European Atherosclerosis Journal
www.eathj.org
EAJ 2024;3:67-72
https://doi.org/10.56095/eaj.v3i3.77

Atherosclerotic cardiovascular disease and measurement of lipoprotein(a) levels in Italy

Elena Olmastroni[1,2], Manuela Casula[1,2], Sining Xie[1], Alberico L. Catapano[1,2]

[1]*Epidemiology and Preventive Pharmacology Service (SEFAP), Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy*
[2]*IRCCS MultiMedica, Sesto San Giovanni (MI), Italy*

ABSTRACT

Background: Lipoprotein(a) [Lp(a)] is a relatively new but underutilized biomarker in the context of atherosclerotic cardiovascular disease (ASCVD).
Objectives: To explore the clinical implementation of Lp(a) measurement and current practices in hospital and specialised settings in Italy.
Methods: An anonymous online questionnaire was distributed to Italian physicians to examine the habits of Italian clinicians regarding Lp(a) measurement. The survey covered three topics: 1) information on the clinical setting of the physicians, 2) questions for physicians who reported not measuring Lp(a), to understand the reasons for not requesting the test, and 3) questions for physicians who measure Lp(a), to investigate its use in patient management.
Results: A total of 978 responses were received. Overall, 63.1% of physicians reported working in a hospital; 12.2% reported being a territorial specialist. Regular Lp(a) measurement was reported by 32.1% of clinicians. Among those who do not measure Lp(a), the main barriers to implementation include high cost and limited availability of the test. The threshold value for defining elevated Lp(a) levels varies significantly among professionals, with 36.7% considering levels above 30 mg/dL to be elevated and 32.7% considering levels above 50 mg/dL to be elevated. Clinical management of patients with elevated Lp(a) primarily includes intensification of lipid-lowering therapy (69.2%), management of cardiovascular risk factors (48.7%), and lifestyle recommendations (37.4%).
Conclusions: The survey highlights the heterogeneity in the approach to managing elevated Lp(a) levels among Italian clinicians, underscoring the importance of clear guidelines and greater accessibility to the test to optimize cardiovascular risk stratification and improve clinical outcomes.

Keywords
Lipoprotein(a); atherosclerotic cardiovascular disease; clinicians; cardiovascular risk management; patient communication simulation

Received 29 october 2024 accepted 28 december 2024

Introduction

Atherosclerotic cardiovascular disease (ASCVD) represents one of the main global health challenges within the landscape of chronic diseases. Characterized by the formation and progression of atherosclerotic plaques in the arteries, ASCVD is a multifactorial condition mostly involving the deposition of lipids and inflammatory cells within the arterial wall [1]. This pathological process can impede blood flow, compromise arterial distensibility, and, in severe cases, lead to complications such as myocardial infarction, stroke, and other cardiovascular conditions.

Understanding the risk factors, prevention methods, and effective management of ASCVD is crucial for promoting cardiovascular health and reducing related morbidity and mortality.

The role of lipoprotein(a) [Lp(a)] in cardiovascular risk assessment has been and continues to be a topic of debate [2]. Lp(a) is a particle similar to low-density lipoprotein (LDL), differing only by the presence of a glycoprotein called apo(a) (which has a high homology with plasminogen) covalently linked to apoB [3]. Unlike other lipoproteins that have a clear biological function as lipid transport molecules in plasma, the function of Lp(a), after more than 50 years of research, remains practically unknown [4].

Corresponding Author
Elena Olmastroni: elena.olmastroni@unimi.it

On the other hand, the role of Lp(a) as a cardiovascular risk factor is well established. Numerous scientific studies indicate that elevated levels of Lp(a) are associated with an increased risk of adverse cardiovascular events, including stroke and myocardial infarction [5]. Therefore, measuring Lp(a) in clinical practice is becoming increasingly important for cardiovascular risk assessment, enabling targeted and personalized preventive interventions.

