ESC European Society of Cardiology

European Journal of Preventive Cardiology (2025) **00**, 1–10
https://doi.org/10.1093/eurjpc/zwaf036

FULL RESEARCH PAPER
CVD risk factors

Impact of diabetes on risk of major adverse cardiovascular events associated with lipoprotein(a) levels in patients with established atherosclerotic cardiovascular disease

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Received 22 August 2024; revised 1 November 2024; accepted 21 January 2025; online publish-ahead-of-print 11 March 2025

Aims Lipoprotein(a) [Lp(a)] is an emerging risk factor for major adverse cardiovascular events (MACE). However, evidence on MACE risk according to Lp(a) level in atherosclerotic patients is insufficient, and more data is needed about whether type 2 diabetes (T2DM) additionally contributes to this risk. We aimed to investigate the association between Lp(a) and MACE in atherosclerotic patients and compare the magnitude of Lp(a)-MACE association in the patients with and without T2DM.

Methods and results Using a retrospective cohort study of atherosclerotic patients with and without T2DM who were screened for Lp(a) between 1 January 2000 to 31 December 2020, we estimated the risk of MACE according to Lp(a) level stratified by quintiles and compared the difference in magnitude of Lp(a)-MACE association according to presence of T2DM with partial likelihood ratio test. The study included 25 826 patients with established atherosclerotic cardiovascular disease, of whom 7535 had T2DM (29.2%) and 18 291 did not (70.8%). During 160 174 person-years (PY) of follow-up, a total of 4836 MACE were observed. Compared to the lowest quintile (Q) of Lp(a) levels, multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for MACEs across Q2 to Q5 were 1.10 (95% CI: 0.94–1.30), 0.98 (95% CI: 0.83–1.16), and 1.25 (95% CI: 1.06–1.46), 1.29 (95% CI: 1.10–1.51) in patients with T2DM, and 0.99 (95% CI: 0.88–1.12), 1.10 (95% CI: 0.98–1.23), 1.01 (95% CI: 0.90–1.13), and 1.13 (95% CI: 1.01–1.27) for those without T2DM. The strength of Lp(a)-MACE association was stronger among the patients with T2DM ($P < 0.001$).

Conclusion Among atherosclerotic patients with and without T2DM, elevated Lp(a) level was significantly associated with a higher risk of MACE. Compared to those without T2DM, the patients with T2DM showed an excess MACE risk, suggesting the need for clinical interventions concerning both Lp(a) level and glycemic control.

Lay Summary

- In a population-based study of 25 826 patients with established atherosclerotic cardiovascular disease, we found a significant association between elevated lipoprotein(a) and an increased risk of incident major adverse cardiovascular events in the patients with and without type 2 diabetes mellitus.

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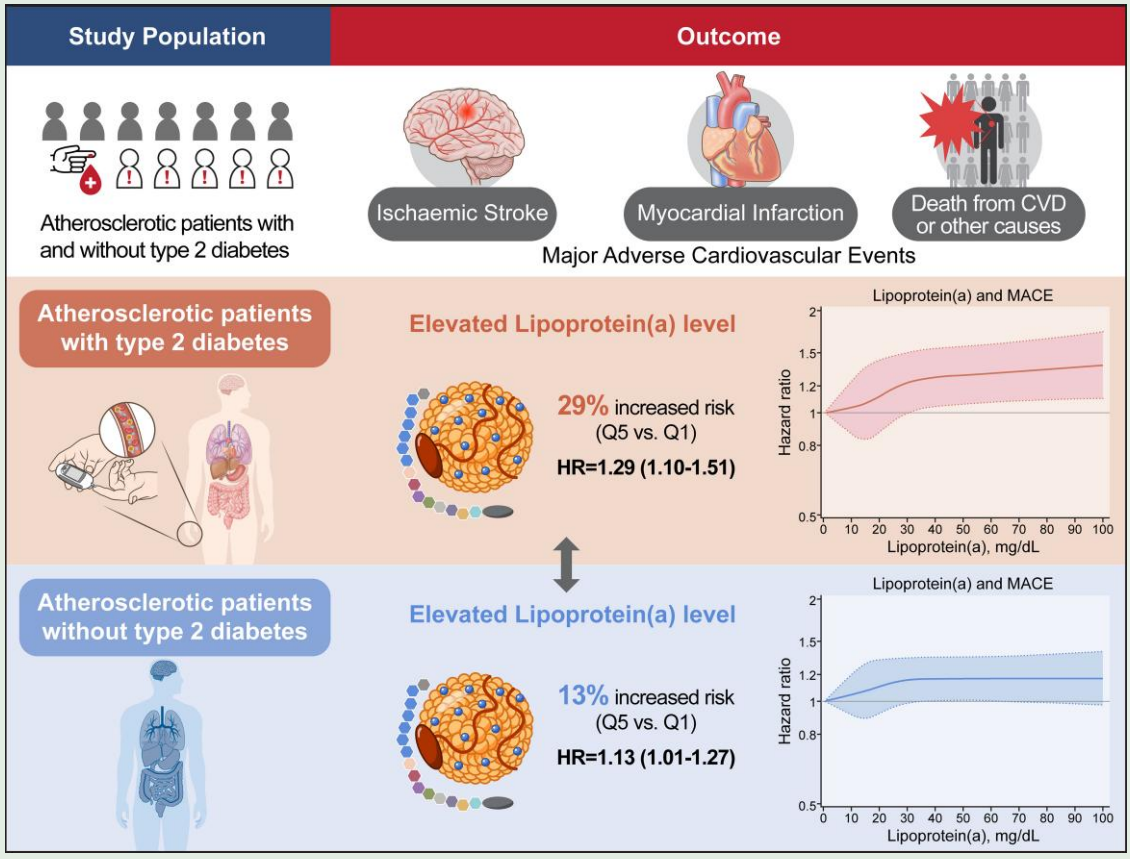
- However, patients with established atherosclerotic cardiovascular disease with type 2 diabetes mellitus exhibited excess risk of major adverse cardiovascular disease for the same unit increase in lipoprotein(a) compared to those without type 2 diabetes mellitus.
- This study highlights the need for additional clinical attention, personalized risk assessment, and prevention strategies for patients with established atherosclerotic cardiovascular disease, particularly among those with type 2 diabetes mellitus.

