Lipoprotein(a) levels and recorded post-test changes in lipid-lowering therapy in a large real-world Polish cohort

Keywords
statins, registries, lipoprotein(a), cardiovascular prevention, lipid-lowering therapy

Abstract

Introduction

Elevated lipoprotein(a) [Lp(a)] is a recognized cardiovascular risk factor, but its association with subsequent lipid-lowering treatment (LLT) patterns is unclear. We assessed whether higher Lp(a) levels were associated with recorded post-test changes in lipid-lowering therapy (LLT).

Material and methods

This retrospective observational study included 23,654 adults tested for Lp(a) within LUX MED, a nationwide private healthcare network in Poland (April 2025-February 2026). Patients were categorized as Lp(a) <62, 62 to <105, or ≥105 nmol/L. Recorded statin initiation, escalation, ezetimibe initiation, and any LLT intensification recorded after Lp(a) testing were compared across categories. Multivariable logistic regression evaluated associations between Lp(a) and LLT initiation and intensification, adjusting for age, sex, body mass index, atherosclerotic cardiovascular disease (ASCVD), current LDL-C, HDL-C, and triglycerides; intensification models additionally adjusted for baseline statin and ezetimibe use.

Results

Current LDL-C increased across categories (P<0.001). Statin initiation was 1.8%, 4.3%, and 9.5%, while any LLT intensification was 2.7%, 5.9%, and 13.2% across increasing Lp(a) categories (both P<0.001). Higher Lp(a) remained associated with LLT initiation (OR 1.93, 95% CI 1.78–2.09) and intensification (OR 1.79, 95% CI 1.68–1.90; both P <0.001) per 1-unit increase in ln[1+Lp(a)]. Associations were stronger in younger patients and, for intensification, in women and patients without ASCVD. However, 86.8% of patients with Lp(a) ≥105 nmol/L had no recorded intensification.

Conclusions

Higher Lp(a) was associated with more frequent recorded post-test LLT initiation and intensification, but absolute rates remained low. These findings suggest an implementation gap but cannot establish that Lp(a) testing itself prompted treatment change.

Lipoprotein(a) levels and recorded post-test changes in lipid-lowering therapy in a large real-world Polish cohort

Running head: Lp(a) levels and recorded therapy changes

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Conclusions: Higher Lp(a) was associated with more frequent recorded post-test LLT initiation and intensification, but absolute rates remained low. These findings suggest an implementation gap but cannot establish that Lp(a) testing itself prompted treatment change.

Keywords: cardiovascular prevention; lipid-lowering therapy; lipoprotein(a); registries; statins

Introduction

Interest in lipoprotein(a) [Lp(a)] as a cardiovascular risk biomarker has intensified in recent years, driven by convergent evidence from genetic, epidemiological, mechanistic, and therapeutic-development studies. Epidemiological studies have consistently demonstrated an association between elevated plasma levels of Lp(a) and an increased risk of atherosclerotic cardiovascular disease (ASCVD) events [1-8]. In addition to its atherogenic effects, Lp(a) carries oxidized phospholipids and has proinflammatory and potentially antifibrinolytic properties, although its relationship with venous thromboembolism remains uncertain [9]. Lp(a) concentrations above 50 mg/dL or 105 nmol/L are considered clinically significant cardiovascular risk modifiers, with risk increasing progressively at higher levels [10,11].

Current guidelines recommend that Lp(a) be measured at least once during adulthood, ideally during the initial lipid profile assessment or at a subsequent evaluation, with results preferably reported in molar units (nmol/L) [12-15]. Measurement may be particularly informative in younger patients with familial hypercholesterolemia or premature ASCVD without other identifiable risk factors, in individuals with a family history of premature ASCVD or elevated Lp(a), and in those at intermediate risk or near a treatment-decision threshold. Despite these recommendations, Lp(a) testing rates remain low in routine clinical practice, and population-level data on Lp(a) distribution and its association with subsequent clinical management are limited, particularly in Central and Eastern Europe [12].

In the absence of approved therapies specifically targeting Lp(a) and proven to reduce cardiovascular events, management currently focuses on intensive control of modifiable risk factors, including low-density lipoprotein cholesterol (LDL-C), with treatment decisions guided by absolute cardiovascular risk and Lp(a) levels [6,13,16-19]. Evidence from multiple randomized, placebo-controlled statin trials indicates that statins do not meaningfully reduce Lp(a) levels [20]. Nevertheless, statins remain the foundation of LDL-C-lowering therapy when

indicated by the patient's overall cardiovascular risk. Accordingly, treatment decisions should consider both the degree of Lp(a) elevation and the patient's overall cardiovascular risk profile [21,22]. An elevated Lp(a) result should therefore prompt comprehensive reassessment of cardiovascular risk, LDL-C goals, and other modifiable risk factors rather than automatic pharmacological intensification [11,13,23]. Several targeted Lp(a)-lowering agents - including antisense oligonucleotides, small interfering RNAs, and oral inhibitors of apo(a) - are currently under investigation in phase III cardiovascular outcomes trials [24,25]. Recent advances in Lp(a) measurement, risk stratification, and therapeutic development have further increased the clinical relevance of systematic testing [16]. The anticipated availability of these therapies further underscores the importance of identifying patients with elevated Lp(a) and understanding how this information is associated with subsequent treatment patterns in routine practice.

However, whether Lp(a) concentrations are associated with subsequent changes in lipid-lowering therapy in routine clinical settings remains insufficiently studied. The objective of the present study was to analyze data from patients in whom Lp(a) concentrations were measured within a large private healthcare network in Poland and to assess the association between Lp(a) levels and subsequent recorded initiation or intensification of lipid-lowering therapy (LLT).

Patients and methods

This was a retrospective observational study based on routinely collected clinical and laboratory data from LUX MED, a large nationwide private healthcare network in Poland [26-28], spanning 14 April 2025 to 19 February 2026. The dataset comprised adults aged ≥18 years undergoing Lp(a) measurement through preventive health assessments and standard clinical pathways. The study population was not selected specifically for established cardiovascular disease or a predefined indication for lipid-lowering therapy. For patients with more than one

Lp(a) measurement during the study period, only the first was included and its date was defined as the index date. Of 26,639 adults with available Lp(a) measurements, 23,654 had values reported in nmol/L (primary cohort) and 2,985 in mg/dL (secondary cohort). Patients with Lp(a) reported in mg/dL were excluded from the primary analysis because direct conversion to nmol/L is unreliable without knowledge of apo(a) isoform size. Because the therapy-change analysis required a uniform reporting unit, it was limited to the primary cohort (n = 23,654).

Lp(a) was measured as part of routine clinical care in collaborating certified diagnostic laboratories. However, assay-level metadata, including the analytical platform, manufacturer, assay principle, calibrator traceability, and reagent lot, were unavailable in the retrospective source dataset, so it could not be confirmed that all measurements used the same assay. Results reported in mg/dL were therefore not converted to nmol/L, because direct conversion is unreliable without knowledge of apo(a) isoform size and would compound this analytical uncertainty; accordingly, only values originally reported in nmol/L were analyzed.

The following demographic and metabolic variables were available: age, sex, body mass index (BMI), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and LDL-C. International Classification of Diseases (ICD)-coded comorbidities were available as binary variables. ASCVD was defined as the presence of coronary artery disease, previous myocardial infarction (MI), or previous stroke/transient ischemic attack (TIA). Information on physician specialty, formal cardiovascular risk scores, family history of premature ASCVD, familial hypercholesterolemia status, smoking status, chronic kidney disease, statin intolerance, treatment adherence, contraindications, maximally tolerated statin dose, and patient preferences was not available. High-sensitivity C-reactive protein measurements were also unavailable and were therefore not included in the analyses.

