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Are We Moving Towards Concordance on the Principle That Lipid Discordance Matters?

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In this issue of *Circulation*, Samia Mora, Julie Buring, and Paul Ridker publish an elegant and clinically-relevant analysis examining discordance of low-density lipoprotein cholesterol (LDL-C) with related laboratory measures and the risk implications.¹ The article should attract attention from a diverse set of contingents, such as those based in preventive cardiology, clinical lipidology, and laboratory medicine, to name just a few. The study addresses the underappreciated concept of discordance between different lipid and lipoprotein measures in individual patients. The investigators address the prevalence of such discordance and its association with long-term incidence of coronary events.

Dr Mora and colleagues analyze participants in the prospective Women's Health Study. With necessary lipid measurements captured on nearly all of the women, the analysis is large, involving 27 533 women aged 45 years. This is a primary prevention population—these women were all free of self-reported cardiovascular disease and cancer at baseline. After baseline risk factor measurements, the women underwent follow-up over a median of 17.2 years for incident coronary events, including nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and coronary death. An Endpoints Committee adjudicated events, which occurred in 1070 women.

A unique aspect of this analysis is the simultaneous availability of directly measured LDL-C, Friedewald-estimated LDL-C, nonhigh-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apoB), and low-density lipoprotein particle concentration (LDL-P). Essentially, these are related, but distinct, measures of the atherogenic lipid burden. Given

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that LDL-C is commonly the first parameter considered in clinical practice, in line with international guidelines,²⁻⁴ having this study center its primary analyses on LDL-C makes the results particularly relevant to daily practice.

Another strength of the study is that the laboratory performing the measurements participates in the Centers for Disease Control and Prevention's Lipid Standardization Program. Ultimately, when we measure lipid parameters, and compare across studies and patients, we want to know that we are measuring the same thing in the same way. This important laboratory program provides accuracy-based standards for total cholesterol, triglycerides, HDL-C, and apoB. It is important to note that non-HDL-C and Friedewald-estimated LDL-C⁵ use inputs from these standardized measures. The other measures in this study (direct LDL-C and LDL-P) are not part of the standardization program.

The study uses a direct assay for LDL-C, specifically the Roche direct homogeneous assay. On the surface, it would seem a virtue to use a direct assay, as it avoids the challenges of LDL-C estimation.^{6,7} However, not all direct techniques are created equal. Whereas the traditional technique is ultra-centrifugation-based, the Roche assay is detergent-based. Moreover, the LDL-C of common parlance—as established by the traditional definition used by Friedewald and by β -quantification—includes not only biological LDL, but also intermediate-density lipoprotein cholesterol and lipoprotein(a) cholesterol [Lp(a)].⁶ A previous analysis showed that the Roche direct LDL assay measures LDL and intermediate-density lipoprotein, but not Lp(a), and showed a significant negative bias attributable to suboptimal calibration between the Roche assay and β -quantification.⁸ Among 4 homogeneous direct LDL-C assays, the Roche assay had the highest total error at 41.6%.⁹ These issues do not negate the importance of this study (especially given the authors also conducted analyses with Friedewald-estimated LDL-C), but must be taken into consideration when comparing the results with other literature.

Going into the analysis, it is also important to understand that LDL-C, non-HDL-C, apoB, and LDL-P, by nature, are expected to carry unique information. LDL-C is the cholesterol content of LDL, intermediate-density lipoprotein, and Lp(a), whereas non-HDL-C adds the cholesterol content of VLDL. ApoB can be viewed as the particle-based counterpart of non-HDL-C, as there is 1 apoB particle per atherogenic lipoprotein particle. In contrast, LDL-P in theory is the particle concentration counterpart of LDL-C, assuming that we are quantifying the cholesterol content and particle concentrations from the same lipoprotein fractions.

Considering these parameters, Mora and colleagues address two key questions: (1) How often is there discordance of LDL-C with non-HDL-C, apoB, or LDL-P? (2) Does discordance matter in terms of coronary prognosis? Amid a field of research wherein studies have often focused on pitting one type of lipid measurement against another to examine average risk in broad populations, the authors should be commended for this more clinically-relevant form of analysis. As the authors insightfully point out, “the clinical utility of these measures may only become apparent among individuals for whom levels are inconsistent (discordant) with LDL-C.”¹ We submit that because discordance is defined at

the level of the patient, discordance analysis should become the preferred standard for future observational studies comparing lipid parameters.

To perform a discordance analysis, Mora and colleagues use the median levels of LDL-C (121 mg/dL), non-HDL-C (154 mg/dL), apoB (100 mg/dL), and LDL-P (1216 nmol/L). The authors then categorize women as discordant if the LDL-C is \geq median and the comparison measure (non-HDL-C, apoB, LDL-P) is $<$ median, or vice versa. The remaining women are classified as concordant. Discordance is present in 11.6% of women in comparison with non-HDL-C, 18.9% with apoB, and 24.3% with LDL-P. It is interesting that the greatest discordance exists between LDL-C and LDL-P, rather than between LDL-C and 1 of the other measures including additional lipoprotein fractions.

