

Lipoprotein(a) and Cumulative Low-Density Lipoprotein Cholesterol as Predictors of Coronary Artery Disease in Statin-Naïve Elderly Individuals with Hyperlipidemia

Statin-Naif Yaşlı Bireylerde Koroner Arter Hastalığı Öngördürücüsü Olarak Lipoprotein(a) ve Kümülatif LDL Kolesterol

ABSTRACT

Objective: Advanced age is a well-recognized risk factor for atherosclerotic cardiovascular disease (ASCVD). Given the ongoing debate regarding the initiation of statin therapy in elderly individuals, identifying those with underlying coronary artery disease (CAD) who may benefit from lipid-lowering treatment is essential. This study aimed to identify predictors of CAD in statin-naïve adults aged ≥ 70 years with elevated low-density lipoprotein cholesterol (LDL-C), with particular emphasis on risk assessment, cumulative LDL-C burden, and lipoprotein(a) [Lp(a)] levels.

Method: The analysis included consecutive patients aged ≥ 70 years with LDL-C ≥ 160 mg/dL, available Lp(a) measurements, no prior history of ASCVD or diabetes, who underwent evaluation for CAD by coronary imaging or functional stress testing. Global ASCVD risk was estimated using the Systematic Coronary Risk Estimation 2-Older Persons (SCORE2-OP) and the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) risk scores.

Results: A total of 202 patients were included (mean age 76 years; 68.3% female). CAD was diagnosed in 30.7% of participants. In multivariable analysis, male sex (odds ratio [OR]: 2.109), Lp(a) level (OR: 1.012 per mg/dL), and cumulative LDL-C (OR: 1.155 per g/dL) were independently associated with CAD. The highest CAD prevalence was observed among individuals with cumulative LDL-C ≥ 14 g/dL and Lp(a) ≥ 50 mg/dL. While the SCORE2-OP algorithm failed to predict CAD, the SAFEHEART risk score was significantly associated with CAD.

Conclusion: In statin-naïve elderly individuals with elevated LDL-C levels, male sex, cumulative LDL-C exposure, and high Lp(a) levels were independently associated with CAD. These findings underscore the potential utility of incorporating cumulative LDL-C and Lp(a) into risk stratification for older adults.

Keywords: Cardiovascular risk stratification, cumulative low-density lipoprotein cholesterol, elderly, primary prevention, Spanish Familial Hypercholesterolemia Cohort Study risk score, statin-naïve, Systematic Coronary Risk Estimation 2-Older Persons

ÖZET

Amaç: İleri yaş, aterosklerotik kardiyovasküler hastalık (ASKVH) riskinde artış ile ilişkilidir. Yaşlı bireylerde statin tedavisinin başlatılmasına yönelik süregelen tartışmalar göz önünde bulundurulduğunda, koroner arter hastalığı (KAH) bulunan ve lipid düşürücü tedaviden fayda görebilecek kişilerin belirlenmesi önemlidir. Bu çalışmanın amacı, statin kullanmayan, LDL-kolesterol (LDL-C) düzeyi yüksek ve ≥ 70 yaş bireylerde KAH öngördürücülerini belirlemek; özellikle risk değerlendirmesinde kümülatif LDL-C ve lipoprotein(a) [Lp(a)] düzeylerinin rolünü incelemektir.

Yöntem: Analize, LDL-C ≥ 160 mg/dL olan, Lp(a) ölçümü mevcut, daha önce ASKVH veya diyabet öyküsü bulunmayan ve koroner görüntüleme ya da fonksiyonel stres testleri ile KAH açısından değerlendirilen ardışık ≥ 70 yaş hastalar dahil edilmiştir. Global ASKVH riski, SCORE2-OP ve SAFEHEART risk skorları kullanılarak hesaplanmıştır.

Bulgular: Toplam 202 hasta çalışmaya dahil edilmiştir (ortalama yaş: 76 yıl, %68,3 kadın). Katılımcıların %30,7'sinde KAH saptanmıştır. Çok değişkenli analizde erkek cinsiyet (OR: 2,109), Lp(a) düzeyi (OR: 1,012, mg/dL başına) ve kümülatif LDL-C (OR: 1,155, g/dL başına) KAH ile bağımsız olarak ilişkili bulunmuştur. KAH prevalansı, kümülatif LDL-C ≥ 14 g/dL ve Lp(a) ≥ 50 mg/dL olan bireylerde en yüksekti. SCORE2-OP algoritması KAH'ı öngörememişken, SAFEHEART risk skoru KAH ile anlamlı ilişkili bulunmuştur.