Plasma levels of Lp(a) in the general population vary widely, ranging from very low, almost undetectable levels (<0.2 mg/dL) to very high levels (>200 mg/dL). This variability primarily depends on the isoforms of apo(a), which differ in the size of the molecule determined by the number of repeat structures, the kringles, particularly the number of kringle 4 type 2 repeats [6].

The polymorphism of the gene encoding apo(a) size is the major predictor of plasma Lp(a) concentration and accounts for 40-70% of the variation in Lp(a) plasma levels [7]. The strong genetic influence on Lp(a) levels results in its asymmetric distribution in the population, unlike other analytes, complicating the role of Lp(a) in cardiovascular risk assessment.

Some peculiar characteristics of Lp(a), such as its significant heterogeneity, the absence of a clear physiological function, and the current difficulty in measuring it reliably and in a standardised manner, limit its use in routine clinical practice [8].

Therefore, the SISA Foundation has promoted a survey on the themes related to 'Atherosclerotic Cardiovascular Disease and the Importance of Measuring Lp(a) Levels,' targeting physicians operating in Italy.

The project's objective is to gather useful information to improve diagnostic and prognostic approaches in the near future. This includes understanding how often Lp(a) is evaluated in daily practice, the criteria used to decide whether or not to test for Lp(a), and the practical factors considered in the decision to perform the test.

This effort aims to collect essential information to determine the resource, process, infrastructure, and funding requirements needed to make Lp(a) evaluation a common practice.

Methods

The questionnaire, consisting of 23 questions, primarily included multiple-choice responses and was structured into three main areas of investigation:

- Information regarding the background and clinical setting of the physicians;
- Specific questions directed at physicians who reported not regularly measuring Lp(a) in clinical practice, to understand the motivations or practical barriers preventing them from requesting the test;
- Specific questions directed at physicians who reported regularly measuring Lp(a) in clinical practice, to delve into their approach in managing patients at high cardiovascular risk.

Participation in the questionnaire was voluntary. Consent was implied with the return of the completed questionnaire.

All responses were managed anonymously. The results were summarized using frequencies and percentages. Statistical analyses were performed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, NC, USA).

Results

A total of 978 clinicians from various settings responded to the survey: the majority reported working primarily in territorial or university hospitals (24.4% and 22.3%, respectively), and 39.2% and 24.7% of them were cardiologists or internal medicine physicians (**Table 1**). The geographical origin of the clinicians participating in the survey is illustrated in **Figure 1**.

Based on the personal experiences of the participants, the

Table 1 | Clinical settings and specializations of the physicians who participated in the survey.

Number of Clinicians	**978**
Practice Setting, %:	
University Hospital	22.29%
Institute for Treatment and Research (IRCCS)	6.44%
Territorial Hospital	24.44%
Territorial Specialist	12.17%
Specialized Lipidology Center	2.97%
Specialized Diabetology Center	2.56%
Specialized Cardiology Center	5.42%
Other	23.72%
Specialization, %:	
Cardiology (Clinical Cardiology, Hemodynamics, Electrophysiology, Interventional Cardiology)	39.16%
Diabetology	4.19%
Endocrinology	6.24%
Lipidology	1.53%
Internal Medicine	24.74%
Other	24.13%

