ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–5
https://doi.org/10.1093/ehjopen/oead035

SHORT REPORT
Coronary artery disease

Lipoprotein(a) concentrations in acute myocardial infarction patients are not indicative of levels at six month follow-up

Efthymios Ziogos [1,2], Michael A. Vavuranakis[1,2], Tarek Harb[1,2], Palmer L. Foran[1], Michael J. Blaha[1,2], Steven R. Jones[1,2], Shenghan Lai[3], Gary Gerstenblith[1,2], and Thorsten M. Leucker [1,2,*]

[1]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; and [3]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD

Received 9 February 2023; revised 16 March 2023; accepted 3 April 2023; online publish-ahead-of-print 5 April 2023

Handling Editor: Magnus Bäck

Aims Lipoprotein(a) [Lp(a)] levels are generally constant throughout an individual's lifetime, and current guidelines recommend that a single measurement is sufficient to assess the risk of coronary artery disease (CAD). However, it is unclear whether a single measurement of Lp(a) in individuals with acute myocardial infarction (MI) is indicative of the Lp(a) level six months following the event.

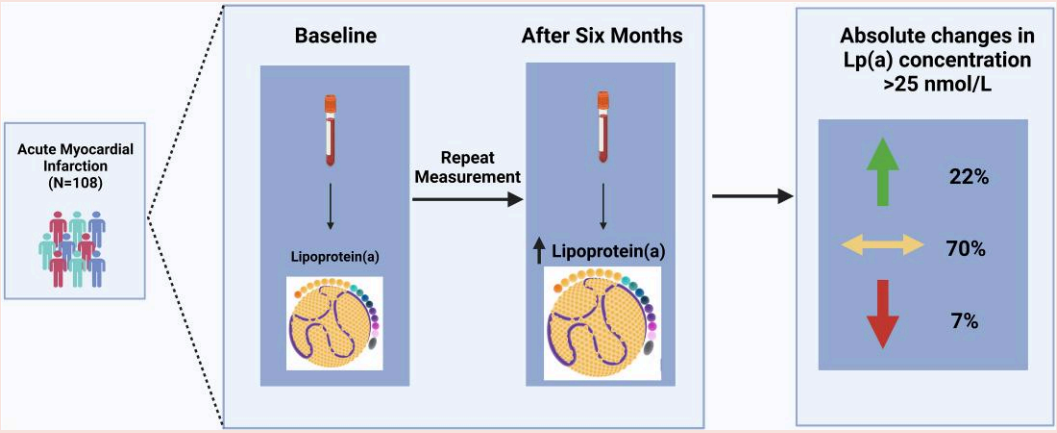
Methods and results Lp(a) levels were obtained from individuals with non–ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) ($n = 99$) within 24 h of hospital admission and after six months, who were enrolled in two randomized trials of evolocumab and placebo, and in individuals with NSTEMI or STEMI ($n = 9$) who enrolled in a small observation arm of the two protocols and did not receive study drug, but whose levels were obtained at the same time points. Median Lp(a) levels increased from 53.5 nmol/L (19, 165) during hospital admission to 58.0 nmol/L (14.8, 176.8) six months after the acute infarction ($P = 0.02$). Subgroup analysis demonstrated no difference in the baseline, six-month, or change between the baseline and six-month Lp(a) values between the STEMI and NSTEMI groups and between the group which received evolocumab and the group that did not.

Conclusion This study demonstrated that Lp(a) levels in individuals with acute MI are significantly higher six months after the initial event. Therefore, a single measurement of Lp(a) in the peri-infarction setting is not sufficient to predict the Lp(a)-associated CAD risk in the post-infarction period.

