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Characteristics and lipid lowering treatment patterns in patients tested for lipoprotein(a): A real-world US study

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ABSTRACT

Objective: Elevated lipoprotein(a) [Lp(a)] is a risk factor for atherosclerotic cardiovascular disease (ASCVD) and has no approved pharmacotherapies. Limited real-world data exists on the proportion of patients with available Lp(a) test results, characteristics of these patients, and their use of lipid lowering therapies (LLTs) for secondary prevention (SP) and primary prevention (PP) of ASCVD.

Methods: Patients with measured Lp(a) receiving LLTs for SP or PP of ASCVD were identified in the Optum Clinformatics® Data Mart database. Lp(a) distribution and LLT utilization including persistence and adherence were assessed. Logistic regression was used to assess the association between Lp(a) levels and low-density lipoprotein cholesterol (LDL-C) levels after index LLT, adjusting for baseline characteristics.

Results: Overall, 2154 SP and 7179 PP patients met eligibility criteria. Of patients with available laboratory data, only 0.7% (SP) and 0.6% (PP) had Lp(a) test results. In the SP cohort, Lp(a) levels ≥125 nmol/L and ≥175 nmol/L were 26.4% and 17.6%, respectively, and the mean (SD) Lp(a) levels (overall SP cohort 90.4 [97.9] nmol/L) were highest in Black patients (123.4 [117.4]; $p<0.001$). Statin monotherapy was the most frequently prescribed LLT in SP patients overall (89.4%). Median (interquartile range [IQR]) persistence of LLTs was 227 (91, 649) days and 33.6% achieved ≥80% proportion of days covered (PDC). Patients with Lp(a) ≥175 nmol/L had 2.1 times greater odds of having elevated LDL-C (≥70 mg/dL) post-LLT than those with Lp(a) <175 nmol/L ($p = 0.031$). Similar findings were observed in the PP population.

Conclusions: Lp(a) screening was rare. Elevated Lp(a) was observed in more than one-quarter of patients receiving LLTs, with the highest mean Lp(a) levels observed in Black patients. Low adherence to LLTs was prevalent and at least half of patients failed to achieve their respective LDL-C target thresholds despite treatment. Finally, high Lp(a) levels were associated with worse LDL-C control.

1. Introduction

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein-like particle in which the apolipoprotein B (apoB) component is linked by a disulfide bond to apolipoprotein(a) [apo(a)] [1]. Lp(a) has been shown to drive monocyte activation and endothelial cell inflammation, thus increasing atherogenic and thrombotic risk [2,3]. Epidemiological, genome-wide association, and Mendelian randomization data provide clear support for Lp(a) as an independent, causal risk factor for atherosclerotic cardiovascular disease (ASCVD) [4–8]. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) guideline highlights Lp(a) values of ≥50 mg/dL or ≥125 nmol/L as risk enhancing factors for ASCVD [9]. It is estimated that 20–30% of people with cardiovascular disease (CVD) have elevated Lp(a) [10,11], with 16% and 25% having Lp(a) levels ≥70 mg/dL and ≥50 mg/dL, respectively [12]. However, little is known regarding the real-world uptake of Lp(a) testing

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in the US since the publication of the ACC/AHA guideline.

Lp(a) levels are primarily genetically determined and are not responsive to lifestyle and/or dietary changes. Despite no approved pharmacotherapy for elevated Lp(a) levels in the US, many treatments are available to modify other risk factors (e.g., high level of low-density lipoprotein cholesterol [LDL-C]) with the goal of optimizing overall ASCVD risk management. Less is known regarding the use of lipid lowering therapies (LLTs) and their treatment patterns among patients with elevated Lp(a) levels.

The objectives of this study were to evaluate the proportion of patients with available Lp(a) test results, distribution of Lp(a) levels, and characteristics of patients receiving LLTs for either secondary prevention (SP) or primary prevention (PP) of ASCVD. Further, the treatment patterns of initial LLTs were described and compared by Lp(a) levels, gender, and race/ethnicity. Finally, LDL-C levels were assessed pre- and post-initiation of LLTs overall and further stratified by Lp(a) levels.

2. Methods

2.1. Study design

This non-interventional, retrospective cohort study used the Optum Clinformatics® Data Mart (CDM) database (January 1, 2007 to December 31, 2020). The Optum CDM database is a widely used longitudinal database that includes detailed eligibility information, de-identified inpatient and outpatient medical claims, pharmacy claims, and laboratory results. The population contained within this database comprises enrollees of a large commercial and Medicare Advantage plan in the US and is geographically diverse across all 50 states and the District of Columbia. In the database, approximately 30% of patients have available laboratory data. The study utilized de-identified data and did not require institutional review board approval.

2.2. Study population

To have a more representative sample to describe the use of LLTs in patients with available Lp(a) values, patients who received LLTs for SP and those who received LLTs for PP were defined and assessed separately. Lp(a) levels provided in nmol/L were included to define the study cohorts; nmol/L, measuring the number of Lp(a) particles, is considered a more accurate and appropriate unit than mg/dl as it is less affected by the large variation in apo(a) isoform size [13]. Lp(a) tests with the mg/dL unit were only included to establish the proportion of patients with any Lp(a) test.

SP cohort: The index date was the first ASCVD-related claim identified from July 1, 2007 to December 31, 2018. These patients were included when they had at least 6 months (baseline period) and 2 years of continuous enrollment prior to and after the index date, respectively. Additionally, they were required to have at least one Lp(a) measurement in nmol/L during the study period as well as a filled prescription for an LLT any time on or after the index date, but not prior to index date. ASCVD was defined based on the 2018 ACC/AHA cholesterol management guideline: ICD-9-CM and ICD-10-CM codes for myocardial infarction (MI), peripheral artery disease (PAD), ischemic stroke, unstable angina, stable angina, transient ischemic attack (TIA) and Healthcare Common Procedure Coding System (HCPCS), Current

