%$ 5-year risk who had a higher baseline LDL-C level and an expected relative reduction of $15\%$ from a 26 mg/dL (0.7 mmol/L) reduction in LDL-C. In contrast, a patient with a $10\%$ 5-year risk, such as patients with chronic coronary heart disease without diabetes mellitus on a statin, would have a 5-year NNT of 100 and a 10-year NNT of 50 from adding ezetimibe to lower LDL-C from 70 to 54 mg/dL (1.8–1.4 mmol/L). Thus, patients could achieve a similar NNT as treatment offering a greater LDL-C reduction in low-risk patients (Table 1).

### Table 1. NNT to Prevent 1 ASCVD Event

<table>
<thead>
<tr>
<th>5-Y ASCVD Rate</th>
<th>Relative Risk Reduction</th>
<th>5-Y NNT; LDL-C Reduction, mg/dL</th>
<th>10-Y ASCVD Rate</th>
<th>Relative Risk Reduction</th>
<th>10-Y NNT; LDL-C Reduction, mg/dL</th>
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ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and NNT, number needed to treat. Adapted from Robinson and Stone. Copyright ©2015, the Authors.

### Table 2. Proposed LDL-C Threshold Approach to Shared Decision Making When Considering Adding a Nonstatin in Statin-Treated Patients

1. Patients treated with maximal statin therapy
   - LDL-C $\geq 130$ mg/dL; (3.4 mmol/L) High-risk* patients likely to benefit from addition of nonstatin
   - LDL-C, 100–129 mg/dL; (2.6–3.4 mmol/L) Very high† risk patients likely to benefit from addition of nonstatin
   - LDL-C<100 mg/dL; (<2.6 mmol/L) Selected very high* risk patients may benefit from addition of nonstatin

2. Choice of a nonstatin based on
   - Reduced CVD events in CV outcomes trials Added to statin: Ezetimibe
     - As monotherapy: Niacin, cholestyramine, fenofibrate, and gemfibrozil‡
     - PCSK9 mAb>>Ezetimibe>>Niacin=Bile acid sequestrant
   - LDL-C–lowering efficacy
     - Ezetimibe>PCSK9 mAb>Bile acid sequestrant>Niacin
   - Safety/tolerability
     - Crystalline niacin<<Extended-release niacin<<cholestyramine/colestipol<<Ezetimibe<<Colesevelam<<PCSK9
   - Cost
     - Perception of benefits and harms, copay, oral vs injection, medication burden

3. Discontinue nonstatin if ≤10% LDL-C reduction

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin 9.

*High risk: As defined in 2013 ACC/AHA cholesterol guideline: clinical cardiovascular disease, untreated LDL-C $\geq 190$ mg/dL, diabetes mellitus aged 40 to 75 years. Also may consider as high-risk equivalents to those patients with $\geq 10\%$ 5-year or $\geq 20\%$ 10-year ASCVD risk (without or with diabetes mellitus).

†Very high risk: clinical ASCVD with diabetes mellitus or familial hypercholesterolemia, or very high–risk equivalents with $\geq 15\%$ 5-year or $\geq 30\%$ 10-year ASCVD risk.

‡Gemfibrozil in contraindicated in statin-treated patients because of excess risk of serious myopathy.
for low-risk patients with CVD, the addition of ezetimibe may be of modest incremental benefit and could have the potential for harm if, for instance, the additional medication jeopardized adherence to other evidence-based drugs because of cost or pill burden.

The relative risk reduction and adverse event rate for proprotein convertase subtilisin/kexin 9 inhibitors, which can lower LDL-C by up to an additional 65% in statin-treated patients, remains to be established in ongoing ASCVD outcomes trials.\footnote{3-8,13-18} In Table 1, NNTs based on 25% to 50% relative risk reductions during 5 and 10 years could be attractive even in low-risk patients based on the magnitude of the absolute risk reduction. However, the high cost and need to inject these agents may limit their widespread use by patients and restrict coverage by payors.

**LDL-C Thresholds a Better Alternative for Now**

Tools are under development to predict CVD risk in statin-treated patients with and without ASCVD. In the meantime, the concept of net benefit from the addition of another LDL-C-lowering drug can be simplified into an LDL-C threshold approach. The LDL-C threshold approach should be reassuring to those who like to have a number to trigger decision making, yet still be consistent with the more robust consideration of the potential for a net benefit for a given patient from added therapy.

Table 2 suggests a step-wise approach for decision making using LDL-C thresholds based on NNT. Extrapolated from NNTs as in Table 1, high-risk patients with LDL-C \(\geq 130\ \text{mg/dL} \) (3.4 mmol/L) are likely to experience a net benefit from moderate additional LDL-C lowering of at least 20% to 25%. When LDL-C is 100 to 129 mg/dL (2.6–3.4 mmol/L), some high-risk and most very high-risk patients are likely to benefit, whereas only very high-risk patients with LDL-C <100 mg/dL (2.6 mmol/L) are likely to benefit from additional moderate LDL-C lowering. Note that LDL-C thresholds are guidance for triggering an assessment of the potential for benefit and shared decision making, rather than mandatory indicators of added therapy.

The choice of nonstatin depends on several factors including demonstration of CVD event reduction randomized trials, adverse event and tolerability profile, cost and availability, and patient preferences. Several randomized trials have found no significant CVD risk reduction during a period of \(\leq 6\) years when LDL-C is lowered by \(\leq 10\%\), especially when LDL-C is <100 mg/dL (2.6 mmol/L).\footnote{19-23} This suggests patients experiencing a \(\leq 10\%\) reduction from the added therapy should have the drug discontinued because they are unlikely to experience a meaningful ASCVD risk reduction benefit while still having the potential to experience the full range of adverse events.

In conclusion, once risk prediction equations are available, personalized estimates of the potential for net benefit could be used to further inform shared decision making. Until that time, LDL-C thresholds can be used to trigger consideration of additional nonstatin therapy to further lower LDL-C and ASCVD risk.

**Disclosures**

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**References**


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