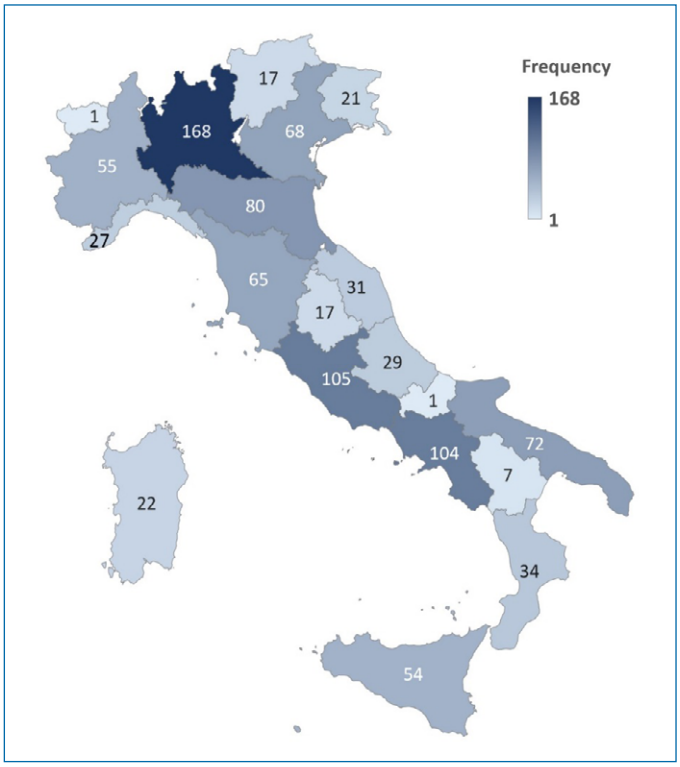

Figure 1 | Geographical distribution of the clinicians participating in the survey.

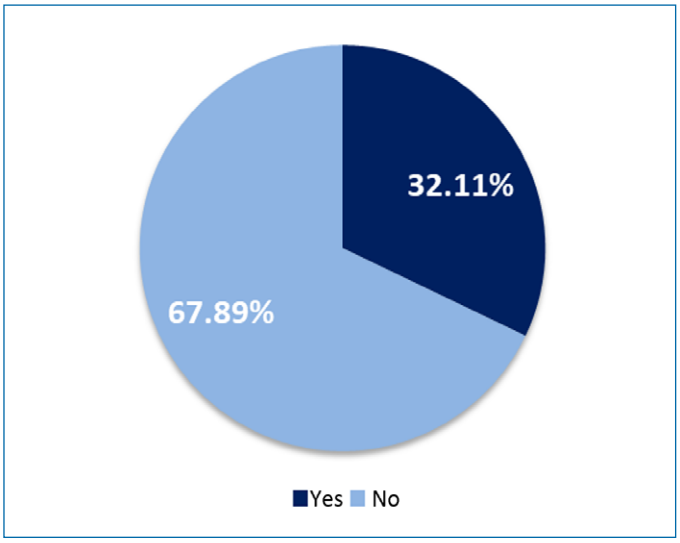

Figure 2 | Proportion of clinicians who regularly measure Lp(a) in clinical practice.

proportion of clinicians who regularly measure Lp(a) in clinical practice was found to be 32.1% (**Figure 2**).

Among the clinicians who do not measure Lp(a) in their clinical practice (N = 664), the most common reasons for not requesting the Lp(a) test were lack of reimbursement by the National Health Service, lack of treatment options for elevated Lp(a) levels, unavailability of the Lp(a) test, and the high cost of the laboratory test (**Figure 3A**). Among these physicians, the availability of specific therapies for the treatment of elevated Lp(a) levels, the availability of the measurement test, and specific recommendations in the guidelines would encourage the inclusion of Lp(a) measurement in their clinical practice (**Figure 3B**).

Among those who regularly measure Lp(a) (N = 314), a high percentage reported requesting the measurement for better cardiovascular risk stratification (**Figure 4**).

The survey shows significant variability among clinicians in the threshold considered for defining high levels of Lp(a) in relation to ASCVD risk (**Figure 5**). Most clinicians (36.7%) consider a value above 30 mg/dL (63 nmol/L) as high, while 32.7% consider a value above 50 mg/dL (105 nmol/L) as high. Only a minority consider higher values as thresholds, with 17.64% indicating 70 mg/dL (150 nmol/L), 8.94% indicating 100 mg/dL (215 nmol/L), and 4.10% considering a value of Lp(a) above 150 mg/dL (325 nmol/L) as high. **Figure 6**, on the other hand, demonstrates that the majority of clinicians adjust their therapeutic approach when Lp(a) levels exceed 50 mg/dL.