Graphical Abstract



Keywords Lipoproteins(a) • Cardiovascular disease • Atherosclerosis • Diabetes mellitus

Introduction

Lipoprotein(a) [Lp(a)] is a unique lipoprotein particle comprising apolipoprotein B-100 linked to apolipoprotein(a) via a disulfide bond.[1,2] While sharing structural similarities with low-density lipoprotein (LDL) cholesterol, Lp(a) exhibits distinctive proatherogenic properties, including pro-inflammatory, prothrombotic, and endothelial dysfunction effects, which eventually increase susceptibility to atherosclerosis and cardiovascular disease (CVD) among individuals with elevated Lp(a) level.[3–6] Recently, several observational studies have shown that elevated Lp(a) level is an independent risk factor for major adverse cardiovascular events (MACE) such as heart failure, coronary heart disease, stroke, or CVD death.[7–15] However, most studies examining this association were conducted among patients without established atherosclerotic cardiovascular disease (ASCVD). Current guidelines from the *American Heart Association (AHA)/American Stroke Association (ASA)* and *European Society of Cardiology (ESC)* highlight the clinical importance of treatment and management of CVD risk factors for patients with established ASCVD.[16,17] Among the CVD risk factors highlighted in the AHA/ASA and ESC guidelines, type 2 diabetes (T2DM) is a well-established risk factor for MACE.[18,19] Notably, a large UK cohort study of nearly 2 million individuals showed that T2DM is associated with 1- to 3-fold increased risk of MACE.[20]

Among atherosclerotic patients with elevated Lp(a), the presence of T2DM may have a potential for excess risk of MACE as compared to those without T2DM.[21,22] In addition, evidence from previous studies suggests that comprehensive approach (i.e. use of glucose-lowering agents such as sodium-glucose cotransporter 2 inhibitor alongside with other medication and lifestyle improvement) should be taken for reduction of CVD risk in patients with T2DM.[23] While a few observational and intervention studies have investigated association of Lp(a) with CVD complications, there is a notable evidence gap regarding the association of Lp(a) level and MACE in patients with established ASCVD. Moreover, evidence regarding the potential effect of T2DM

on the association between Lp(a) level and MACE among patients with established ASCVD remains insufficient and inconclusive.

To address this evidence gap, the aim of this study was to investigate the association of Lp(a) and MACE in patients with established ASCVD with and without T2DM. We also tested the hypothesis that T2DM exacerbates the MACE risk in the patients with high Lp(a) levels by comparing the difference in magnitude of this association using a population-based cohort.

Methods

Study design, population, and data collection

We identified patients with established ASCVD (unstable angina or myocardial infarction [MI], stable angina, asymptomatic coronary artery disease [CAD], transient ischemic attack or ischaemic stroke, and peripheral artery disease) aged 18 years or older admitted to Asan Medical Center (AMC) in Seoul, Republic of Korea between 1 January 2000 to 31 December 2020 who were screened for Lp(a) at or within 6 months prior to the admission (i.e. measurement date nearest to the admission date was used). Only those with complete data for all variables of interest were included in the final study cohort and subsequent analyses. Details of ASCVD classification in clinical research data warehouse based on ICD-10 codes and medical utilization are available in Supplementary material online, Table *S1*.Of these 29 868 patients with established ASCVD, those with history of hemorrhagic or lacunar stroke ($n = 455$), systolic blood pressure (BP) > 180 mmHg or diastolic BP >110 mmHg ($n = 1727$), or history of cancer ($n = 1860$) were excluded. Finally, a total of 25 826 patients were enrolled in the analytic cohort (*Figure 1*). Details of the clinical research data warehouse derived from the AMC are available elsewhere.[24] This study was approved by the Institutional Review Board (IRB) at AMC (IRB No.: 20 231 001) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. To ensure the privacy of the patients, all data were anonymized before constructing the cohort and conducting data analysis following the guidelines established by the AMC (Seoul, Republic of Korea).

Assessment of lipoprotein(a) level and type 2 diabetes

Among the patients with established ASCVD, Lp(a) concentration was quantified with immune-nephelometric assay (BN II, Behring, Germany), and the results were calibrated to internal reference samples provided by Simens Health Diagnostics in mg/dL and categorized into quintiles. T2DM was defined with *International Classification of Diseases, Tenth Revision (ICD-10)* codes E11–E14 and glycated hemoglobin (HbA1c) level greater than or equal to 6.5% at the time of Lp(a) measurement according to the *European Association for the Study of Diabetes*, which is also in compliance with the *American Diabetes Association* and *World Health Organization* criteria.[25–27] In addition, antidiabetic medication (biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose cotransporter 2 [SGLT2] inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, and insulin) were documented among patients with T2DM. Based on the diagnostic criteria and medication data, patients with Lp(a) measurements were categorized as those with T2DM ($n = 7535$) and those without T2DM ($n = 18\,291$).

Covariate assessment

Using the unique personal identity number assigned to each citizen by the Ministry of Public Administration and Security in the Republic of Korea, we identified subtypes of established ASCVD (unstable angina or MI, stable angina, asymptomatic CAD, transient ischemic attack or ischaemic stroke, and peripheral artery disease), chronic kidney disease (CKD), and hypertension within the AMC clinical research data warehouse based on ICD-10 codes and medical utilization (see Supplementary material online, Table *S1* in Supplement *S1*). Demographic characteristics, lifestyle factors, and health status were assessed concurrently with Lp(a) measurement. Clinical data, such as medication history and laboratory test results, were collected either at the time of Lp(a) measurement or within the preceding 12 months. From the demographic and clinical information, the patients were categorized by age (≤39, 40–59, 60–69, ≤ 70 years), sex (male, female), cigarette smoking (never smoker, past smoker, current smoker), medication use (statin, ezetimibe, other lipid-lowering treatments [fibrate, niacin, and cholestyramine], aspirin, P2Y purinergic receptor 12 [P2Y12] inhibitors, beta-blockers, renin–angiotensin–aldosterone system [RAAS] inhibitors), and calcium channel blockers were also identified. Measurements of body mass index (BMI), systolic or diastolic BP, triglycerides, LDL-cholesterol, and high-density lipoprotein (HDL)-cholesterol, urinary albumin, and creatinine were collected as continuous variables.