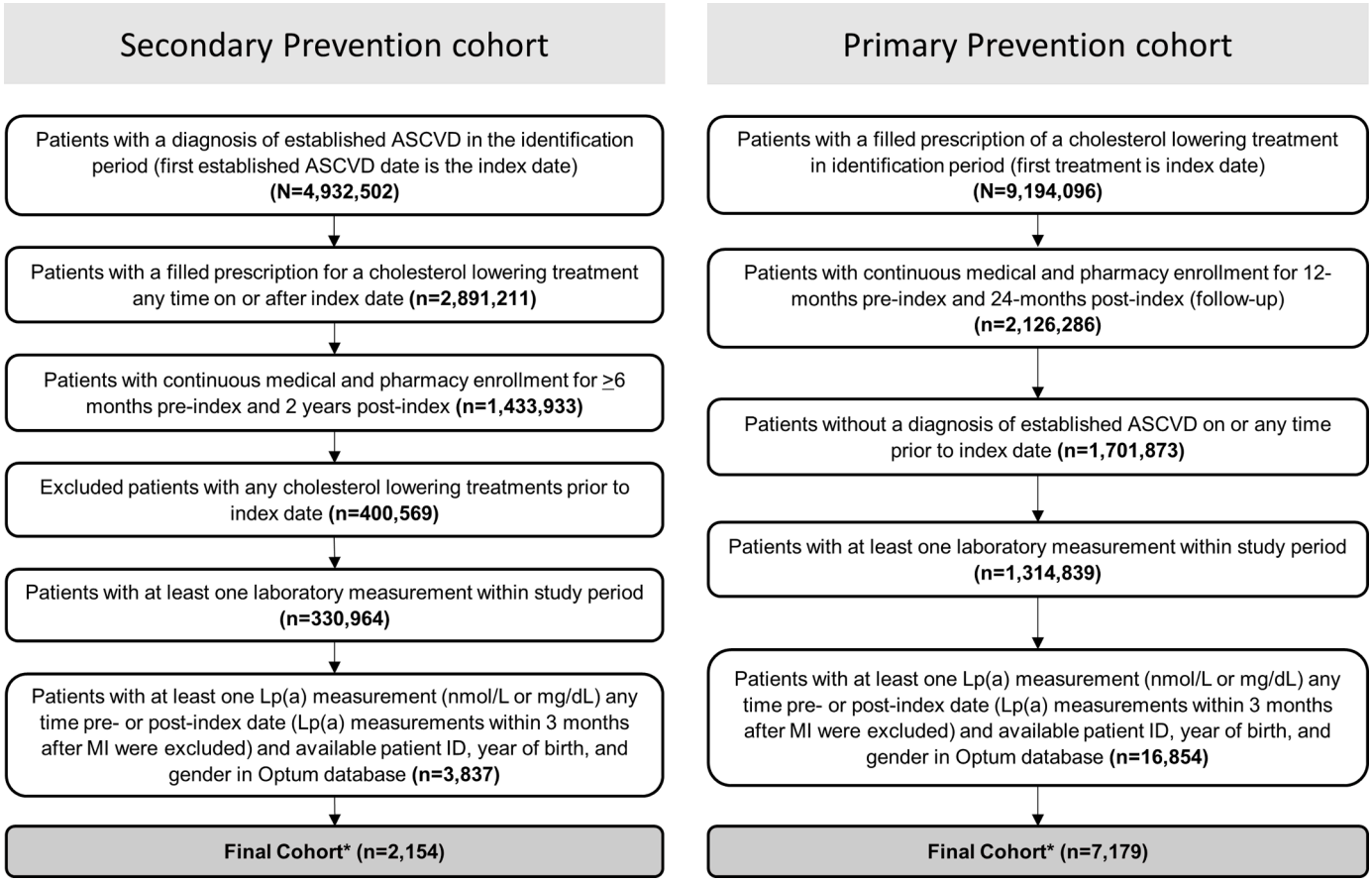


Fig. 1. Sample attrition and cohort identification for secondary and primary prevention patients
* Contains only patients with an Lp(a) test in nmol/L
Study period: Jan 1, 2007 – Dec 31, 2020; Identification period: Jul 1, 2007 - Dec 31, 2018 (SP), Jan 1, 2008 - Dec 31, 2018 (PP)
Abbreviation: ASCVD, atherosclerotic cardiovascular disease; **Lp(a)**, lipoprotein (a); **MI**, myocardial infarction.

Procedural Terminology (CPT), and ICD-9/10-PCS codes for revascularization procedures [9]. Lp(a) measurements taken within 3 months after MI were excluded to prevent the impact of acute coronary syndrome on Lp(a) values.

PP cohort: The identification period for the PP cohort was January 1, 2008 until December 31, 2018, and the PP index date was defined as the first LLT prescription during this period. Similarly, at least 12 months (baseline period) and 24 months of continuous enrollment prior to and after the index date, respectively, and at least one Lp(a) measurement (nmol/L) were required. Those who were qualified as PP patients required no diagnosis of ASCVD identified as above on or any time prior to the index date.

2.3. Study measures

Baseline demographic characteristics assessed included age at index, gender, race/ethnicity, and health plan type. Baseline clinical characteristics included index ASCVD (SP only), cardiovascular and other comorbidities, Deyo-Charlson comorbidity index (DCCI), medications/procedures, presence of familial hypercholesterolemia (FH; identified using ICD-10 code E78.01), LDL-C levels, and Lp(a) levels.

Lp(a) screening was measured as the proportion of secondary or primary prevention patients with available laboratory data that had any Lp(a) test result during the study period. Due to lack of detailed provider information from Optum CDM's laboratory data, the types of providers requesting Lp(a) tests were estimated based on patients' medical and/or pharmacy claims data on the same day of the Lp(a) test.

The initial LLTs were assessed as monotherapy and combination therapy (second agent added or fixed dose combination therapy prescribed). Monotherapy was assigned based on the first prescription for any of the LLTs in patients without any other LLTs within 30 days after initial LLTs. Combination therapy was assigned when an additional LLT was started within 30 days after the first LLT prescription or if a fixed dose combination was used from the beginning. Adherence was defined as the proportion of days covered (PDC), which was calculated as the number of days with drug on hand (or number of days exposed to drug) divided by the 24-month follow-up period, regardless of discontinuation. A PDC of greater than 80% was considered adherent. Persistence was defined as the duration of time from initiation to discontinuation of the initial LLTs allowing a 60-day gap.

According to the ACC/AHA guideline [9], elevated LDL-C was defined as LDL-C levels ≥70 mg/dL for SP and ≥100 mg/dL for PP. The closest LDL-C measurements prior to the index date was used as the index LDL-C levels.

2.4. Statistical analyses

Continuous variables were reported as mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum. To compare PDC and persistence, Mann-Whitney U test was used between Lp(a) levels (<175 nmol/L vs. ≥175 nmol/L), gender, and treatment types (mono vs. combination therapy) and an ANOVA test was used for race/ethnicity. Categorical variables were reported as frequency counts and percentages and compared using the Chi-square test of proportions. A McNemar's test was conducted to compare the proportion of patients with elevated LDL-C between baseline and post-LLT (within 6 to 12 months after index treatment). Logistic regression was used to assess the odds of having elevated LDL-C after index LLT with elevated Lp(a) levels (≥175 nmol/L), adjusting for baseline LDL-C, age, gender, race/ethnicity, and treatment types (statin only and other therapies). All statistical tests were two-tailed with an *a priori* significance level set at 0.05. Analyses were performed using SAS Studio 3.81 (SAS Institute, Cary, NC).

Table 1
Baseline characteristics.

