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FULL RESEARCH PAPER
Cardiovascular Disease

Finding very high lipoprotein(a): the need for routine assessment

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Aims To validate the reported increased atherosclerotic cardiovascular disease (ASCVD) risk associated with very high lipoprotein(a) [Lp(a)] and to investigate the impact of routine Lp(a) assessment on risk reclassification.

Methods and results We performed a cross-sectional case-control study in the Amsterdam UMC, a tertiary hospital in The Netherlands. All patients in whom a lipid blood test was ordered between October 2018 and October 2019 were included. Individuals with Lp(a) >99th percentile were age and sex matched to individuals with Lp(a) ≤20th percentile. We computed odds ratios (ORs) for myocardial infarction (MI) and ASCVD using multivariable logistic regression adjusted for age, sex, and systolic blood pressure. Furthermore, we assessed the additive value of Lp(a) to established ASCVD risk algorithms. Lipoprotein(a) levels were determined in 12 437 individuals, out of whom 119 cases [Lp(a) >99th percentile; >387.8 nmol/L] and 119 matched controls [Lp(a) ≤20th percentile; ≤7 nmol/L] were included. Mean age was 58 ± 15 years, 56.7% were female, and 30.7% had a history of ASCVD. Individuals with Lp(a) levels >99th percentile had an OR of 2.64 for ASCVD [95% confidence interval (CI) 1.45–4.89] and 3.39 for MI (95% CI 1.56–7.94). Addition of Lp(a) to ASCVD risk algorithms led to 31% and 63% being reclassified into a higher risk category for Systematic Coronary Risk Evaluation (SCORE) and Second Manifestations of ARTerial disease (SMART), respectively.

Conclusion The prevalence of ASCVD is nearly three-fold higher in adults with Lp(a) >99th percentile compared with matched subjects with Lp(a) ≤20th percentile. In individuals with very high Lp(a), addition of Lp(a) resulted in one-third of patients being reclassified in primary prevention, and over half being reclassified in secondary prevention.