Ascertainment of outcomes

The primary endpoint of this study was MACE, a composite outcome MI, ischemic stroke, or death from CVD or other causes. MI was defined as outpatient visit, hospitalization, or emergency room admission along with records for coronary angiography or percutaneous coronary intervention within a week from the initial diagnosis date according to the ICD-10 codes I21-I23. Ischaemic stroke (ICD-10 code: I63) events were identified with at least one brain imaging with computed tomography or magnetic resonance imaging within a week from the initial diagnosis date. Records on death date and cause of death were collected from in-hospital death certificates. MACE cases were confirmed by at least two specialists with previously established criteria for the AMC database.

Statistical analysis

Patients were follow-up from the index date [i.e. Lp(a) screening date] to the first date of MACE or 31 December 2020, whichever occurred first. We calculated incidence rate (IR) per 1000 person-years (PYs) by dividing the number of MACE by the total PYs in each quintile of Lp(a) level. After checking the proportionality assumption with Schoenfeld residual, we calculated age-and sex-adjusted and multivariable-adjusted hazard ratio (HR) and 95% confidence intervals (CIs) using Cox proportional hazards model after adjusting for age, sex, cigarette smoking, BMI, hypertension, triglyceride, HDL-C, LDL-C, CKD, statin, ezetimibe use, other lipid-lowering drugs, and Lp(a) screening year. The partial likelihood ratio test was employed to assess the comparative magnitude of the association between Lp(a) level and MACE risk among the patients with and without T2DM. To further investigate the association of Lp(a) level and MACE in ASCVD patients with and without T2DM, we fitted the restricted cubic spline model with four knots placed at the 5th, 35th, 65th, and 95th percentiles using the confounding variables in the multivariable-adjusted Cox regression model. We conducted subgroup analyses according to age (<70 years, ≥ 70 years), sex (male, female), cigarette smoking (non-smoker, smoker), BMI (<25.0 kg/m^2, ≥ 25.0 kg/m^2), triglyceride (<150 mg/dL, ≥ 150 mg/dL), LDL-C (<55 mg/dL, ≥ 55 mg/dL), statin use (yes, no), CKD (yes, no), and ASCVD subtypes (stable angina, asymptomatic CAD, others). Interaction terms were assessed using likelihood ratio tests across all subgroups.

In sensitivity analyses, several approaches were undertaken. First, we applied inverse probability of treatment weighting (IPTW) to create a weighted pseudo-population cohort using the same variables included in the multivariable Cox regression model. In this approach, the weight corresponding to the inverse probability of being T2DM was assigned to each participant based on the confounding variables. The IPTW aimed to balance baseline characteristics between exposure groups, which was verified by examining standardized differences. Subsequently, Lp(a) level and MACE in ASCVD patients with and without T2DM were assessed in the cohort of pseudo-population. Second, we excluded MACE events that occurred up to 5 years of follow-up to minimize bias from risk estimates attributable to immortal time (i.e. patients under observation who are not yet fully exposed to the risk associated with the study outcome). Third, we additionally

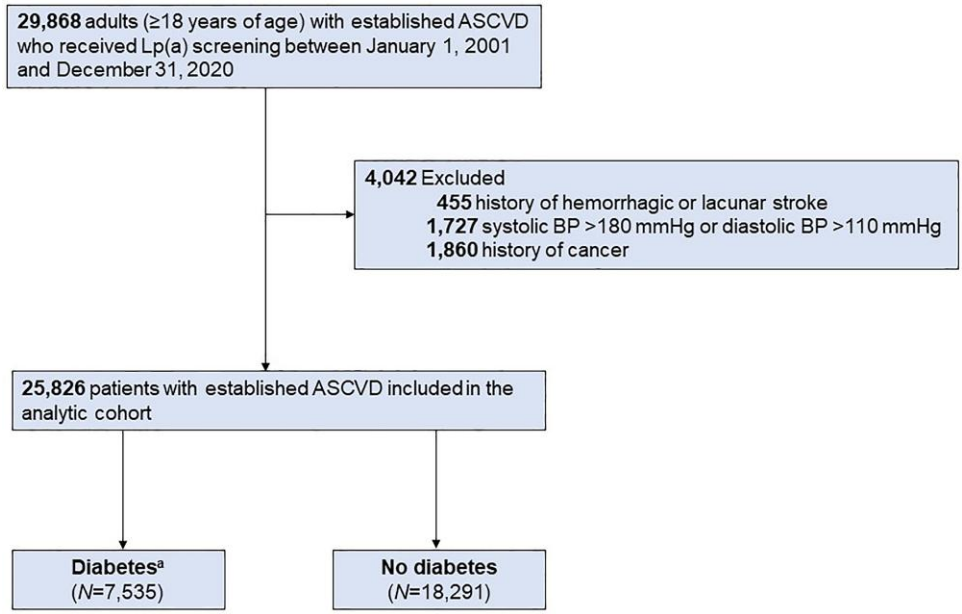


Figure 1 Flow diagram for study population selection. [a]Diabetes was defined with ICD-10 codes E11–E14 and glycated hemoglobin (HbA1c) level greater than or equal to 6.5% according to the *American Diabetes Association* criteria. Abbreviations/Acronyms: ASCVD, Atherosclerotic Cardiovascular Disease; BP, blood pressure; Lp(a), lipoprotein (a); ICD-10, International Classification of Diseases, tenth revision.