Registration Evolocumab in Acute Coronary Syndrome Trial [EVACS I] NCT03515304, Evolocumab in Patients with Acute Myocardial Infarction [EVACS II], NCT04082442

* Corresponding author. Tel: +410-502-9453, Fax: 410-367-2224, Email: tleucke1@jhmi.edu

Graphical Abstract



Keywords Lipoprotein(a) • Acute myocardial infarction • Repeat measurement

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein like particle containing apolipoprotein B covalently linked to a carbohydrate-rich protein termed apolipoprotein(a) [apo(a)]. Mechanistic and epidemiologic studies indicate that Lp(a) levels are significantly associated with cardiovascular risk, and Mendelian randomization studies indicate a causal link.[1,2] Although serum concentrations vary greatly among individuals, epidemiologic studies indicate that each individual's level is relatively constant, consistent with genetic studies indicating 70–95% heritability. Repeat testing of Lp(a) levels in UK Biobank participants demonstrated that Lp(a) concentrations are generally stable[3], and current guidelines recommend that a single level is sufficient to assess Lp(a)-related cardiovascular risk in stable primary and secondary prevention settings.[1,2,4]

However, a single Lp(a) measure obtained during an acute infarction may not be indicative of subsequent values in the stable setting. Lipoprotein(a) levels are decreased in individuals with severe, life-threatening conditions, such as sepsis and severe burns.[1] Lipoprotein(a) may be an acute-phase reactant[5], and cytokine release associated with the inflammatory response to the infarct may result in acute changes similar to those seen in other inflammatory conditions.[1] Additionally, statin therapy is often instituted or up titrated in the hospital setting, and statins may influence Lp(a) levels. For these reasons, we tested whether an Lp(a) level obtained at the time of an acute myocardial infarction is indicative of a subsequent level obtained in the stable outpatient setting six months following the event.

Baseline Lp(a) measurements were obtained in individuals with non–ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) within 24 h of hospital admission and after 6 months from 99 participants, who were enrolled in two randomized, double-blind trials of evolocumab and placebo (Evolocumab in Acute Coronary Syndrome [EVACS I]; *ClinicalTrials.gov*, NCT03515304 and Evolocumab in Patients With STEMI [EVACS II]; *ClinicalTrials.gov* Identifier: NCT04082442).[6] The results from the evolocumab and placebo groups are combined for this report comparing baseline, and repeat Lp(a) values as the baseline values were obtained before the one-time only administration of the study drug during the index admission, and the follow-up values were obtained after at least six months following the administration of either placebo or evolocumab, which has a half-life of 11–17 h.[7] We also included nine patients with acute infarctions enrolled in a small observation arm of the above protocols who did not receive study drug but whose levels were obtained at the same time points. Additionally, high-sensitivity C-reactive protein (hsCRP) levels were measured in the entire cohort to assess inflammation.

Lipoprotein(a) levels are expressed in nmol/L and were calculated using the Quest Diagnostics immunoturbidimetric assay at both baseline and follow-up. Lipoprotein(a) values were not normally distributed and are presented as medians (Q1 and Q3) and compared using the Wilcoxon matched pairs signed rank test. *Table 1* presents the demographic and clinical variables of the enrolled participants. Mean (±SD) age was 59.3 ± 12.3 years, 35% were women and 32% were African American. The median Lp(a) level was 53.5 nmol/L (19, 165) at baseline. After six months, Lp(a) increased to 58.0 nmol/L (14.8, 176.8), $P = 0.02$ (*Figure 1A*). Subgroup analysis of the groups revealed that Lp(a) levels increased from baseline to after six months in both the group which received evolocumab ($P = 0.038$) and the group which did not ($P = 0.016$). There were also no differences in Lp(a) between the two groups at baseline ($P = 0.12$) and at six months ($P = 0.25$), and in the change from baseline to six months ($P = 0.79$). Further subgroup analysis based on the type of infarct revealed that Lp(a) was higher after six months when compared to baseline in both individuals with NSTEMI ($P = 0.016$) and those with STEMI ($P = 0.039$). Comparison of individuals with NSTEMI and STEMI also showed no differences in Lp(a) levels at baseline ($P = 0.86$) and at six months ($P = 0.54$) and in the change from baseline to follow-up ($P = 0.27$). Generalized estimation analysis adjusting for group assignment (received evolocumab or did not receive evolocumab) and type of myocardial infarction (MI) (NSTEMI or STEMI) demonstrated that neither the group assignment ($P = 0.46$) nor the type of MI ($P = 0.24$) influenced the change in Lp(a) levels. Although the median Lp(a) change in the entire cohort was modest, 32 of 108 participants had an absolute change of at least 25 nmol/L; 24 with an increase of >25 nmol/L and 8 with a decrease of >25 nmol/L (*Figure 1C*). In addition, we created quartiles based on the baseline distribution of Lp(a) and determined how many patients changed quartiles based on the second measurement. We observed that 21 of the 108 participants changed quartiles; 12 moved up one quartile and 9 moved down one quartile. A linear regression analysis demonstrated that for each 1 nmol/L higher baseline Lp(a), there was an increase between the baseline and follow-up Lp(a) levels of 0.13 nmol/L