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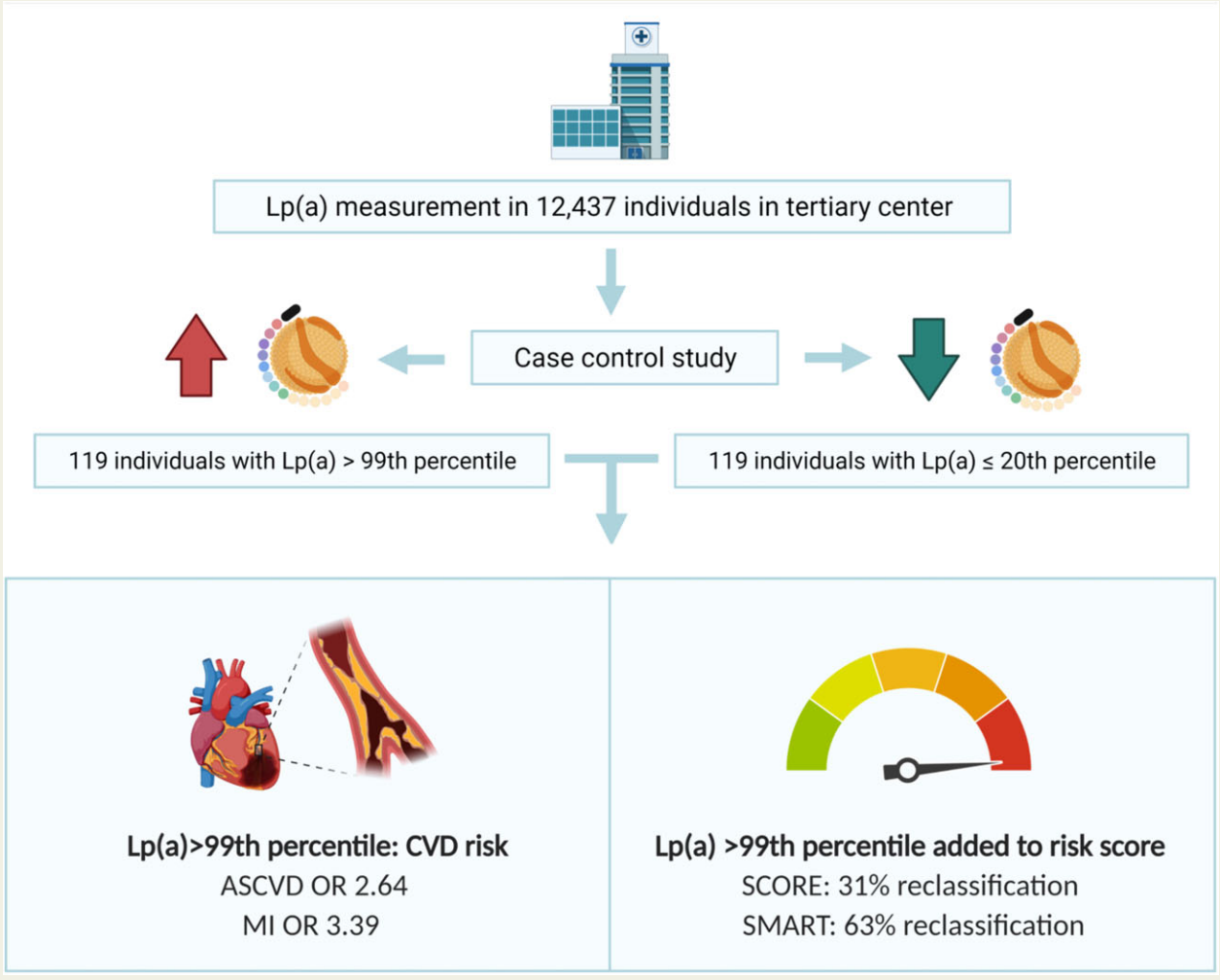
Graphical Abstract



Overview of study design and results of included participants in this study. Controls were matched to cases according to age and sex.

Keywords Lipoprotein(a) • Cardiovascular risk • Reclassification

Introduction

Lipoprotein(a) [Lp(a)], consisting of a lipid-laden apoB-100 particle covalently bound to an apolipoprotein(a) [apo(a)] tail, is an independent and likely causal risk factor for atherosclerotic cardiovascular disease (ASCVD).[1–4] Individuals with very high Lp(a) levels (>430 nmol/L; ∼180 mg/dL) are considered to have a more than three-fold increased lifetime risk of ASCVD, which is comparable to heterozygous familial hypercholesterolaemia (FH) patients.[5] Even though very high Lp(a) is ∼2.5 times more prevalent than heterozygous FH (1:100 vs. 1:250), the vast majority of individuals remains unidentified because standard lipid profiling does not include Lp(a) measurement.[5–7]

The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias recommend to measure Lp(a) at least once in every person's life.[8] Yet, routine lipid assessment does not include Lp(a) in the majority of hospitals, nor do modern-day ASCVD risk algorithms such as the Systematic Coronary Risk Evaluation (SCORE)[9] and Second Manifestations of ARTerial disease (SMART) incorporate Lp(a).[10] The cause of this deviation from guidelines is likely multifactorial.[11] First, national guidelines still report conflicting cut-offs for Lp(a) elevation, which is further complicated by the use of a wide variety of Lp(a) assays, reporting either Lp(a) mass or particle concentration. Second, the use of Lp(a) as a dichotomous rather than continuous parameter results in minimal improvements in risk stratification: Lp(a) levels of 50 mg/dL would be considered to carry the same risk as very high Lp(a) levels (>180 mg/dL), even though the linear relationship between increasing Lp(a) levels and ASCVD risk has been well established. Finally, the absence of available specific Lp(a)

lowering interventions has restricted therapeutic consequences of Lp(a) elevation.