used log-transformed values for categorizing Lp(a) into quintiles to stabilize variance and approximate a more normal distribution. Fourth, we assessed the risk of MACE per 10-to-50-unit increment in original Lp(a) levels as well as per 10-unit and one standard deviation (SD) increase in log-transformed Lp(a) levels, treating these as continuous variables.[28,29] The analyses were conducted using both age- and sex-adjusted and multivariable-adjusted models. Additionally, partial likelihood ratio tests were performed to compare the magnitude of the association between Lp(a) level and MACE risk in ASCVD patients with and without T2DM. Fifth, we excluded the T2DM patients with antidiabetic medication prescriptions to minimize the potential confounding effects of these drugs on Lp(a) levels.[30,31] To further address the clinical relevance of Lp(a) levels and T2DM associated with MACE, we developed two prediction models with Cox regression (Model 1: Lp(a) and Model 2: Lp(a) and T2DM) and evaluated their predictive performance using time-dependent area under the receiver operating characteristic curve (AUC) accounting for the time-to-event nature of the data.

We established statistical significance at a threshold of 2-sided *P*-values less than 0.05. Data collection and statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, NC, USA) and Python version 3.10.12 (Python Software Foundation, Wilmington, DE, USA) for predictive models.

Results

The study cohort comprised 25 826 patients with established ASCVD, including 7535 patients with T2DM (29.2%) and 18 291 patients without T2DM (70.8%). The patients with diabetes were older, had higher blood pressure and triglyceride levels, and were more likely to be prescribed statins and other medications compared to those without diabetes (*Table 1*). Lp(a) levels were categorized into quintiles (Q1–Q5), each representing a range of Lp(a) concentrations. The median Lp(a) levels and their corresponding interquartile ranges (IQR) for each quintile were as follows: 5.8 (4.6–6.9) mg/dL for Q1, 11.3 (9.7–13.0) mg/dL for Q2, 19.3 (17.0–21.9) mg/dL for Q3, 32.2 (28.2–37.2) mg/dL for Q4, and 65.8 (52.7 to 85.5) mg/dL for Q5, respectively. Among these patients with and without T2DM, a total of 4836 MACEs occurred during 160 174 PYs of follow-up.

The IR per 1000 PYs varied among quintiles of lipoprotein(a) levels, ranging from 33.8 in the Q1 to 44.2 in the Q5 for the patients with T2DM, and from 26.0 to 30.0 for those without T2DM. Compared to the lowest quintile of Lp(a) level, the multivariable-adjusted HRs and 95% CIs for MACE across Q2–Q5 were 1.10 (0.94–1.30), 0.98 (0.83–1.16), 1.25 (1.06–1.46), 1.29 (1.10–1.51) in patients with T2DM and 0.99 (0.88–1.12), 1.10 (0.98–1.23), 1.01 (0.90–1.13), 1.13 (1.01–1.27) in those without T2DM (*Table 2*). The magnitude of the association between elevated Lp(a) and MACE was significantly higher among the patients with T2DM as compared to those without T2DM (<0.001). The restricted cubic spline analysis demonstrated a significant association between Lp(a) levels and MACE risk, showing a continuous positive relationship across the entire Lp(a) range in patients with and without T2DM. This association was more pronounced in patients with T2DM, with the HR for MACE exceeding 1.2 at an Lp(a) level of 50 mg/dL and consistently increasing across the entire range of Lp(a) level up to 100 mg/dL. However, patients without T2DM exhibited a less steep, non-linear relationship, with the HR plateauing at approximately 1.20 for Lp(a) levels above 30 mg/dL. Among patients without T2DM, the confidence intervals partially overlapped the null effect at higher Lp(a) levels, suggesting attenuated statistical significance (*Figure 2*). In subgroup analyses of the patients with T2DM examining whether the association of elevated Lp(a) with increased MACE risk remains unchanged across the clinically important factors, the overall association remained generally consistent for all subgroups. However, interaction effects were found in the elderly (≥70 years), smoker, non-obese (<25.0 kg/m^2), without CKD, and ASCVD subtypes (stable angina, asymptomatic CAD, and others). Similar patterns of associations

Table 1 Baseline characteristics of atherosclerotic patients with and without diabetes