ORIGINAL ARTICLE KLİNİK ÇALIŞMA

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Sonuç: Statin kullanmayan yaşlı bireylerde yüksek LDL-C düzeyi varlığında, erkek cinsiyet, artmış kümülatif LDL-C maruziyeti ve yüksek Lp(a) düzeyleri KAH ile bağımsız olarak ilişkili bulunmuştur. Bu sonuçlar, yaşlı bireylerde risk sınıflamasında kümülatif LDL-C ve Lp(a) ölçümlerinin kullanılmasının potansiyel değerini vurgulamaktadır.

Anahtar Kelimeler: Kardiyovasküler risk sınıflaması, kümülatif düşük yoğunluklu lipoprotein kolesterol, yaşlı, birincil korunma, İspanyol Ailevi Hiperkolesterolemi Kohort Çalışması, statin-naif, Sistematik Koroner Risk Tahmini 2 – Yaşlı Kişiler

Atherosclerotic cardiovascular disease (ASCVD) continues to be the leading cause of death worldwide. Elevated levels of low-density lipoprotein cholesterol (LDL-C), a major modifiable risk factor, play a pivotal role in the development of atherosclerotic cardiovascular disease and are strongly associated with increased cardiovascular risk.¹

Low-density lipoprotein cholesterol reduction remains the cornerstone of ASCVD prevention.² In individuals without established ASCVD, diabetes, or familial hypercholesterolemia (FH), LDL-C targets are determined based on overall cardiovascular risk. For risk estimation, current American College of Cardiology (ACC) guidelines recommend the ASCVD risk estimator for individuals aged 40–75 years, while European guidelines recommend the Systematic Coronary Risk Estimation 2 (SCORE2) for individuals aged 40–70 years and the Systematic Coronary Risk Estimation 2–Older Persons (SCORE2–OP) for individuals aged ≥ 70 years.^{3,4} However, although elderly individuals are frequently classified as high risk, they often receive weaker recommendations for statin therapy due to concerns about polypharmacy, frailty, and limited evidence of mortality benefit.⁴

Cumulative LDL-C exposure, reflecting both the level and duration of LDL-C elevation, is a recognized driver of atherosclerosis and may better predict ASCVD than a single LDL-C measurement.⁵ However, interindividual differences exist: some older adults develop ASCVD despite high LDL-C levels, while others with FH may remain disease-free.⁶ This variability may be influenced by additional risk modifiers such as lipoprotein(a) [Lp(a)], a genetically determined, highly atherogenic lipoprotein structurally similar to LDL-C.^{7,8} Unlike LDL-C, Lp(a) levels are not significantly reduced by statins or other conventional lipid-lowering therapies. Currently, ASCVD prevention in individuals with elevated Lp(a) relies primarily on intensive LDL-C reduction, due to the lack of approved therapies specifically targeting Lp(a).⁴

This study aimed to identify individuals at higher ASCVD risk and to determine key predictors of ASCVD in statin-naïve older adults, with a particular focus on Lp(a) and cumulative LDL-C exposure. By identifying those at increased risk within this population, we sought to clarify which elderly individuals with high LDL-C are most likely to benefit from lipid-lowering therapy.

Materials and Methods

Study Approval

This retrospective study was approved by the Ethics Committee of Koç University (Approval Number: 2022.467. IRB1.184, Date: 23.12.2022), and conducted in accordance

ABBREVIATIONS

ACC	American College of Cardiology
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body Mass Index
BP	Blood pressure
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CRP	C-reactive protein
CVD	Cardiovascular disease
ESC	European Society of Cardiology
FH	Familial hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MDRD	Modification of Diet in Renal Disease
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study
SBP	Systolic blood pressure
SCORE2–OP	Systematic Coronary Risk Estimation 2–Older Persons
WHO	World Health Organization

with the Declaration of Helsinki. The study was conducted using anonymized data obtained under the hospital's routine institutional research consent.

Study Design and Population

Data were collected from patients who visited the cardiology outpatient clinic of a tertiary university hospital between December 2020 and December 2023. Patients aged 70 years and older were consecutively screened for eligibility. Inclusion criteria were: (1) no prior history of ASCVD; (2) undergoing diagnostic testing for coronary artery disease (CAD), including coronary computed tomography angiography (CCTA), conventional coronary angiography, myocardial perfusion scintigraphy (MPS), or stress echocardiography; (3) statin-naïve status; (4) LDL-C levels ≥ 160 mg/dL; and (5) availability of Lp(a) measurements. An LDL-C threshold of ≥ 160 mg/dL was chosen to identify elderly individuals with markedly elevated LDL-C levels, consistent with European Society of Cardiology (ESC) guideline statements indicating that this level increases the probability of familial hypercholesterolemia.⁹

Exclusion criteria included known ASCVD, diabetes mellitus, active or prior malignancy, liver failure, renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²), chronic inflammatory disease, acute infection or inflammation [defined by leukocytosis, C-reactive protein (CRP) > 10 mg/L, fever, or recent antibiotic use], and hypothyroidism. The flowchart outlining the inclusion of the study population is presented in Figure 1.