In the present study, we set out to evaluate the clinical impact of a single routine measurement of Lp(a) on cardiovascular disease (CVD) risk reclassification and the potential implications for guideline-based preventive therapy in patients with very high Lp(a) levels.[6] To this end, we aimed to substantiate the increased ASCVD risk associated with very high Lp(a) levels. Next, we determined what proportion of these individuals would be reclassified to a higher risk category by adding Lp(a) to the SCORE and SMART algorithms. For this purpose, we routinely measured Lp(a) during 1 year in all individuals undergoing clinical lipid profiling in a tertiary hospital setting.

Methods

Study design and participants

Lipoprotein(a) levels were determined in all patients who underwent clinical lipid profiling between October 2018 and October 2019 in the Amsterdam University Medical Centre. Patients were defined as case if they had very high Lp(a) levels >99th percentile, consistent with the 2019 ESC/EAS Guidelines.[12] Cases were matched by age and sex to a random selection of individuals with low Lp(a) levels (≤20th percentile) from the same sample in a 1:1 ratio. All patients aged 18 years or older who fulfilled the criteria for case or control were included. All data were collected from electronic medical records. Patients were asked for consent for the use of clinical data through an opt-out procedure, which was approved.

Lipid measurements

Lipoprotein(a) concentrations were measured in nmol/L by an isoform independent, second-generation assay (Roche Diagnostics, Mannheim, Germany). Plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured in a core laboratory from the same plasma sample as Lp(a). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula and corrected for Lp(a) cholesterol by subtracting 17.3% of total Lp(a) mass from LDL-C, based on recent insights from a direct Lp(a) cholesterol quantification assay.[13]

Primary and secondary outcomes

The primary outcome consisted of ASCVD prevalence, which was a composite of prior fatal or non-fatal myocardial infarction (MI), revascularization therapy (coronary artery bypass graft surgery and percutaneous coronary intervention), ischaemic stroke, and peripheral arterial disease. Prevalence of MI was studied as a key secondary outcome. Other secondary outcomes consisted of the use of lipid-lowering therapy (LLT), the achievement of LDL-C treatment targets for primary and secondary prevention and the effect of Lp(a) addition to established ASCVD risk algorithms on risk classification. Patients without data available on the primary outcome were excluded.

Statistical analysis

Baseline characteristics are described as mean ± standard deviation for normally distributed data, as median [interquartile range (IQR)] for non-normally distributed data or as number (percentage) for count data, and were compared using the unpaired *T*-test, Mann–Whitney *U* test, and χ^2 test, respectively. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the primary and secondary outcomes using multivariable logistic regression. Models were adjusted for age, sex, and systolic blood pressure.

To determine the achievement of LDL-C treatment targets in a primary prevention setting, we first stratified patients without clinically manifest CVD into established risk categories based on their 10-year predicted risk of CVD mortality according to the SCORE.[9] Patients with a 10-year predicted risk <5% were classified as low risk, 5–10% as intermediate risk, and ≥10% as high risk. Next, we calculated the percentage of high- and intermediate-risk patients who achieved LDL-C levels <2.6 mmol/L, which is the recommended target by Dutch national guidelines in patients with a 10-year risk of CVD mortality ≥5%.[14] To assess the achievement of LDL-C treatment targets in secondary prevention, we applied the same Dutch guidelines, which recommend an LDL-C level <1.8 mmol/L in all patients with overt CVD.[14] For both primary and secondary prevention, we also calculated the proportion of patients treated with LLT that reached their guideline-recommended treatment target of 2.6 and 1.8 mmol/L, respectively.