Characteristics	All (n = 25 826)	With Diabetes (n = 7535)	Without Diabetes (n = 18 291)
Age			
≤39	455 (1.8)	52 (0.7)	403 (2.2)
40–59	9133 (35.4)	2277 (30.2)	6856 (37.5)
60–69	9463 (36.6)	3038 (40.3)	6425 (35.1)
≥70	6775 (26.2)	2168 (28.8)	4607 (25.2)
Sex			
Male	17 958 (69.5)	5113 (67.9)	12 845 (70.2)
Female	7868 (30.5)	2422 (32.1)	5446 (29.8)
Cigarette smoking			
Never smoker	13 878 (53.7)	4194 (55.7)	9684 (52.9)
Past smoker	5276 (20.4)	1417 (18.8)	3859 (21.2)
Current smoker	6672 (25.9)	1924 (25.5)	4748 (14.9)
Body mass index, mean (SD), kg/m^2	24.8 (2.9)	24.9 (2.9)	24.8 (2.8)
Systolic blood pressure, mean (SD), mmHg	124.7 (19.2)	127.0 (19.7)	123.6 (18.9)
Diastolic blood pressure, mean (SD), mmHg	73.1 (11.9)	72.5 (11.7)	73.4 (12.0)
Triglycerides, mean (SD), mg/dL	135.3 (79.6)	142.9 (86.0)	132.1 (76.6)
LDL-C, mean (SD), mg/dL	93.1 (36.1)	86.6 (35.2)	95.8 (36.2)
HDL-C, mean (SD), mg/dL	42.9 (11.6)	40.9 (11.2)	43.8 (11.7)
Urinary albumin, median (IQR), mg/dL	2.1 (0.7–11.7)	2.5 (0.7–16.0)	1.6 (0.6–7.6)
Creatinine, median (IQR), mg/dL	89.0 (53.9–138.4)	86.9 (53.5–136.9)	90.8 (54.5–139.9)
eGFR, median (QIR), mL/min/1.73 m^2	50.0 (36.0–56.0)	47.0 (24.0–55.0)	52.0 (41.1–57.0)
Chronic kidney disease	12 472 (48.3)	4157 (55.2)	8315 (45.5)
Medication use[a]			
Statins	13 823 (53.5)	4431 (58.8)	9392 (51.4)
Ezetimibe	60 (0.2)	34 (0.5)	26 (0.1)
Other lipid-lowering treatments[b]	288 (1.1)	190 (2.5)	98 (0.5)
Aspirin or P2Y12 inhibitors	1004 (3.9)	266 (3.5)	738 (4.0)
Beta-blockers	6826 (26.4)	2124 (28.2)	4702 (25.7)
RAAS inhibitors[c]	2680 (10.4)	1070 (14.2)	1610 (8.8)
Calcium channel blocker	1204 (4.7)	561 (7.5)	643 (3.5)
Established ASCVD			
Unstable angina or MI	7841 (30.4)	1990 (26.4)	5851 (32.0)
Stable angina	10 866 (42.1)	3094 (41.1)	7772 (42.5)
Asymptomatic CAD	4832 (18.7)	1516 (20.1)	3316 (18.1)
Transient ischaemic attack or ischaemic stroke	1860 (7.2)	667 (8.9)	1193 (6.5)
Peripheral artery disease	876 (3.4)	454 (6.0)	422 (2.3)
Lipoprotein(a), median (IQR), mg/dL			
Q1	5.8 (4.6–6.9)	5.7 (4.4–6.9)	5.9 (4.7–6.9)
Q2	11.3 (9.7–13.0)	11.2 (9.7–13.1)	11.3 (9.7–13.0)
Q3	19.3 (17.0–21.9)	19.4 (17.0–22.0)	19.2 (16.9–21.8)
Q4	32.2 (28.2–37.2)	32.3 (28.3–37.1)	32.3 (28.2–37.3)
Q5	65.8 (52.7–85.5)	67.0 (52.8–88.7)	65.0 (52.6–84.6)
HbA1c, %, median (IQR)	6.6 (5.8–7.6)	7.4 (6.9–8.5)	5.7 (5.5–6.0)
Antidiabetic medication[a]			
Biguanides	—	1348 (17.9)	—
Sulfonylureas	—	4231 (56.2)	—
Meglitinides	—	298 (4.0)	—
Thiazolidinediones	—	1097 (14.6)	—
DPP-4 inhibitors	—	2816 (37.4)	—
SGLT2 inhibitors	—	495 (6.6)	—

Continued

Table 1 *Continued*

Characteristics	All ($n = 25\,826$)	With Diabetes ($n = 7535$)	Without Diabetes ($n = 18\,291$)
GLP-1 receptor agonists	—	66 (0.9)	—
Insulin	—	931 (12.4)	—
Follow-up, mean (IQR), y	5.0 (1.4–10.3)	4.5 (1.3–9.4)	5.3 (1.5–10.7)

Data shown above are presented as *n* (%) unless otherwise specified. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for lipoprotein(a) to nanomoles per liter, multiply by 2.5.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DPP-4, Dipeptidyl Peptidase-4; eGFR, estimated Glomerular Filtration Rate; GLP, Glucagon-Like Peptide-1; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; Q, quintile; RAAS, Renin–Angiotensin–Aldosterone System; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; y, years.
[a]Defined as more than 30 days of prescription.
[b]Fibrate, niacin, and cholestyramine.
[c]ACE inhibitors, ARB, or aldosterone antagonist.

Table 2 Association between lipoprotein(a) level and major adverse cardiovascular events in atherosclerotic patients with and without diabetes

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Diabetes ($n = 7535$)					
No. of events	271	323	311	361	402
Person-years	8010	8407	9122	8222	9095
IR (per 1000 person-years)	33.8	38.4	34.1	43.9	44.2
HR (95% CI)					
Age-and sex-adjusted	1 (Reference)	1.16 (0.98–1.36)	1.04 (0.88–1.22)	1.33 (1.14–1.56)[b]	1.37 (1.17–1.60)[b]
Multivariable-adjusted[a]	1 (Reference)	1.10 (0.94–1.30)	0.98 (0.83–1.16)	1.25 (1.06–1.46)[b]	1.29 (1.10–1.51)[b]
No diabetes ($n = 18\,291$)					
No. of events	526	607	682	665	688
Person-years	20 260	24 159	24 375	25 601	22 923
IR (per 1000 person-years)	26.0	25.1	28.0	26.0	30.0
HR (95% CI)					
Age- and sex-adjusted	1 (Reference)	0.99 (0.88–1.11)	1.12 (1.00–1.25)[b]	1.05 (0.93–1.17)	1.18 (1.06–1.33)[b]
Multivariable-adjusted[a]	1 (Reference)	0.99 (0.88–1.12)	1.10 (0.98–1.23)	1.01 (0.90–1.13)	1.13 (1.01–1.27)[b]

MACE includes composite outcomes of deaths from cardiovascular disease or other causes, incident myocardial infarction (non-fatal), and ischaemic stroke (non-fatal). Median and interquartile range for each lipoprotein(a) quintile are as follows (unit: mg/dL): Q1: 5.8 (4.6–6.9), Q2: 11.3 (9.7–13.0), Q3: 19.3 (17.0–21.9), Q4: 32.2 (28.2–37.2), and Q5: 65.8 (52.7–85.5). To convert the values for lipoprotein(a) to nanomoles per liter, multiply by 2.5.
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IR, incidence rate; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; PY, person-years; Q, quintile.
[a]Adjusted for age, sex, cigarette smoking, body mass index, hypertension, triglyceride, HDL-C, LDL-C, chronic kidney disease, statin, ezetimibe use, other lipid-lowering drugs, Lp(a) screening year in the Cox proportional hazards regression model.
[b]$P < 0.05$.

were observed when the patients without T2DM were stratified into the subgroups, albeit with attenuated statistical significance regarding the association between elevated Lp(a) level and increased MACE risk in each category (*Figure 3*).