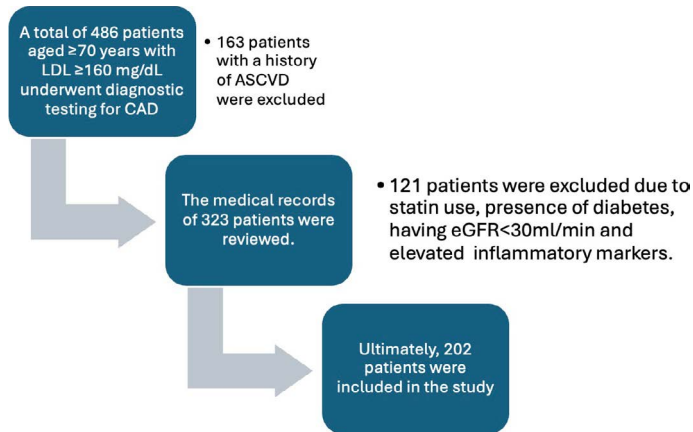


Figure 1. Flowchart of the study population inclusion.

Data Collection and Definitions

Demographic and clinical data were recorded, including sex, age, Body Mass Index (BMI), systolic blood pressure (SBP), and smoking status. Laboratory parameters included serum creatinine, estimated glomerular filtration rate calculated using the MDRD (Modification of Diet in Renal Disease) formula (eGFR), LDL-C measured with a direct assay, triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C), glucose, hemoglobin A1c (HbA1c), and Lp(a).

Cumulative LDL-C exposure was calculated by multiplying the LDL-C level (mg/dL) by age (years) and expressed in grams per deciliter (g/dL). Lp(a) levels were measured using the Roche Cobas Tina-quant Lipoprotein(a) Gen 2 assay via an immunoturbidimetric method in an accredited local laboratory.

Hypertension was defined as a previous diagnosis or office SBP ≥ 140 mmHg and/or diastolic blood pressure (BP) ≥ 90 mmHg on two separate occasions. Diabetes mellitus—an exclusion criterion—was defined as a known diagnosis, fasting glucose > 126 mg/dL, or HbA1c $> 6.5\%$. ASCVD was defined as a history of CAD, coronary revascularization, cerebrovascular disease, or peripheral artery disease. CAD was diagnosed based on $> 50\%$ stenosis in epicardial coronary arteries (detected by invasive or computed tomography [CT] angiography) or the presence of myocardial ischemia on functional testing.

The SCORE2-OP risk score (for high-risk countries) and the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk equation scores were calculated using baseline data obtained prior to CAD diagnosis.^{10,11} SCORE2-OP is a cardiovascular risk prediction tool specifically designed for older adults (≥ 70 years). It estimates the 10-year risk of ASCVD based on key variables including sex, age, SBP, smoking status, and non-high density lipoprotein cholesterol levels. The SAFEHEART risk equation is designed to estimate the 5- and 10-year ASCVD incidence in individuals with familial hypercholesterolemia.¹¹ It was developed using data from the Spanish SAFEHEART registry, a large, prospective cohort of patients with heterozygous FH. The equation incorporates key clinical predictors, including sex, age, history of ASCVD, smoking status, BMI, LDL-C, and Lp(a) levels (Appendix Data).

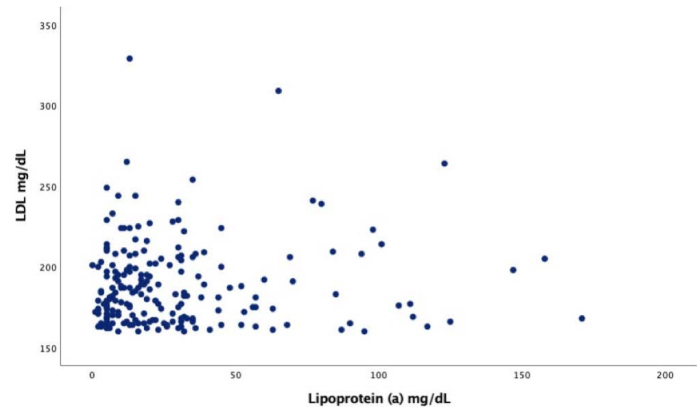


Figure 2. Distribution of LDL-C and Lp(a) in the study population.

The cohort was stratified based on the median cumulative LDL-C value (14 g/dL) and Lp(a) cutoffs of < 30 mg/dL, 30–49 mg/dL, and ≥ 50 mg/dL to assess CAD risk stratification according to cumulative LDL-C and Lp(a) levels.

