

Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications

Hiperlipidemili Yaşlı Hastalarda Kümülatif LDL-C ve Lipoprotein(a): Metodolojik Hususlar ve Klinik Etkileri

To the Editor,

We read with great interest the article by Yurtseven et al.,¹ recently published in the Archives of the Turkish Society of Cardiology, which investigated lipoprotein(a) [Lp(a)] and cumulative low-density lipoprotein cholesterol (LDL-C) as predictors of coronary artery disease (CAD) in statin-naïve elderly individuals with hyperlipidemia.

The authors found that male sex, cumulative LDL-C, and elevated Lp(a) independently predict CAD in individuals aged ≥ 70 years with LDL-C ≥ 160 mg/dL. The SAFEHEART risk score outperformed SCORE2-OP in this population.¹ Given the ongoing debate regarding statin initiation in elderly patients, these findings are clinically relevant. However, we would like to highlight several methodological and interpretive considerations that warrant further evaluation.

First, the cumulative LDL-C exposure approach, which multiplies a single measurement by age, should be interpreted with caution. The authors acknowledge that this method may overestimate lifelong LDL-C burden, as LDL-C levels tend to increase with age. A single cross-sectional measurement cannot accurately reflect decades-long LDL-C exposure. Mendelian randomization studies by Ference et al.² suggest that integrating serial LDL-C measurements over time provides a more physiologically accurate estimate of cumulative exposure.

Second, the SAFEHEART risk equation was developed and validated in patients with familial hypercholesterolemia (FH). However, its application in this cohort—where only 5.4% met the Dutch Lipid Clinic Network criteria for probable FH—raises concerns regarding external validity. The incorporation of Lp(a) into the equation may explain its apparent superiority over SCORE2-OP in this Lp(a)-enriched cohort, rather than reflecting its performance in the broader elderly hyperlipidemia population. Therefore, before recommending its widespread clinical use, SAFEHEART should be prospectively validated in non-FH elderly populations.³

Third, the study population was predominantly female (68.3%), which may have influenced the observed effect sizes and limited generalizability to elderly men. Although interaction terms between sex and both Lp(a) and cumulative LDL-C were not statistically significant, the study was likely underpowered to detect such interactions given the sample size of 202 patients. In light of evidence suggesting that sex-specific Lp(a) cut-off values may be warranted for cardiovascular risk stratification, sex-stratified analyses or the inclusion of a larger cohort would strengthen the conclusions.⁴

Fourth, Lp(a) levels were reported in mg/dL rather than nmol/L. Given the well-recognized interindividual variability in Lp(a) particle size, reporting in nmol/L is increasingly preferred in contemporary guidelines and improves cross-study comparability. Additionally, the absence of genetic testing for FH mutations or LPA kringle-IV type 2 (KIV-2) repeat number leaves the molecular basis of elevated Lp(a) uncharacterized in this cohort, thereby limiting mechanistic interpretation.⁵

LETTER TO THE EDITOR EDİTÖRE MEKTUP

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Received: March 01, 2026

Accepted: March 06, 2026

Cite this article as: Aydın F. Cumulative LDL-C and Lipoprotein(a) in Elderly Patients with Hyperlipidemia: Methodological Considerations and Clinical Implications. *Türk Kardiyol Dern Ars.* 2026;54(3):286-287.

DOI: 10.5543/tkda.2026.46309



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Finally, the retrospective, single-center design involving a referred, symptomatic population introduces Berkson-type bias and limits the generalizability of the findings to community-dwelling elderly individuals. Prospective studies with longitudinal follow-up, incorporating incident cardiovascular events as endpoints rather than prevalent CAD, will be essential to confirm the prognostic utility of cumulative LDL-C and Lp(a) in this age group.

In conclusion, Yurtseven et al.¹ identify Lp(a) and cumulative LDL-C as underappreciated risk indicators in elderly patients with hyperlipidemia. In this vulnerable and growing population, future prospective studies should address the methodological considerations outlined above to strengthen the evidence base for lipid-lowering therapy strategies.

Conflict of Interest: The author have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

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