LDL-C values were obtained from routine laboratory records. The source dataset did not indicate whether individual LDL-C results had been measured directly or calculated by the performing laboratory. Current LDL-C was available for 12,696 patients (53.7% of the cohort), including 99 patients (0.4% of the full cohort) in whom LDL-C was calculated using the Friedewald equation because a recorded LDL-C value was unavailable but the required lipid components were present and triglycerides were ≤400 mg/dL. No adjustment for Lp(a)-cholesterol and no back-calculation of untreated or pretreatment LDL-C were performed; the current, as-reported LDL-C was used in all analyses. Lp(a) was analyzed as a continuous variable and categorized using thresholds of <62, 62 to <105, and ≥105 nmol/L that align with the updated ESC/EAS recommendations and support clinically interpretable comparisons of treatment patterns. In a supplementary sensitivity analysis, patients were reclassified using the Polish Cardiac Society and Polish Lipid Association thresholds of <75, 75 to <125, and ≥125 nmol/L.

Statin intensity was classified according to the recorded statin type and dose using a simplified rule-based approach reflecting low-, moderate-, and high-intensity therapy (Supplementary Table S1). Baseline therapy was defined using the medication record closest to, but preceding, the index date, whereas post-test therapy was defined using the closest available medication record following the index date. No fixed post-test observation interval was imposed; consequently, the interval between Lp(a) measurement and the subsequent medication record could vary among patients. The following outcomes were evaluated: statin initiation, defined as the absence of a recorded statin therapy before and its presence after Lp(a) testing; any statin escalation, defined as statin initiation and/or an increase in the recorded statin dose or intensity; ezetimibe initiation, defined analogously; and any LLT intensification, defined as any statin escalation and/or ezetimibe initiation. Any LLT initiation was defined as the recorded initiation of a statin and/or ezetimibe among patients receiving neither treatment

at baseline. All outcomes were ascertained using the corresponding pre- and post-test medication records. For analyses of LLT initiation, patients receiving baseline statin or ezetimibe therapy were excluded. Analyses of LLT intensification were performed in the full cohort. These outcomes represent differences between the recorded pre- and post-test medication states and do not establish that the Lp(a) result itself directly prompted treatment modification.

In an additional exploratory analysis, statin deintensification was assessed among patients with a statin documented both before and after Lp(a) testing. Deintensification was defined as a reduction in the recorded dose of the same statin or a transition to a lower statin-intensity category. Patients without a post-test statin record were not classified as having discontinued or deintensified treatment because the absence of a record could reflect incomplete medication documentation. Ezetimibe initiation among patients with statin deintensification was also assessed.

This study was approved by the Bioethics Committee at the Regional Medical Chamber in Krakow (approval number OIL/KBL/13/2026), and the requirement for informed consent was waived owing to the retrospective, anonymized nature of the data.

Statistical analysis

All continuous variables were non-normally distributed and are presented as median (interquartile range [IQR]). Categorical variables are presented as number (percentage). Between-group comparisons were performed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. For the therapy-change analysis, the primary cohort was stratified by Lp(a) category. Frequencies of statin initiation, any statin escalation, ezetimibe initiation, and any LLT intensification were compared across categories

using the chi-square test. The frequency of statin deintensification was compared across Lp(a) categories in the restricted subgroup with statin therapy documented both before and after the index measurement. A sensitivity analysis repeated the categorical comparisons using the alternative Lp(a) thresholds of <75, 75 to <125, and ≥125 nmol/L recommended by the Polish Cardiac Society and Polish Lipid Association. Multivariable logistic regression models were used to evaluate whether Lp(a) levels were independently associated with any LLT initiation and any LLT intensification. Lp(a) was analyzed both as a continuous log-transformed variable and as a categorical variable using the thresholds defined above. The LLT initiation model was restricted to patients without baseline statin or ezetimibe therapy and adjusted for age, sex, BMI, ASCVD status, current LDL-C, HDL-C, and triglycerides. The LLT intensification model was performed in the full cohort with additional adjustment for baseline statin and ezetimibe use. Multivariable analyses were performed using complete cases for all model covariates. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). To explore potential effect modification, multiplicative interaction terms between log-transformed Lp(a) and selected modifiers - ASCVD status, current LDL-C category (<100 vs. ≥100 mg/dL), sex, and age group (<65 vs. ≥65 years) - were included in the multivariable models. Interaction results are reported using the corresponding P values for interaction. All tests were two-sided, and *P* <0.05 was considered statistically significant. Given the exploratory nature of the interaction and sensitivity analyses, no adjustment for multiple comparisons was applied. Analyses were performed using Python 3.13.5 (Python Software Foundation, Wilmington, DE, USA), with the pandas, SciPy, statsmodels, and matplotlib packages.

Results

A total of 23,654 patients with Lp(a) measurements were included. Based on prespecified Lp(a) categories, 18,440 patients had Lp(a) <62 nmol/L, 1,381 had Lp(a) 62 to <105 nmol/L, and 3,833 had Lp(a) ≥105 nmol/L. Baseline characteristics differed across categories; in particular, patients with higher Lp(a) levels had higher current LDL-C, higher total cholesterol, and more frequent baseline LLT and ASCVD, whereas HDL-C was similar across groups (Table 1). Current LDL-C increased across Lp(a) categories, with median values of 106.7 mg/dL (IQR, 86.2–129.9) in patients with Lp(a) <62 nmol/L, 109.8 mg/dL (IQR, 87.3–135.0) in those with Lp(a) 62 to <105 nmol/L, and 117.8 mg/dL (IQR, 95.9–143.5) in those with Lp(a) ≥105 nmol/L (P <0.001). The distribution of current LDL-C categories also differed significantly across Lp(a) groups (P <0.001), with a lower proportion of patients having lower LDL-C levels and a higher proportion remaining in the highest LDL-C category among those with elevated Lp(a) levels (Figure 1).

The frequency of recorded post-test treatment modification increased progressively across Lp(a) categories (Figure 2, Supplementary Table S2). Statin initiation increased from 1.8% in patients with Lp(a) <62 nmol/L to 4.3% in those with Lp(a) 62 to <105 nmol/L and 9.5% in those with Lp(a) ≥105 nmol/L (P <0.001). Similarly, any statin escalation increased from 2.3% to 5.1% and 11.6% (P <0.001), ezetimibe initiation from 0.7% to 1.7% and 3.8% (P <0.001), and any LLT intensification from 2.7% to 5.9% and 13.2% (P <0.001). Despite this gradient, 86.8% of patients with Lp(a) ≥105 nmol/L had no recorded LLT intensification after testing. Initiation of acetylsalicylic acid was rare and did not differ significantly across Lp(a) categories.

Findings were consistent in the sensitivity analysis using the Lp(a) categories recommended by the Polish Cardiac Society and Polish Lipid Association. Statin initiation occurred in 1.9%, 5.8%, and 10.1% of patients with Lp(a) <75, 75 to <125, and ≥125 nmol/L, respectively. Corresponding rates were 2.3%, 6.7%, and 12.4% for any statin escalation; 0.7%,

2.3%, and 4.0% for ezetimibe initiation; and 2.7%, 7.5%, and 14.1% for any LLT intensification (all *P* <0.001; Supplementary Table S3).

In the exploratory analysis of 1,397 patients with a statin documented both before and after Lp(a) testing, statin deintensification was recorded in 125 patients (8.9%). Its frequency did not differ significantly across Lp(a) categories: 83 of 909 patients (9.1%) with Lp(a) <62 nmol/L, 8 of 84 (9.5%) with Lp(a) 62 to <105 nmol/L, and 34 of 404 (8.4%) with Lp(a) ≥105 nmol/L (*P*=0.90). Ezetimibe initiation was recorded in 18 of the 125 patients with statin deintensification (14.4%; Supplementary Table S4).