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 9.4.1 (GraphPad Software, San Diego, CA, USA). Normality of distributions was assessed using the Shapiro-Wilk test. Quantitative variables were reported as mean \pm standard deviation (SD) or median (interquartile range, IQR), and categorical variables as proportions. Between-group differences were examined using the chi-square or Fisher's exact test for categorical data and Student's t test or Mann-Whitney U test for continuous data, as appropriate. Univariate and multivariate logistic regression analyses were performed to determine associations between risk factors and CAD. A multivariate logistic regression model predicting CAD was developed based on variables that were significant in univariate analysis. Additionally, two further models were constructed: one incorporating the variables included in the SCORE2-OP algorithm and another incorporating both SCORE2-OP variables and Lp(a). A p-value < 0.05 was considered statistically significant. Bland-Altman analysis was conducted and presented in Appendix Figure 1 to assess agreement between the SCORE2-OP and SAFEHEART scores.

Results

The study included 202 elderly patients with a mean age of 75.9 ± 5.0 years; 68.3% were female. According to the Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia, 43.6% of the cohort was classified as possible FH and 5.4% as probable FH. The mean LDL-C level was 188.43 ± 26.32 mg/dL, while the median Lp(a) level was 18 mg/dL (Q1–Q3: 8–35 mg/dL) (Figure 2). Evaluation for CAD included coronary angiography in 43.6% of patients, MPS in 31.2%, CCTA in 19.3%, and stress echocardiography in 5.9%. Overall, 30.7% ($n = 62$) of patients were diagnosed with CAD.

Patients with CAD were more likely to be male (46.8% vs. 25.0%, $P = 0.002$), had lower HDL-C levels [52 mg/dL (Q1–Q3: 43–62.25) vs. 58 mg/dL (Q1–Q3: 50–69.75), $P = 0.003$],

Table 1. Baseline characteristics of the study population

Variables	CAD (-) (n = 140)	CAD (+) (n = 62)	P
Demographic variables			
Sex (female), n (%)	105 (75)	33 (53.2)	0.002
Age (mean ± SD)	75.49 ± 4.94	76.79 ± 5.00	0.088
BMI, kg/m ² (mean ± SD)	27.29 ± 5.49	28.57 ± 4.00	0.154
Current smokers, n (%)	28 (20%)	18 (29%)	0.224
Hypertension, n (%)	97 (69.3%)	42 (68.9%)	0.951
SBP, mmHg (mean ± SD)	135.82 ± 19.88	133.07 ± 16.40	0.379
SCORE2-OP, % (mean ± SD)	30.69 ± 12.06	33.03 ± 11.17	0.195
SAFEHEART score, 5 years, % (median, Q1-Q3)*	0.94 (0.87-2.12)	2.09 (0.94-2.62)	0.001
SAFEHEART score, 10 years, % (median, Q1-Q3)*	1.99 (1.86-4.49)	4.42 (1.99-5.52)	0.001
Medications, n (%)			
Antiplatelet therapy	38 (27.10)	19 (30.64)	0.349
Beta-blockers	42 (30.00)	22 (35.48)	0.513
RAS blockers	77 (55.00)	28 (48.38)	0.260
Biochemical analysis			
eGFR, mL/min/1.73 m ² (mean ± SD)	72.73 ± 35.37	69.84 ± 22.20	0.559
Glucose (mean ± SD)	104.89 ± 11.05	106.66 ± 11.59	0.153
HbA1C (mean ± SD)	5.76 ± 0.40	5.91 ± 2.32	0.087
Total cholesterol, mg/dL (mean ± SD)	260.84 ± 27.13	262.27 ± 40.74	0.770
HDL-C, mg/dL (median, Q1-Q3)*	58 (50-69.75)	52 (43-62.25)	0.003
LDL-C, mg/dL (mean ± SD)	186.19 ± 21.19	193.39 ± 34.98	0.073
Triglycerides, mg/dL (median, Q1-Q3)*	142 (105.25-191.25)	158 (119.25-206.25)	0.091
Non-HDL cholesterol (mean ± SD)	200.37 ± 27.10	208.02 ± 41.20	0.123
hsCRP, mg/L (median, Q1-Q3)*	2.8 (1.2-6.45)	3.1 (1.2-8.05)	0.168
Lp(a), mg/dL (median, Q1-Q3)*	17 (6-32.75)	19.5 (12-47.25)	0.017
Cumulative LDL, g/dL (mean ± SD)	14.18 ± 1.90	15.59 ± 2.7	<0.001

BMI, Body mass index; CAD, Coronary artery disease; eGFR, Estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; hsCRP, High-sensitivity C-reactive protein; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); SBP, Systolic blood pressure. *Continuous variables not normally distributed are presented as median (Q1-Q3), and nonparametric statistical tests were applied due to the absence of normal distribution.

higher cumulative LDL-C exposure (14.06 ± 1.97 g/dL vs. 15.59 ± 2.7 g/dL, P < 0.001), and elevated Lp(a) levels [19.5 mg/dL (Q1-Q3: 12-47.25) vs. 17 mg/dL (Q1-Q3: 6-32.75), P = 0.017] (Table 1).