To assess the additive value of Lp(a) levels to established ASCVD risk algorithms, we first calculated the 10-year predicted risk of recurrent vascular events using the SMART and the 10-year predicted risk of CVD mortality using SCORE for patients with and without overt ASCVD, respectively.[9,10] Randomly missing variables were imputed using multiple imputation by chained equations. We created 25 imputed copies of the original data set and pooled the estimates from the regression analyses. For SMART, the 10-year predicted risk of recurrent ASCVD events was classified into five categories: <10% was classified as low risk, 10–20% as moderate risk, 20–30% as high risk, 30–40% as very high risk, and ≥40% as extremely high risk.[10] Next, we multiplied the SCORE and SMART score with ORs for Lp(a) increase above the population average from two observational cohorts in both primary and secondary prevention. For primary prevention, we added Lp(a) to the SCORE algorithm using the following formula: 10-year predicted SCORE risk × 1.16 ^ [(Lp(a) in nmol/L − 28.2 nmol/L)/105 nmol/L]. This formula was based on the observation by Langsted *et al.*[3] that every 105 nmol/L Lp(a) increase above the median level results in a hazard ratio of 1.16 for CVD mortality. For secondary prevention, we added Lp(a) to the SMART algorithm using this formula: 10-year predicted SMART risk × 1.04 ^ [(Lp(a) in nmol/L − 28.2 nmol/L)/50 nmol/L]. This formula was based on the observation by Patel *et al.*[15] that every 50 nmol/L Lp(a) increase above the median level results in a hazard ratio of 1.04 for recurrent ASCVD events. All statistical analyses were performed using R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between October 2018 and October 2019, Lp(a) levels were determined in 12 437 patients who underwent clinical lipid profiling (Graphical abstract) in our centre. In our study population, the 99th Lp(a) percentile corresponded to 387.8 nmol/L. Twenty-four patients were not included in the analysis because they refused consent through the opt-out procedure for data collection from their electronic medical records. Of the remaining 12 413 patients, 122 individuals with very high Lp(a) levels fulfilled the inclusion criteria, three of which were excluded because of missing data on the primary outcome. The included 119 cases were matched to an equal number of control subjects with Lp(a) ≤20th percentile. The mean age of all included patients was 57.8 ± 15 years and 56.7% (135) were female (*Table 1*). In total, 30.7% (73) patients had a history of ASCVD. The median Lp(a) in the very high Lp(a) group was 460 nmol/L (IQR 418–533), compared with 7 nmol/L (IQR 7–7) in the low Lp(a) group

Table 1 Baseline characteristics of patients with very high and low lipoprotein(a) levels

	Lp(a) >99th percentile	Lp(a) ≤20th percentile	*P*-value
Number of individuals	119	119	
Age (years)	59 (14)	57 (16)	0.372
Women	68 (57.1)	67 (56.3)	1.000
Lp(a) (nmol/L)	459.6 (417.9–532.7)	7.0 (7.0–7.0)	<0.001
Total cholesterol (mmol/L)	5.14 (1.57)	4.73 (1.30)	0.032
LDL cholesterol, Lp(a) corrected (mmol/L)	2.08 (1.32)	2.52 (1.03)	0.007
HDL cholesterol (mmol/L)	1.47 (0.47)	1.46 (0.46)	0.894
Triglycerides (mmol/L)	1.29 (0.92–1.84)	1.29 (0.78–1.84)	0.875
Body mass index (kg/m^2)	26.9 (4.9)	25.4 (5.1)	0.456
Systolic blood pressure (mmHg)	134 (17)	131 (18)	0.097
Diastolic blood pressure (mmHg)	81 (12)	79 (12)	0.238
eGFR (mL/min/1.73 m^2)	64 (23)	74 (18)	0.001
Hypertension	72 (60.5)	49 (41.2)	0.004
Diabetes mellitus type 2	28 (23.5)	16 (13.4)	0.066
Current smoker	18 (15.9)	24 (22.2)	0.308
Lipid-lowering therapy	83 (70.3)	50 (42.0)	<0.001
Antihypertensives	75 (63.0)	58 (48.7)	0.037
Antidiabetics	27 (23.1)	18 (15.3)	0.174
Antiplatelet therapy	49 (41.5)	26 (21.8)	0.002
Anticoagulants	8 (6.8)	12 (10.1)	0.508
ASCVD	48 (40.3)	25 (21.0)	0.002
Myocardial infarction	27 (22.7)	10 (8.4)	0.004
Revascularization therapy	27 (22.7)	9 (7.6)	0.002
Ischaemic stroke	12 (10.1)	7 (5.9)	0.339
Peripheral arterial disease	11 (9.2)	8 (6.7)	0.632