Category	Secondary prevention patients (N = 2154)	Primary prevention patients (N = 7179)
Age at index		
Mean (SD)	63.7 (11.8)	58.2 (12.9)
Median (Q1, Q3)	66 (55, 72)	58 (49, 69)
Gender		
Female	50.3%	49.5%
Male	49.7%	50.5%
Race/Ethnicity		
Asian	3.3%	5.1%
Black	13.7%	10.5%
Hispanic	12.8%	12.6%
White	66.9%	68.1%
Other	3.3%	3.8%
Health plan type		
Commercial	42.5%	63.9%
Medicare	57.5%	36.1%
ASCVD index diagnosis		
Myocardial infarction (MI)	10.4%	
Peripheral arterial disease (PAD)	38.8%	
Ischemic stroke	10.9%	
Transient ischemic attack (TIA)	11.9%	
Unstable Angina	5.9%	
Stable Angina	14.8%	
Post-revascularization	7.3%	
Cardiovascular comorbidities[a]		
Hypertension	73.3%	52.8%
Heart failure	9.6%	2.5%
Atrial fibrillation	8.5%	3.0%
Aortic valve stenosis	5.8%	2.3%
Cardiac amyloidosis	0.2%	0.1%
Other comorbidities[a]		
Dyslipidemia	71.9%	77.7%
Depression/mental disorder	41.9%	31.2%
Diabetes	29.7%	22.3%
Obesity	20.7%	14.6%
Anemia	17.6%	12.7%
Cancer	16.2%	12.1%
Sleep apnea	13.2%	9.7%
Chronic obstructive pulmonary disease (COPD)	12.5%	7.5%
Liver disease	9.8%	6.2%
Chronic kidney disease (stage III)	5.2%	2.4%
Rheumatoid arthritis	5.0%	2.0%
Cognitive Impairment & Dementia	2.0%	0.8%
Alzheimer Disease	1.8%	0.8%
Chronic kidney disease (stage IV-V)	0.9%	0.5%
Deyo-Charlson comorbidity index (DCCI)		
Mean (SD)	2.3 (2.0)	1.0 (1.5)
Median (Q1, Q3)	2 (1, 3)	0 (0, 1)
Baseline medications		
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARBs)	31.6%	31.4%
Beta-blockers	21.7%	16.5%
Anti-depressants	18.1%	18.9%
Anti-diabetics	12.6%	14.6%
Hormone replacement therapy	3.9%	5.5%
Antiplatelets	2.6%	2.2%
Baseline procedure		
Dialysis	0.1%	0.1%
Familial hypercholesterolemia (FH) and apheresis procedure in baseline and follow-up period[b]		
FH	0.2%	3.4%
Apheresis procedure	0.04%	0.05%
Baseline LDL-C (mg/dL)[c]		
Patients with LDL-C measurements	737 (34.2%)	2985 (41.6%)
Mean (SD)	121.9 (34.8)	134.9 (41.1)
Median (Q1, Q3)	119 (99, 143)	134 (108,160)
≥190 mg/Dl	24 (3.3%)	249 (8.3%)
Lp(a) (nmol/L)[d]		
Mean (SD)	90.4 (97.9)	92.6 (100.4)

(*continued on next page*)

Table 1 (*continued*)

Category	Secondary prevention patients ($N = 2154$)	Primary prevention patients ($N = 7179$)
Median (Q1, Q3)	48.1 (21.0, 130.0)	48.0 (19.2, 142.0)
≥125 nmol/L	26.4%	28.5%
≥175 nmol/L	17.6%	18.6%

[a] Any time prior to index date (earliest ASCVD date for secondary prevention, earliest treatment date for primary prevention).
[b] The duration between index date and the end of study period for familial hypercholesterolemia (FH), between the closest Lp(a) measurement to the index date and the end of study period for apheresis.
[c] Closest LDL-C measurement prior to the index date.
[d] Closest Lp(a) measurement prior to or after index date.
Abbreviations: FH, familial hypercholesterolemia; **LDL-C**, low-density lipoprotein cholesterol; **Lp(a)**, lipoprotein (a); **SD**, standard deviation.

3. Results

3.1. Study population attrition and patient characteristics

Lp(a) measurements in either nmol/L or mg/dL, were available for 1.2% and 1.3% of SP and PP patients, respectively. Proportions were similar by gender and race/ethnicity. The majority of the Lp(a) tests were requested by family practitioners/general practice (38%) and internists (37%), followed by cardiologists (24%). Patients meeting the full eligibility criteria, and with only Lp(a) tests results in nmol/L, totaled 2154 (0.7%) in the SP cohort and 7179 (0.6%) in the PP cohort (Fig. 1).

The mean age of SP patients was 63.7 years, half were female (50.3%), and two thirds were White (66.9%), followed by Black (13.7%), Hispanic (12.8%), and Asian (3.3%) (Table 1). The gender distribution of PP patients was fairly even as seen in SP, though patients were relatively younger with fewer in the Medicare advantage plan.

The most common index ASCVD diagnosis in SP patients was PAD (38.8%), followed by stable angina (14.8%), and TIA (11.9%) (Table 1). Prior MI and ischemic stroke accounted for 10.4% and 10.9% ASCVD diagnoses, respectively. The most common cardiovascular comorbidity was hypertension (73.3%), followed by heart failure (9.6%), and atrial fibrillation (8.5%). The most common non-cardiovascular comorbidity was dyslipidemia (71.9%), followed by depression/mental disorder (41.9%), and diabetes (29.7%). Mean (SD) DCCI was 2.3 (2.0). The most common baseline medications (other than LLT) were angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) (31.6%), followed by beta-blockers (21.7%) and antiplatelets (2.6%). Few patients had FH in the baseline and follow-up period defined as a diagnosis of FH (0.2%) or any LDL-C level ≥190 mg/dL (3.3%) (indicative of FH in adults). Similar clinical characteristics were observed in the PP cohort.

3.2. Lp(a) distribution

The mean (SD) Lp(a) level in SP patients was 90.4 (97.9) nmol/L with more than one quarter (26.4%) having Lp(a) values of ≥125 nmol/L (Fig. 2). Lp(a) levels greater than or equal to 175 nmol/L and 225 nmol/L accounted for 17.6% and 10.4%, respectively. The mean Lp(a) level in Black patients (123.4 nmol/L) was significantly higher than those observed for other races/ethnic groups (77.6–87.0 nmol/L, $p<0.001$) (Fig. 3). More than a third of Black patients had Lp(a) levels ≥125 nmol/L (34.7%), and around one-quarter had Lp(a) ≥175 nmol/L (24.5%) which was a significantly higher proportion compared with other races/ethnic groups ($p<0.001$). Similar Lp(a) distributions overall and across racial/ethnical groups were observed in the PP cohort.