SCORE2-OP scores did not differ significantly between the CAD and non-CAD groups; however, nearly all participants were classified as having a very high 10-year ASCVD risk according to SCORE2-OP, except for two individuals with an estimated risk below 15%. In contrast, the SAFEHEART risk score was significantly higher in patients with CAD for both 5-year risk estimation [0.94 (IQR: 0.87-2.12) vs. 2.09 (IQR: 0.94-2.62), P = 0.001] and 10-year risk estimation [1.99 (IQR: 1.86-4.49) vs. 4.42 (IQR: 1.99-5.52), P = 0.001] (Figure 3).

In univariate logistic regression analysis, male sex (odds ratio [OR]: 2.636, 95% confidence interval [CI]: 1.406-4.493, P = 0.003), lower HDL-C levels (OR: 0.973, 95% CI: 0.953-0.994, P = 0.013), and higher Lp(a) levels (OR: 1.012, 95% CI: 1.003-1.021, P = 0.009) were significantly associated with

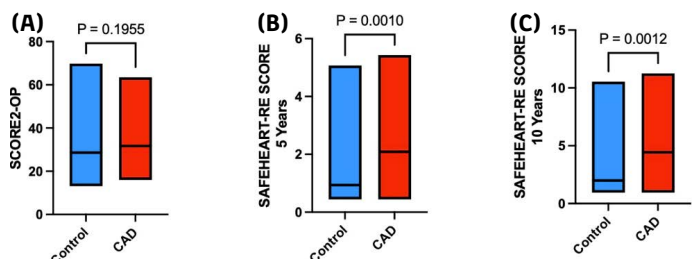


Figure 3. Comparison of risk scores between patients diagnosed with CAD and those without CAD. (A) Comparison of SCORE2-OP between groups. (B) Comparison of SAFEHEART risk score for 5-year risk prediction between groups. (C) Comparison of SAFEHEART risk score for 10-year risk prediction between groups.

CAD. The SCORE2-OP algorithm was not predictive of CAD (OR: 1.017, 95% CI: 0.992-1.042, P = 0.196), whereas the SAFEHEART score was predictive (OR: 1.605, 95%CI:1.130-1.209, P = 0.001).

Table 2. Predictors of CAD (Model 1)

Variables	OR	95% CI	P
Male sex	2.109	1.070-4.160	0.031
Lp(a)	1.012	1.002-1.022	0.023
HDL-C	0.978	0.956-1.001	0.060
Cumulative LDL	1.155	1.009-1.322	0.037

CAD, Coronary artery disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); OR, Odds ratios; CI, Confidence interval.

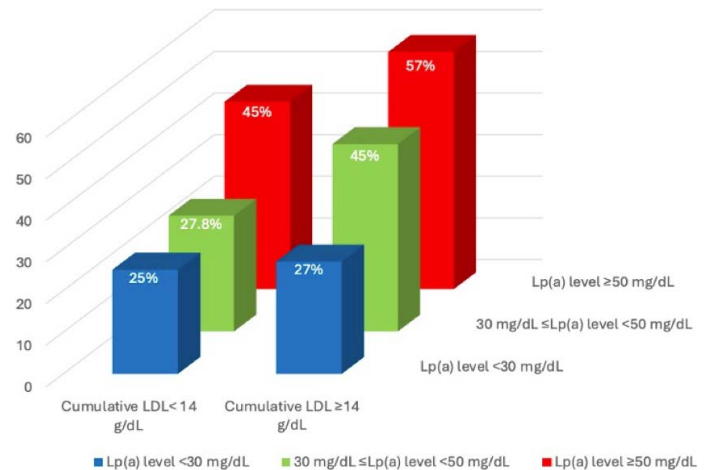
Multivariable analysis included all variables that were significant in univariate analysis. Independent predictors of CAD were male sex (OR: 2.109, 95% CI: 1.070-4.160, $P = 0.031$), Lp(a) (OR: 1.012, 95% CI: 1.002-1.022, $P = 0.023$), and cumulative LDL-C (OR: 1.155, 95% CI: 1.009-1.322, $P = 0.037$). The protective association of HDL-C with lower CAD risk did not reach statistical significance (OR: 0.978, 95% CI: 0.956-1.001, $P = 0.060$) (Table 2). In this model, the interaction terms for Lp(a) and sex (OR: 1.003, 95% CI: 0.983-1.023, $P = 0.760$) and for cumulative LDL-C and sex (OR: 1.078, 95% CI: 0.810-1.433, $P = 0.607$) were not statistically significant.