Table 1 Population characteristics and baseline and 6-months lipoprotein(a), other lipid, and hsCRP levels

Variable	Total cohort ($n = 108$)
Age (years), mean ± SD	59.3 ± 12.3
STEMI	33 (31%)
NSTEMI	75 (69%)
Women	38 (35%)
African American	35 (32%)
BMI (kg/m2), mean ± SD	29.2 ± 6.4
Diabetes mellitus	34 (31%)
Insulin-treated	16 (15%)
Hypertension	69 (64%)
Current cigarette smoking	31 (29%)
Previous myocardial infarction	25 (23%)
PCI	71 (66%)
CABG	13 (12%)
Peripheral artery disease	5 (5%)

Statin treatment	Baseline ($n = 108$)	After 6 months ($n = 108$)
No statin or low-intensity statin	55 (51%)	5 (5%)
Moderate- or high-intensity statin	53 (49%)	103 (95%)

Lipid levels and hsCRP	Baseline ($n = 108$)	After 6 months ($n = 108$)	*P*-value
Total cholesterol (mg/100 mL), mean ± SD	162.7 ± 40.7	138.1 ± 36.2	<0.0001
Triglycerides (mg/100 mL), median (IQR)	98 [71.5, 150]	95 [74, 163.5]	0.95
HDL-C (mg/100 mL), mean ± SD	48.6 ± 14.6	48.2 ± 12.5	0.35
LDL-C (mg/100 mL), mean ± SD	93 ± 34.8	69.1 ± 30.5	<0.0001
Non–HDL-C (mg/100 mL), mean ± SD	114 ± 38	89.9 ± 35.3	<0.0001
ApoB (mg/100 mL), mean ± SD	82.8 ± 22.1	71.6 ± 25.6	<0.0001
Lipoprotein(a) (nmol/L), median (IQR)	53.5 [19, 165]	58 [14.8, 176.8]	0.02
hsCRP (mg/dL), median (IQR)	12.9 [4.1, 54.9]	1.5 [0.7, 3.9]	<0.0001

ApoB, apolipoprotein B; BMI, body mass index; CABG, coronary artery bypass graft during admission; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention during admission; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

($P = 0.006$). Generalized estimated equation analysis was also performed to examine whether the extent of myocardial necrosis, assessed by the peak troponin I level during the hospital admission, was associated with the changes in Lp(a) values and showed no correlation between the two variables. In addition, a linear regression model with the Lp(a) difference as the outcome variable revealed that baseline statin therapy as well as the change in statin therapy during the trial did not impact the change of Lp(a) levels between baseline and follow-up ($P > 0.5$). In contrast to the trajectory of Lp(a), hsCRP significantly decreased from 12.9 mg/dL during index hospital admission to 1.5 mg/dL after six months, $P < 0001$ (*Figure 1D*), and the changes in the two values were not correlated.

Pathophysiologic studies indicate that Lp(a) has proatherogenic effects similar to and independent of those of LDL-cholesterol[8] as well as proinflammatory effects, potentially due to oxidized phospholipids carried by the Lp(a) molecule. Additionally, apo(a) contains a sequence that structurally resembles plasminogen and may therefore have prothrombotic and antifibrinolytic effects. The early post-acute infarct setting is associated with an increased risk for recurrent events, and management strategies are often instituted in the hospital setting to decrease that risk. Although there are no currently available therapeutic options that specifically lead to Lp(a) reduction, emerging antisense oligonucleotide and small interfering RNA treatments[9,10] targeting hepatic production of apo(a) are currently being tested in phase 3 clinical trials. The clinical decision as to whether to implement those therapies is likely to be dependent, in part, on the extent to which the values obtained in the hospital setting during the event are indicative of subsequent values.