Data are presented as mean (standard deviation) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables. ASCVD consisted of fatal or non-fatal myocardial infarction, revascularization therapy (coronary artery bypass graft surgery or percutaneous coronary intervention), ischaemic stroke, and peripheral arterial disease.
ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); HDL, high-density lipoprotein.

(*Table 1*; $P < 0.001$). As expected, uncorrected LDL-C levels were higher in the very high Lp(a) group compared to the low Lp(a) group (3.01 ± 1.30 vs. 2.53 ± 1.03 mmol/L; $P = 0.003$), while corrected LDL-C levels were lower in the very high Lp(a) group (2.08 ± 1.32 vs. 2.52 ± 1.03 mmol/L; $P = 0.007$). Use of antihypertensive and antiplatelet therapy was significantly higher among individuals with very high Lp(a) levels than in controls. Missing data percentages were 1.3% for systolic blood pressure, 7.1% for smoking, 5.9% for LDL-C, 4.2% for HDL-C, 4.6% for total cholesterol, and 7.6% for estimated glomerular filtration rate (eGFR). The baseline table shows the original, non-imputed values.

Prevalence of atherosclerotic cardiovascular disease and myocardial infarction

The prevalence of ASCVD was 40.3% in the very high Lp(a) group compared with 21.0% in the low Lp(a) group ($P = 0.002$). Prevalence of MI was also significantly higher in patients with very high Lp(a) levels compared to patients with low Lp(a) levels (22.7% vs. 8.4%; $P = 0.004$). Multivariable-adjusted ORs were 2.64 (95% CI 1.46–4.88, $P = 0.002$) for ASCVD and 3.39 (95% CI 1.56–7.93, $P = 0.003$) for MI (*Table 2*). Mean age of first ASCVD event was 54 ± 12 years in the very high Lp(a) group and 58 ± 11 years in the low Lp(a) group ($P = 0.232$). For MI, this was 56 ± 11 and 60 ± 9 years for very high and low Lp(a) levels, respectively ($P = 0.315$). Since eGFR differed significantly between the two groups at baseline, we performed an additional regression analysis including eGFR, which did not materially impact the findings.

Use of lipid-lowering therapy and achievement of low-density lipoprotein cholesterol targets

In the very high Lp(a) group, 70.3% patients used at least one type of LLT, compared with 42.0% patients with low Lp(a) levels (*Table 3*; $P < 0.001$). In patients with very high Lp(a) levels, LLT predominantly consisted of statins (90.4%), followed by ezetimibe (50.6%), PCSK9 inhibitors (13.3%), and fibrates (2.4%). In the low Lp(a) group, this was 90.0%, 20.0%, 6.0%, and 4.0% for statins, ezetimibe, PCSK9 inhibitors, and fibrates, respectively. Two or more types of LLT were used by 33.9% patients with very high Lp(a) levels and 8.4% patients with low Lp(a) levels (*Table 3*; $P < 0.001$). In primary prevention, 51.3% of patients with intermediate or high risk according to SCORE reached

Table 2 Odds ratios for atherosclerotic cardiovascular disease and myocardial infarction

	Model 1: ASCVD			Model 2: MI		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Lp(a) >99th percentile	2.64	1.45–4.89	0.002	3.39	1.56–7.94	0.003

ASCVD consisted of fatal or non-fatal myocardial infarction, revascularization therapy (coronary artery bypass graft surgery or percutaneous coronary intervention), ischaemic stroke, and peripheral arterial disease.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; Lp(a), lipoprotein(a); MI, myocardial infarction; OR, odds ratio.