Coronary artery disease incidence increased with both higher cumulative LDL-C and elevated Lp(a) levels. Among patients with cumulative LDL-C ≥ 14 g/dL, CAD was diagnosed in 57% of those with Lp(a) ≥ 50 mg/dL, 45% with Lp(a) between 30 and 49 mg/dL, and 27% with Lp(a) < 30 mg/dL. In comparison, among those with cumulative LDL-C < 14 g/dL, CAD incidence was 45%, 27.8%, and 25%, respectively (Figure 4). A cumulative LDL-C level ≥ 14 g/dL combined with Lp(a) ≥ 30 mg/dL was an independent predictor of CAD (OR: 2.730, 95% CI: 1.286-5.810), with an even greater risk observed in patients with Lp(a) ≥ 50 mg/dL (OR: 3.309; 95% CI: 1.096-9.986).

Although SCORE2-OP was not predictive in our cohort, a model incorporating SCORE2-OP variables identified male sex as an independent predictor of CAD (OR: 2.747, 95% CI: 1.428-5.284, $P = 0.002$). When Lp(a) was added, it also emerged as an independent predictor (OR: 1.011, 95% CI: 1.001-1.020, $P = 0.034$), alongside male sex (OR: 2.586, 95% CI: 1.329-5.033, $P = 0.005$) (Table 3). In the multivariable logistic regression analysis using SAFEHEART-related variables, male sex and Lp(a) were independently associated with the presence of ASCVD (OR: 4.35, 95% CI: 1.91-9.89, $P < 0.001$; and OR: 1.01, 95% CI: 1.00-1.03, $P = 0.026$, respectively) (Appendix Table 1).

Discussion

Our study demonstrated that in statin-naïve individuals aged ≥ 70 years with elevated LDL-C levels, the presence of CAD was associated with greater cumulative LDL-C exposure, higher Lp(a) levels, lower HDL-C levels, and male sex. Multivariate analysis identified cumulative LDL-C, Lp(a), and male sex as independent predictors of CAD. Notably, the highest incidence of CAD was observed among individuals with both cumulative LDL-C > 14 g/dL and Lp(a) ≥ 50 mg/dL. While the SCORE2-OP algorithm did not effectively discriminate risk in this elderly cohort, the SAFEHEART risk score was significantly associated with CAD, supporting its potential utility in this population.

**Figure 4. Incidence of CAD according to cumulative LDL-C and Lp(a) levels.****Table 3. Predictors of CAD (Model 2 with SCORE2-OP variables)**

Variables	OR	95% CI	P
Age	1.052	0.980-1.1120	0.108
Male sex	2.737	1.431-5.235	0.002
Smoking	1.634	0.803-3.326	0.175
Systolic blood pressure	1.005	0.988-1.022	0.540
Non-HDL-C	1.007	0.998-1.017	0.148
After inclusion of Lp(a)			
Age	1.055	0.991-1.124	0.095
Male sex	2.586	1.329-5.033	0.005
Smoking	1.479	0.716-3.059	0.291
Systolic blood pressure	1.004	0.987-1.021	0.662
Non-HDL-C	1.007	0.997-1.017	0.155
Lp(a)	1.011	1.001-1.020	0.034

CAD, Coronary artery disease; HDL-C, High-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); SCORE2-OP, Systematic Coronary Risk Estimation 2-Older Persons; OR, Odds ratios; CI, Confidence interval.

It is well known that some elderly individuals are spared from ASCVD despite having very high LDL-C levels. In the Spanish SAFEHEART cohort, Pérez de Isla et al.¹² demonstrated that female patients with FH who had lower Lp(a) levels and higher HDL-C levels may be protected from CAD. Although this study did not specifically focus on patients with FH, due to the high LDL-C levels, 43.6% of the cohort was classified as possible FH and 5.4% as probable FH according to the Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia.¹³ In our statin-naïve study group, cumulative LDL-C demonstrated high predictive value for CAD. Prolonged exposure to elevated LDL-C levels in these patients is similar to that seen in individuals with FH, who are subjected to lifelong high LDL-C concentrations.¹⁴ Our findings are consistent with those of the SAFEHEART cohort, which highlighted the protective effects of female sex and low Lp(a) levels in elderly patients with high LDL-C levels.

