EDITORIAL COMMENT

LDL-Cholesterol Targets After the ACC/AHA 2013 Guidelines*
Evidence That Lower Is Better?

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Approximately 25 years ago, the first Adult Treatment Panel (ATP) guidelines set the stage for low-density lipoprotein cholesterol (LDL-C) as both a risk factor and a target of therapy (1). Since then, ever-accumulating evidence on the role of LDL-C in atherosclerosis, coupled with the availability of more potent statins and data that “lower is better,” have led to what appears to be an inexorable march toward lower LDL-C goals, particularly for secondary prevention. ATP-III (2), published in 2001, defined the optimal LDL level as <100 mg/dl, to be followed in an update in 2004, which established a goal of <70 mg/dl as an option in very high-risk patients (3).

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a much-anticipated guideline update, in which the most surprising and controversial change was the abandonment of LDL-C targets and dose titration (4). Instead, either moderate- or high-intensity statin therapy was recommended on the basis of underlying risk categories, irrespective of LDL-C response. Measurement of on-therapy LDL-C was recommended only for the purpose of assessing adherence. Notably, the American Association of Clinical Endocrinology (5) as well as the National Lipid Association (6) refused to endorse the new recommendations.

In this issue of the Journal, Boekholdt et al. (7) report a patient-level meta-analysis of data from large statin trials, which informs the discussion surrounding the 2013 ACC/AHA guidelines. The authors provide important information on the variability of lipoprotein levels achieved with treatment, as well as the cardiovascular risk reduction associated with different lipoprotein levels attained. The key question they address is whether there is evidence that patients who achieve lower LDL levels, <100 mg/dl, <70 mg/dl, or even <50 mg/dl, have a reduced cardiovascular risk. With this objective, they analyzed individual patient data (provided by the investigators) from 8 large-scale randomized trials.

The authors found that more than 40% of the participants in these trials did not reach an LDL-C level <70 mg/dl despite being prescribed high-dose statin therapy, defined as rosuvastatin 20 mg or atorvastatin 80 mg. Findings were similar when the data were analyzed for apolipoprotein B and for non–high-density lipoprotein cholesterol, 2 measurements that may be better than LDL-C as risk predictors, but which are not as familiar to the general public (8).

In terms of risk reduction, there was a clear relationship between LDL-C level attained and cardiovascular risk, with the major cardiovascular event rate at 1 year increasing incrementally from 4.4% in those with LDL-C levels <50 mg/dl, to 10.9% for LDL-C between 50 and <70 mg/dl, 16% between 70 and <100 mg/dl, and up to 34.4% in those with LDL-C ≥190 mg/dl. This relationship supports the premise that “lower is better” when it comes to LDL-C goals.

An important limitation of the large statin trials conducted to date—and therefore by extension this meta-analysis by Boekholdt et al. (7)—is that these trials (with the exception of the limited dose titration in 4S [Scandinavian Simvastatin Survival Study] (9) and AFCAPS/TexCAPS [Air Force/Texas Coronary

* Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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Atherosclerosis Prevention Study [10]) examined fixed doses of statins. The different LDL-C levels attained were therefore not due to a strategy of individualized goal attainment, which would have involved dose titration and possibly the addition of other agents, such as ezetimibe or nicotinic acid, but due to the complex interaction between the statin (including the dose) and the individual patient’s biology. Indeed, only a small number of subjects in each trial achieved an LDL-C level of <50 mg/dl (11% in the pooled population). These patients are different from those with a less robust response; hence, it remains unclear whether it is the LDL-C level achieved or the patient’s ability to respond to a statin dose that is the key determinant of the better outcomes.

Several important questions remain. Is it acceptable if a patient reaches a desired LDL-C level at a less-than-moderate or high-intensity statin dose, or is there an additional benefit to receiving a higher dose of a statin? Also uncertain is whether a statin sparing combination therapy would be as efficacious as high-intensity agents. Although data from statin trials such as the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study [11] suggest that adverse events in patients achieving LDL-C levels <50 mg/dl are no different from in those who do not, an increased incidence of diabetes exists. In addition, there are undoubtedly patients who cannot tolerate the highest statin doses.

There are many factors that may affect LDL-C reduction and achieved LDL-C levels. Patient compliance and starting LDL-C levels are the most obvious and probably most important. But underlying biology also plays a role. A relatively small population of patients, termed “hyper-responders,” can be identified who achieve low LDL-C levels (typically on relatively low doses of statins) and have very low event rates. However, the mechanisms driving hyper-responsiveness are poorly understood. Factors favoring greater LDL-C reduction that were identified in a pooled analysis of data from more than 21,000 patients included the presence of diabetes mellitus, black race, and male sex, but these factors had only a modest overall effect [12]. Particularly intriguing is the possible role of the PCSK9 gene, with loss of function associated with an increased response to statins [13], but the genetic response to statins is likely polygenic and is still poorly understood.

Beyond the LDL-C level attained, cardiovascular risk reduction may also vary by underlying disease and metabolic state. In an analysis of data from the 4S study, it was shown that patients with low HDL-C cholesterol and elevated triglycerides along with elevated LDL-C (lipid triad) benefited much more from simvastatin use than did patients with isolated elevated LDL-C, who had only marginal benefit [14].

The strengths of the meta-analysis by Boekholdt et al. [7] include the patient-level analysis and the large number of patients. The main limitation, beyond the post-hoc observational nature of the data and the different inclusion criteria, which the authors acknowledged, is that the LDL-C levels attained may have been influenced by a myriad of factors, which in themselves may affect cardiovascular risk. In this regard, the present meta-analysis does not disprove the 2013 ACC/AHA guidelines contention [4] that there are inadequate data at the present time to indicate specific LDL-C targets of therapy. Unfortunately, even the much-anticipated IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which is randomizing patients to simvastatin alone versus simvastatin/ezetimibe therapy, is unlikely to be definitive in this regard, as it too is largely fixed-dose based, with the only response related titration being the increase in simvastatin dose from 40 to 80 mg in those with LDL-C >79 mg/dl [15]. It has been estimated that with the current ACC/AHA guidelines, 56 million U.S. patients are eligible for statin therapy [16]. It is indeed regrettable that more than 25 years after the first ATP guidelines, we still do not have clear-cut evidence on what the appropriate LDL-C targets of therapy should be. The findings from the present meta-analysis will hopefully further spur the design and implementation of lipid trials assessing specific LDL-C targets rather than specific drug doses.

REFERENCES


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KEY WORDS guidelines, LDL-cholesterol, LDL-cholesterol goal, statins