3.3. Treatment patterns for initial LLTs

Statins were the most prescribed initial LLT in SP patients (89.4%), 27.7% of which were high intensity, followed by fibrates (2.5%) and bile acid sequestrants (2.4%). Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) were initiated in 0.5% of SP patients (Table 2). Few patients initiated their LLT with combination therapy (2.5%). The median (Q1, Q3) persistence of LLTs was 227 (91, 649) days and the median PDC was 0.6 (0.2, 0.9), with approximately one third adherent (33.6%) (PDC ≥80%) over 2 years. Patients with combination therapy had significantly higher persistence and adherence compared to monotherapy ($p = 0.004$). The most commonly prescribed LLT in SP patients with elevated Lp(a) of ≥175 nmol/L was statins (87.4%). SP patients with elevated Lp(a) levels of ≥175 nmol/L had greater median persistence (246 [91, 630] vs. 224 [91, 649]) and adherence (35.3% vs. 33.2%) to their LLTs than patients with <175 nmol/L Lp(a) (Table 3). Both median persistence and adherence differed significantly by gender and race/ethnicity. Lower persistence (202 days vs. 269 days, $p<0.001$) and adherence to LLTs (PDC: 0.5 vs. 0.6, $p = 0.005$) were observed in females compared to males. Black patients exhibited the lowest levels of persistence (189 days) and adherence (24.2%) over 2 years compared

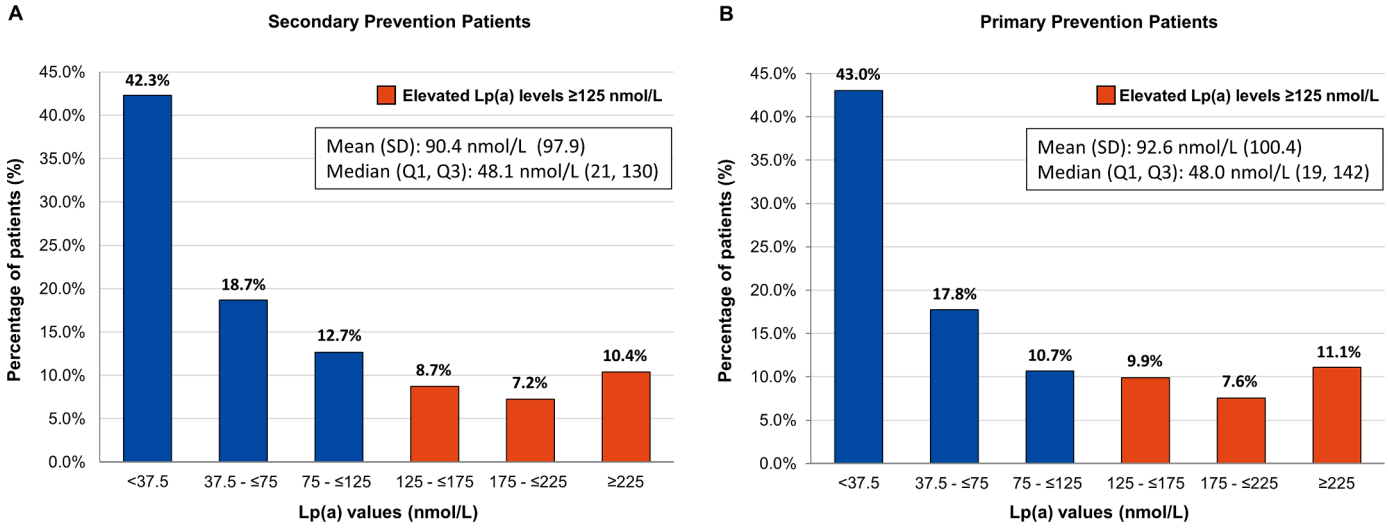
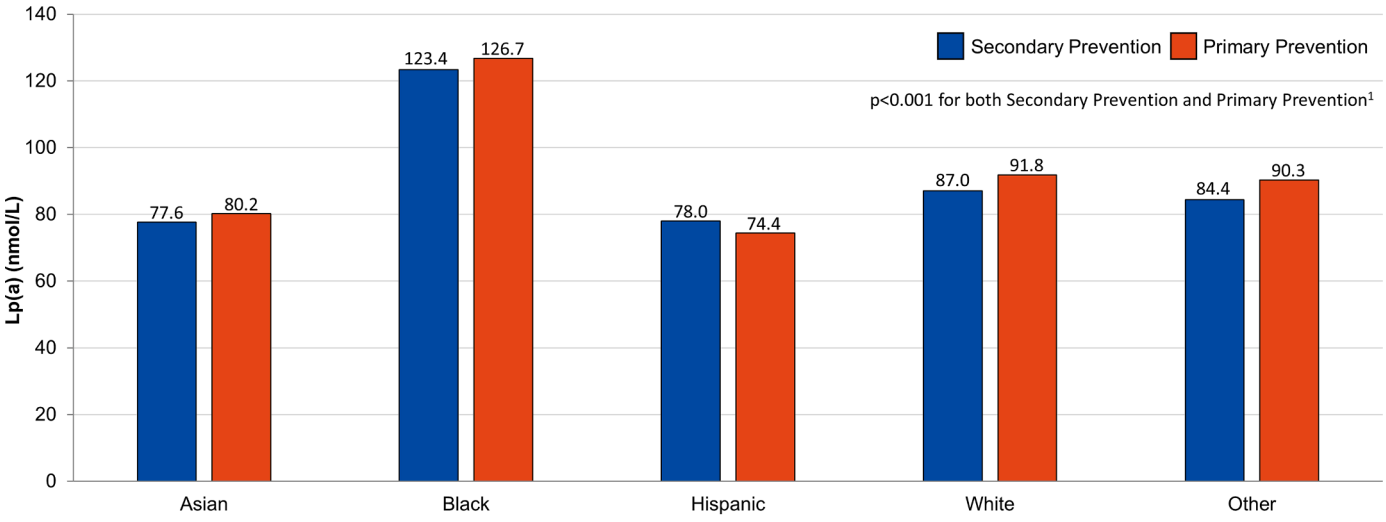


Fig. 2. Lp(a) distribution in secondary and primary prevention patients
Abbreviation: Lp(a), lipoprotein (a).



Percentage of patients with ≥125 and ≥175 nmol/L Lp(a) by race/ethnicity

Lp(a) levels	Asian	Black	Hispanic	White	Other
Secondary prevention (N,%)	72 (100.0%)	294 (100.0%)	275 (100.0%)	1,441 (100.0%)	72 (100.0%)
≥125 nmol/L	19.4%	34.7%	21.5%	26.0%	25.0%
≥175 nmol/L	12.5%	24.5%	15.6%	17.1%	13.9%
Primary prevention (N,%)	365 (100.0%)	753 (100.0%)	902 (100.0%)	4,888 (100.0%)	271 (100.0%)
≥125 nmol/L	22.2%	39.0%	21.1%	28.8%	27.7%
≥175 nmol/L	14.3%	28.3%	12.8%	18.7%	17.0%

Fig. 3. Distribution of Lp(a) value by race/ethnicity
[1] ANOVA test compared Lp(a) value across race/ethnicity within secondary prevention and primary prevention.
Abbreviation: Lp(a), lipoprotein (a).

with other races/ethnic groups ($p = 0.003$ and <0.001, respectively). Similar LLT patterns overall and by Lp(a) levels, gender, and race/ethnicity were observed in the PP cohort (**Supplementary Appendix A, B**).

