The Future of Low-Density Lipoprotein Cholesterol in an Era of Nonfasting Lipid Testing and Potent Low-Density Lipoprotein Lowering

Article, see p 10

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Lipid testing plays a major role in cardiovascular risk stratification and management in clinical practice. Fasting samples have long been the standard for assessing low-density lipoprotein cholesterol (LDL-C) and triglycerides because fasting is believed to reduce variability and to allow more accurate derivation of the commonly used Friedewald-calculated LDL-C. In 2009, the Danish guidelines recommended nonfasting lipid testing across Denmark. In 2014, the US Department of Veterans Affairs, the Joint British Societies, and the National Clinical Guideline Center practice guidelines recommended nonfasting lipids for cardiovascular risk assessment. In 2016 to 2017, several additional clinical guidelines and expert consensus statements[1–3] from Europe, Canada, and the United States have also recommended nonfasting lipid testing for most routine clinical evaluations (Figure). As more of the worldwide medical community moves toward obtaining nonfasting lipids for routine testing,[3] the time is opportune for reassessing whether Friedewald LDL-C or other methods for determining LDL-C could result in improved accuracy of LDL-C, whether assessed nonfasting or fasting.

In their seminal article published in 1972, which is among the top 100 most highly cited articles of all time, Friedewald and colleagues[4] set out to determine a method to accurately calculate LDL-C without having to use expensive and laborious ultracentrifugation techniques (total cholesterol, triglycerides, and high-density lipoprotein concentration [HDL-C] can all be measured without ultracentrifugation). They proposed an equation to calculate LDL-C based on data derived from the plasma of 448 fasting patients and demonstrated that very low-density lipoprotein cholesterol (VLDL-C) could be approximated by a ratio of triglycerides/5 (in mg/dL) or triglycerides/2.2 (in mmol/L). When this ratio was substituted into the Friedewald equation, LDL-C (mg/dL)=total cholesterol–HDL-C–(triglycerides/5), a generally good correlation was obtained with the gold-standard measurement of LDL-C by ultracentrifugation for plasma triglyceride levels up to 400 mg/dL. However, perhaps because of its relative simplicity, clinicians and laboratories have largely relied on the original calculation method, which has acceptable accuracy when LDL-C is average or high and when triglycerides are not elevated.

However, the Friedewald LDL-C has several limitations that have become more relevant today than previously. First, its accuracy depends on the error in measuring 3 other lipids (total cholesterol, HDL-C, triglycerides). Second, it includes cholesterol not only from LDL particles but also from lipoprotein(a), which is usually higher in blacks or renal patients (eg, nephrotic syndrome). Third, it assumes a constant ratio of triglycerides to cholesterol in very low-density lipoprotein particles. This is not met in patients with hypertriglyceridemia from certain dyslipidemias (eg, type III hyperlipoproteinemia), diabetes mellitus, insulin resistance, or obesity. Furthermore, nonfasting samples may not always meet these assumptions because chylo-

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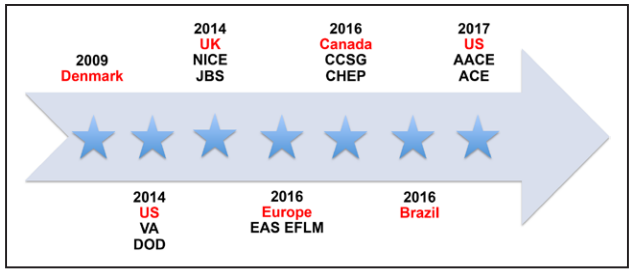

Figure. Timeline of countries and the respective guidelines advocating nonfasting lipid tests as preferred or acceptable alternative to fasting lipids.
AACE/ACE indicates American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease; CCSG, Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult; CHEP, Canadian Hypertension Education Program; EAS/EFLM, European Atherosclerotic Society/European Federation of Clinical Chemistry and Laboratory Medicine joint consensus statement; JBS, Joint British Societies guidelines on prevention of cardiovascular disease in clinical practice; NICE, National Institute for Health and Care Excellence cardiovascular disease: risk assessment and reduction, including lipid modification clinical guideline; and VA DOD, Veterans Affairs/Department of Defense clinical practice guideline for the management of dyslipidemia for cardiovascular risk reduction.

microns are present and are more triglycerides-rich than very low-density lipoprotein particles. Finally, concerns have been raised recently about the inaccuracy of Friedewald LDL-C (underestimating the true LDL-C) when LDL-C is low, in particular if triglycerides are concomitantly moderately elevated or higher (>200 mg/dL).[5–7] Extremely low LDL-C (eg, ≤10 mg/dL) is more common now in the era of potent LDL lowering for high-risk patients, for whom guidelines recommend targeting LDL-C <70 mg/dL or even lower with therapies such as high-intensity statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors. High-risk patients may be potentially undertreated if Friedewald LDL-C is used.

The question for clinicians who rely on LDL-C for management decisions then becomes, can we still accurately calculate LDL-C in light of all these factors, and if not, is there a better estimator than the Friedewald equation?