In multivariable analysis restricted to patients without baseline statin or ezetimibe therapy, higher Lp(a) levels remained independently associated with any LLT initiation after adjustment for age, sex, BMI, ASCVD status, current LDL-C, HDL-C, and triglycerides (Supplementary Table S5). For continuous Lp(a), the adjusted odds ratio (OR) was 1.93 (95% CI 1.78–2.09; *P* <0.001) per 1-unit increase in log-transformed Lp(a). Compared with Lp(a) <62 nmol/L, the adjusted OR was 2.99 (95% CI 2.06–4.33; *P* <0.001) for Lp(a) 62 to <105 nmol/L and 6.18 (95% CI 4.97–7.68; *P* <0.001) for Lp(a) ≥105 nmol/L. Higher Lp(a) levels were likewise independently associated with any LLT intensification after additional adjustment for baseline statin and ezetimibe use. For continuous Lp(a), the adjusted OR was 1.79 (95% CI 1.68–1.90; *P* <0.001). Compared with Lp(a) <62 nmol/L, the adjusted OR was 2.75 (95% CI 2.04–3.71; *P* <0.001) for Lp(a) 62 to <105 nmol/L and 5.20 (95% CI 4.39–6.17; *P* <0.001) for Lp(a) ≥105 nmol/L.

In the sensitivity analysis using alternative categorical thresholds, the adjusted ORs for LLT initiation were 4.17 (95% CI 3.01–5.77) for Lp(a) 75 to <125 nmol/L and 6.35 (95% CI 5.07–7.95) for Lp(a) ≥125 nmol/L, compared with Lp(a) <75 nmol/L (Supplementary Table S3). The corresponding ORs for LLT intensification were 3.55 (95% CI 2.71–4.65) and 5.35 (95% CI 4.49–6.38), respectively (all *P* <0.001).

Interaction analysis revealed that the association between Lp(a) levels and treatment change was not modified by current LDL-C category (<100 vs. ≥100 mg/dL) for either LLT initiation (*P* for interaction = 0.87) or LLT intensification (*P* for interaction = 0.32). No significant interaction with sex was observed for LLT initiation (*P* for interaction = 0.47), although a modest interaction was present for LLT intensification (*P* for interaction = 0.008), with a somewhat stronger association in women than in men (Supplementary Table S6). Female sex was nevertheless associated with lower overall odds of treatment modification; therefore, the interaction should not be interpreted as indicating higher absolute intensification rates in women. Age group significantly modified the association between Lp(a) levels and both LLT initiation (*P* for interaction = 0.002) and LLT intensification (*P* for interaction = 0.015), with a stronger association in patients aged <65 years than in those aged ≥65 years, particularly for LLT initiation. ASCVD status did not significantly modify the association between Lp(a) levels and LLT initiation (*P* for interaction = 0.14), but a significant interaction was observed for LLT intensification (*P* for interaction <0.001), with a stronger association in patients without ASCVD than in those with established ASCVD (Supplementary Table S6).

Discussion

In this real-world retrospective observational study of more than 23,600 adults from the LUX MED network in Poland, higher Lp(a) levels were independently associated with a greater likelihood of recorded post-test LLT initiation or intensification. These findings describe associations between Lp(a) concentrations and subsequent treatment patterns but do not establish that the Lp(a) result itself directly prompted treatment modification. Importantly, despite the progressive increase in treatment-change rates across Lp(a) categories, the absolute frequency of LLT modification remained low.

The number of Lp(a) measurements performed in Poland has been rising steadily, yet comprehensive epidemiological data describing Lp(a) distribution in the Polish population remain scarce. Burzyńska et al. analyzed 2,475 consecutive patients admitted to two cardiology centers within the cross-sectional STAR (Specialist Care Patients) Lp(a) study conducted between March 2022 and January 2024. Their analysis focused exclusively on individuals in primary prevention [29]. They reported a median Lp(a) concentration of 8.5 mg/dL, with 21.5% of participants having levels ≥30 mg/dL (≥75 nmol/L) and 13.5% meeting or exceeding 50 mg/dL (≥125 nmol/L) [29]. Similarly, in a cohort of 800 adults aged 49 (44–53) years participating in the "Małopolska coronary artery disease prophylactic program for individuals over 40 years", conducted from May to October 2022, the prevalence of Lp(a) >50 mg/dL was 17.8% [30]. In our cohort, median Lp(a) was 12.7 nmol/L (IQR, 7.0–47.0). When Lp(a) values were categorized using corresponding clinically relevant thresholds (<62, 62 to <105, and ≥105 nmol/L), the overall three-category distribution was 78.0%, 5.8%, and 16.2%. Although direct comparison with the above studies is limited by differences in units, assay methodology, and population characteristics, the proportion of patients with markedly elevated Lp(a) in our cohort was broadly consistent with prior Polish estimates. The lack of assay-level information in our dataset should nevertheless be considered because inter-assay variability may have resulted in some misclassification around the category thresholds. Reassuringly, the findings remained consistent when the alternative thresholds of <75, 75 to <125, and ≥125 nmol/L recommended by Polish experts were applied [12].

In the Women's Health Study (n = 27,791), Suk Danik et al. [31] reported weak correlations between Lp(a) and TC (Spearman ρ = 0.14) and LDL-C (ρ = 0.17), and Waldeyer et al. [32] reported similar relationships in over 52,000 individuals. These modest correlations may partly be explained by the structural composition of Lp(a), which includes an LDL-like particle [33]. Nissen et al., in the Lp(a) HERITAGE study, further noted that Lp(a) cholesterol

may contribute to standard LDL-C measurements, though on average less than 10% of Lp(a) cholesterol is captured by conventional assays [34]. Accordingly, the increase in routinely reported current LDL-C across Lp(a) categories may partly reflect cholesterol carried within Lp(a). We did not apply an Lp(a)-cholesterol correction because Lp(a) was reported in nmol/L, assay-level characteristics were unavailable, and the cholesterol content of Lp(a) varies between individuals. The routinely reported LDL-C value was also the clinically relevant measure potentially available during treatment assessment. These results support the concept that Lp(a) contributes to cardiovascular risk assessment independently of traditional lipid measures.

The young median age, low prevalence of established ASCVD, and preventive-care context indicate that the cohort predominantly reflected primary-prevention and general health-assessment pathways rather than specialist secondary-prevention care. The well-established association between elevated Lp(a) and ASCVD risk has been confirmed in large prospective studies. Patel et al. analyzed over 460,500 middle-aged participants from the UK Biobank and found a clear linear association between Lp(a) concentration and ASCVD risk, with each 50 nmol/L increase corresponding to an 11% higher risk (HR 1.11; 95% CI 1.10–1.12) over a median follow-up of 11.2 years [10]. Similarly, Hoogeveen et al. reported that individuals with Lp(a) ≥50 mg/dL had a significantly increased risk of ASCVD (HR 1.31; 95% CI 1.15–1.50) and CAD (HR 1.49; 95% CI 1.27–1.75; both P <0.001) compared with those with Lp(a) <10 mg/dL in a cohort of nearly 16,000 participants [35]. The higher prevalence of baseline LLT observed in patients with elevated Lp(a) in our cohort could therefore be partly attributable to the higher prevalence of ASCVD and other unmeasured clinical indications for treatment. However, the demographic profile of our cohort differs substantially from that of older or dedicated secondary-prevention populations and limits the generalizability of the observed treatment patterns.