Among the categories of patients that clinicians consider eligible for Lp(a) measurement, the majority (67.7%) indicated patients with recurrent cardiovascular events despite LDL cholesterol reduction is important, followed by 64.2% who assess Lp(a) levels in patients with a family history of early cardiovascular events. A significant number of clinicians (48.6%) consider measuring Lp(a) levels important in patients with a history of myocardial infarction, and 45.2% in those with familial hypercholesterolemia. Overall, only 44.2% of clinicians find it useful to measure Lp(a) at least once in the life of every adult patient.

Faced with elevated Lp(a) levels in patients with ASCVD, most clinicians (69.2%) stated that they intensify dyslipidaemia treatment, while 48.7% actively manage other risk factors. Lifestyle

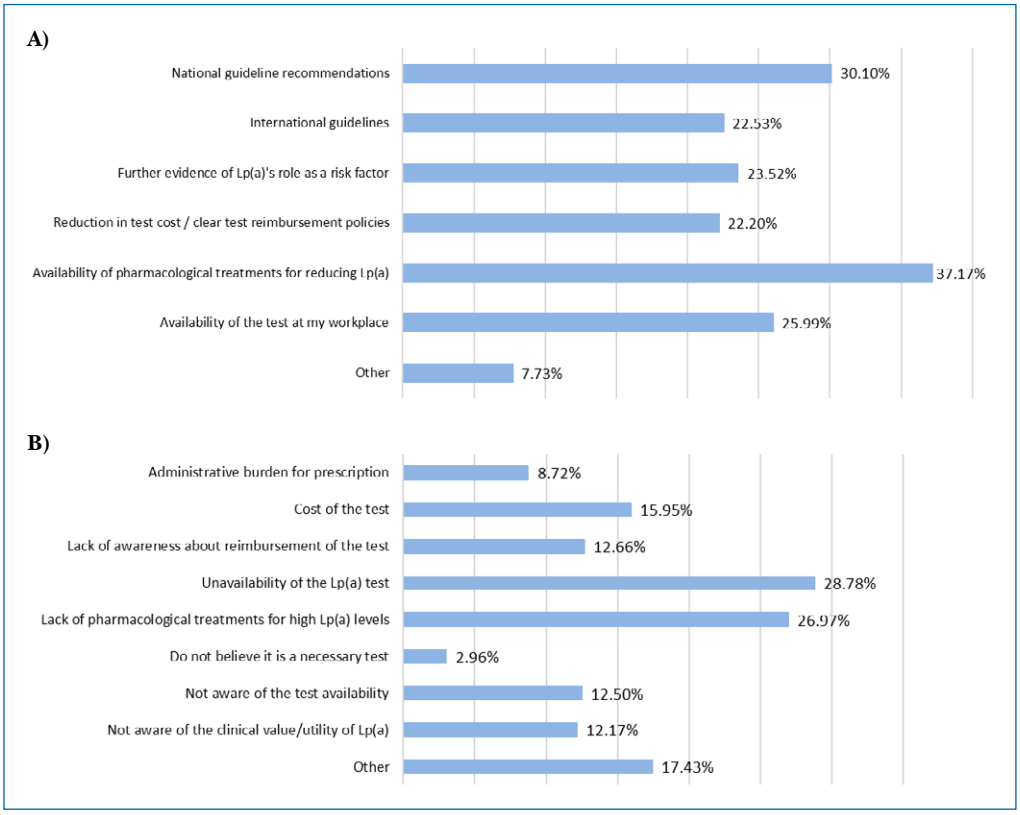

Figure 3 | Among clinicians who do not measure Lp(a) in their clinical practice, panel A shows the reasons for not requesting the Lp(a) test, while panel B shows what clinicians think would be necessary to start testing Lp(a) in clinical practice. Clinicians were allowed to provide multiple answers.