In the cohort of pseudo-population with inverse probability of treatment weighting, the results were generally consistent with the main analysis for both patients with T2DM (HR = 1.28; 95% CIs: 1.10–1.50) and without T2DM (HR = 1.20; 95% CIs: 1.06–1.34) (see Supplementary data online, *Table S2*).

Excluding MACE occurred up to 5 years showed generally consistent results to the main analysis, but we observed slightly attenuated statistical significance and reduced effect size among the patients without T2DM (see Supplementary data online, *Table S3*). Categorization of quintiles with natural log-transformed Lp(a) level did not significantly alter the association of elevated Lp(a) level with increased MACE risk in both patients with T2DM (HR = 1.28; 95% CIs: 1.10–1.50) and those without T2DM (HR = 1.01–1.27) (see Supplementary data online, *Table S4*). In the exploratory analyses of treating Lp(a) and log-transformed Lp(a) levels as continuous variables, the multivariable-adjusted HRs and 95% CI for MACE associated with Lp(a) levels differed significantly between the patients with T2DM and without T2DM across all categories. For each 10 mg/L and 50 mg/dL increase in Lp(a), the multivariable-adjusted HRs and 95% CIs were 1.03 (1.01–1.04) and 1.15 (1.06–1.24) among T2DM patients and 1.01 (0.99–1.02) and 1.04 (0.97–1.10) among those without T2DM, respectively (*P*-value for interaction <0.001 for all comparisons) (see Supplementary data online, *Table S5*). Similar associations were found per 10 mg/dL increase and per one SD increase in log-transformed Lp(a) and MACE among the

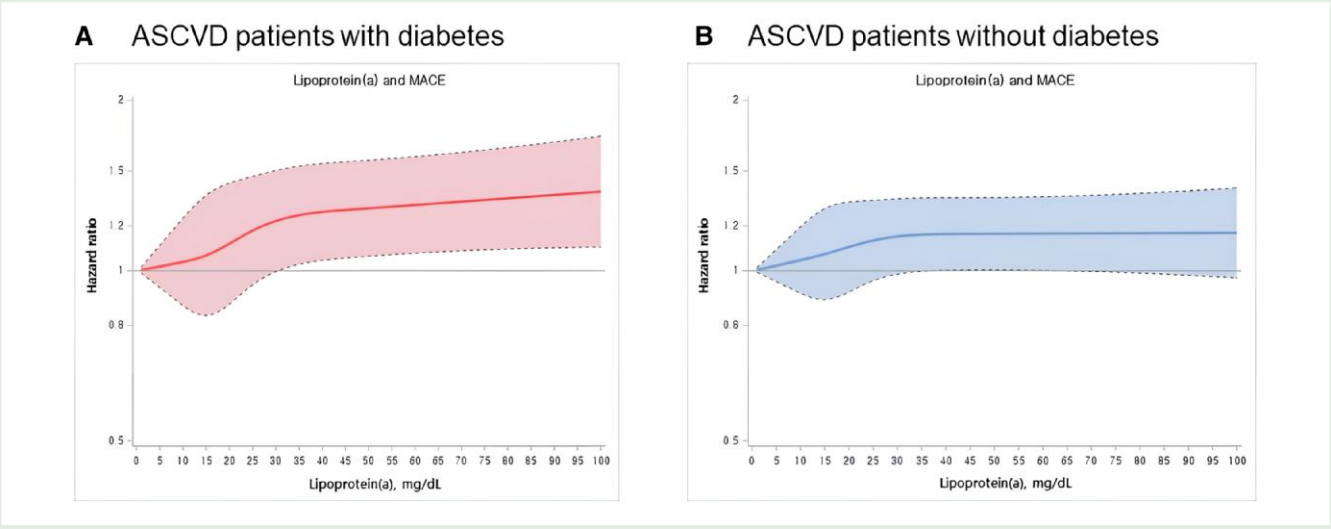


Figure 2 Restricted cubic spline model for association between lipoprotein(a) and major adverse cardiovascular events in atherosclerotic patients with and without diabetes. Model was adjusted for age, sex, cigarette smoking, body mass index, hypertension, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, chronic kidney disease, statin, ezetimibe use, other lipid-lowering drugs, lipoprotein(a) screening year.

