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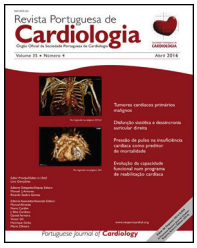

EDITORIAL COMMENT

In search of accurate estimates of low-density lipoprotein cholesterol levels – a better compass

Em busca de estimativas corretas dos níveis de colesterol LDL – uma bússola melhor

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The ''basic lipid profile'', composed of total cholesterol, high-density lipid protein cholesterol (HDL-C), and triglycerides, is among the most requested and performed blood tests in our outpatient clinics across the country. Notably, the ''absent'' parameter (low-density lipid cholesterol, LDL-C) is the one with the greatest implications for patient management. The pivotal role of LDL-C in atherosclerotic disease, backed by overwhelming evidence from genetic, epidemiological, and clinical studies, justifies its center-stage locus, translated into practice using LDL-C targets according to each patient's cardiovascular risk.[1,2] However, unlike its basic lipid profile counterparts, LDL-C is not so easy and inexpensive to measure.

For decades, the simplest way of assessing LDL-C was to estimate its level using the Friedewald formula. The underlying principle is quite simple. Since total cholesterol is essentially the sum of HDL-C, LDL-C, and very-low-density lipoprotein (VLDL) cholesterol, one can calculate LDL cholesterol by subtracting HDL-C and VLDL-C from the total cholesterol level. Even though VLDL-C is also not simple to measure directly, Friedewald et al. noted in 1972 that there was a relatively stable relationship between the level of measured triglycerides and the level of the VLDL particles, with an average ratio of 5:1.[3] So, simply dividing triglyceride levels by a factor of 5 would provide a reasonable estimate of VLDL-C, enabling us to calculate LDL-C.

For many years, this method served us well. Despite some known limitations (notably its non-applicability in patients with triglyceride levels >400 mg/dL), it provided a relatively straightforward way to assess the LDL-C levels of our patients. However, recent data have shown convincingly that high triglyceride levels (>400 mg/dL) are not the only setting where the formula provides inaccurate estimates of LDL-C. Much milder elevations of triglyceride levels tend to increase the ratio of triglycerides/VLDL-C above the 5.0 figure, leading to an underestimation of LDL-C levels. Perhaps more importantly, this underestimation also occurs (by a similar mechanism) in patients with lower total cholesterol levels, a situation that is becoming increasingly common with the mounting use of high intensity lipid lowering therapies.

To overcome these issues, Martin et al. developed a new way to estimate LDL-C that has become known as the Martin-Hopkins method (a designation combining the names of its first author and of the University where it was developed).[4] In their seminal work published in 2013, they used around 1.3 million lipid profiles to establish more accurate triglyceride/VLDL-C ratios, dependent on both triglyceride and non-HDL-C levels. In the proposed table, the

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triglyceride/VLDL-C relationship varies from a ratio of about 3.5 to almost 12. Using the direct measurement of LDL-C as gold standard, this new Martin-Hopkins method proved to be more accurate than the Friedewald formula. Importantly, they also showed its robustness in patients with high triglyceride levels, overcoming an important limitation of the previous method.

Despite its numerous merits, the Martin-Hopkins method was developed from a single dataset of patients living in the United States of America, and could not be applied here in Portugal without prior validation. In this issue of the Portuguese Journal of Cardiology, Ferrinho et al. provide this validation using a cohort of 1688 patients from the e_COR study, which aimed to assess the prevalence of cardiovascular risk factors in the Portuguese population.[5] In brief, the authors confirm the excellent correlation between LDL-C estimated by the Martin-Hopkins method and LDL-C measured directly. Moreover, they corroborate the superiority of the Martin-Hopkins method over the Friedewald equation, especially in patients with diabetes, hypertriglyceridemia, and/or LDL-C<100 mg/dL, where the underestimation by the said equation tends to be greater. Finally, this study offers us a glimpse of what to expect when applying this method in our patients with very high or high cardiovascular risk, suggesting that a significant proportion of those we consider to be on target, are in fact above their desired LDL-C levels.

Even though these results were somewhat expected, they are a fundamental and necessary step toward the use of the Martin-Hopkins method in our patients, and the authors should be credited for this. The main strength of this study is its representativeness of the Portuguese population in its diversity of risk and clinical scenarios. On the other hand, for physicians who see mostly patients with very high cardiovascular risk, the relatively low number of patients in this category is probably also the main constraint of the e_COR cohort.

So, exactly what are the implications of this study and the method it validates? Perhaps an example can help us better understand the possible repercussions. Mr. Silva is a diabetic patient who suffered a myocardial infarction one year ago. He is currently on a high potency statin and comes to the clinic with a basic lipid profile showing total cholesterol levels of 134 mg/dL, HDL-C 30 mg/dL, and triglycerides of 248 mg/dL in the context of poor glycemic control. Using the Friedewald equation, we would estimate this patient's LDL-C at 54 mg/dL, just below the 55 mg/dL limit recommended for very high risk patients. If we used the newer (and more accurate) Martin-Hopkins equation, the result would be quite different, since this patient's LDL-C would be estimated at 71 mg/dL, considerably above his goal and probably prompting changes in his lipid lowering medication. By revealing these previously disguised cases of above-target LDL-C, the Martin-Hopkins method may become a valuable ally in fighting therapeutic inertia and getting more patients to their lipid targets. In a sense, this new tool can be compared to a better compass that helps us to determine more accurately our patients' positions in the LDL-C charts. This, of course, is a fundamental step in discovering how to get them to their goals. Let's all use it, then.

Conflicts of interest

Dr. Ferreira has received speaker and consulting fees from MSD Portugal, Organon Portugal, and Amgen Portugal.

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