Journal of the American College of Cardiology Vol. 62, No. 8, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.027

Living With Imprecision*

John C. LaRosa, MD

Brooklyn, New York

One of the most vexing conundrums in the science and practice of medicine is the designation of arbitrary "cut-points" separating what we will consider normal from abnormal. We can pretend that a blood pressure of 121 mm Hg is different from one of 119 mm Hg, but we should not take that literally.

In this issue of the *Journal*, Martin et al. (1) present such a conundrum, in this case, involving the determination of the "estimated" low-density lipoprotein cholesterol (LDL-C) level in the circulation. This estimated LDL-C is calculated by the formula: LDL − C = TC − [TG/5 + HDL-C], where TC is total cholesterol in mg/dl, TG is total triglyceride in mg/dl, and HDL-C is high-density

See page 732

lipoprotein cholesterol in mg/dl. Dividing TG by 5 has been accepted as an approximation of very low-density lipoprotein cholesterol (VLDL-C) as long as TG levels are <400 mg/dl. In a nutshell, Martin et al (1) demonstrate that this assumption is very weak and, even at TG levels <400 mg/dl, underestimates LDL-C when compared to levels measured directly in the ultracentrifuge. This is not the first study to question this method of estimating LDL-C, but its gargantuan sample size makes it by far the largest.

Should we, as a result of this large and well-executed study, abandon estimated LDL-C for a more precise parameter? There is no shortage of candidates. The simplest (and cheapest) is the non–HDL-C obtained by the formula: TC − HDL-C = non–HDL-C.

This provides an estimate of the cholesterol content of the apo-B–containing, atherogenic lipoproteins in the blood, including LDL, VLDL, and intermediate-density lipoprotein. Because of its inclusiveness, this should be a broader estimate of circulating atherogenicity than LDL-C alone. It also (by subtraction) takes into account the presumed antiatherogenic properties of HDL, so that the higher the HDL-C level, the lower the non–HDL-C. It requires only measurement of TC and HDL-C, which are widely available and can be measured even by fingerstick methods. Conversely, it leaves us dependent on the cholesterol content of the lipoprotein, which is not a stoichiometric constant.

Direct measurement of apolipoprotein B in the plasma might be a better bet because there is 1 molecule of apolipoprotein B in each molecule of LDL. It is a widely available, standardized measurement and does not depend on the cholesterol content of the particle. It does not, however, include any estimate of HDL, in which it is not present.

Finally, there are ratios of atherogenic to antiatherogenic particles, including LDL-C/HDL-C and apolipoprotein B/apolipoprotein A (the major apolipoprotein of HDL), which, like non-HDL, try to express the net atherogenicity of the blood sample. These have a long history of popularity in observational epidemiology but have had less acceptance in clinical practice. The reasons for this are not entirely clear but may be related to the fact that they might encourage clinicians to ignore treatment of elevated LDL-C levels in patients who also have high HDL-C. Unfortunately, our evidence base concerning HDL-C is still sufficiently confused to preclude withholding treatment of LDL based solely on a high HDL level.

Needless to say, there are many strong and vocal champions for widespread use of each of these parameters. Unfortunately, there is not consistent evidence that any of them are reproducibly better than any other, including estimated LDL-C, in predicting future risk of atherogenic events (2,3).

So what should we do with this carefully executed and elegant report? First, we should not use it to justify the notion that we can comfortably abandon following lipid parameters as we treat patients with lipid-altering drugs. As a result of agents now under development, we will soon have the ability to lower LDL-C levels well below 70 mg/dl. As a result, we will have to contend with the possibility that we can do harm as well as good if lipid levels fall too low. At this point, we do not know where, if at all, such a lower limit might be.

As we examine alternatives to estimated LDL-C, we should be mindful that none of the alternatives has been convincingly demonstrated to be a better risk predictor and that changing recommended parameters in clinical settings is a long, slow process, even when the data are more solid than they are today. As a start, we might

*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.

From the SUNY Downstate Medical Center, Brooklyn, New York. Dr. LaRosa is an occasional consultant for Amgen and Pfizer.

encourage clinicians and trialists to calculate, and report, non–HDL-C levels. That requires no additional cost. Non–HDL-C is less cumbersome than estimated LDL-C and would represent an evolutionary, not revolutionary, step forward.

Reprint requests and correspondence: Dr. John C. LaRosa, Department of Medicine, SUNY Downstate Medical Center, 450 Clarkson Avenue, B7-512, Brooklyn, New York 11203. E-mail: jclarosa@downstate.edu.

REFERENCES

1. Martin SS, Blaha MJ, Elshazly MB. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Card 2013;62:732–9.
2. Asia Pacific Cohort Studies Collaboration. A comparison of lipid variables as predictors of cardiovascular disease in the Asia Pacific region. Ann Epidemiol 2005;15:405–13.
3. The Emerging Risk Factors Collaborative. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499–506.

Key Words: Friedewald equation ■ low-density lipoprotein cholesterol ■ very low-density lipoprotein cholesterol.