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Permalink

<https://escholarship.org/uc/item/5h7219k9>

Journal

JAMA cardiology, 2(12)

ISSN

2380-6583

Author

Waters, David D

Publication Date

2017-12-01

DOI

10.1001/jamacardio.2017.3943

Peer reviewed

Invited Commentary

Are Cholesterol Treatment Targets a Deterrent to Optimal Lipid-Lowering Therapy?

David D. Waters, MD

“A good decision is based on knowledge and not on numbers” - Plato

History has not been kind to those who assigned numbers to define normal or optimal cholesterol levels. In the 1963 table of normal laboratory values in the *New England Journal of Medicine*, normal total cholesterol was listed as 150-280 mg/dL (to convert to millimoles per liter, multiply by 0.0259),¹ referenced to an article published in 1916. Because most patients with coronary disease thus had “normal” cholesterol levels, the hypothesis that cholesterol was a primary cause of atherosclerosis faced stiff headwinds before finally being accepted.

The Cholesterol and Recurrent Events (CARE) trial was an important and influential early statin trial. Among 4159 postinfarction patients, those randomized to pravastatin 40 mg/d experienced a 32% reduction in low-density lipoprotein cholesterol (LDL-C) and a 24% reduction in the primary end point, coronary death, or myocardial infarction over 5 years of follow-up.² Based on an analysis of their data, the authors opined that although their finding could not be considered definitive and required confirmation, an LDL-C level of 125 mg/dL may be an approximate lower boundary for a clinically important influence of the LDL-C level on coronary disease. Most patients with myocardial infarction present with an LDL-C level

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of less than 125 mg/dL. Fortunately, subsequent trials rapidly established that statins are of benefit to patients after myocardial infarction irrespective of their LDL-C level.

Early cholesterol guidelines established specific cut points both for initiation of treatment and as treatment targets: 190 mg/dL, 160 mg/dL, 130 mg/dL, 100 mg/dL, and later 70 mg/dL.³ These numbers were eliminated in the 2013 American College of Cardiology/American Heart Association cholesterol treatment guideline but persist in the 2016 European guideline and in guidelines from other countries.³ Clinical trial data indicate that statins reduce cardiovascular (CV) events across a broad range of baseline LDL-C, down to a level less than 50 mg/dL,⁴ and that for each millimoles per liter reduction in LDL-C, CV events are reduced by 22%.⁵

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk

In this issue, Giugliano et al⁶ describe the benefits of LDL-C lowering with evolocumab in high-risk patients with a baseline LDL-C level of less than 70 mg/dL in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial.⁶ Overall, 27 564 patients with established vascular disease plus other high-risk features were randomized to evolocumab or placebo on top of statin therapy and were followed for a median of 2.2

years.⁷ Treatment with evolocumab was associated with a 59% reduction in LDL-C levels, from a mean of 92 mg/dL to 30 mg/dL and a 15% reduction in the primary end point (HR, 0.85; 95% CI, 0.79-0.92; $P < .001$). This degree of CV event reduction is less than expected based on the amount of LDL-C reduction.⁸

To be eligible for FOURIER, patients had to have had an LDL-C level of at least 70 mg/dL or a non-high-density lipoprotein cholesterol level of at least 100 mg/dL on baseline statin therapy. In this article,⁶ the 2034 patients with a baseline LDL-C level of less than 70 mg/dL are compared with most of the FOURIER patients who had a baseline LDL-C level of at least 70 mg/dL. As a consequence of the inclusion criterion requiring that they have a non-high-density lipoprotein cholesterol level of at least 100 mg/dL, the LDL group was enriched with patients with diabetes (48.5% vs 35.6%) and the metabolic syndrome (72.8% vs 58.2%) and had lower levels of high-density lipoprotein cholesterol (38.5 mg/dL vs 44.0 mg/dL) and higher triglyceride levels (181 mg/dL vs 131 mg/dL; to convert to millimoles per liter, multiply by 0.0113).

Evolocumab reduced the risk of the primary composite end point by 20% (HR, 0.80; 95% CI, 0.60-1.07) in patients with a baseline LDL-C level of less than 70 mg/dL, compared with 14% (HR, 0.86; 95% CI, 0.79-0.92) in patients with an LDL-C level of at least 70 mg/dL. There was no evidence of treatment effect modification by baseline LDL-C level. These results indicate that high-risk patients with an LDL-C level of less than 70 mg/dL benefit from further LDL-C reduction.

Treating to a Target

These results also call into question the validity of specific LDL-C targets such as a level of 70 mg/dL. A bigger issue is that although guidelines have recommended for many years that physicians treat to a specific numerical LDL-C target, this approach had not been rigorously tested in an adequately sized clinical trial until now.

In the just presented but not yet published Standard vs Intensive Statin Therapy for Hypercholesterolemic Patients With Diabetic Retinopathy (EMPATHY) study, 5042 patients in Japan were randomized to either standard therapy, targeting an LDL-C level of 100mg/dL to 120 mg/dL, or to intensive therapy, targeting an LDL-C level of less than 70 mg/dL.⁹ After a median follow-up of 37 months, the CV event rate was reduced, but not significantly, in the intensive therapy group (HR, 0.84; 95% CI, 0.67-1.07; $P = .15$).

However, less than half of the patients in the intensive therapy group actually attained the LDL-C goal of less than 70 mg/dL. In a post hoc analysis restricted to patients who achieved their LDL-C targets, a large reduction in CV events was observed (HR, 0.48; 95% CI, 0.28-0.82; $P = .007$).

The failure of more than half of patients to reach their target of less than 70 mg/dL despite more than 3 years of treatment within the strict confines of a clinical trial suggests that the whole concept of treating to target is flawed. Japanese physicians tend to prescribe smaller doses of most drugs, including statins, and it is possible that a higher proportion of patients may have attained goal if the trial was performed elsewhere. Nevertheless, it seems reasonable for guideline-writing committees to stop recommending the treating to target approach until credible evidence shows that it works.

Practical Implications

High-risk patients benefit from aggressive LDL-C lowering whether their baseline level is greater or less than 70 mg/dL. The degree of risk reduction will be less at lower baseline LDL-C

levels because treatment lowers LDL-C as a percentage of the baseline level, while benefit is proportional to the absolute reduction (22% per mmol/L). Proprotein convertase subtilisin/kexin type 9 inhibitors, such as evolocumab, are usually not cost-effective at their current price, so statin dose should be maximized as a first step. New drugs that lower LDL-C levels now being developed have the potential to strengthen and diversify our therapeutic armamentarium.

Low-density lipoprotein cholesterol levels in patients receiving treatment have steadily decreased from significantly more than 100 mg/dL in the early statin trials to 30 mg/dL in evolocumab-treated patients in FOURIER. Perhaps patients attain the maximum benefit from LDL-C lowering at 30 mg/dL because there is not much room to go lower. We have come a long way since 1963.

ARTICLE INFORMATION

Author Affiliations: Division of Cardiology, Zuckerberg San Francisco General Hospital, San Francisco, California; Department of Medicine, University of California, San Francisco.

Corresponding Author: David D. Waters, MD, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, 5G1, San Francisco, CA 94110 (david.waters@ucsf.edu).

Published Online: November 1, 2017.
doi:10.1001/jamacardio.2017.3943

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Waters has received remuneration for participating in clinical trial committees from the Medicines Company, Pfizer, Regeneron, and Sanofi-Aventis. No other disclosures were reported.

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