Our results expand on earlier studies by providing not only a description of patients undergoing Lp(a) testing but also an assessment of the association between clinically interpretable Lp(a) categories and subsequent recorded treatment patterns. In a cross-sectional and longitudinal claims-based analysis of the German population, Stürzebecher et al. demonstrated an increase in LLT use among patients who underwent Lp(a) testing - particularly in those with both an Lp(a) measurement and established ASCVD. Treatment intensity following Lp(a) assessment was higher compared with the year preceding the test [36]. Parsa et al. [37], using Veterans Affairs electronic health record data, analyzed 10,384 individuals who underwent Lp(a) testing. Assessment of Lp(a) was associated with increased LLT intensification (OR 2.11) and higher rates of LDL-cholesterol goal achievement (OR 1.22). Patients with elevated Lp(a) levels (>50 mg/dL) were more likely to undergo treatment intensification (OR 1.73); however, those with markedly high concentrations (>100 mg/dL) were less likely to reach LDL-C goals. These findings indicate that Lp(a) testing and elevated Lp(a) concentrations were associated with more intensive subsequent lipid management, although achieving LDL-C targets was more challenging in individuals with very high Lp(a) levels [37]. Additionally, Mangla et al. [38] examined the relationship between Lp(a) levels and the initiation or intensification of LLT in more than 16,400 individuals within the Northwell Health System. The proportion of patients who initiated or escalated LLT increased progressively across Lp(a) categories: 12.8% for Lp(a) <75 nmol/L, 17.5% for 75 to <125 nmol/L, 20.2% for 125 to <200 nmol/L, and 22.1% for ≥200 nmol/L (P <0.001) [38]. The investigators reported a positive relationship between rising Lp(a) levels and the likelihood of initiating or intensifying LLT. Compared with these earlier reports, our study demonstrated notably stronger adjusted associations between Lp(a) levels and therapy changes. The adjusted OR for LLT initiation in patients with Lp(a) ≥105 nmol/L was 6.18 (vs. <62 nmol/L), and for LLT intensification 5.20 - substantially larger than the effect sizes reported by Parsa et al. (OR

1.73 for elevated Lp(a)) or the unadjusted proportional increases observed by Mangla et al. [37,38]. Direct comparison of these estimates should be cautious because the studies differed in population characteristics, outcome definitions, Lp(a) thresholds, follow-up periods, and covariate adjustment. Nevertheless, the direction of the associations was consistent across studies, with higher Lp(a) concentrations generally accompanied by more frequent subsequent LLT modification.

Despite these associations, the absolute rates of therapy modification remained modest even among patients with markedly elevated Lp(a). Statin initiation occurred in only 9.5% and any LLT intensification in 13.2% of patients with Lp(a) ≥105 nmol/L. Thus, 86.8% of patients in the highest Lp(a) category had no documented LLT intensification after testing. This limited translation of elevated Lp(a) into subsequent recorded management may be one of the most clinically important findings of the study. Similarly, Kelly et al. [39] recently reported that among patients with elevated Lp(a), fewer than one quarter had LLT modified within 30 days of the result, with ezetimibe addition and statin intensification being the most frequent interventions. In Poland, Nowowiejska-Wiewióra et al. also demonstrated persistent gaps in lipid management even within a structured post-myocardial infarction care program, in which combination therapy remained underused and only approximately one-fifth of patients achieved LDL-C <55 mg/dL [40]. Several factors may explain the low absolute treatment-change rates in our cohort. The study population was young, had a low prevalence of established ASCVD, and included many patients undergoing preventive assessment. Elevated Lp(a) is a cardiovascular risk modifier but does not automatically constitute an indication for pharmacological treatment irrespective of current LDL-C, absolute cardiovascular risk, comorbidities, treatment tolerance, and patient preferences. Some patients may also have had limited opportunity for further escalation because they were already receiving treatment. Conversely, the low rates may reflect an implementation gap, including limited awareness of

how elevated Lp(a) should modify overall risk assessment, insufficient structured follow-up, and clinical inertia. Because individualized LDL-C goals, physician specialty, formal risk estimates, statin intolerance, contraindications, adherence, patient preferences, and treatment outside the network were unavailable, absence of recorded intensification cannot be classified as inappropriate care in every individual patient. Statin deintensification was recorded in 8.9% of patients with a statin documented both before and after Lp(a) testing and did not differ significantly across Lp(a) categories. Ezetimibe initiation was recorded in 14.4% of patients with statin deintensification. These exploratory findings suggest that deintensification was relatively infrequent and showed no evident variation according to Lp(a) category. However, the exact timing and clinical reasons for dose reduction, switching, or ezetimibe initiation were unavailable.

A key finding of this study is that age modified the association between Lp(a) levels and both the initiation (P = 0.002) and intensification (P = 0.015) of LLT. This association was stronger in individuals younger than 65 years, especially for treatment initiation. One possible explanation is that elevated Lp(a) provides additional information regarding lifetime risk in younger patients, whereas older patients may more often already have established treatment indications or baseline LLT. This interpretation remains hypothesis-generating. A significant interaction was also observed for LLT intensification (P <0.001), with a more pronounced association in patients without ASCVD than in those with established disease. Patients with ASCVD were more frequently receiving LLT at baseline, potentially leaving less therapeutic opportunity for further escalation using the statin- and ezetimibe-based outcomes captured in this study. In addition, elevated Lp(a) may provide less new risk information in patients already classified as being at very high cardiovascular risk. Nevertheless, the weaker association in patients with ASCVD should not be interpreted as evidence that they were optimally treated

because individualized LDL-C goals, maximally tolerated therapy, and the complete use of nonstatin agents were not available.

No significant sex interaction was observed for LLT initiation, whereas the association between Lp(a) and LLT intensification was somewhat stronger in women than in men. This finding requires careful interpretation because female sex was associated with lower overall odds of treatment modification. Thus, women did not have higher absolute intensification rates; rather, the relative treatment gradient across increasing Lp(a) concentrations was steeper in women. Elevated Lp(a) may have provided a more prominent additional risk signal in women whose short-term cardiovascular risk might otherwise have been perceived as lower. Hormonal and metabolic changes during the menopausal transition may also be relevant because menopause is associated with adverse changes in lipid metabolism and cardiovascular risk [41]. However, menopausal status, age at menopause, reproductive history, and hormone therapy were unavailable, and this explanation should be regarded as hypothesis-generating.

The association between Lp(a) and treatment modification was not materially modified by current LDL-C category. This indicates that the association between Lp(a) and recorded treatment change was present across the examined LDL-C categories, although it does not establish that Lp(a) directly determined the prescribing decision. These findings are consistent with recommendations that Lp(a) should be considered a cardiovascular risk modifier and that other modifiable risk factors should be optimized when Lp(a) is elevated [13]. In patients not receiving LLT, an elevated Lp(a) result should prompt reassessment of the complete cardiovascular risk profile and may contribute to decisions regarding treatment initiation when supported by the overall level of risk.

Several practical measures may improve the translation of Lp(a) testing into effective cardiovascular prevention. Lp(a) measurement should be incorporated consistently into adult cardiovascular risk assessment, with results reported in nmol/L using clearly interpretable

categories. An elevated result should prompt reassessment of overall cardiovascular risk, current LDL-C and individualized LDL-C goals, treatment adherence and tolerance, and other modifiable risk factors rather than automatic pharmacological escalation. Standardized laboratory comments, electronic clinical decision support, clinician and patient education, and structured referral pathways may facilitate appropriate follow-up. Family-based testing should also be considered because Lp(a) concentrations are predominantly genetically determined.

This issue is particularly relevant in Poland, where the national 'My Health' preventive program includes once-in-a-lifetime Lp(a) measurement within its extended diagnostic package, with eligibility determined by age and questionnaire-derived risk factors [42]. Broader access to testing provides an important opportunity to identify individuals with elevated inherited risk but also increases the need for clear interpretation and defined management pathways. Recent analyses of the Polish landscape similarly emphasize that expanded screening must be accompanied by comprehensive cardiovascular risk assessment, optimization of modifiable risk factors, and structured follow-up [43].

Looking ahead, the anticipated availability of targeted Lp(a)-lowering agents may fundamentally change the therapeutic implications of Lp(a) testing [25]. Our findings show that conventional LLT modification was recorded more frequently among patients with higher Lp(a), although the reasons for individual treatment decisions were unavailable. As specific therapies become available, structured Lp(a) screening programs and standardized reporting of results in clinically actionable categories may further amplify the impact of testing on cardiovascular risk management. However, broader testing must be linked to effective follow-up to avoid increasing diagnosis without a corresponding improvement in preventive care.