3.4. LDL-C levels pre- and post-LLTs and by Lp(a) levels

To compare the LDL-C levels between baseline and within 6 to 12 months after initial LLT, only patients with LDL-C measurements both in baseline and post-LLT were included (SP: 365, PP: 1419). Elevated LDL-C levels were ubiquitous at baseline (94.2%) in the SP cohort (Table 4). This proportion was significantly reduced to 66.6% ($p<0.001$) after initiation of LLTs for at least 6 to 12 months. Multivariable logistic regression showed that compared with those with Lp(a) levels <175 nmol/L, patients with Lp(a) levels ≥175 nmol/L had significantly greater odds of having elevated LDL-C levels at follow-up after the initiation of LLTs (OR: 2.11 [95% CI: 1.07–4.14], $p = 0.031$) (Table 5). A similar trend was observed in PP patients. For sensitivity analysis, the logistic regression using continuous Lp(a) levels with 25 nmol/L as an increment was conducted (**Supplementary Appendix C**). SP patients had 8% greater odds of having elevated LDL-C for every 25 nmol/L increase in Lp(a) levels ($p = 0.028$).

Central Illustration. Association of risk-enhancing factors with annual CAC progression in South Asian American adults. Eight risk-enhancing factors were evaluated in the association with coronary artery calcium, among South Asian American participants in the MASALA Study. Among participants with any CAC progression, having three or more of these risk-enhancing factors was associated with an approximately 2-times higher rate of CAC progression, compared with having no risk-enhancing factors.

4. Discussion

The results of this investigation show that, despite increasing awareness of elevated Lp(a) as a risk factor for ASCVD, in practice Lp(a) testing rates are still extremely low. Among patients with available laboratory data in this study, slightly over 1% showed any evidence of an Lp(a) test being taken any time during the study (average combined pre- and post-index periods were 9.2 years for SP patients and 10.3 years for PP). Despite guideline recommendations, lack of clinician awareness and knowledge of Lp(a) as an independent, genetically driven, causal, and prevalent risk factor for ASCVD [15], and lack of consensus on how to integrate this biomarker into risk assessments may play an important role leading to the low screening of Lp(a) in the US. Additionally, no approved treatment is currently available, although multiple novel therapies for Lp(a) lowering are in various stages of clinical trials [16, 17]. However, even without an approved treatment, early detection of elevated Lp(a) is crucial for risk reclassification and may support the early introduction of interventions (e.g., statins) that modify other risk factors. Other possible reasons for low testing rates include lack of standardization and harmonization of assays to properly and accurately quantify Lp(a), and unfamiliarity of the new ICD-10 diagnosis code of elevated Lp(a) [15]. The proportion of patients identified in the current study using the new ICD-10 diagnosis code for elevated Lp(a) (ICD10: E78.41, Z83.430) was indeed low (2.6% for SP and 3.1% for PP). The results of proxy provider data suggest that family doctors and internists may currently account for the majority of requested Lp(a) tests. This could mean that Lp(a) testing may remain less of a priority for specialists such as cardiologists, despite the ACC/AHA guideline. More research, education, and multi-disciplinary efforts across different stakeholders in the healthcare system are needed to address the above challenges and to

Table 2
Treatment patterns by initial lipid-lowering therapy among secondary prevention patients.

Category	Overall N (%)	Persistence (days),[a] Median (Q1, Q3)	PDC,[a] Median (Q1, Q3)	PDC ≥ 80%,[a] N (%)
Overall	2154 (100%)	227 (91, 649)	0.6 (0.2, 0.9)	723 (33.6%)
Monotherapy	2100 (97.5%)	224 (91, 639)	0.6 (0.2, 0.9)	697 (33.2%)
Statin (overall)	1925 (89.4%)	262 (91, 696)	0.6 (0.3, 0.9)	669 (34.8%)
High intensity[b]	534 (27.7%)	294 (91, 730)	0.6 (0.3, 0.9)	203 (38.0%)
Low/moderate intensity[b]	1373 (71.3%)	249 (91, 673)	0.6 (0.3, 0.9)	466 (33.9%)
PCSK9i (alirocumab and evolocumab)	11 (0.5%)	188 (31, 649)	0.8 (0.3, 0.9)	5 (45.5%)
Ezetimibe	30 (1.4%)	91 (37, 396)	0.2 (0.1, 0.6)	6 (20.0%)
Fibrates	54 (2.5%)	92 (56, 215)	0.2 (0.1, 0.6)	10 (18.5%)
Niacin	28 (1.3%)	135 (77, 256)	0.3 (0.1, 0.7)	5 (17.9%)
BAS	52 (2.4%)	31 (31, 98)	0.1 (0.0, 0.3)	2 (3.9%)
Combination therapy	54 (2.5%)	395 (154, 730)	0.7 (0.5, 0.9)	26 (48.2%)
Statin + Niacin	22 (1.0%)	373 (153, 673)	0.7 (0.5, 0.9)	7 (31.8%)
Statin + Fibrates	7 (0.3%)	542 (109, 730)	0.8 (0.5, 0.9)	3 (42.9%)
Statin + BAS	4 (0.2%)	730 (493, 730)	0.8 (0.6, 0.9)	3 (75.0%)
Statin + Ezetimibe	15 (0.7%)	191 (129, 582)	0.8 (0.7, 0.9)	9 (60.0%)
Other	6 (0.3%)	730 (363, 730)	1.0 (0.7, 1.0)	4 (66.7%)

[a] Mann-Whitney U test was used to compare persistence and PDC and Chi-square test was used to compare the proportion of patients with PDC ≥ 80% between monotherapy and combination therapy. All p-values were significant at <0.05.

[b] Only statin with available dose were included for statin intensity analysis. Statin procedures or missing dose were excluded from statin intensity categories. Percentage was calculated based on overall statin users.

Abbreviations: BAS, bile acid sequestrants; **PCSKi9i**, proprotein convertase subtilisin/kexin type 9 inhibitors; **PDC**, proportion of days covered.

increase the screening for Lp(a) in both SP and PP settings.

The prevalence of elevated Lp(a) levels observed in our SP and PP cohorts are consistent with the literature, with approximately one-quarter having Lp(a) values of ≥125 nmol/L. A US study assessing the distribution of Lp(a) levels derived from a referral lab ($n = 543,114$) and a tertiary referral center ($n = 915$) showed the prevalence of elevated Lp (a), ≥50 mg/dL or 125 nmol/L, at 24% and 29%, respectively [11]. Another study using the AIM-HIGH trial cohort similarly reported one-quarter of patients with prior ASCVD had Lp(a) levels as high as at least 50 mg/dL [12]. Focusing on a large sample ($n = 460,506$) from the UK biobank with Lp(a) levels measured, Patel et al. reported the prevalence of elevated Lp(a) in 12.2% of those without and 20.3% of those with preexisting ASCVD [18]. However, their threshold for elevated Lp (a) was defined as ≥150 nmol/L whilst the current study used the ACC/AHA guideline recommendation of ≥125 nmol/L, thus capturing a larger group of patients at risk.