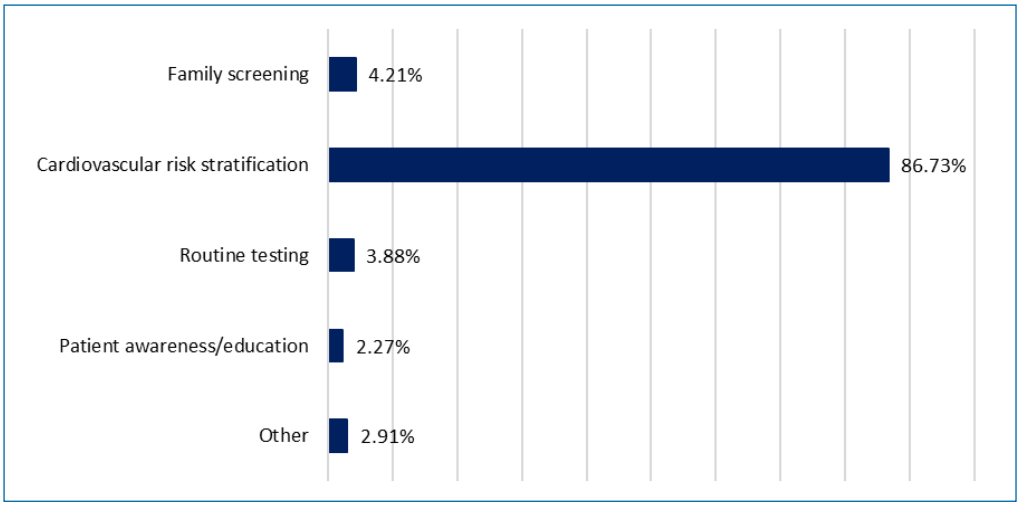

Figure 4 | Additional information for clinicians who regularly measure Lp(a) in their clinical practice. Reasons for requesting an Lp(a) test.

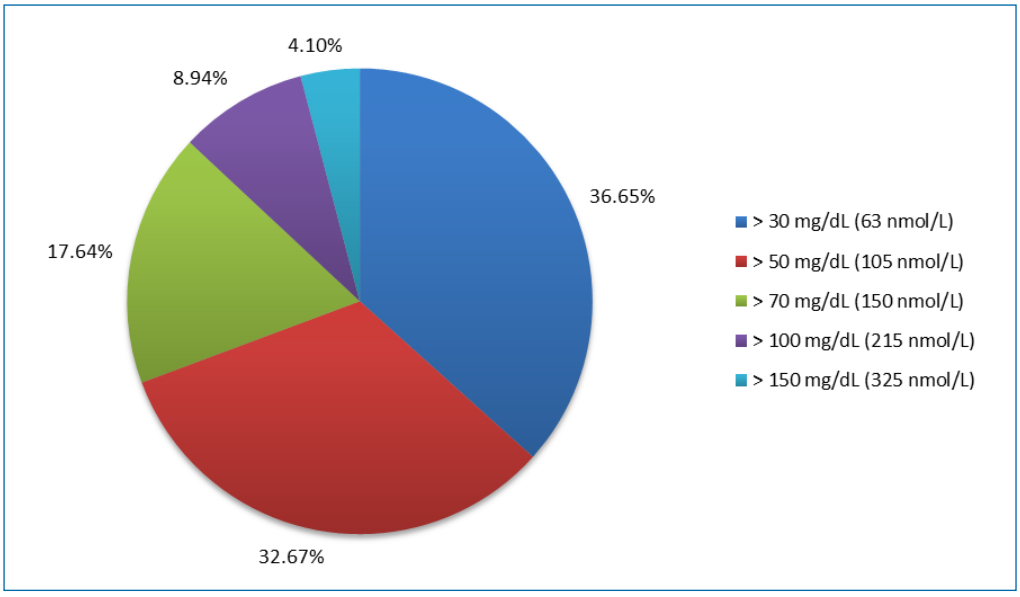

Figure 5 | Proportions of clinicians considering different levels of Lp(a) as high in relation to atherosclerotic cardiovascular disease.