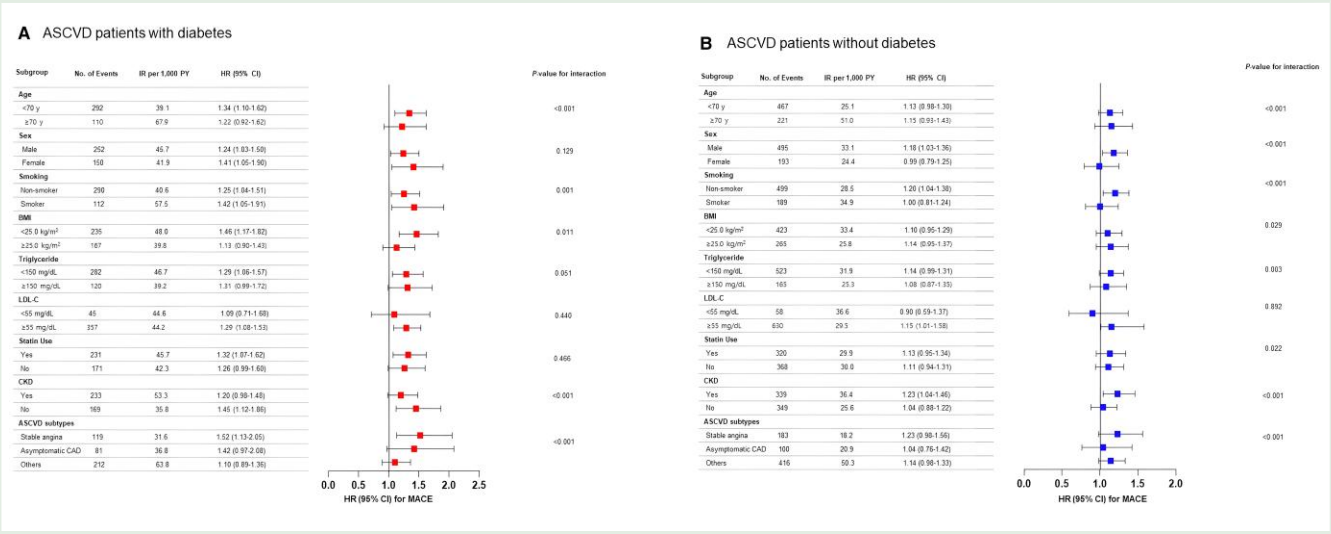


Figure 3 Subgroup analyses for the association between elevated lipoprotein(a) level and major adverse cardiovascular events in atherosclerotic patients with and without diabetes by demographic and clinical characteristics. Each subgroup analysis was conducted using the Cox proportional hazards model to compute hazard ratios (HRs) along with their corresponding 95% confidence intervals (CIs). These analyses compared the highest quintile (Q5) to the lowest quintile (Q1) and were adjusted for various covariates, including age, sex, cigarette smoking status, body mass index, hypertension, triglyceride levels, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, chronic kidney disease diagnosis, statin use, ezetimibe use, and the utilization of other lipid-lowering medications, as well as the screening year for lipoprotein(a), except for the relevant category.

patients with and without T2DM (*P*-value for interaction <0.001 for all comparisons) (see Supplementary data online, *Table S6*). When the analysis was limited to the T2DM patients who were not using antidiabetic drugs, the results remained generally consistent. However, the reduced sample size in this group led to wider confidence intervals (see Supplementary data online, *Table S7*). For prediction model, the time-dependent AUC for MACE using Lp(a) alone was 0.717 (95% CI: 0.708–0.725). The addition of T2DM to the model resulted in a marginal improvement in predictive performance with an AUC of 0.719 (95% CI: 0.710–0.727).

Discussion

In this population-based cohort study of patients with established ASCVD, elevated Lp(a) level was associated with a significantly increased

risk of MACE in the patients with and without T2DM. Among the patients with elevated Lp(a) level, those with T2DM had a substantially higher risk for MACE as compared to their counterpart population without T2DM. Dose–response relationship was also observed for Lp(a) and MACE association, but the strength of this association was stronger among the patients with T2DM as the point estimates for MACE were consistently above the statistically significant level in this group. Also, similar association of elevated Lp(a) level with an increased risk of MACE were observed across clinically important subgroups.

Comparison with other studies

Our findings of increased MACE risk associated with elevated Lp(a) in patients with established ASCVD are consistent with observational evidence from the general population in Europe and North America. The Copenhagen City Heart Study (CCHS) consisting of 9330 general Danish adult population over a 10-year follow-up period showed that, individuals with progressively higher levels of Lp(a) have a stepwise increased risk for myocardial infarction (MI) with the highest levels (i.e. 95th percentile vs. 5th percentile) associated with up to approximately 4-fold increased risk for MI as compared to those with the lowest levels.[13] In a cross-sectional analysis of a nationally representative cohort using data from the U.S. National Health and Nutrition Examination Survey (NHANES) III, an odds ratio of 1.41 (95% CI: 1.14–1.75) was found per SD increase in Lp(a) was found.[14] Also, a recent international multicenter study found that more than a quarter of patients with established ASCVD had Lp(a) levels that exceed the established threshold (i.e. approximately 50 mg/dL) for high CVD risk, suggesting the potential need for clinical intervention among those with elevated Lp(a) level.[32] The current study extends the evidence that elevated Lp(a) level is associated with an increased risk of MACE in patients with established ASCVD, a population that may need additional clinical attention for management of CVD risk factors.

There is a paucity of literature addressing the association of Lp(a) level and MACE risk in atherosclerotic patients and whether the effect size of this association differs among those with and without T2DM. Currently, a few plausible biological mechanisms may support our findings of elevated Lp(a) level associated with a significantly increased MACE risk in atherosclerotic patients. Elevated Lp(a) levels have been implicated in promoting atherosclerotic plaque formation and thrombosis, potentially contributing to the risk of myocardial infarction.[33,34] In addition, elevated Lp(a) level may stimulate the proliferation of smooth muscle cells within the arterial lumen, narrowing the vessel and potentially leading to ischemia.[35] Moreover, Lp(a) possesses anti-fibrinolytic properties by competitively inhibiting plasminogen conversion to plasmin, a key enzyme responsible for fibrinolysis.[36] Also, Lp(a) might inhibit tissue factor pathway inhibitor, a natural anticoagulant, potentially promoting thrombosis at sites of plaque rupture.[37] Finally, insulin suppresses apolipoprotein(a) synthesis at the posttranscriptional level and reduces apo(a) promoter activity, leading to decreased production of Lp(a), which contributes to the typically lower Lp(a) levels observed in patients with T2DM and chronic hyperinsulinemia.[38] Despite this reduction, the paradoxical increase in cardiovascular risk in type 2 diabetes reflects broader metabolic disturbances. Lp(a) affects systemic triglyceride and Very Low-Density Lipoprotein (VLDL) metabolism. Notably, the Lp(a)-raising allele rs10455872-G is linked to smaller VLDL particle diameters.[39] In patients with T2DM and elevated Lp(a), these factors interact to induce atherosclerosis and thrombosis risk. At the molecular level, hyperglycemia-induced glycation of Lp(a) may further elevate its atherogenic properties.[40]