Of note in this study was the difference observed in Lp(a) levels by race/ethnicity. In both the SP and PP cohorts, Black patients showed higher mean Lp(a) levels compared to other races/ ethnic groups. Given the evidence for a causal relationship between elevated Lp(a) levels and high risk of CVD [4–6], this could indicate a higher risk and greater burden of future CVD in Black patients. This is supported by Patel et al., who observed that, whilst risk per 50 nmol/L increment in Lp(a) concentration was similar across all races/ethnic groups investigated, Black patients exhibited a higher average Lp(a) concentration, suggesting that they are likely to be subject to a higher risk of incident as well as recurrent CVD events [18]. However, race/ethnicity was not the only factor associated with risk of CVD in patients with elevated Lp(a) levels. Diabetes was one of the most prevalent comorbidities observed within the SP and PP cohorts, with 29.7% and 22.3% of respective patients found to have diabetes at baseline. Diabetes status is reported to have a significant effect on patients' risk of cardiovascular (CV)-related morbidity and mortality [19]. The relationship between Lp(a) levels and CVD risk in the presence of diabetes may warrant further investigation in the future.

The most commonly used LLTs in overall SP patients and those with elevated Lp(a) were statins, with just over one-quarter using high intensity statin treatments. The median persistence and the adherence to statin treatments were greater compared to other LLTs (excluding PCSK9i for which there was a very small sample size). A greater proportion of patients with Lp(a) levels of ≥175 nmol/L used high intensity statins compared with those with <175 nmol/L. The high prevalence of statin use is to be expected given that statins are recommended as a first-line therapy for elevated LDL-C [9]. Persistence to all LLTs was less than one year in SP patients, and only one-third of patients were adherent to LLTs. This aligns with other studies in which overall adherence and persistence is seen to be low in SP patients. Recent data presented by Smith et al. showed that adherence and persistence of existing LLTs were suboptimal at both 12 and 24 months [20].

In this study, female SP patients had both lower persistence and lower adherence than male patients. Additionally, Black patients had the lowest persistence and adherence of all races/ ethnic groups. Such findings are consistent with prior studies exploring potential gender and race/ethnic disparities in LLT treatment patterns. A similar trend was observed in a recent assessment of 284,954 adult patients receiving SP for ASCVD from the OptumLabs Data Warehouse, in which women were reportedly less likely to adhere to their LLTs medications than men [21]. In the same study, all minority populations (e.g., Black, Hispanic, Asian) exhibited relatively low medication adherence compared with White patients [21]. Women and Black, Hispanic, and Asian patients have been shown to be less likely to be prescribed statins than men and White individuals, respectively [21]. Discontinuation of statins has been reported to be significantly more common in patients that do not have a history of statin use [22]. Moreover, high statin persistence has been shown to be more common among individuals with an area-level median income of ≥$37,257, which may disproportionately favor the White population in the US [22].

This study explored the potential relationship between Lp(a) levels and the control of LDL-C levels after the initiation of LLTs. Elevated Lp (a) was associated with greater odds of having an LDL-C ≥ 70 mg/dL, suggesting that high Lp(a) levels may be associated with worse LDL-C control. The cholesterol content of Lp(a) is included in nearly all currently available clinical assays quantifying LDL-C [23]. Given the majority of LLTs have little or no effect on Lp(a), patients with high Lp (a) levels are more likely to have higher LDL-C levels than those without high Lp(a) levels even after LLTs, and thus actual LDL-C levels may be overestimated. Besides LDL-C reduction, several studies have shown that PCSK9is have a moderate effect on Lp(a) lowering [24–26], and ASCVD risk reduction [24]. However, the number of patients initiated with a PCSK9i observed in our study was low for both the SP and PP so it was not possible to assess this in the current investigation. Nevertheless, adding Lp(a)-lowering therapy may further benefit the LDL-C control in those with high Lp(a).

4.1. Limitations

As with all studies that rely on claims data, there are some limitations to be acknowledged. This observational study relied on claims data from

Table 3
Treatment patterns by Lp(a) level, gender, and race/ethnicity among secondary prevention patients.

Category	Overall N (%)	Persistence (days),[a] Median (Q1, Q3)	PDC,[a] Median (Q1, Q3)	PDC ≥ 80%,[a] N (%)	Statins, N (% over Overall N)[a,b]			Combo therapy,[a] N (% over Overall N)
					Overall statins	High intensity	Low/moderate intensity	
Lp(a) level								
<175 nmol/L	1774 (82.4%)	224 (91, 649)	0.6 (0.2, 0.9)	589 (33.2%)	1593 (89.8%)	433 (24.4%)	1142 (64.4%)	42 (2.4%)
≥175 nmol/L	380 (17.6%)	246 (91, 630)	0.6 (0.3, 0.9)	134 (35.3%)	332 (87.4%)	101 (26.6%)	231 (60.5%)	12 (3.2%)
Gender								
Female	1084 (50.3%)	**202 (89, 568)**	**0.5 (0.2, 0.9)**	344 (31.7%)	967 (89.2%)	**226 (20.9%)**	**735 (67.8%)**	23 (2.1%)
Male	1070 (49.7%)	**269 (91, 701)**	**0.6 (0.3, 0.9)**	379 (35.4%)	958 (89.5%)	**308 (28.8%)**	**638 (59.6%)**	31 (2.9%)
Race/Ethnicity								
Asian	72 (3.3%)	**366 (91, 730)**	**0.6 (0.3, 0.9)**	**25 (34.7%)**	60 (83.3%)	15 (20.8%)	43 (59.7%)	4 (5.6%)
Black	294 (13.7%)	**189 (79, 569)**	**0.5 (0.2, 0.8)**	**71 (24.2%)**	263 (89.5%)	86 (29.3%)	177 (60.2%)	8 (2.7%)
Hispanic	275 (12.8%)	**198 (74, 478)**	**0.4 (0.2, 0.8)**	**75 (27.3%)**	237 (86.2%)	60 (21.8%)	172 (62.6%)	5 (1.8%)
White	1441 (66.9%)	**254 (91, 702)**	**0.6 (0.3, 0.9)**	**529 (36.7%)**	1303 (90.4%)	356 (24.7%)	937 (65.0%)	34 (2.4%)
Other	72 (3.3%)	**265 (85, 531)**	**0.6 (0.3, 0.9)**	**23 (31.9%)**	62 (86.1%)	17 (23.6%)	44 (61.1%)	3 (4.2%)

[a] Mann-Whitney U test was used to compare persistence and PDC by Lp(a) level (<175 nmol/L vs. ≥175 nmol/L) and gender (female vs. male), and ANOVA test was used to compare persistence and PDC by race/ethnicity. Chi-square test was used to compare proportion of patients with PDC ≥ 80%, statins, and combination therapy.
[b] Only statin with available dose were included for statin intensity analysis. Statin procedures or missing dose were excluded from statin intensity categories.
Note: Bold text refers to significance level <0.05
Abbreviations: Lp(a), lipoprotein (a); **PDC**, proportion of days covered.