This study has several limitations. First, it relied on the retrospective analysis of routinely collected data from a single private healthcare provider (LUX MED) in Poland, and patients accessing private healthcare may differ from the general population in socioeconomic

characteristics, health-seeking behavior, and baseline comorbidity burden, potentially limiting generalizability. Furthermore, the cohort was remarkably young and had a low prevalence of established ASCVD. Therefore, the findings should not be extrapolated directly to the general Polish population, older adults, patients treated exclusively within the public healthcare system, or dedicated secondary-prevention populations. Second, the study population comprised a mixture of primary- and secondary-prevention patients, meaning that the overall estimates may reflect a clinically heterogeneous population rather than a well-defined screening cohort. However, the young age distribution and preventive-care setting indicate that primary-prevention patients predominated. Third, clinical conditions were ascertained from available ICD-coded diagnoses, and underdetection or misclassification cannot be excluded, particularly where diagnostic coding was incomplete or relevant events occurred outside the captured healthcare pathway. This concern applies especially to composite cardiovascular endpoints and to conditions such as prior myocardial infarction, stroke/TIA, and other cardiovascular comorbidities. Moreover, the ASCVD composite should be considered a pragmatic approximation, as it did not encompass carotid artery disease without prior cerebrovascular events or peripheral arterial disease. Fourth, the study was not designed to assess incident cardiovascular events or the long-term prognostic implications of elevated Lp(a) levels. Although post-test medication records followed the index Lp(a) measurement, no standardized follow-up interval was imposed, and the interval between testing and the subsequent medication record could vary among patients. Patients with longer intervals may have had a greater opportunity for treatment modification to be recorded. Fifth, analyses of therapy initiation and intensification following Lp(a) testing reflect observational associations in prescribing patterns and should not be interpreted as evidence that the Lp(a) result itself directly prompted therapeutic change. The identity of the prescribing clinician, the clinical indication for treatment modification, intermediate consultations, additional laboratory results, and clinical events

occurring between the pre- and post-test medication records were not available. Consequently, temporal ordering alone cannot establish causality. Sixth, the source dataset did not indicate whether individual LDL-C values had been measured directly or calculated by the performing laboratory. For 0.4% of patients without a recorded LDL-C value, LDL-C was calculated using the Friedewald equation when the required lipid components were available. No back-calculation of untreated or pretreatment LDL-C was performed in the revised analysis. In addition, routinely reported LDL-C includes cholesterol carried within Lp(a), and no Lp(a)-cholesterol correction was applied. Current LDL-C was available for only 53.7% of the cohort, and the multivariable analyses were consequently based on complete-case subsets. Selection related to the availability of lipid measurements therefore cannot be excluded. Seventh, Lp(a) measurements were performed in collaborating certified laboratories, but assay-level metadata, including the analytical platform, manufacturer, assay principle, calibrator traceability, and reagent lot, were unavailable. Consequently, we could not confirm that all measurements were performed using the same assay, and inter-assay variation may have resulted in some misclassification around category thresholds. To reduce additional analytical uncertainty, the primary analysis was restricted to results originally reported in nmol/L, and no conversion between mass and molar units was performed. Eighth, several clinically important variables that may have influenced both the decision to measure Lp(a) and subsequent treatment changes were unavailable in the dataset. These included familial hypercholesterolemia status, family history of premature ASCVD, smoking status, chronic kidney disease, cardiovascular risk scores, specialty of the ordering or treating physician, and Lp(a) assay characteristics. High-sensitivity C-reactive protein was also unavailable; therefore, inflammatory status could not be incorporated into the multivariable models. The absence of these data introduces the possibility of confounding by indication and residual confounding that cannot be fully addressed in the present analysis. In addition, information on statin intolerance, prior adverse effects,

contraindications, patient preferences, and maximally tolerated statin dose was not available, limiting interpretation of non-intensification as clinical inertia [44]. Menopausal status, age at menopause, reproductive history, and hormone therapy were also unavailable, precluding further evaluation of the observed sex interaction. Moreover, PCSK9-targeted therapies, including monoclonal antibodies and inclisiran, as well as bempedoic acid and other nonstatin agents, were not captured and were not included in the primary definition of LLT intensification, which may have underestimated the rate of treatment escalation. Treatment prescribed outside the LUX MED network may likewise have been missed. Finally, medication documentation may have been incomplete or inconsistent for some patients, which could have influenced estimates of post-test treatment modification. For this reason, the absence of a post-test statin record was not interpreted as treatment discontinuation in the exploratory deintensification analysis.

Conclusions

In this real-world analysis of over 23,600 adults, higher Lp(a) levels were independently associated with more frequent recorded post-test initiation and intensification of LLT, even after adjustment for available demographic, clinical, and lipid variables, including ASCVD status and current LDL-C. This association was not materially modified by current LDL-C category but appeared stronger in younger patients and, for therapy intensification, somewhat stronger in women and in patients without established ASCVD. However, absolute treatment-change rates remained low: only 13.2% of patients with Lp(a) ≥105 nmol/L had any recorded LLT intensification, leaving 86.8% without documented intensification. This limited translation of elevated Lp(a) into subsequent recorded management highlights the need for standardized interpretation, comprehensive cardiovascular risk reassessment, clinician and patient education,

and structured follow-up pathways. Because of the retrospective observational design and the absence of information on the reasons for individual treatment decisions, these findings do not establish that the Lp(a) result itself directly prompted treatment modification.

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Conflict of interest: The authors declare no conflict of interest.

Data availability: The individual-level data analyzed in this study were derived from electronic health records within the LUX MED network and cannot be made publicly available because of legal, contractual, and patient-privacy restrictions. Access may be considered upon reasonable request to the data custodian and is subject to institutional approval, applicable data-protection regulations, and an appropriate data-use agreement.

AI statement: The authors declare that generative artificial intelligence (Claude Opus 4.8; Anthropic) was used solely for language editing and stylistic improvement during manuscript preparation. All AI-assisted content was reviewed and edited by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Table 1. Baseline characteristics according to lipoprotein(a) category.

Characteristic	Total (N = 23,654)	Lp(a) <62 nmol/L (N = 18,440)	Lp(a) 62 to <105 nmol/L (N = 1,381)	Lp(a) ≥105 nmol/L (N = 3,833)	*P* value
Age, years, median (IQR)	34.0 (29.0–40.0)	34.0 (28.0–39.0)	34.0 (29.0–39.0)	35.0 (29.0–41.0)	<0.001
Age ≥65 years, n (%)	968 (4.1%)	733 (4.0%)	47 (3.4%)	188 (4.9%)	0.01
BMI, kg/m², median (IQR)	24.2 (21.5–27.5)	24.2 (21.5–27.5)	24.1 (21.5–27.5)	24.5 (21.9–27.8)	<0.001
Obesity (BMI ≥30 kg/m²), n (%)	3,005 (12.7%)	2,309 (12.5%)	176 (12.7%)	520 (13.6%)	0.21
Female sex, n (%)	15,212 (64.3%)	11,854 (64.3%)	905 (65.5%)	2,453 (64.0%)	0.59
Lipid parameters / treatment					
Current LDL-C, mg/dL, median (IQR)	108.7 (87.8–132.8)	106.7 (86.2–129.9)	109.8 (87.3–135.0)	117.8 (95.9–143.5)	<0.001
Total cholesterol, mg/dL, median (IQR)	188.1 (165.0–215.0)	186.0 (163.2–212.4)	189.5 (166.0–213.1)	198.0 (173.8–225.6)	<0.001
HDL-C, mg/dL, median (IQR)	57.3 (47.5–69.2)	57.3 (47.4–69.1)	58.3 (47.6–70.1)	57.0 (47.9–69.1)	0.84
Triglycerides, mg/dL, median (IQR)	91.5 (67.1–129.3)	91.0 (67.0–128.5)	89.7 (65.2–126.7)	95.0 (69.1–133.0)	<0.001
Baseline statin and/or ezetimibe therapy, n (%)	2,891 (12.2%)	2,059 (11.2%)	167 (12.1%)	665 (17.3%)	<0.001
Comorbidities					
ASCVD, n (%)	739 (3.1%)	527 (2.9%)	38 (2.8%)	174 (4.5%)	<0.001
Type 1 diabetes mellitus, n (%)	163 (0.7%)	124 (0.7%)	9 (0.7%)	30 (0.8%)	0.74
Type 2 diabetes mellitus, n (%)	634 (2.7%)	489 (2.7%)	33 (2.4%)	112 (2.9%)	0.51