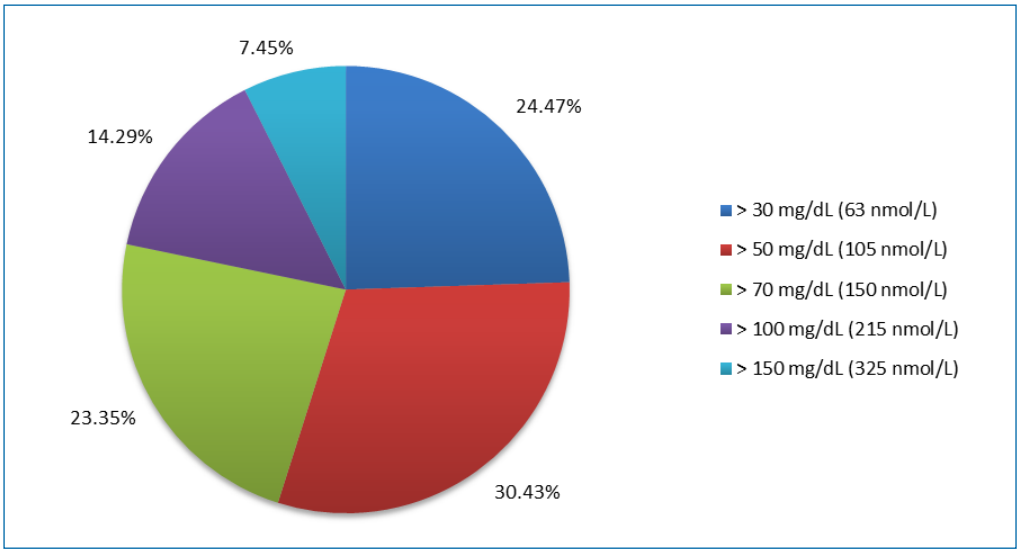

Figure 6 | Proportions of clinicians modifying therapeutic approach based on different levels of Lp(a) in atherosclerotic cardiovascular disease.

recommendations are provided by 37.4% of clinicians. Approximately 20.3% of clinicians refer patients to a colleague specializing in lipid management, and a minority (4.8%) take no action.

Finally, the majority of clinicians (76.4%) reported discussing the Lp(a) test results with the patient, explaining the clinical implications of elevated Lp(a) levels; of these, about 61% also recommend Lp(a) testing for family members. Among clinicians who choose not to discuss these results with patients, one of the most cited reasons is the lack of specific treatment to reduce elevated Lp(a) levels. This concern was highlighted by 40.4% of clinicians, underscoring a significant challenge in managing this biomarker.

Discussion

This survey depicts a detailed overview of clinicians' practices and opinions regarding Lp(a) in the management of ASCVD. The survey involved a broad sample of clinicians from various centres, predominantly those working in territorial and university hospitals. The most common specialization among the participants is cardiology, followed by internal medicine. This reflects a diverse representation of professionals managing patients with cardiovascular diseases, contributing to a comprehensive view of clinical experiences and practices.

One of the key aspects highlighted by the study is the variety of approaches in the measurement and management of Lp(a) among clinicians. While 32.1% of the participants indicated that they regularly measure Lp(a), a significant percentage cited obstacles such as the high cost of tests and the lack of reimbursement as reasons for not regularly performing this test. This evidence confirmed the results of a similar survey on European lipid clinics (12), and underscores the need to improve the accessibility and availability of the Lp(a) test in various clinical settings, especially considering the potential impact of elevated Lp(a) levels on the development of cardiovascular diseases.

Additionally, the variability in thresholds used to define elevated Lp(a) levels among clinicians reflects the lack of clear consensus in clinical guidelines (13). Most of the physicians who participated in this survey tend to consider lower levels (above 30 mg/dL or 50 mg/dL) as indicative of high risk, reflecting greater caution in identifying patients at risk of atherosclerotic cardiovascular disease. This may suggest a growing awareness of the importance of monitoring relatively low levels of Lp(a) as part of cardiovascular risk management and presents an opportunity to develop standardized criteria that can guide a more uniform and evidence-based management of patients with elevated Lp(a) levels.