Table 3 Use of lipid-lowering therapy in primary and secondary prevention

	Lp(a) >99th percentile	Lp(a) ≤20th percentile	*P*-value
Primary prevention			
≥1 lipid-lowering drug	39/70 (55.7%)	28/94 (29.8%)	0.001
≥2 lipid-lowering drugs	22/70 (31.4%)	4/94 (4.3%)	<0.001
Secondary prevention			
≥1 lipid-lowering drug	44/48 (91.7%)	22/25 (88%)	0.931
≥2 lipid-lowering drugs	18/48 (37.5%)	6/25 (24%)	0.367

Data are presented as numbers, percentages, or ratios.
Lp(a), lipoprotein(a).

their recommended LDL-C target of <2.6 mmol/L. In secondary prevention, 27.4% of patients reached their recommended LDL-C target of <1.8 mmol/L. The proportion of patients in both primary and secondary prevention treated with LLT reaching their recommended LDL-C target was 39.8% in the very high Lp(a) group compared to 58.0% in the low Lp(a) group ($P = 0.041$).

Risk reclassification

After incorporating Lp(a) levels into the SCORE algorithm, the mean estimated 10-year CVD mortality risk increased from 2.8% to 3.9% in the primary prevention subset. In the very high Lp(a) group, this resulted in the upward reclassification of 31.0% of patients (*Table 4* and *Figure 1A*). Incorporation of Lp(a) levels in the SMART algorithm led to an increase in the mean estimated 10-year recurrent ASCVD risk from 24.8% to 32.5% in the secondary prevention subset. This led to reclassification of 62.5% of patients with very high Lp(a) levels to a higher risk category (*Table 4* and *Figure 1B*).

Discussion

We show that patients with Lp(a) levels >99th percentile have an OR of 3.4 for MI and 2.6 for ASCVD compared with age- and sex-matched patients with low Lp(a) ≤20th percentile. Incorporation of Lp(a) into ASCVD risk algorithms resulted in the reclassification of 31% and 63% of individuals with very high Lp(a) levels to a higher risk category for SCORE (primary prevention) and SMART (secondary prevention), respectively. Despite more intensive LLT, patients with very high Lp(a) levels were less likely to achieve their LDL-C treatment target than patients in the low Lp(a) group. Collectively, these data underscore the profound impact of a single Lp(a) measurement on risk reclassification of patients with very high Lp(a) levels, lending further support to routinely measure Lp(a) in patients evaluated for cardiovascular risk management.

Atherosclerotic cardiovascular disease risk associated with very high lipoprotein(a)

The observed risks of ASCVD and MI in individuals with very high Lp(a) levels in our study are in accordance with the previously reported three- to four-fold increased risk observed in population studies, which evaluated both genetically predicted and plasma Lp(a) concentrations.[1,5,15] This confirms that the ASCVD risk associated with very high Lp(a) is equivalent to that of heterozygous FH. Importantly, very high Lp(a) may even have a greater impact on the overall population burden of ASCVD, since very high Lp(a) elevation is an approximately two to three times more prevalent condition than heterozygous FH. Unfortunately, in absence of routine Lp(a) testing the vast majority of individuals with very high Lp(a) remains unidentified, even after having experienced an ASCVD event. Timely identification as well as treatment initiation in these individuals, even in absence of specific Lp(a) lowering therapies, could greatly reduce their ASCVD burden.