Next, the authors demonstrate the significance of discordance between lipid parameters in individual patients as it relates to risk of coronary heart disease events. In risk models, direct LDL-C under- or overestimated coronary risk by \approx 20-50% when discordant with the other related parameters. Regarding the outcomes implications of discordance between lipid and lipoprotein parameters, only a handful of previous papers have examined this topic. Dr Sniderman and colleagues conducted a discordance analysis of Friedewald-estimated LDL-C, apoB, and non-HDL-C in men who participated in the Quebec Cardiovascular Study, with findings compatible with those in this report.¹⁰ Dr Cromwell and colleagues examined LDL-P versus Friedewald-estimated in the Framingham Heart Study, finding that in persons classified as discordant, risk tracked more closely with LDL-P.¹¹ More recently, Dr Otvos, along with other colleagues, including Dr Mora, reached a similar result in the more diverse Multi-Ethnic Study of Atherosclerosis cohort.¹²

Future discordance analyses are needed in diverse populations from prospective studies with the best available measurement techniques. This current Women's Health Study is limited to only women (almost exclusively Caucasian). Triglycerides (and thus related atherogenic particles) may be a stronger risk factor in women compared with men¹³ and thus the risk conferred by LDL discordance may differ by gender, which could not be assessed in the current study. Moreover, some of the significant findings were lost when using Friedewald-estimated LDL-C instead of direct LDL-C. This highlights the need for additional investigations using ultracentrifugation-based direct LDL-C and novel methods for LDL-C estimation.⁷

Another limitation of this current study is that it is not reported how many patients were on statins at baseline or initiated a statin during follow-up. This can impact coronary risk prediction and confound the relationship between baseline lipid parameters and outcomes. Not only will each atherogenic parameter change if statin therapy is initiated during follow-up, previous studies have shown that there is a differential impact of statins on LDL-C, non-HDL-C, and apoB such that their relationships are altered.¹⁴ Moreover, the central context where we consider residual risk—defined as that risk remaining after adequate statin treatment and in part related to measures beyond LDL-C—is in statin-treated patients. Although the latest US guidelines⁴ do not endorse titrating drugs or adjusting medication regimens to fixed lipid targets, one may want to assess the residual risk related to lipids on-

treatment, and so the concept of discordance on-treatment is another area worthy of future attention.

As emphasized by the latest American College of Cardiology (ACC)/American Heart Association (AHA) guidelines,⁴ the baseline decisions about initiating statin treatment are more related to global risk prediction using lipid parameters in addition to other risk factors. For lipid parameter inputs, the risk calculator incorporates total cholesterol and HDL-C, rather than LDL-C, non-HDL-C, apoB, or LDL-P. In the future, it may become feasible and desirable to replace total cholesterol and HDL-C with other lipid parameters in the ACC/AHA risk calculator. If 1 of these atherogenic lipid parameters were used, this would allow one to understand the modifiable component to lipid related risk. A very clinically relevant question is what risk can be directly targeted with treatment? For this question, total cholesterol and HDL-C are not ideal because, to date, we have not identified a treatment that improves clinical outcomes by directly targeting HDL-C. Total cholesterol is a crude measure of atherogenic lipid and lipoprotein burden.

Another important question is what the most relevant clinical end point of interest is. A virtue of the new ACC/AHA guidelines⁴ is the emphasis on stroke prevention, in addition to coronary disease prevention. Although the authors focused on coronary disease risk only, it will be helpful if future studies of this kind frame the question of discordance on the broader end point of atherosclerotic cardiovascular disease risk, including strokes. This is especially important for female or black populations, in whom strokes tend to be a more common end point compared with other demographic groups.

Although percutaneous coronary intervention and coronary artery bypass grafting are clinically important outcomes, they are subject to a higher risk of bias and geographic variation. Therefore, it would have been nice to see whether results were still robust using hard end points of myocardial infarction and coronary death. This is especially the case given that revascularization outcomes were not included in the 2013 ACC/AHA guidelines risk calculator.⁴

Another consideration as this line of research matures is definitions of discordance. To define discordance, the authors chose median cutpoints because there is no physiological cut-point for discordance. However, greater discordance between LDL-C and non-HDL-C occurs at lower LDL-C levels.¹⁵ It is notable that the methods to date for defining discordance have been discordant, ranging from 12 percentile units difference¹² to Framingham percentiles and guideline cutpoints.¹⁶ In moving forward, we as a research community should settle on a standard approach to discordance analysis, so that we can best synthesize the studies, and reach the ultimate goal of translating the concept into optimizing care of the individual patient.

In summary, the authors have nicely demonstrated that discordance is common, that this discordance may lead to over- or underestimation of clinically significant coronary risk, and this may have important implications for developing future risk prediction calculators. However, further study is needed regarding how to best apply these findings in the clinical

management of individual discordant patients, especially in the new era of “abandoning” specific lipid targets.

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