Coronary artery disease, n (%)	556 (2.4%)	388 (2.1%)	25 (1.8%)	143 (3.7%)	<0.001
Previous MI, n (%)	29 (0.1%)	17 (0.1%)	0 (0.0%)	12 (0.3%)	<0.001
Arterial hypertension, n (%)	4,484 (19.0%)	3,378 (18.3%)	266 (19.3%)	840 (21.9%)	<0.001
Hyperlipidemia, n (%)	7,896 (33.4%)	5,505 (29.9%)	483 (35.0%)	1,908 (49.8%)	<0.001
Atrial fibrillation or flutter, n (%)	258 (1.1%)	185 (1.0%)	17 (1.2%)	56 (1.5%)	0.04
Aortic valve stenosis, n (%)	40 (0.2%)	29 (0.2%)	5 (0.4%)	6 (0.2%)	0.20
Previous pulmonary embolism, n (%)	79 (0.3%)	57 (0.3%)	8 (0.6%)	14 (0.4%)	0.23
Heart failure, n (%)	193 (0.8%)	136 (0.7%)	15 (1.1%)	42 (1.1%)	0.04
Previous stroke/TIA, n (%)	220 (0.9%)	169 (0.9%)	14 (1.0%)	37 (1.0%)	0.91
Obstructive sleep apnea, n (%)	486 (2.1%)	366 (2.0%)	36 (2.6%)	84 (2.2%)	0.24
Major depressive disorder, single episode, n (%)	1,968 (8.3%)	1,539 (8.3%)	102 (7.4%)	327 (8.5%)	0.40
Recurrent depressive disorder, n (%)	867 (3.7%)	683 (3.7%)	42 (3.0%)	142 (3.7%)	0.45
Alzheimer's disease, n (%)	4 (0.0%)	2 (0.0%)	0 (0.0%)	2 (0.1%)	0.18
Psoriasis, n (%)	677 (2.9%)	536 (2.9%)	36 (2.6%)	105 (2.7%)	0.72
Seropositive rheumatoid arthritis, n (%)	80 (0.3%)	58 (0.3%)	4 (0.3%)	18 (0.5%)	0.31
Other rheumatoid arthritis, n (%)	189 (0.8%)	141 (0.8%)	15 (1.1%)	33 (0.9%)	0.39
Systemic sclerosis, n (%)	11 (0.0%)	10 (0.1%)	0 (0.0%)	1 (0.0%)	0.54

Data are presented as median (IQR) or n (%) as appropriate.

Current LDL-C was available for 12,696 patients: 9,808, 736, and 2,152 patients in the respective Lp(a) categories. Baseline lipid-lowering therapy was defined as recorded statin

and/or ezetimibe use before the index Lp(a) measurement. ASCVD was defined as coronary artery disease, previous myocardial infarction, or previous stroke/TIA.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TIA, transient ischemic attack.

Figure Legends

Figure 1. Distribution of current low-density lipoprotein cholesterol categories across lipoprotein(a) categories.

The distribution differed significantly across Lp(a) categories (P <0.001).

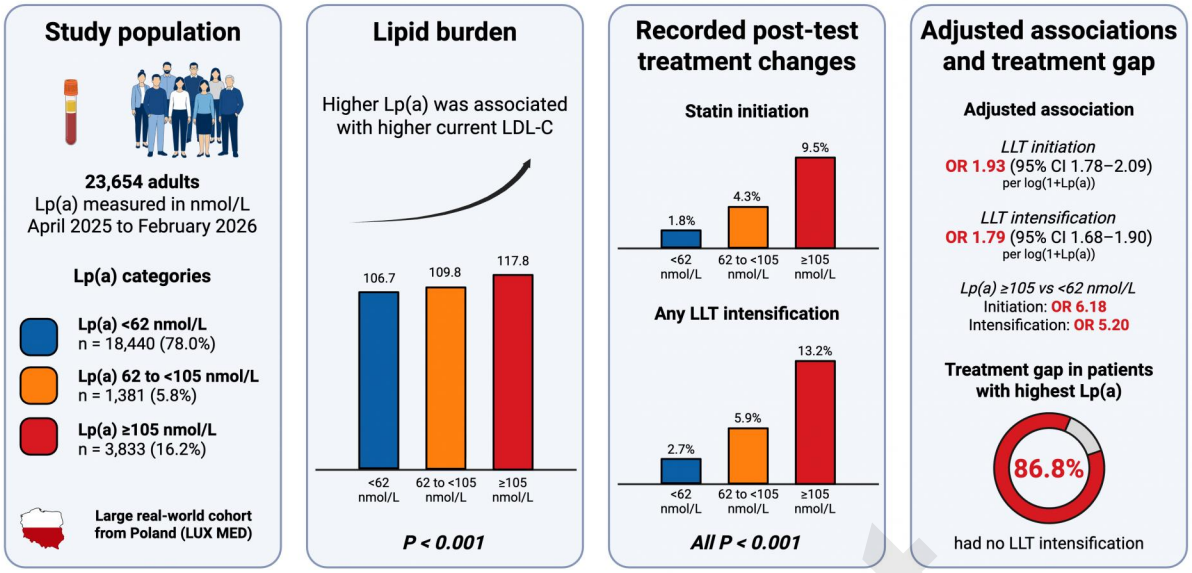
Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

Figure 2. Frequencies of recorded post-test lipid-lowering therapy changes according to lipoprotein(a) category.

The outcomes shown include statin initiation, any statin escalation, ezetimibe initiation, and any LLT intensification. All outcomes differed significantly across Lp(a) categories (P<0.001). Treatment changes represent differences between the recorded pre- and post-test medication states and do not establish that the Lp(a) result directly prompted treatment modification.

Abbreviations: LLT, lipid-lowering therapy; Lp(a), lipoprotein(a).

Lipoprotein(a) levels and post-test lipid-lowering therapy changes in routine practice



Higher Lp(a) levels were independently associated with more frequent recorded LLT initiation and intensification, but most patients with high Lp(a) still had no recorded treatment change.

Supplementary Table S1. Prespecified rule-based classification of statin intensity.

Statin	Low intensity	Moderate intensity	High intensity
Atorvastatin	<10 mg	10 to <40 mg	≥40 mg
Rosuvastatin	<5 mg	5 to <20 mg	≥20 mg
Simvastatin	<20 mg	≥20 mg	—
Pitavastatin	<2 mg	≥2 mg	—

Statin intensity was classified using the recorded statin type and daily dose. The categories represent a simplified rule-based classification used to identify changes in treatment intensity within the available medication records. An increase or decrease in intensity was defined as movement to a higher or lower category, respectively. The em dash indicates that no high-intensity category was assigned for the respective statin. Combination with ezetimibe was assessed separately and did not alter the assigned statin-intensity category.

Supplementary Table S2. Recorded post-test lipid-lowering therapy changes, stratified by Lp(a) category.

Outcome	Lp(a) <62 nmol/L (n=18,440)	Lp(a) 62 to <105 nmol/L (n=1,381)	Lp(a) ≥105 nmol/L (n=3,833)	*P* value
Statin initiation, n/N (%)	339/18,440 (1.8%)	60/1,381 (4.3%)	364/3,833 (9.5%)	<0.001
Any statin escalation, n/N (%)	429/18,440 (2.3%)	70/1,381 (5.1%)	446/3,833 (11.6%)	<0.001
Ezetimibe initiation, n/N (%)	128/18,440 (0.7%)	24/1,381 (1.7%)	144/3,833 (3.8%)	<0.001
Any LLT intensification, n/N (%)	497/18,440 (2.7%)	81/1,381 (5.9%)	505/3,833 (13.2%)	<0.001

Treatment changes were identified by comparing the recorded medication states before and after the index Lp(a) measurement. Statin initiation was defined as a post-test statin record in a patient without a recorded pre-test statin. Any statin escalation included statin initiation, an increase in the recorded dose of the same statin, or a change to a higher statin-intensity category. Ezetimibe initiation was defined as a post-test ezetimibe record in a patient without recorded pre-test ezetimibe use. Any LLT intensification was defined as statin initiation, statin escalation, and/or ezetimibe initiation. Recorded treatment changes do not establish that the Lp(a) result directly prompted treatment modification.

