Over the last 30 years, since release of the first National Cholesterol Education Program’s Adult Treatment Panel (NCEP-ATP) Guidelines, LDL cholesterol (LDL-C) has been the focus of, and basis for, therapeutic decisions, both for when to start drug therapy and for what goals to achieve (1). Although the recent American Heart Association and American College of Cardiology (AHA/ACC) guidelines (2) minimize LDL-C treatment goals, the majority of guidelines throughout the world continue to recommend therapeutic targets similar to those of NCEP-ATP III (3–5). Furthermore, given the substantial controversy and debate since the release of the AHA/ACC guidelines, it is unclear how successfully they will ultimately influence physician practice regarding the use of LDL-C treatment targets (6, 7). Thus, measurement of LDL-C remains a vital component of our decision making in terms of even the new “nontarget” guidelines.

From the outset, the NCEP recognized the importance of accurate and reproducible assessment for LDL-C and convened an expert panel of laboratory scientists to address the standardization of the lipid measurements included in the guidelines (8, 9). It was recognized that there was no simple and accurate method for actual LDL-C measurement, and thus calculation of LDL-C using the Friedewald formula, which was widely accepted as an accurate and cost-effective alternative to the reference method, preparative ultracentrifugation (PUC), was recommended for routine clinical purposes in patients with triglycerides (TG) <400 mg/dL (4.52 mmol/L) (8–10). The formula described and validated against PUC in 1972 calculated LDL-C using total cholesterol (TC), TG, and HDL-C (10).

However, over the last 20 years, as clinical outcome trials provided additional data indicating that lower LDL-C is associated with further reductions in the risk of cardiovascular disease, treatment goals for LDL-C have been adjusted downward (3–5).

In comparing the performance of the Friedewald formula, it is important to consider that measurements of TC and HDL-C are common components of, and were therefore identical to, both the Friedewald formula and PUC. Thus, any differences between them relate solely to the calculation of very-low-density lipoprotein cholesterol (VLDL-C), which the Friedewald formula assumes to be one-fifth, or 0.2, of the TG concentration if values are in milligrams per deciliter (10). Two large studies over the next 2 decades reexamined the relationship between LDL-C calculated by Friedewald and measured by PUC (11, 12). The study by De Long et al. (11) compared 10,483 participants in the Lipid Research Clinics prevalence studies and concluded that VLDL-C was better represented by a factor of TG/6 or 0.16 × TG, when reported in milligrams per deciliter (0.37 when reported in millimoles per liter). McNamara et al. (12) assessed 4797 samples from a wide range of patients using various formulas for calculating VLDL-C and the effect on calculated LDL-C to PUC. They found that the best representation of VLDL-C varied by TG concentration and suggested different formulas based on the TG value [TG/4 (ratios were not provided for TG in mmol/L) for concentrations ≥50 mg/dL (0.56 mmol/L); TG/4.5 for TG >50–200 mg/dL (0.56–2.26 mmol/L); and TG/5 for TG >200–400 mg/dL (2.26–4.52 mmol/L)] (12). However, the differences in the actual calculated LDL-C with the various factors were small and likely clinically insignificant. Despite finding values slightly more consistent with PUC, neither study resulted in adoption of a new formula and Friedewald endured.

The Friedewald formula was originally validated based on a relatively small number of samples from 3 lipid patient populations: 96 subjects considered “normal” in whom LDL-C ranged from 62 to 185 mg/dL (1.6 to 4.78 mmol/L); 204 subjects with Fredrickson type II hyperlipidemia (HLP) with LDL-C ranging from 173 to 840 mg/dL (4.47 to 21.7 mmol/L); and 111 Fredrickson type IV HLP patients with TG <400
mg/dL (4.52 mmol/L) and LDL-C from 46.4 to 232.0 mg/dL (1.2 to 6.0 mmol/L). Although the numbers of subjects at the newer lower thresholds of clinical interest were not specified, from the data graphically depicted, fewer than 40 subjects had LDL-C ≤ 100 mg/dL (2.59 mmol/L) and only 6 had LDL-C ≥ 70 mg/dL (1.81 mmol/L) (10).

In 2001, Scharnagl et al. (13) first reported that the Friedewald formula significantly underestimated LDL-C in patients with low LDL-C undergoing apheresis. Now, more than a decade later, a number of recent studies from patients undergoing lipid measurement in routine clinical practice have provided confirmatory data that Friedewald formula–calculated LDL-C values, compared to more directly measured LDL-C, may not be accurate and underestimate LDL-C when it decreases below 70 mg/dL (1.81 mmol/L) (14, 15). The largest of these studies, reported by Martin et al. (14), compared Friedewald with LDL-C measured by density gradient, single, vertical spin ultracentrifugation [vertical auto profile (VAP)] in 1310440 patients, of whom 191333 had calculated LDL-C < 70 mg/dL (1.81 mmol/L) and derived a replacement formula (“Hopkins” or “novel”) that used a 180-cell array of TG/VLDL-C factors based on triglyceride and non–HDL-C concentrations (14). The novel formula reclassified many of those with LDL-C < 70 mg/dL (1.81 mmol/L) by Friedewald to > 70 mg/dL (1.81 mmol/L) in better agreement with VAP-measured LDL-C (14).