Implications

While the precise biological mechanisms of the stronger Lp(a)-CVD association in T2DM patients as compared to those without remain unclear, emerging evidence from preclinical studies may suggest some potential pathways. In vitro studies using cynomolgus monkey hepatocytes have demonstrated an inverse relationship between insulin and Lp(a) levels.[41] This finding suggests that increased insulin may suppress the synthesis of apo(a), a key Lp(a) component, leading to lower Lp(a) concentrations. Conversely, insulin deficiency, a common characteristic of diabetes, might contribute to elevated Lp(a) levels.[42,43] Also, a study conducted in Turkey with a small sample of patients with T2DM (n = 85) showed a positive correlation between leptin and Lp(a) level.[44] Elevated leptin, which is frequently observed in diabetic patients in clinical settings, could potentially contribute to increased level of Lp(a) and additionally contribute to subsequent MACE risk.[44]

Two observational studies of patients with a history of myocardial infarction may add evidence to elevated Lp(a) levels associated with increased risk MACE in patients with diabetes, despite these patients often showing lower Lp(a) levels than those without diabetes due to insulin's inhibitory effect on Lp(a) synthesis.[45,46] The underlying mechanisms may involve pro-inflammatory effects of elevated Lp(a) level along with promotion of endothelial dysfunction, contribution to atherosclerotic plaque formation, prothrombotic properties, susceptibility to oxidation, and role in vascular calcification.[47] Genetic factors, including LPA gene variants, also may play a role.[45] Therefore, the combination of diabetes and elevated Lp(a) may create a synergistic effect, with glycation of Lp(a) potentially enhancing vascular endothelium damage. However, these findings require further validation through *in vivo* and clinical studies to determine their relevance to MACE risk in ASCVD patients with T2DM.

Strengths and limitations

This study has several strengths including the use of well-validated clinical data to identify atherosclerotic patients screened for Lp(a) level with and without T2DM according to the *European Association for the Study of Diabetes* criteria with data on HbA1c level. Data on MACE was also ascertained by rigorously reviewing electronic medical records by trained cardiologists. However, a few limitations should be considered when interpreting the results of this study. First, our analytic cohort of atherosclerotic patients was limited to those with complete data on Lp(a) measurement. Also, follow-up data on Lp(a) measurement were not available. Second, we lacked information on socioeconomic status, physical activity level, high-sensitivity C-reactive protein, and dietary behavior. Furthermore, clinical information of the patients collected prior to their initial visit to AMC was not available. However, we were able to include a wide range of information from the database upon their initial presentation at AMC such as detailed information on types of antidiabetic medication. Third, clinical records of atherosclerotic patients identified from the AMC database exclusively represent a single ethnicity (i.e. Korean descendants). Therefore, the generalizability of the findings in this study should be tested in ethnically diverse population-based cohorts. Fourth, the small proportion of patients with T2DM receiving cardioprotective antidiabetic medication (i.e. SGLT2 inhibitors and GLP-1 receptor agonists) partially limit the generalizability of our findings in contemporary clinical practice. Future studies examining the potential mitigating effect of these medications on the increased risk of MACE associated with elevated Lp(a) level in patients with T2DM are necessary. Fifth, we were only able to assess diabetes status at the beginning of the study time and lacked information regarding follow-up data on diabetes management such as glycaemic control, adherence to

antidiabetic medication, and lifestyle modification to further investigate whether effective diabetes management may attenuate the increased risk of MACE in patients with T2DM. Thus, future research incorporating longitudinal diabetes management data is warranted to clarify this association. Sixth, we were not able to specifically assess the effect of Proprotein Subtilisin/Kexin Type 9 (PCSK9) inhibitors on lowering Lp(a) levels and subsequent MACE risk in the patients with and without T2DM, primarily due to the recent approval and limited availability of PCSK9 inhibitors in the Republic of Korea. Well-established evidence, especially the findings from the FOURIER trial showed that PCSK9 inhibitors such as evolocumab can significantly reduce Lp(a) levels and cardiovascular outcomes.[48] Therefore, future studies are needed to assess how PCSK9 inhibition might influence the Lp(a)-MACE association specifically in T2DM patients. Lastly, other limitations include single-time-point Lp(a) measurements, which may not capture intra-individual variability,[49] unavailability of genetic analysis to establish the relationship independent of LDL-cholesterol,[50] lack of information on diet for calculating the Life's Simple 7 Cardiovascular Health Score to further assess its association with Lp(a),[51] and absence of advanced imaging techniques to precisely characterize plaque composition and severity.[52] Future studies need to address these points to further understand the role of Lp(a) in evaluating MACE risk in atherosclerotic patients with and without T2DM.

Conclusion

In conclusion, in a population-based cohort of atherosclerotic patients with and without T2DM, an elevated level of Lp(a) was associated with a significantly increased risk of MACE. As compared to those without T2DM, the magnitude of increased MACE risk associated with elevated Lp(a) level was stronger among those with T2DM, suggesting the need for comprehensive MACE risk reduction interventions concerning both Lp(a) level and glycemic status according to the well-established clinical guidelines.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

We would like to thank Heejun Kang (Asan Institute for Life Science, Asan Medical Center, Seoul, Republic of Korea) for administrative support. We would like to thank Suhyun Chae (Ewha Womans University Medical Center, Seoul, Republic of Korea) and June Yong Jeon for the design concept used in the Graphical Abstract.

Author contribution

K.K., M.K., T.J.J., and Y.K. contributed to the conception and design of the study. M.K. and T.J.J. contributed to the acquisition, analysis, and interpretation of the data. K.K. and M.K. prepared the initial draft of the manuscript. All authors reviewed and critically revised the manuscript for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Funding

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, the Republic of Korea (Grant No.:HR21C0198).

Conflicts of interest: The authors declare no competing interests.

Role of the sponsors

The funding source did not participate in any aspects of the study, including its design and execution, data collection, management, data analysis, data interpretation, manuscript preparation, manuscript review, manuscript approval, or the decision to submit the manuscript for publication.

Data availability

The data supporting the findings of this study cannot be further provided to other individuals or organizations due to the patient data privacy regulations of the Asan Medical Center (Seoul, the Republic of Korea).

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