Lipoprotein(a) is a genetically determined, proatherogenic, and prothrombotic lipoprotein composed of apolipoprotein B and apolipoprotein(a).^{7,15} Lp(a) levels remain largely unchanged across the lifespan, although an increase is often observed in women following the menopausal transition.^{16,17} The median Lp(a) level in our cohort (18 mg/dL) was higher than the estimated national average in the Turkish population (12–16 mg/dL), likely reflecting the high proportion of postmenopausal women in the study.¹⁸ Consistent with previous studies, elevated Lp(a) levels in our cohort were associated with CAD and retained their independent predictive value following multivariable adjustment.^{19,20}

At present, no approved pharmacologic therapies specifically target Lp(a) reduction. Therefore, management of patients with elevated Lp(a) focuses on optimizing modifiable risk factors, with particular emphasis on LDL-C reduction.^{3,4,21} Nevertheless, the role of LDL-C-lowering treatment in elderly patients remains controversial, and it is still debated which individuals in this age group benefit most from statins. Statin therapy in older individuals is inconsistently recommended in national guidelines. The ESC Prevention Guidelines provide only a weak recommendation for statin therapy in individuals over 70 years of age, even for those classified as at very high risk.⁴ Similarly, the ACC Prevention Guideline offers limited clarity regarding preventive treatment in this population.³

As the population continues to age, uncertainties surrounding ASCVD prevention and treatment strategies in older individuals have become increasingly prominent, partly due to their underrepresentation in clinical trials. The higher incidence of non-cardiac mortality and the presence of competing risks further complicate cardiovascular risk evaluation in the elderly population.^{22,23} Existing clinical studies indicate that statins reduce ASCVD events in elderly individuals to a similar extent as in younger patients.²⁴ However, in the ASPREE trial (Aspirin in Reducing Events in the Elderly), a U-shaped relationship between LDL-C levels and mortality was observed, raising concerns about potential harm at very low LDL-C levels in older individuals.^{25,26} These contradictory findings, combined with the lack of strong evidence demonstrating a clear mortality benefit, as well as concerns related to polypharmacy and frailty, limit the strength of recommendations for statin therapy in the elderly. Therefore, the use of risk scores and identification of specific parameters to help select elderly individuals most likely to benefit from treatment are important.

To address this issue, the SCORE2-OP risk prediction algorithm was developed by the SCORE2-OP Working Group for four different geographical regions with varying cardiovascular disease (CVD) prevalence and risk levels, as defined by the World Health Organization (WHO).¹⁰ According to this model, a 10-year cardiovascular risk above 15% is classified as very high risk, and the latest ESC prevention guidelines recommend the use of SCORE2-OP for risk estimation in individuals aged 70 years and older.⁴ However, particularly in risk algorithms developed for high-risk countries, the majority of individuals aged 70 years and above are classified as very high risk, as age itself is a major risk enhancer. In our study population, drawn from a high-risk country, nearly all patients, except for two, were categorized as very high risk, despite approximately 70% of participants being free of obstructive CAD.

The superiority of the SAFEHEART risk score over SCORE2-OP in our cohort suggests that including additional clinical and lipid-related parameters, such as Lp(a), may improve CVD risk prediction in elderly individuals with elevated LDL-C levels.

An additional distinction between the two risk scores relates to the characteristics of their derivation cohorts. The SCORE2-OP algorithm was developed based on data from the CONOR study (Cohort of Norway), which included Norwegian individuals and a diverse group of immigrants residing in Norway, populations exposed to relatively uniform healthcare systems and environmental influences.²⁷ In contrast, the SAFEHEART registry is based on a Spanish cohort.¹¹ Given that both our study population and the SAFEHEART cohort are Mediterranean, they may share common dietary patterns, cultural habits, and lifestyle characteristics, enhancing the applicability of the SAFEHEART score in our setting. Second, baseline lipid profiles also differ across cohorts. The mean LDL-C level in our population more closely resembled that of the SAFEHEART cohort (177.8 mg/dL) than that of the SCORE2-OP population, which reported a non-HDL cholesterol level of 189.5 mg/dL.^{10,11} Finally, the SCORE2-OP calculator tends to classify nearly all elderly individuals in high-risk countries into the very high-risk category. This broad classification may diminish its discriminative power.

Strengths and Limitations

This study has several noteworthy strengths. It addresses a critical gap in the literature by focusing on primary prevention in statin-naïve elderly individuals with elevated LDL-C levels, a population frequently underrepresented in clinical research and guideline development. The use of cumulative LDL-C as a risk marker, rather than relying on a single-point measurement, provides a more comprehensive assessment of lifelong exposure and may improve individualized risk stratification. The incorporation and comparative evaluation of multiple risk prediction models, including SCORE2-OP and SAFEHEART, offer additional insights into risk assessment in this specific elderly cohort. Importantly, the real-world nature of the study population, consisting of elderly individuals for whom guidelines are often unclear and treatment decisions are particularly challenging, enhances the clinical relevance of the findings.