Abbreviations: LLT, lipid-lowering therapy; Lp(a), lipoprotein(a).

Supplementary Table S3. Sensitivity analysis of recorded post-test lipid-lowering therapy changes using lipoprotein(a) categories recommended by the Polish Cardiac Society and Polish Lipid Association

Panel A. Crude frequencies of recorded post-test treatment changes

Outcome	Lp(a) <75 nmol/L (N=18,887)	Lp(a) 75 to <125 nmol/L (N=1,544)	Lp(a) ≥125 nmol/L (N=3,223)	P value
Statin initiation, n/N (%)	350/18,887 (1.9%)	89/1,544 (5.8%)	324/3,223 (10.1%)	<0.001
Any statin escalation, n/N (%)	442/18,887 (2.3%)	103/1,544 (6.7%)	400/3,223 (12.4%)	<0.001
Ezetimibe initiation, n/N (%)	131/18,887 (0.7%)	35/1,544 (2.3%)	130/3,223 (4.0%)	<0.001
Any LLT intensification, n/N (%)	513/18,887 (2.7%)	116/1,544 (7.5%)	454/3,223 (14.1%)	<0.001

Panel B. Adjusted associations with recorded post-test treatment changes

Outcome	Lp(a) comparison	Adjusted OR (95% CI)	P value
Recorded LLT initiation	75 to <125 vs <75 nmol/L	4.17 (3.01–5.77)	<0.001
Recorded LLT initiation	≥125 vs <75 nmol/L	6.35 (5.07–7.95)	<0.001
Recorded LLT intensification	75 to <125 vs <75 nmol/L	3.55 (2.71–4.65)	<0.001
Recorded LLT intensification	≥125 vs <75 nmol/L	5.35 (4.49–6.38)	<0.001

Values in Panel A are n/N (%). P values were calculated using the chi-square test. In Panel B, values are adjusted odds ratios with 95% confidence intervals from complete-case multivariable logistic regression models, with Lp(a) <75 nmol/L as the reference category. The LLT initiation model was restricted to patients without recorded baseline statin or ezetimibe use; the outcome was initiation of either treatment. Models of LLT initiation were adjusted for age, sex, BMI, ASCVD, current LDL-C, HDL-C, and triglycerides. Models of LLT intensification were additionally adjusted for baseline statin and ezetimibe use.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); OR, odds ratio.

Supplementary Table S4. Recorded statin deintensification according to lipoprotein(a) category

Outcome	Total	Lp(a) <62 nmol/L	Lp(a) 62 to <105 nmol/L	Lp(a) ≥105 nmol/L	P value
Statin deintensification, n/N (%)	125/1,397 (8.9%)	83/909 (9.1%)	8/84 (9.5%)	34/404 (8.4%)	0.90

Additional descriptive outcome	Total
Ezetimibe initiation among patients with statin deintensification, n/N (%)	18/125 (14.4%)

The statin-deintensification analysis was restricted to patients with a statin documented both before and after the index Lp(a) measurement. Statin deintensification was defined as a reduction in the dose of the same statin or a change to a lower statin-intensity category. An absent post-test statin record was not classified as treatment discontinuation.

Abbreviation: Lp(a), lipoprotein(a).

Supplementary Table S5. Multivariable logistic regression models for recorded post-test lipid-lowering therapy changes.

	Recorded LLT initiation		Recorded LLT intensification	
Covariate	**Continuous Lp(a)**	**Categorical Lp(a)**	**Continuous Lp(a)**	**Categorical Lp(a)**
Complete-case sample, N/events	9,737 / 471	9,737 / 471	12,301 / 733	12,301 / 733
Lp(a) terms				
Lp(a), per 1-unit increase in ln[1+Lp(a)]	1.93 (1.78–2.09)*	—	1.79 (1.68–1.90)*	—
Lp(a) 62 to <105 nmol/L vs. <62 nmol/L	—	2.99 (2.06–4.33)*	—	2.75 (2.04–3.71)*
Lp(a) ≥105 nmol/L vs. <62 nmol/L	—	6.18 (4.97–7.68)*	—	5.20 (4.39–6.17)*
Other covariates				
Age, per year	1.07 (1.06–1.08)*	1.07 (1.06–1.08)*	1.06 (1.05–1.06)*	1.06 (1.05–1.07)*
Female sex	0.63 (0.50–0.79)*	0.66 (0.52–0.83)*	0.67 (0.56–0.80)*	0.69 (0.58–0.83)*
BMI, per kg/m²	1.02 (1.00–1.04)	1.02 (1.00–1.05)	1.02 (1.00–1.04)	1.02 (1.00–1.04)
ASCVD	1.42 (0.81–2.49)	1.48 (0.84–2.58)	1.29 (0.95–1.75)	1.31 (0.97–1.78)
Current LDL-C, per mg/dL	1.02 (1.02–1.02)*	1.02 (1.02–1.02)*	1.01 (1.01–1.02)*	1.01 (1.01–1.02)*
HDL-C, per mg/dL	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Triglycerides, per mg/dL	1.00 (1.00–1.01)*	1.00 (1.00–1.01)*	1.00 (1.00–1.00)*	1.00 (1.00–1.00)*
Baseline statin use	—	—	0.69 (0.56–0.85)*	0.70 (0.57–0.86)*

Baseline ezetimibe use	—	—	0.26 (0.18–0.39)*	0.27 (0.18–0.39)*

Values are adjusted odds ratios with 95% confidence intervals. Continuous and categorical Lp(a) were evaluated in separate models. In the continuous models, Lp(a) was modeled per 1-unit increase in ln[1+Lp(a)]. The reference category in the categorical models was Lp(a) <62 nmol/L. All models included age, sex, BMI, ASCVD, current LDL-C, HDL-C, and triglycerides. Models of LLT intensification additionally included baseline statin and ezetimibe use. Analyses were restricted to patients with complete data for all variables included in the respective model. The em dash indicates that the variable was not applicable or was not included in the model. *P* <0.05.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); OR, odds ratio.

Supplementary Table S6. Interaction and stratified analyses of the association between lipoprotein(a) and recorded post-test lipid-lowering therapy changes

Panel A. Recorded LLT initiation

Effect modifier	Reference stratum	Lp(a) OR (95% CI)	N/events	Comparison stratum	Lp(a) OR (95% CI)	N/events	Interaction OR (95% CI); P value
Current LDL-C category	<100 mg/dL	1.97 (1.50–2.59)	3,886/39	≥100 mg/dL	1.89 (1.74–2.05)	5,851/432	0.98 (0.75–1.28); P=0.87
Sex	Male	1.85 (1.65–2.08)	3,153/232	Female	2.00 (1.79–2.25)	6,584/239	1.06 (0.90–1.24); P=0.47
Age group	<65 years	1.99 (1.83–2.16)	9,565/439	≥65 years	1.15 (0.82–1.62)	172/32	0.57 (0.40–0.81); P=0.002
ASCVD status	Absent	1.96 (1.80–2.12)	9,596/449	Present	1.41 (0.96–2.08)	141/22	0.73 (0.47–1.11); P=0.14

Panel B. Recorded LLT intensification

Effect modifier	Reference stratum	Lp(a) OR (95% CI)	N/events	Comparison stratum	Lp(a) OR (95% CI)	N/events	Interaction OR (95% CI); P value

Current LDL-C category	<100 mg/dL	1.60 (1.39–1.85)	4,844/129	≥100 mg/dL	1.81 (1.69–1.94)	7,457/604	1.08 (0.93–1.26); P=0.32
Sex	Male	1.64 (1.50–1.79)	4,491/361	Female	1.96 (1.79–2.14)	7,810/372	1.18 (1.04–1.33); P=0.008
Age group	<65 years	1.85 (1.73–1.98)	11,422/623	≥65 years	1.52 (1.29–1.78)	879/110	0.81 (0.68–0.96); P=0.015
ASCVD status	Absent	1.87 (1.75–1.99)	11,656/655	Present	1.28 (1.06–1.54)	645/78	0.71 (0.58–0.86); P<0.001

Values are adjusted odds ratios with 95% confidence intervals for the association between Lp(a) and the respective outcome per 1-unit increase in ln[1+Lp(a)]. Stratum-specific ORs were estimated in separate adjusted models. Interaction ORs represent the multiplicative change in the association between Lp(a) and the outcome in the comparison stratum relative to the reference stratum. The LLT-initiation analysis was restricted to patients without recorded baseline statin or ezetimibe use and was adjusted for age, sex, BMI, ASCVD, current LDL-C, HDL-C, and triglycerides. The LLT-intensification analysis included the same covariates with additional adjustment for baseline statin and ezetimibe use. Interaction analyses were exploratory, and no adjustment for multiple comparisons was applied.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); OR, odds ratio.