Thus, besides increased TG, a second previously unrecognized factor, low LDL-C, was shown to influence the accuracy of the Friedewald formula. How could this go 3 or more decades before being discovered? When LDL-C concentrations are relatively high, the impact of slight variations in calculating VLDL-C is small. For example, when LDL-C is at the 3 cut points of 130, 160, and 190 mg/dL (3.36, 4.14, and 4.91 mmol/L) designated by NCEP-ATP III for commencing treatment based on various risk factors, and TG is moderately increased at 200 mg/dL (2.26 mmol/L), VLDL-C will range from 31.3 mg/dL (0.81 mmol/L) for Friedewald formula to 40.2 mg/dL (1.04 mmol/L) for De Long formula. Thus, the impact on LDL-C in the 130–190 mg/dL (3.36–4.91 mmol/L) range will be 8.9 mg/dL (0.23 mmol/L), a maximum difference of 6.8% at 130 mg/dL (3.36 mmol/L) and 4.6% at 190 mg/dL (4.91 mmol/L). However, as LDL-C decreases, even this relatively small variability in calculating VLDL-C translates into a 12.7% and 17.8% difference in LDL-C, at 70 (1.81 mmol/L) and 50 mg/dL (1.29 mmol/L), respectively.

In the current study, by Meeusen et al., LDL-C is compared by both the Friedewald and the novel formulas against the gold-standard measurement of LDL-C by PUC (also referred to as beta quantification) in 23055 patients (15). PUC is the method that has been used in the validation of other more direct methods including VAP, nuclear magnetic resonance, and detergent based direct or homogeneous assays (14). Although detergent-based assays for LDL-C have been widely adopted in routine clinical laboratories, they have been shown to vary from generation to generation and have significant bias compared with PUC, especially in dyslipidemic patients (16). In addition, none of these alternative LDL-C assays has been thoroughly validated at lower LDL-C concentrations or against PUC.

Meeusen et al. (15) found that over the entire LDL-C range, the 2 formulas were very similar in correctly classifying patients compared to PUC, at 77% and 78% for the Friedewald and novel formula, respectively. However, both formulas deviated from the reference method when LDL-C was < 70 mg/dL (1.81 mmol/L): the novel formula resulted in reclassification of 8.7% of patients as > 70 mg/dL (1.81 mmol/L) compared with the Friedewald equation (15). The authors also suggested that in considering the implications to patient care, it is important to note that in the current standard of practice it is the Friedewald-calculated LDL-C and not LDL-C by PUC that has been used in guidelines. Although this was true in the original guidelines, that was before the treatment LDL-C goal for certain patients was reduced to < 70 mg/dL (1.81 mmol/L) and the concern and subsequent demonstration that Friedewald underestimated LDL-C and had not been validated at lower LDL-C concentrations.

Even with these new large studies, the Friedewald formula remains a reliable and cost-effective method for measuring LDL-C in routine clinical practice and clinical trials when LDL-C is > 100 mg/dL (2.59 mmol/L), and TG is < 400 mg/dL (4.52 mmol/L). However, as LDL-C decreases below 70 mg/dL (1.81 mmol/L), calculating LDL-C will lead to moderate underestimation of true LDL-C, and this increases substantially as LDL-C decreases further, potentially leading to undertreatment of patients. The novel formula, however, appears to overestimate LDL-C < 70 mg/dL (1.81 mmol/L), with more patients not achieving this treatment goal, perhaps leading to overtreatment of patients.

Given the uncertainty of these formulas when LDL-C approaches 70 mg/dL (1.81 mmol/L), an alternative is to use the secondary target of therapy, namely non–HDL-C, introduced in NCEP-ATP III for patients with increased TG (> 200 mg/dL or 2.26 mmol/L) (3). The non–HDL-C goal, which is 30 mg/dL (0.78 mmol/L) higher than the LDL-C goal, is not dependent on TG or VLDL-C. This may well compensate for the under- or overestimation of discrepancies in the LDL-C calculation by Friedewald or other formulas in terms of clinical decision making. Comparing the 2
formulas in both the Meeusen and Martin study databases and already published cardiovascular outcome trials with other parameters such as non-HDL-C and apolipoprotein B may provide better guidance for clinicians when LDL-C is decreased to lower concentrations (14, 15).

In the interim, Meeusen et al. quite rightly conclude, based on their data, that whereas the novel formula has some benefits, it is unclear whether improvements over the Friedewald calculation are large enough to justify making a change in routine clinical practice and to improve patient outcomes at this time.

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