Table 4
Proportion of elevated LDL-C in baseline period and within 6 to 12 months after index treatment by Lp(a) levels.

Lp(a) Level	Patients with elevated LDL-C[a]				*p*-value[b]
	Baseline		Post-treatment		
	N	%	N	%	
Secondary prevention patients					
Overall (*n* = 365)	344	94.2%	243	66.6%	<0.001
<175 nmol/L (*n* = 299)	280	93.6%	190	63.5%	<0.001
≥175 nmol/L (*n* = 66)	64	97.0%	53	80.3%	0.002
Primary prevention patients					
Overall (*n* = 1419)	1138	80.2%	690	48.6%	<0.001
<175 nmol/L (*n* = 1182)	942	79.7%	558	47.2%	<0.001
≥175 nmol/L (*n* = 237)	196	82.7%	132	55.7%	<0.001

[a] Elevated LDL-C: ≥70 mg/dL for secondary prevention and ≥100 mg/dL for primary prevention. To compare LDL-C before and after treatment, only patients with LDL-C measurements in both baseline and post-treatment were included.
[b] McNemar's test was used to compare proportion of patients with elevated LDL-C between baseline and post-treatment.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; **Lp(a)**, lipoprotein (a).

the Optum CDM database and may not be generalizable to the entire US population, thus no causal inferences can be made. The identification of a random sample of eligible patients from the broader population is not possible within retrospective studies utilizing administrative claims for sample selection. Consequently, unobserved factors may have introduced selection bias into our sample. For instance, patients with Lp(a) levels available are self-selected by the ordering physicians for such measurements and are therefore not a random sample of either the general SP or PP cohorts. Nevertheless, our findings regarding Lp(a) distribution are consistent with data from other studies and represent the real-world characteristics of patients who have been tested for Lp(a) [11,14,27]. Moreover, in this sample, patients with and without any Lp (a) test were generally similar in terms of demographics and clinical characteristics (**Supplementary Appendix D**). An additional, fundamental limitation of using real-world data collected and abstracted from claims databases is the completeness of the data. Only 30% of patients in the Optum CDM database contain information on laboratory measurements. Given the sample included in this study was selected based on the presence of any Lp(a) test results, our findings may not be fully representative of the rest of the sample without available laboratory data.

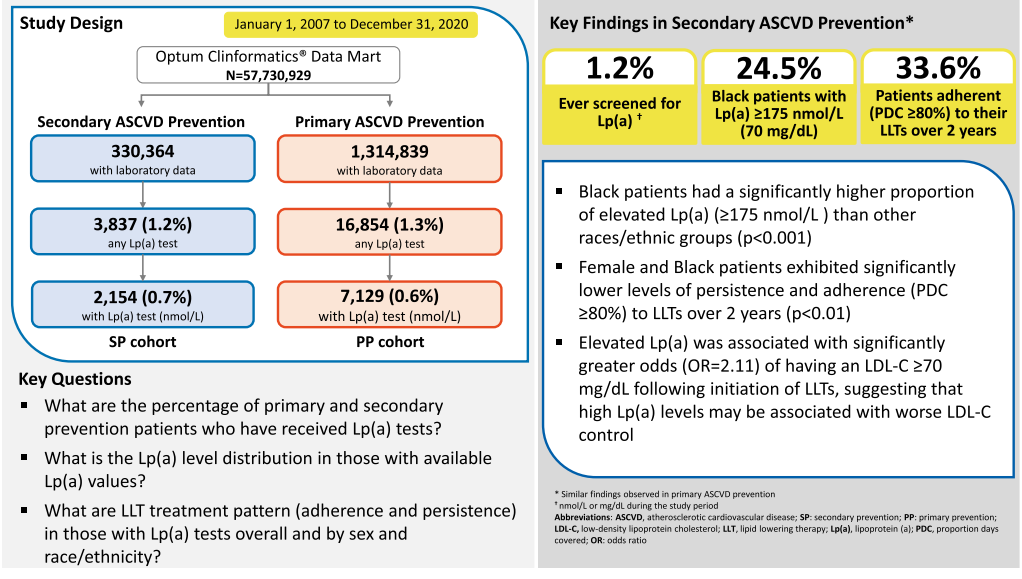


Table 5
Logistic regression for elevated LDL-C within 6 to 12 months after index treatment.

Effect	Category	Secondary prevention patients ($n = 365$)				Primary prevention patients ($n = 1419$)			
		Odds Ratio	Lower 95% CI	Upper 95% CI	*p*-value	Odds Ratio	Lower 95% CI	Upper 95% CI	*p*-value
Lp(a) levels	≥175 nmol/L (v. <175 nmol/L)	2.11	1.07	4.14	0.031	1.25	0.92	1.68	0.150
Baseline LDL-C	Elevated (v. controlled)[b]	4.42	1.58	12.40	0.005	5.02	3.63	6.94	<0.001
Age	Continuous	0.97	0.95	1.00	0.015	0.98	0.97	0.99	<0.001
Gender	Female (v. Male)	1.63	1.03	2.60	0.038	1.63	1.30	2.04	<0.001
Race/Ethnicity[a]	Non-White (v. White)	0.82	0.51	1.31	0.398	1.04	0.83	1.31	0.746
LLT	Statin only (v. other treatments)	0.19	0.06	0.56	0.003	0.48	0.35	0.66	<0.001

[a] Due to small sample size, Asian, Black, Hispanic, and other race/ethnicity were categorized into 'Non-White' group.
[b] Elevated LDL-C was defined as ≥70 mg/dL for secondary prevention and ≥100 mg/dL for primary prevention.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; **LLT**: lipid-lowering therapy; **Lp(a)**, lipoprotein (a).

5. Conclusions

The proportion of patients with available Lp(a) measurements was low in patients receiving LLTs for SP or PP of ACVSD, despite guideline recommendations and the need to consider Lp(a) as an important risk factor. Future research is needed to better understand the clinical and non-clinical mechanisms driving Lp(a) screening across systems of care in the US. In this study, Black patients had an average Lp(a) level close to the risk threshold, suggesting that this group may be disproportionally affected by Lp(a)-driven CVD risk. Statins were the predominant LLTs for SP and PP of ASCVD, but only one third of patients were adherent to any LLT, and the majority still had elevated LDL-C levels within 6 to 12 months after index treatment. The association between LDL-C control and high Lp(a) levels warrants future investigation to better understand the role of Lp(a) in the clinical practice of lipid control and optimized ASCVD management.

