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EDITORIAL COMMENT

Lipoprotein(a) Cholesterol Masquerading as Low-Density Lipoprotein Cholesterol

Catch Me if You Can*

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Lipoprotein(a) is recognized as an independent, causal risk factor for cardiovascular diseases. Considerable evidence from epidemiological and genetic studies has established its role in risk of atherothrombotic disease[1] and aortic valve stenosis.[2] Indeed, there are now multiple RNA-based therapeutics at various stages of clinical development. Although this is an exciting prospect for primary and secondary prevention, the introduction of a new lipid fraction into clinical practice will bring challenges to both clinicians and medical laboratories. This is very well-illustrated by the report from Yeang et al[3] in this issue of the *Journal of the American College of Cardiology*. The report stems from the intriguing observation that pelacarsen, an antisense oligonucleotide targeting the lipoprotein(a) gene, unexpectedly decreased low-density lipoprotein cholesterol (LDL-C) levels by up to 26% and total

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apoB levels by up to 16%. Although pelacarsen is not known to directly affect apoB production, it raises the possibility of a physiological effect. An alternative explanation is confounding of laboratory measurements of LDL-C by lipoprotein(a). Indeed, lipoprotein(a) is derived from low-density lipoprotein through the covalent binding of apo(a) to apoB, the main apolipoprotein of low-density lipoproteins. As standard LDL-C assays do not distinguish low-density lipoproteins from lipoprotein(a), the reported cholesterol is effectively the sum of cholesterol contained by both low-density lipoprotein and lipoprotein(a).

Yeang et al[3] shed light on this question by applying a novel method to directly measure lipoprotein(a)-associated cholesterol [Lp(a)-C] in participants from the phase 2 pelacarsen trial.[4] The previously described method[5] works by first isolating Lp(a) from plasma and then measuring cholesterol directly, with improved sensitivity and linear range compared with other assays. Use of this method enabled calculation of corrected LDL-C (LDL-$C_{corrDirectLp(a)}$). LDL-$C_{corrDirectLp(a)}$ is defined as the quantity of cholesterol present on low-density lipoproteins after exclusion of lipoprotein(a) particles. Consistent with the expected effect of pelacarsen, LDL-$C_{corrDirectLp(a)}$ showed an attenuated decrease compared with noncorrected LDL-C. These results have 3 important clinical implications. First, they provide further proof that in individuals with elevated Lp(a) (>150 nmol/L in the phase 2 pelacarsen trial), the contribution of Lp(a) to LDL-C is non-negligible using standard assays, with 13-16 mg/dL lower LDL-C postcorrection. Second, they confirm that the effect of Lp(a) inhibitors is likely to be mostly confined to Lp(a), as would be expected. Finally, and perhaps more importantly, the authors highlight the need to improve clinical reporting of lipid fractions to properly treat LDL-C and Lp(a) in high-risk patients. Patients with elevated Lp(a) will have a correspondingly high LDL-C using standard assays; yet, the value reflects both LDL-C and Lp(a)-C. Conversely, treatment with

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Lp(a) inhibitors will lead to an apparent decrease in LDL-C with current assays.

There are a few limitations to the study by Yeang et al[3] that should be considered. First, the study was conducted in a population selected for elevated Lp(a). Although findings are likely to be applicable to a more general population, the confounding effect of elevated Lp(a) on LDL-C can nonetheless be expected to be smaller, or even negligible, in patients with normal or low Lp(a) through either natural or pharmacological means. In other words, if and when Lp(a) becomes a therapeutic target, residual Lp(a) might not be high enough to have a material effect on LDL-C measurements, even with current methods. Additionally, it remains to be demonstrated whether the novel assay and correction proposed will be sensitive enough at these lower levels. Second, the association of $\text{LDL-C}_{\text{corrDirectLp(a)}}$ with pelacarsen is attenuated compared with LDL-C; yet, a trend remains, and in fact, is still statistically significant in certain groups. Perhaps a small indirect physiological effect is indeed present, or the method does not fully adjust for Lp(a)-C. A third limitation, especially for clinical applications, is the availability of the assay used in the study. Beyond availability, it is also likely to be more expensive given the additional laboratory steps needed.

The report from Yeang et al[3] provides an additional insight that mitigates the aforementioned limitations. The authors considered not only LDL-C but also apoB, which is particularly important as apo(a) is covalently bound to apoB with a 1:1 stoichiometry on Lp(a). As each low-density lipoprotein carries a single apoB apolipoprotein, measurement of both apoB and Lp(a) on a molar basis provides a complete picture of the effect of pelacarsen on low-density lipoprotein numbers. In other words, non-Lp(a) apoB can be calculated by simply subtracting Lp(a) from total apoB concentration when both are expressed in molar units (ie, number of proteins per volume of plasma). Tellingly, the decrease in total apoB observed with pelacarsen is restricted to Lp(a) as no change was observed with non-Lp(a) apoB. As apoB has already been shown to be superior to LDL-C for risk prediction in both epidemiological[6] and genetic studies,[7] these results provide another compelling rationale for wider adoption of apoB. Furthermore, apoB has also been shown to be superior to LDL-C to estimate on-treatment residual risk,[8] an important consideration in patients likely to have both elevated Lp(a) and/or be on Lp(a) inhibitors. Both apoB and Lp(a) measurements are already offered by most clinical laboratories. The observation made by Yeang et al[3] provides an additional impetus for laboratories to report them in the more biologically relevant molar units rather than mass units.

In summary, Yeang et al[3] present a detailed analysis of the effect of pelacarsen on Lp(a)-C and corrected LDL-C. The report starts from an interesting observation from the phase 2 trial of pelacarsen, raising relevant questions on measurement and reporting of LDL-C, Lp(a), and apoB. Through meticulous and innovative investigative work, Yeang et al[3] hone in and catch the suspect red-handed: current LDL-C assays measure both bona fide LDL-C and Lp(a)-C. With the impending introduction of Lp(a) in clinical practice, these questions will grow in importance. Fortunately, Yeang et al[3] not only raise these questions, but also provide solutions through a novel method for measurement of Lp(a)-associated cholesterol and compelling data arguing for broader use of apoB. The report paves the way for future studies investigating the clinical utility of these additional measurements to initiate and monitor lipid-lowering therapy.

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REFERENCES

1. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361:2518–2528.

2. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–512.

3. Yeang C, Karwatowska-Prokopczuk E, Su F, et al. Effect of pelacarsen on lipoprotein(a) cholesterol and corrected low-density lipoprotein cholesterol. *J Am Coll Cardiol*. 2022;79:1035–1046.

4. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med*. 2020;382:244–255.

5. Yeang C, Witztum JL, Tsimikas S. Novel method for quantification of lipoprotein(a)-cholesterol: implications for improving accuracy of LDL-C measurements. *J Lipid Res*. 2021;62:100053.

6. Marston NA, Giugliano RP, Melloni GEM, et al. Association of Apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without atherosclerosis: distinguishing between particle concentration, type, and content. *JAMA Cardiol*. Published online November 13, 2021. https://doi.org/10.1001/jamacardio.2021.5083

7. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364–373.

8. Johannesen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. *J Am Coll Cardiol*. 2021;77:1439–1450.

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