To our knowledge, this is the first study to assess the change in Lp(a) levels between those obtained in the acute infarction setting and those obtained six months following the event. Our results demonstrate that Lp(a) significantly increases by at least 25 nmol/L in over 20% of patients. The trajectory is not similar to that of hsCRP and suggests that Lp(a) does not behave as an acute-phase reactant in the acute infarct setting. A limitation of the study is that it was not possible to obtain levels in the participants prior to the infarction. The lower level we observed in the acute infarction setting may not necessarily be due to a transient decrease as it is possible that the higher levels we observed six months following the event may be a long-term consequence of the infarct, rather than a return to lower, prior infarct values. In addition, it is

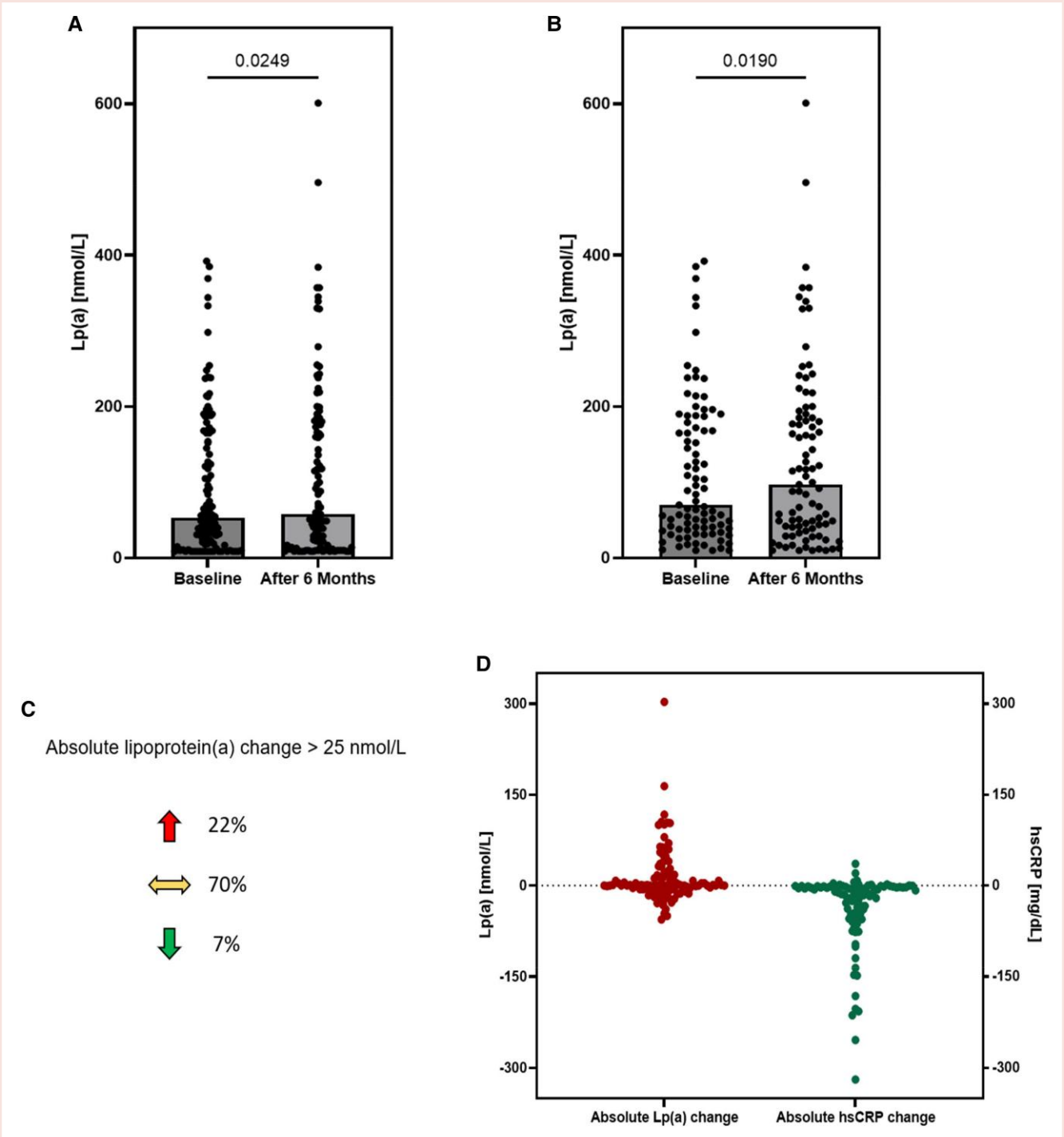


Figure 1 (*A*, *B*) Scatterplots depicting data points representing the paired baseline and follow-up Lp(a) values, presented as medians with interquartile ranges, $n = 108$. Levels below 9 nmol/L were not detectable and are censored for the data in *B*, $n = 89$. (*C*) Graphical illustration indicating percentage of study participants with an absolute Lp(a) change greater than (up arrow) and less than (down arrow) 25 nmol/L from baseline to follow-up. (*D*) Scatterplots depicting data points representing the absolute Lp(a) and hsCRP changes from baseline to after six month follow-up. Lp(a), lipoprotein(a); hsCRP, high-sensitivity C-reactive protein.

not clear that the differences we observed between the baseline and six-month values are clinically meaningful as the changes are relatively modest and only re-classified the original quartile in a minority of the patients. This is particularly true for those with a low Lp(a) baseline level as any change is not likely to result in an increase sufficient to impact treatment decisions. Regardless, we can conclude that a level obtained in the infarct setting alone may not necessarily be relied upon to predict the long-term risk imparted by Lp(a).

Lead author biography