Impact of lipoprotein(a) on cardiovascular risk stratification

Several studies have evaluated the effect Lp(a) addition to ASCVD risk prediction scores, reporting improved risk classification.[12,16–18] However, overall improvements were modest due to the use of specific Lp(a) cut-offs rather than continuous values, the use of different Lp(a) assays, and the previous lack of predictive power to adequately

Table 4 Reclassification tables of lipoprotein(a) addition to clinical risk algorithms in the very high lipoprotein(a) group

A SCORE without Lp(a)	SCORE with Lp(a)				Reclassified into higher risk category	
	High risk	Intermediate risk	Low risk	Total	Number	Total (%)
High risk	4			4		
Intermediate risk	**11**	1		12	**11**	15.5
Low risk	**0**	**11**	44	55	**11**	15.5
Total	16	12	44	71	**22**	31.0

B SMART without Lp(a)	SMART with Lp(a)						Reclassified into higher risk category	
	Extremely high risk	Very high risk	High risk	Moderate risk	Low risk	Total	Number	Total (%)
Extremely high risk	10					10		
Very high risk	**4**	0				4	**4**	8.3
High risk	**3**	**5**	0			8	**8**	16.7
Moderate risk	**0**	**1**	**11**	6		18	**12**	25.0
Low risk	**0**	**0**	**0**	**6**	2	8	**6**	12.5
Total	16	7	11	12	2	48	**30**	62.5

(A) Risk reclassification table of Lp(a) addition to SCORE in primary prevention. (B) Risk reclassification table of Lp(a) addition to SMART in secondary prevention. Data are presented as numbers or percentages. Numbers in red represent the number of Lp(a) patients with very high Lp(a) who were reclassified into a higher risk category.
Lp(a), lipoprotein(a); SCORE, Systematic Coronary Risk Evaluation; SMART, Second Manifestations of ARTerial disease.

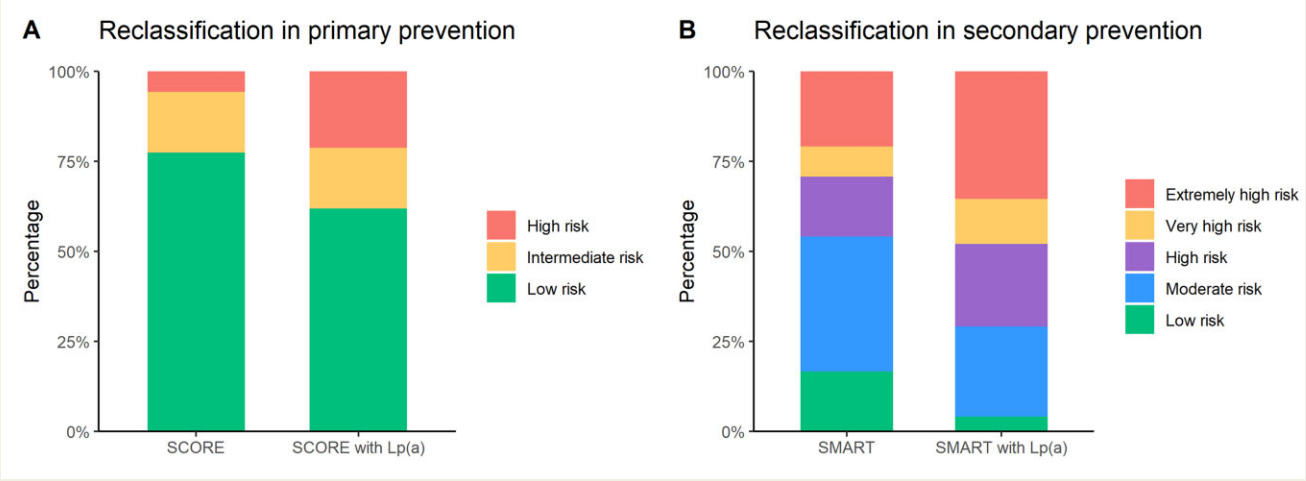


Figure 1 Risk reclassification in patients with very high lipoprotein(a) in primary and secondary prevention setting. Stacked bar charts showing the proportional distribution of patients in the very high lipoprotein(a) group across different risk categories based on the SCORE (*A*) and SMART (*B*) algorithm without lipoprotein(a) (left bar) and after addition of lipoprotein(a) (right bar). Lp(a), lipoprotein(a); SCORE, Systematic Coronary Risk Evaluation; SMART, Second Manifestations of ARTerial disease.