In this context, Sathiyakumar and colleagues[8] in this issue of *Circulation* examined the accuracy of Friedewald LDL-C compared with a novel method they had previously derived.[9] In 2013, Martin and colleagues[9] published their first report of a novel LDL-C calculation method (LDL-C_N) that substituted a sophisticated derivation of the variable triglycerides to VLDL-C ratio into the Friedewald original formula. Using a large subset derived from close to 1.3 million lipid profiles from a single database (Very Large Database of Lipids), they were able to create a 2×2 table based on triglycerides and non–HDL-C levels that provided more precise values for ratios of triglycerides to VLDL-C ratios across a spectrum of non–HDL-C and triglycerides. Derivation of this variable ratio was preceded by an exploration of the contributions of age, sex, and individual lipid profile characteristics of the participants. Unlike the Friedewald equation, their original formula derivation included those with triglycerides >400 mg/dL. Using a second population from the same database, they were able to validate their formula by comparing its accuracy and that of the standard Friedewald equation with LDL-C measurement obtained by vertical autoprofile ultracentrifugation method. The results demonstrated the superiority of their novel method compared with the Friedewald formula across a range of clinically derived LDL-C cut points, with the greatest advantage being seen in those with LDL-C <70 mg/dL. Despite very promising results, this method did not reach widespread use, perhaps related to the need for validation in other populations.

Sathiyakumar and coauthors now use this novel, more personalized method and the previously derived triglycerides:VLDL-C table, with the additional advantage of assessing the accuracy of their formula compared with the Friedewald equation depending on the fasting status of participants. Using the second wave of data from the same database, they included an even larger number of patient samples (≈1.5 million), about one third of which were nonfasting (defined as <10 hours since the last meal). However, unlike their original ratio derivation study, those patients with triglycerides ≥400 mg/dL were excluded from this analysis to provide a more direct comparison with the Friedewald formula. In addition, the actual time since last meal and information on race, obesity, and insulin resistance were not available.

These results corroborate findings from their previous study; the novel method was found to be consistently more accurate than the Friedewald formula across previously described clinical cut points for target LDL-C. This superiority was upheld in both fasting and nonfasting samples. In those with LDL-C <70 mg/dL, LDL-C_N provided closer approximation to direct LDL-C by the vertical autoprofile ultracentrifugation method than the Friedewald equation and indeed, on the basis of their findings, was minimally affected by fasting status compared with the Friedewald equation. As triglycerides levels increased, the accuracy of both methods decreased for patients with low LDL-C, but LDL-C_N still was superior. The overall message therefore is that the Friedewald equation is not as reliable in patients, especially among those with low LDL-C and at least moderately high triglycerides.

It should be noted, however, that the median ratio of triglycerides to VLDL-C in the fasting and nonfasting groups was 4.9 and 5.3, respectively, so the absolute

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difference in the numbers derived for LDL-C would be small compared with using the fixed ratio of 5 for patients who fall into less extreme ranges of triglycerides and LDL-C. This is part of the reason that the Friedewald equation has been applicable for most patients. However, as we continue to evolve into the field of precision medicine, this study highlights specific patients who would benefit from the novel method that greatly improves the accuracy of LDL-C calculation without added expense.

The main strength of this study lies in the novel, more personalized calculation of the ratio of triglycerides to VLDL-C and the immense and national sample size, with >500 000 patients in the nonfasting group. It should be noted that whether the patients actually had fasted for at least 10 hours before giving blood samples could not be verified, and it is known that in the community, strict fasts are not maintained by some. In this instance, however, the volume of data should be sufficient to account for any small degree of misclassification. Another potential limitation in accurate LDL-C determination by the LDL-C_N would be the fact that the ratios of triglycerides to VLDL-C were not originally adjusted for other factors such as race, obesity, and insulin resistance that may affect triglycerides and VLDL-C levels and hence the ratio. In addition, the study excluded patients with triglycerides ≥400 mg/dL. These are higher-risk individuals for whom we would expect decreased accuracy of both the Friedewald equation and the novel method, and it would be interesting to see how the novel method compares with direct LDL-C measurement in these patients. These 2 issues open up areas for continued investigation.

In the United States, the emphasis of recent guidelines has shifted away from absolute LDL-C cut points to focus on percent and risk reduction with tools that do not require absolute LDL-C.[10] Nonetheless, a baseline lipid profile is often the first screening test obtained by providers, and accurate LDL-C levels are still of value to both providers and, perhaps more important, to patient education and to optimal treatment of high-risk patients. This study highlights important limitations with the Friedewald calculation, especially in nonfasting patients and those with low LDL-C and higher triglycerides. For those patients, for whom knowledge of absolute LDL-C would be desired, the novel method offers a superior calculation method, with no additional cost to patients or the healthcare system. Indeed, a national laboratory was proactive and has already adopted this innovative method for patient care, including for nonfasting lipid testing.[11]

In summary, to address the limitations of the Friedewald LDL-C in an era of nonfasting lipids and potent LDL lowering, Sathiyakumar and colleagues have provided an innovative, personalized, and cost-effective LDL calculation that could be a valuable addition to, or an alternative for, non–HDL-C or apolipoprotein B measurements in optimally treating LDL-related risk, whether assessed fasting or nonfasting.

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DISCLOSURES

Dr Farukhi reports no conflicts. Dr Mora has received institutional research grant support from Atherotech Diagnostics; served as consultant to Amgen, Lilly, Pfizer, and Quest Diagnostics; and is listed as a coinventor on a patent for biomarker-based prediction of colorectal cancer incidence and mortality.

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FOOTNOTES

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