Dr. Ziogos holds a medical degree from the Medical School of the University of Ioannina, Greece. After his graduation, he joined the Division of Cardiology at the Johns Hopkins University School of Medicine as a postdoctoral research fellow, working under the direct guidance of Drs Thorsten Leucker and Gary Gerstenblith. His main area of interest is atherosclerotic cardiovascular disease, with an emphasis on prevention and acute coronary syndromes.

Author contributions

E.Z., G.G., and T.M.L. contributed to the conception and design of the work. E.Z., G.G., T.M.L., T.H., M.A.V., and P.L.F. contributed to the acquisition and interpretation of the data. E.Z., G.G., T.M.L., M.B., and S.R.J. contributed to the interpretation of the data. S.L. and M.A.V. contributed to the statistical analysis. E.Z, G.G., and T.M.L. drafted the manuscript. All critically revised the manuscript and gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data availability

The data and analytical methods that support the findings of this study are available from the corresponding author on reasonable request.

Acknowledgements

The investigators thank the patients who participated in this study; the members of the Data Safety and Monitoring Board, Dr John W. McEvoy, Dr Gregory P. Prokopowicz, and Dr Chang Yu; and their research coordinators, Frances A. Kirkland, Christine McLeod, and Shannon Kelley.

Funding

T.L. reports a relationship with the American Heart Association and National Institutes of Health that includes funding grants. T.L. reports that financial support for this study was provided by Amgen. M.B. reports a relationship with American Heart Association and National Institutes of Health that includes funding grants. M.B. reports a relationship with US Food and Drug Administration that includes grant support voting member status on the EMDAC. M.B. reports a relationship with Amgen that includes funding grants. M.B. reports a relationship with Aetna Inc. that includes funding grants. M.B. reports a relationship with Novo Nordisk Pharmaceuticals SA that includes board membership. M.B. reports a relationship with Bayer AG that includes board membership. M.B. reports a relationship with Novartis that includes board membership. M.B. reports a relationship with Amgen that includes board membership. M.B. reports a relationship with Sanofi that includes board membership. M.B. reports a relationship with Regeron that includes board membership. M.B. reports a relationship with Akcea Therapeutics that includes board membership.