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CRediT authorship contribution statement

Xingdi Hu: Conceptualization, Methodology, Writing – review & editing, Supervision. **Joaquim Cristino:** Conceptualization, Writing – review & editing, Supervision. **Raju Gautam:** Methodology, Writing – review & editing. **Rina Mehta:** Conceptualization, Methodology, Writing – review & editing. **Diana Amari:** Conceptualization, Methodology, Writing – review & editing. **Ji Haeng Heo:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Siwei Wang:** Formal analysis, Writing – review & editing. **Nathan D. Wong:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Xingdi Hu reports a relationship with Novartis Pharmaceuticals Corporation that includes: employment. Joaquim Cristino reports a relationship with Novartis Pharmaceuticals Corporation that includes: employment. Nathan D. Wong reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory. Nathan D. Wong reports a relationship with Novo Nordisk Inc that includes: consulting or advisory. Yingjie Ding reports a relationship with Genesis Research LLC that includes: employment. Diana Amari reports a relationship with Genesis Research LLC that includes: employment. Ji Haeng Heo reports a relationship with Genesis Research LLC that includes: employment. Siwei Wang reports a relationship with Genesis Research LLC that includes: employment.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100476.

References

[1] Maranhao RC, Carvalho PO, Strunz CC, Pileggi F. Lipoprotein (a): structure, pathophysiology and clinical implications. Arq Bras Cardiol Jul 2014;103(1):76–84. https://doi.org/10.5935/abc.20140101.
[2] Schnitzler JG, Hoogeveen RM, Ali L, et al. Atherogenic lipoprotein(a) increases vascular glycolysis, thereby facilitating inflammation and leukocyte extravasation. Circ Res May 8 2020,;126(10):1346–59. https://doi.org/10.1161/CIRCRESAHA.119.316206.
[3] Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol Feb 14 2017;69(6):692–711. https://doi.org/10.1016/j.jacc.2016.11.042.
[4] Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med Dec 24 2009;361(26):2518–28. https://doi.org/10.1056/NEJMoa0902604.
[5] Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA Jun 10 2009;301(22):2331–9. https://doi.org/10.1001/jama.2009.801.
[6] Luke MM, Kane JP, Liu DM, et al. A polymorphism in the protease-like domain of apolipoprotein(a) is associated with severe coronary artery disease. Arterioscler Thromb Vasc Biol Sep 2007;27(9):2030–6. https://doi.org/10.1161/ATVBAHA.107.141291.
[7] Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J Dec 2010;31(23):2844–53. https://doi.org/10.1093/eurheartj/ehq386.
[8] Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European atherosclerosis society consensus statement. Eur Heart J Oct 14 2022;43(39):3925–46. https://doi.org/10.1093/eurheartj/ehac361.
[9] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2019;73(24):3168–209. https://doi.org/10.1016/j.jacc.2018.11.002. Jun 25.
[10] van Buuren F, Horstkotte D, Knabbe C, Hinse D, Mellwig KP. Incidence of elevated lipoprotein (a) levels in a large cohort of patients with cardiovascular disease. Clin Res Cardiol Suppl Mar 2017;12(Suppl 1):55–9. https://doi.org/10.1007/s11789-017-0087-y.
[11] Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. Arterioscler Thromb Vasc Biol Nov 2016;36(11):2239–45. https://doi.org/10.1161/ATVBAHA.116.308011.
[12] Wong ND, Zhao Y, Sung J, Browne A. Relation of first and total recurrent atherosclerotic cardiovascular disease events to increased lipoprotein(a) levels

among statin treated adults with cardiovascular disease. Am J Cardiol Apr 15 2021; 145:12–7. https://doi.org/10.1016/j.amjcard.2020.12.075.

[13] Cegla J, France M, Marcovina SM, Neely RDG. Lp(a): when and how to measure it. Ann Clin Biochem Jan 2021;58(1):16–21. https://doi.org/10.1177/0004563220968473.

[14] Lahoz R, Laguna A, Ferber P, et al. LP(A) distribution and correlation with LDL-C in patients with atherosclerotic cardiovascular disease (ASCVD) in the US. J Am Coll Cardiol 2021;77(18_Supplement_1):1564. https://doi.org/10.1016/S0735-1097(21)02921-1. 2021/05/11-1564.

[15] Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American heart association. Arterioscler Thromb Vasc Biol Jan 2022;42(1):e48–60. https://doi.org/10.1161/ATV.0000000000000147.

[16] Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med Jan 16 2020;382(3):244–55. https://doi.org/10.1056/NEJMoa1905239.

[17] Nissen SE, Wolski K, Balog C, et al. Single ascending dose study of a short interfering RNA targeting lipoprotein(a) production in individuals with elevated plasma lipoprotein(a) levels. JAMA May 3 2022,;327(17):1679–87. https://doi.org/10.1001/jama.2022.5050.

[18] Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. Arterioscler Thromb Vasc Biol Jan 2021;41(1):465–74. https://doi.org/10.1161/ATVBAHA.120.315291.

[19] Leon BM, Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes Oct 10 2015;6(13):1246–58. https://doi.org/10.4239/wjd.v6.i13.1246.

[20] Smith JL, N'Dri L, Jiang Z, Singhal M, Electricwala B. Real-world treatment patterns among patients with atherosclerotic cardiovascular disease (ASCVD) using lipid-lowering therapy in the HealthCore Integrated Research Database (HIRD). In: Presented at: 16th annual cardiometabolic health congress; 2021.

[21] Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. JAMA Netw Open 2020;3(11):e2025505. https://doi.org/10.1001/jamanetworkopen.2020.25505. -e2025505.

[22] Booth 3rd JN, Colantonio LD, Chen L, et al. Statin discontinuation, reinitiation, and persistence patterns among medicare beneficiaries after myocardial infarction: a cohort study. Circ Cardiovasc Qual Outcomes Oct 2017;10(10). https://doi.org/10.1161/CIRCOUTCOMES.117.003626.

[23] Fatica EM, Meeusen JW, Vasile VC, Jaffe AS, Donato LJ. Measuring the contribution of Lp(a) cholesterol towards LDL-C interpretation. Clin Biochem 2020; 86:45–51. https://doi.org/10.1016/j.clinbiochem.2020.09.007. 2020/12/01/.

[24] Szarek M, Bittner VA, Aylward P, et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: Odyssey outcomes trial. Eur Heart J Nov 21 2020; 41(44):4245–55. https://doi.org/10.1093/eurheartj/ehaa649.

[25] O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation Mar 19 2019;139(12):1483–92. https://doi.org/10.1161/circulationaha.118.037184.

[26] Wong ND, Young D, Zhao Y, et al. Prevalence of the American college of cardiology/American heart association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US adults using the National health and nutrition examination survey 2011-2012. J Clin Lipidol Sep-Oct 2016;10(5): 1109–18. https://doi.org/10.1016/j.jacl.2016.06.011.

[27] Nissen SE, Wolski K, Cho L, et al. Lipoprotein(a) levels in a global population with established atherosclerotic cardiovascular disease. Open Heart 2022;9:e002060. https://doi.org/10.1136/openhrt-2022-002060.