Reply to Letter regarding Keto CTA Study

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We thank Drs Lopez-Moreno, and Lopez-Gil, for their interest in our manuscript[1], and cordial commentary and for the opportunity to address these points.

Regarding the primary outcome presented in Figure 1, we would like to clarify that the pooled median change in non-calcified plaque volume (NCPV) was 18.9 mm^3, which corresponds to a 42.8% relative change. We apologize for this omission in the original publication and welcome the opportunity to provide that information here. This was a sincere oversight, not intentional selective reporting. Additionally, we'll highlight that the mean change in NCPV was 31.5 mm^3 with a standard deviation also of 31.5 mm^3. This highlights the impressive degree of heterogeneity in NCPV change. Even within a self-selected group like this one, some individuals display rapid plaque progression, and we do not want our results to be interpreted as if we believe all lean mass hyper-responders (LMHRs) to be of uniform risk.

In our table comparing plaque progression with other populations (Supplemental Table 1), we aimed to emphasize plaque progression was highly heterogeneous across the baseline cardiovascular risk spectrum using Percentage Atheroma Volume (PAV) because, in contrast with NCPV it considers changes in vessel volume and provides a more holistic report insofar as it takes into account multiple types of plaque and is less influenced by patient-specific factors.[2] We also emphasize that between studies comparisons are challenging because of variations in data acquisition, methods, and inclusion criteria of the study population. In this regard, we acknowledged the lack of a control group in our study as one of its limitations. Nonetheless, a carefully matched comparison[3] of 80% of this cohort showed similar plaque metrics after 4.7 years in a ketogenic diet when compared to participants in MiHeart[4], which has comparable risk factors but with lower LDL-C. While there is no consensus on what "stable plaque" means for NCPV changes, we would like to emphasize that, since most participants showed low-baseline plaque values, relative changes are expected to be magnified. As readers will be able to see for themselves in the table mentioned above, the majority of the participants showed PAV changes below the agreed upon definition for rapid plaque progression of >1% per year[4].

Regarding the analytical points brought forward, we are aware of the relevance of linear assumptions to obtain accurate estimators. Since residual plot evaluation can also be subjective, we followed their suggestion and re-ran all models with robust linear regression (using the MASS::rlm function in R, version 4.4.3). While, as expected, there were small differences with the published estimates, all models using robust regression were consistent with what was reported. Additionally, we would like to emphasize that Bayes Factors should not be interpreted as the probability of any hypothesis being true. They are a quantitative way of evaluating how much a given hypothesis should be updated against or towards the null. The words used for their interpretation (i.e. "moderate" or "strong") come from "Jeffrey's scale," a commonly used semiquantitative scale for this purpose.[5]

We agree that being able to identify patients with rapid plaque progression, and gaining better understanding of the mechanisms that mediate its pace (i.e. insulin resistance, inflammation, different dietary composition elements, etc.) is paramount. We plan to address these risk factors in future reports. Nonetheless, we would like to point out that we did test for the influence of diet

adherence (which was defined physiologically and not with the dietary recalls) and for the best-studied dietary component influencing cardiovascular disease, saturated fat, and with a null association.

We acknowledge the short follow-up time in our study as one of its limitations in our discussion. However, despite its short duration and thanks to the high sensitivity of the image acquisition methods we used, we did observe meaningful plaque changes in some participants.

As a clarification, the Central Illustration was not focused on sensitivity analyses with a smaller sample size, but rather displays a panel with change in NCPV (our primary outcome) using the full sample size (panel C in Figure 2).

Finally, we completely agree our exploratory results (especially those suggesting a null association between plaque progression and ApoB) should be interpreted with caution and that all patients should still seek personalized medical advice, including individual consideration of treatment guidelines based on their level of risk. Nonetheless, our results are useful to remind clinicians to be mindful of risk factors beyond the lipid panel and to help risk stratify patients exhibiting the LMHR phenotype.

Moreover, our results are compatible with a causal role of ApoB in atherosclerosis, as we have openly acknowledged and supported in previous publications.[6] Along the same lines, we would like to clarify that our title was not meant to be a statement about causality. “Plaque begets plaque” (which, of course, mirrors the proverb “Money begets money”) is frequently used to highlight the strong and clinically relevant association of baseline plaque values with plaque progression rate[7]. In retrospect, we might have chosen “Longitudinal Data from the KETO-CTA Study” as alternative phrasing to avoid misinterpretations.

References

1. Soto-Mota, A., Norwitz, N. G., Manubolu, V. S., Kinninger, A., Wood, T. R., Earls, J., Feldman, D., & Budoff, M. (2025). Plaque Begets Plaque, ApoB Does Not: Longitudinal Data From the KETO-CTA Trial. *JACC. Advances*, 101686. Advance online publication. doi: 10.1016/j.jacadv.2025.101686
2. van Rosendael, A. R., Lin, F. Y., Ma, X., van den Hoogen, I. J., Gianni, U., Al Hussein, O., Aref, S. J., Peña, J. M., Andreini, D., Al-Mallah, M. H., Budoff, M. J., Cademartiri, F., Chinnaiyan, K., Choi, J. H., Conte, E., Marques, H., de Araújo Gonçalves, P., Gottlieb, I., Hadamitzky, M., Leipsic, J. A., Chang, H. J. (2020). Percent atheroma volume: Optimal variable to report whole-heart atherosclerotic plaque burden with coronary CTA, the PARADIGM study. Journal of cardiovascular computed tomography, 14(5), 400–406. https://doi.org/10.1016/j.jcct.2020.01.012
3. Budoff M, Manubolu VS, Kinninger A, Norwitz NG, Feldman D, Wood TR, Fialkow J, Cury R, Feldman T, Nasir K. Carbohydrate Restriction-Induced Elevations in LDL-

Cholesterol and Atherosclerosis: The KETO Trial. JACC Adv. 2024 Aug 28;3(8):101109. doi: 10.1016/j.jacadv.2024.101109.

4. Han D, Berman DS, Miller RJH, Andreini D, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Conte E, Marques H, de Araújo Gonçalves P, Gottlieb I, Hadamitzky M, Leipsic J, Maffei E, Pontone G, Shin S, Kim YJ, Lee BK, Chun EJ, Sung JM, Lee SE, Virmani R, Samady H, Stone P, Narula J, Bax JJ, Shaw LJ, Lin FY, Min JK, Chang HJ. Association of Cardiovascular Disease Risk Factor Burden With Progression of Coronary Atherosclerosis Assessed by Serial Coronary Computed Tomographic Angiography. JAMA Netw Open. 2020 Jul 1;3(7):e2011444. doi: 10.1001/jamanetworkopen.2020.11444.
5. Jeffreys, H. (1961). Theory of Probability (3rd ed.). Oxford University Press
6. Norwitz, N. G., Mindrum, M. R., Giral, P., Kontush, A., Soto-Mota, A., Wood, T. R., D'Agostino, D. P., Manubolu, V. S., Budoff, M., & Krauss, R. M. (2022). Elevated LDL-cholesterol levels among lean mass hyper-responders on low-carbohydrate ketogenic diets deserve urgent clinical attention and further research. *Journal of clinical lipidology*, *16*(6), 765–768. doi: 10.1016/j.jacl.2022.10.010
7. Yoon, H.C., Emerick A.M., Hill J.A., Gjertson D.W., Goldin J.G. (2002). Calcium begets calcium: progression of coronary artery calcification in asymptomatic subjects Radiology, 224(1):236-41. doi: 10.1148/radiol.2241011191