However, the study also has limitations. The retrospective, single-center design of the study and its modest sample size may restrict the extent to which these findings can be generalized. The lack of longitudinal follow-up precludes assessment of long-term outcomes such as incident ASCVD events or mortality, limiting the ability to evaluate the prognostic impact of cumulative LDL-C and Lp(a) levels.

A key source of selection bias arises from the study population: most participants were referred to a cardiology outpatient clinic and underwent advanced diagnostic testing (e.g., coronary CT angiography, invasive angiography, or myocardial perfusion imaging) due to suspected CAD. As a result, the cohort likely represents a higher-risk, symptomatic, or physician-referred group rather than a community-based elderly population. This introduces the possibility of Berkson-type bias, which may further restrict the applicability of the findings to the broader elderly population with elevated LDL-C levels. The use of multiple diagnostic modalities (invasive angiography, CCTA, and functional stress testing) may have introduced variability in CAD

detection, particularly given the known limitations of CCTA in elderly individuals with severe coronary calcification; therefore, some degree of diagnostic misclassification cannot be excluded. Moreover, the absence of obstructive CAD may not be sufficient to exclude a substantial 10-year cardiovascular event risk.

Although interaction terms between sex and both Lp(a) and cumulative LDL-C were statistically insignificant, the predominance of female participants may have influenced the observed associations, thereby limiting the generalizability of the results to elderly men. In addition, cumulative LDL-C exposure was estimated by multiplying a single LDL-C measurement by age, which may not accurately reflect true lifetime exposure, especially given that LDL-C levels tend to rise with age. This approach may have led to a modest overestimation of cumulative LDL-C burden.

Lp(a) levels were reported in milligrams per deciliter (mg/dL) rather than nanomoles per liter (nmol/L), which limits comparability across studies due to interindividual variability in Lp(a) particle size. Furthermore, genetic testing for FH or specific LPA variants was not performed, leaving the contribution of monogenic or polygenic lipid disorders to elevated LDL-C and Lp(a) levels uncharacterized.

Conclusion

Among elderly individuals aged ≥ 70 years with elevated LDL-C levels, male sex, greater cumulative LDL-C exposure, and higher Lp(a) concentrations emerged as independent correlates of CAD. In particular, individuals with cumulative LDL-C ≥ 14 g/dL and Lp(a) ≥ 30 mg/dL may represent a subgroup of elderly patients who would derive the greatest benefit from statin therapy, despite current uncertainties and weaker recommendations in clinical guidelines. In this context, the SAFEHEART risk score demonstrated superior discriminatory ability compared to SCORE2-OP and may offer a more appropriate tool for risk stratification in elderly patients with substantial lipid burden. If confirmed in larger prospective cohorts, this risk score may provide an alternative approach to risk stratification among elderly individuals with elevated LDL-C levels.

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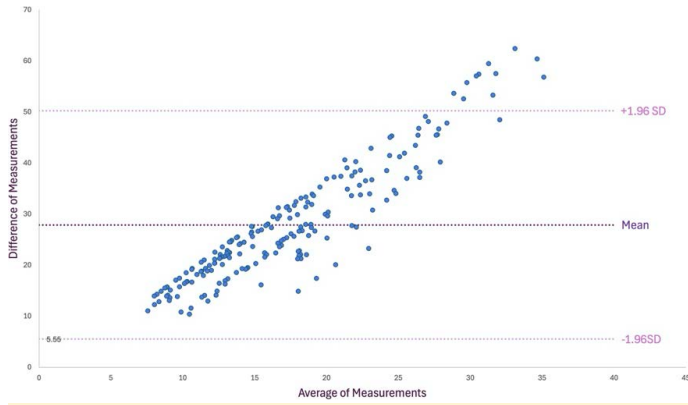
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Appendix Figure 1. Bland-Altman analysis showing a mean difference of 27.90 (\pm 11.40) between SCORE2-OP and SAFEHEART risk scores, indicating that SCORE2-OP systematically overestimated cardiovascular risk compared to SAFEHEART.

Appendix Table 1. Predictors of CAD (Model 3 with SAFEHEART variables)

Variables	OR	95% CI	P
Age (years)	1.03	0.95-1.12	0.423
BMI	1.09	0.98-1.18	0.058
Male sex	4.35	1.91-9.89	<0.001
Smoking	1.65	0.69-3.91	0.259
LDL-C	1.01	0.99-1.02	0.128
Lp(a)	1.01	1.00-1.03	0.026

BMI, Body mass index; CAD, Coronary artery disease; CI, Confidence interval; LDL-C, Low-density lipoprotein cholesterol; Lp(a), Lipoprotein(a); OR, Odds ratios; SAFEHEART, Spanish Familial Hypercholesterolemia Cohort Study.