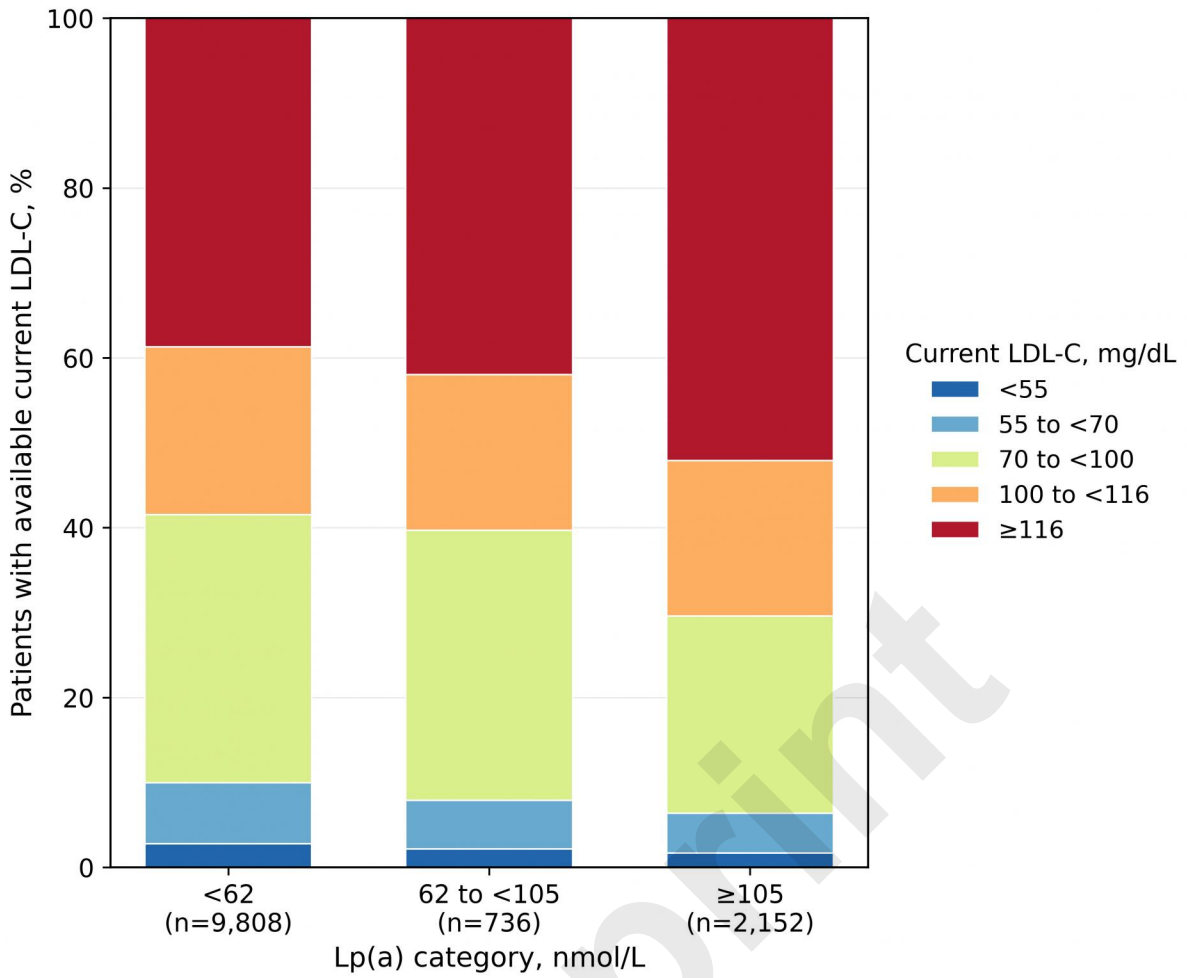


Figure 1. Distribution of current low-density lipoprotein cholesterol categories across lipoprotein(a) categories.

The distribution differed significantly across Lp(a) categories (P <0.001).
Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

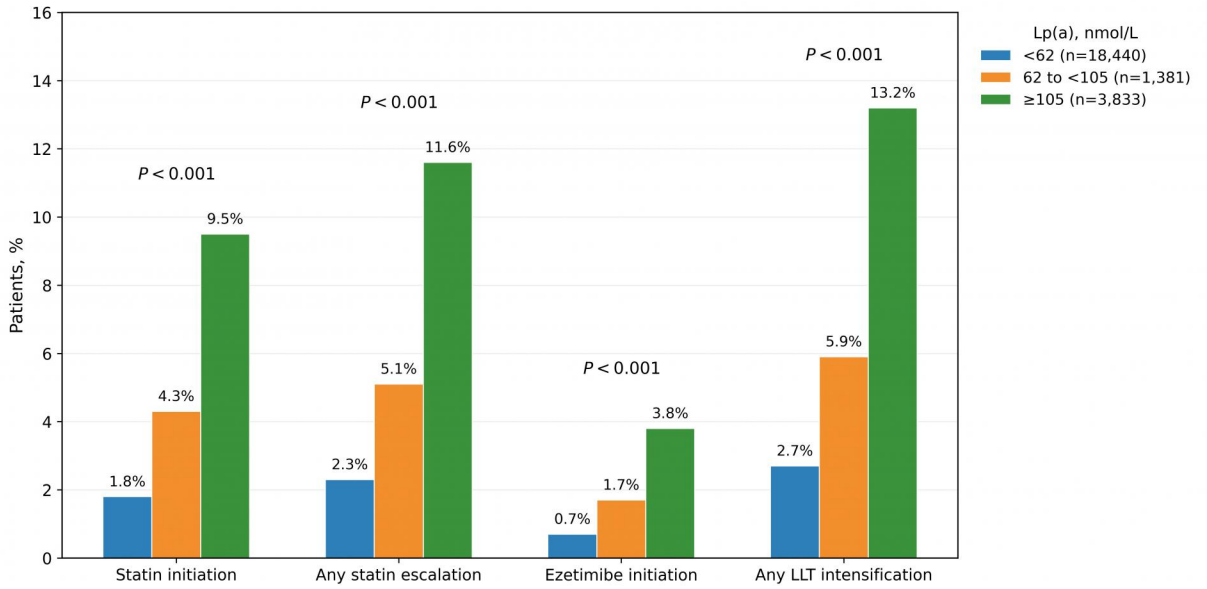


Figure 2. Frequencies of recorded post-test lipid-lowering therapy changes according to lipoprotein(a) category.
The outcomes shown include statin initiation, any statin escalation, ezetimibe initiation, and any LLT intensification. All outcomes differed significantly across Lp(a) categories (P<0.001). Treatment changes represent differences between the recorded pre- and post-test medication states and do not establish that the Lp(a) result directly prompted treatment modification.
Abbreviations: LLT, lipid-lowering therapy; Lp(a), lipoprotein(a).