The survey results on clinicians' management of elevated Lp(a) levels are particularly interesting. These data indicate that the prevailing strategy among clinicians to manage elevated Lp(a) levels involves intensifying lipid-lowering therapy and overall management of cardiovascular risk factors. Lifestyle recommendations are also considered an important component of management. However, a significant portion of clinicians feels the need to consult experts, suggesting that there may be a need for further knowledge or specialist support in this area. The reduced percentage of clinicians who do not take any action suggests a widespread awareness of the importance of addressing elevated Lp(a) levels in the management of cardiovascular diseases (14).

In contemporary medical practice, effective communication of Lp(a) test results plays a crucial role in providing personalized and rational care (15). However, it is interesting to note that some clinicians report not discussing these results with patients primarily due to the lack of a specific treatment to reduce elevated Lp(a) levels. These clinicians likely find it challenging to inform a patient about a risk factor without being able to provide a way to counteract it. This evidence underscores the critical need for medical staff education and updates regarding the currently available alternatives to counteract the increased cardiovascular risk associated with elevated Lp(a) levels. Intensifying the control of other known risk factors is currently the only strategy, and promoting this approach must become an urgent priority for scientific societies to produce and disseminate shared guidelines.

Going forward, integrating Lp(a) measurement into clinical practice is crucial for improving cardiovascular risk stratification and optimizing preventive therapies (16). This study highlights the importance of an integrated and multidisciplinary approach in the management of Lp(a), emphasizing the need for innovations in diagnostic and therapeutic practices to improve the clinical outcomes of patients with cardiovascular diseases. Continuous evolution in research and clinical practice will be essential to effectively address this critical component of cardiovascular pathology.

Authors contributions

EO and ALC were responsible for the study concept and design. SX was responsible for study management and data collection. EO and SX provided methodological knowledge and performed the analysis. MC and ALC contributed to the interpretation of the results. EO and SX wrote the article. ALC and MC critically revised for important intellectual content and approved the final article.

Funding/Support

The survey was conducted thanks to the collaboration with Novartis Farma SpA.

The work of Alberico L Catapano has been supported by Italian Ministry of Health-IRCCS MultiMedica RF-2019-12370896, SISA Lombardia, and Fondazione SISA. The work of Alberico L Catapano, Manuela Casula, and Federica Galimberti has been also supported by Italian Ministry of Health - Ricerca Corrente - IRCCS MultiMedica.

Conflict of interest disclosures

All authors declare no support from any organization for the submitted work.

ALC received research funding and/or honoraria for advisory boards, consultancy or speaker bureau from Amarin, Amgen, Amryt, AstraZeneca, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Medscape, Menarini, Merck, Novartis, Peer Voice, Pfizer, Recordati, Regeneron, Sandoz, Sanofi, The Corpus, Ultragenyx, Viatris.

MC received honoraria for consultancy or speaker bureau from Sobi and Ultragenyx.

References

[1] Della Corte V, Todaro F, Cataldi M, Tuttolomondo A. Atherosclerosis and Its Related Laboratory Biomarkers. Int J Mol Sci 2023 Oct 24; 24(21):15546.

[2] Duarte Lau F, Giugliano RP. Lipoprotein(a) and its Significance in Cardiovascular Disease: A Review. JAMA Cardiol 2022 Jul 1;7(7):760-769. https://doi.org/10.1001/jamacardio.2022.0987. Erratum in: JAMA Cardiol. 2022 Jul 1; 7(7):776.

[3] Jauhiainen M, Metso J, Koskinen P, Ehnholm C. Characterization of the enzyme activity of human plasma lipoprotein (a) using synthetic peptide substrates. Biochem J 1991 Mar 1; 274 (Pt 2) (Pt 2):491-6.