assess the risk of ASCVD associated with very high Lp(a) levels. Contemporary Lp(a) assays and large-scale data from population studies have substantiated the linear relationship between increasing Lp(a) levels and ASCVD risk. By providing a quantitative risk estimate per unit Lp(a) increase, we were able to incorporate the risk associated with Lp(a) into ASCVD risk algorithms on the individual patient level instead of the previously used 50 mg/dL cut-off. The observed high rate of reclassification in patients with very high Lp(a) but no ASCVD in the present study underscores a valuable role for Lp(a) in refining ASCVD risk assessment in patients at the far end of the Lp(a) spectrum. In primary prevention, 75% of patients with very high Lp(a) were initially classified as low risk according to the conventional SCORE algorithm.

The majority of these patients would not have qualified for cardiovascular risk management in absence of the Lp(a) screening. After incorporating their Lp(a) levels into the SCORE algorithm, one-third of primary prevention patients with high Lp(a) were reclassified into a higher risk category. In secondary prevention, more than half of all patients with very high Lp(a) were reclassified into a higher risk category after incorporation of Lp(a) into the SMART algorithm.

Target attainment in individuals with very high lipoprotein(a)

Our study demonstrates that patients with ASCVD and very high Lp(a) levels were less successful in attaining their LDL-C treatment target than patients with low Lp(a) levels, despite higher as well as more intensive use of LLT. With over 90% of patients with ASCVD and very high Lp(a) levels using at least one lipid-lowering drug and a combination of several LLTs, only one in four achieved the recommended LDL-C target of 1.8 mmol/L in secondary prevention. The large difference in the proportion of treated patients reaching their LDL-C target between very high vs. low Lp(a) subjects most likely reflects the inability to potently reduce LDL-C levels in very high Lp(a) subjects, because measured LDL-C in these patients mainly reflects high Lp(a) cholesterol. Statin therapy has even been shown to increase circulating Lp(a) levels by ~10–20%.[6,19] With standard of care LLTs being less effective, these patients could benefit from more intensive LDL-C lowering [e.g. by PCSK9 inhibitors, which also modestly lower Lp(a)], or a specific Lp(a) lowering compound such as apo(a) antisense, when approved.[20–22]

Study limitations

Several limitations of this study require closer attention. First, data were ascertained through electronic patient records, which may have contained incomplete or outdated information. Second, the researchers collecting the data from electronic medical records were not blinded to participants' exposure status, i.e. Lp(a) values, which may have introduced bias in collecting the data. To minimize any potential bias, data collection was checked by a third independent researcher. Third, due to privacy and capacity restrictions, we were only able to assess the group of patients with very high Lp(a) levels. It is likely that there would be considerable reclassification at lower Lp(a) levels as well. Last, data were obtained in a large academic hospital, which may limit generalizability to the general population, since Lp(a) levels and prevalence of other ASCVD risk factors in included patients could be higher than in the general population as a result from hospital selection bias. Future studies will need to address these questions to validate the generalizability of our observations.

Conclusions

The prevalence of ASCVD and MI is approximately three-fold higher in adults with Lp(a) levels >99th percentile compared to adults with Lp(a) levels ≤20th percentile. The incorporation of Lp(a) into established ASCVD risk algorithms results in reclassification for one-third of individuals with very high Lp(a) in primary prevention and more than half of individuals with very high Lp(a) in secondary prevention. Our findings highlight the profound impact of Lp(a) on cardiovascular risk stratification, lending further support to routine measurement of Lp(a) as an integral part of cholesterol measurement.

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The graphical abstract in this manuscript was created with BioRender.com.

Data availability statement

The data underlying this article cannot be shared publicly due to privacy regulations. The data will be shared on reasonable request to the corresponding author.

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