This work was funded by Amgen Inc. Amgen, the funder of the study, had no role in the design of the study, the collection, management, or interpretation of the data, or the statistical analysis. The funder reviewed the first submitted version of the article but was not involved in the writing or approval of the article or the decision to submit the article for publication. There is no other relevant funding information.

Conflict of interest: None declared.

References

1. 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;**43**:3925–3946.
2. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, Lloyd-Jones DM, Marcovina SM, Yeang C, Koschinsky ML. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol* 2022;**42**:e48–e60.
3. Trinder M, Paruchuri K, Haidermota S, Bernardo R, Zekavat SM, Gilliland T, Januzzi J, Natarajan P. Repeat measures of lipoprotein(a) molar concentration and cardiovascular risk. *J Am Coll Cardiol* 2022;**79**:617–628.
4. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Mueller C, Drexel H, Aboyans V, Corsini A, Doehner W, Farnier M, Gigante B, Kayikcioglu M, Krstacic G, Lambrinou E, Lewis BS, Masip J, Moulin P, Petersen S, Petronio AS, Piepoli MF, Pintó X, Räber L, Ray KK, Reiner Ž, Riesen WF, Roffi M, Schmid J-P, Shlyakhto E, Simpson IA, Stroes E, Sudano I, Tselepis AD, Viigimaa M, Vindis C, Vonbank A, Vrablik M, Vrsalovic M, Zamorano JL, Collet J-P, Koskinas KC, Casula M, Badimon L, John Chapman M, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee D, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen S, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Nibouche D, Zelveian PH, Siostrzonek P, Najafov R, van de Borne P, Pojskic B, Postadzhiyan A, Kypris L, Špinar J, Larsen ML, Eldin HS, Viigimaa M, Strandberg TE, Ferrières J, Agladze R, Laufs U, Rallidis L, Bajnok L, Gudjónsson T, Maher V, Henkin Y, Gulizia MM, Mussagaliyeva A, Bajraktari G, Kerimkulova A, Latkovskis G, Hamoui O, Slapikas R, Visser L, Dingli P, Ivanov V, Boskovic A, Nazzi M, Visseren F, Mitevska I, Retterstøl K, Jankowski P, Fontes-Carvalho R, Gaita D, Ezhov M, Foscoli M, Giga V, Pella D, Fras Z, de Isla LP, Hagström E, Lehmann R, Abid L, Ozdogan O, Mitchenko O, Patel RS. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
5. Noma A, Abe A, Maeda S, Seishima M, Makino K, Yano Y, Shimokawa K. Lp(a): an acute-phase reactant? *Chem Phys Lipids* 1994;**67–68**:411–417.
6. Vavuranakis MA, Jones SR, Ziogos E, Blaha MJ, Williams MS, Foran P, Schindler TH, Lai S, Schulman SP, Gerstenblith G, Leucker TM. The trajectory of lipoprotein(a) during the peri- and early postinfarction period and the impact of proprotein convertase subtilisin/kexin type 9 inhibition. *Am J Cardiol* 2022;**171**:1–6.
7. Kasichayanula S, Grover A, Emery MG, Gibbs MA, Somaratne R, Wasserman SM, Gibbs JP. Clinical pharmacokinetics and pharmacodynamics of evolocumab, a PCSK9 inhibitor. *Clin Pharmacokinet* 2018;**57**:769–779.
8. Rikhi R, Hammoud A, Ashburn N, Snavely AC, Michos ED, Chevli P, Tsai MY, Herrington D, Shapiro MD. Relationship of low-density lipoprotein-cholesterol and lipoprotein(a) to cardiovascular risk: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2022;**363**:102–108.
9. O'Donoghue ML, Rosenson RS, Gencer B, López JAG, Lepor NE, Baum SJ, Stout E, Gaudet D, Knusel B, Kuder JF, Ran X, Murphy SA, Wang H, Wu Y, Kassahun H, Sabatine MS. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. *N Engl J Med* 2022;**387**:1855–1864.
10. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif J-C, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, Xia S, Guerriero J, Viney NJ, O'Dea L, Witztum JL. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med* 2020;**382**:244–255.