[4] Kronenberg F. Lipoprotein(a). Handb Exp Pharmacol 2022; 270:201-232.

[5] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, McNeal CJ, Moriarty PM, Natarajan P, Nordestgaard BG, Parhofer KG, Virani SS, von Eckardstein A, Watts GF, Stock JK, Ray KK, Tokgözoğlu LS, Catapano AL. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022 Oct 14; 43(39):3925-46.

[6] Koschinsky ML, Marcovina SM. Lipoprotein(a): structural implications for pathophysiology. Int J Clin Lab Res 1997; 27(1):14-23.

[7] Enkhmaa B, Anuurad E, Zhang W, Tran T, Berglund L. Lipoprotein(a): genotype-phenotype relationship and impact on atherogenic risk. Metab Syndr Relat Disord 2011 Dec; 9(6):411-8.

[8] Catapano AL, Daccord M, Damato E, Humphries SE, Neely RDG, Nordestgaard BG, Pistollato M, Steinhagen-Thiessen E. How should public health recommendations address Lp(a) measurement, a causative risk factor for cardiovascular disease (CVD)? Atherosclerosis 2022 May; 349:136-43.

[9] Vinci P, Di Girolamo FG, Panizon E, Tosoni LM, Cerrato C, Pellicori F, Altamura N, Pirulli A, Zaccari M, Biasinutto C, Roni C, Fiotti N, Schincariol P, Mangogna A, Biolo G. Lipoprotein(a) as a Risk Factor for Cardiovascular Diseases: Pathophysiology and Treatment Perspectives. Int J Environ Res Public Health 2023 Sep 6; 20(18):6721.

[10] Reyes-Soffer G, Yeang C, Michos ED, Boatwright W, Ballantyne CM. High lipoprotein(a): Actionable strategies for risk assessment and mitigation. Am J Prev Cardiol. 2024 Apr 3; 18:100651.

[11] Kelsey MD, Mulder H, Chiswell K, Lampron ZM, Nilles E, Kulinski JP, Joshi PH, Jones WS, Chamberlain AM, Leucker TM, Hwang W, Milks MW, Paranjape A, Obeid JS, Linton MF, Kent ST, Peterson ED, O'Brien EC, Pagidipati NJ. Contemporary patterns of lipoprotein(a) testing and associated clinical care and outcomes. Am J Prev Cardiol. 2023 Mar 1; 14:100478.

[12] Catapano AL, Tokgözoğlu L, Banach M, Gazzotti M, Olmastroni E, Casula M, Ray KK; Lipid Clinics Network Group. Evaluation of lipoprotein(a) in the prevention and management of atherosclerotic cardiovascular disease: A survey among the Lipid Clinics Network. Atherosclerosis 2023 Apr; 370:5-11.

[13] Ansari S, Neely RDG, Payne J, Cegla J. Lipoprotein(a) testing in lipid clinics across the UK: Results of a national survey. J Clin Lipidol 2024 May-Jun; 18(3):e477-e481.

[14] Reyes-Soffer G, Yeang C, Michos ED, Boatwright W, Ballantyne CM. High lipoprotein(a): Actionable strategies for risk assessment and mitigation. Am J Prev Cardiol 2024 Apr 3; 18:100651.

[15] Khan TZ. Raised lipoprotein(a): real-world examples of communication and clinical management. Br J Cardiol 2024 Aug; 31(suppl 1):S21-S25.

[16] Chiesa G, Zenti MG, Baragetti A, Barbagallo CM, Borghi C, Colivicchi F, Maggioni AP, Noto D, Pirro M, Rivellese AA, Sampietro T, Sbrana F, Arca M, Averna M, Catapano AL. Consensus document on Lipoprotein(a) from the Italian Society for the Study of Atherosclerosis (SISA). Nutr Metab Cardiovasc Dis 2023 Oct; 33(10):1866-1877.