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ORIGINAL RESEARCH

Lipoprotein (a) Testing in Patients With Atherosclerotic Cardiovascular Disease in 5 Large US Health Systems

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BACKGROUND: Lipoprotein (a) is an independent risk factor for atherosclerotic cardiovascular disease. However, lipoprotein (a) testing remains variable and it is unclear what factors influence testing and if testing changes clinical management.

METHODS AND RESULTS: A retrospective study using electronic medical record data from 5 health systems identified an atherosclerotic cardiovascular disease cohort divided into those with and without a lipoprotein (a) test between 2019 and 2021. Baseline characteristics and lipid-lowering therapy patterns were assessed. Multivariable regression modeling was used to determine factors associated with lipoprotein (a) testing. Among 595 684 patients with atherosclerotic cardiovascular disease, only 2587 (0.4%) were tested for lipoprotein (a). Those who were older or Black individuals were less likely to have lipoprotein (a) testing, while those with familial hypercholesterolemia, ischemic stroke/transient ischemic attack, peripheral artery disease, prior lipid-lowering therapy, or low-density lipoprotein cholesterol ≥130 mg/dL were more likely to be tested. Those with a lipoprotein (a) test, regardless of the lipoprotein (a) value, were more frequently initiated on any statin therapy (30.3% versus 10.6%, $P<0.001$), ezetimibe (7.65% versus 0.8%, $P<0.001$), or proprotein convertase substilisin/kexin type 9 inhibitor (6.7% versus 0.3%, $P<0.001$) compared with those without a test. Those with an elevated lipoprotein (a) level more frequently initiated ezetimibe (11.5% versus 5.9%, $P<0.001$) or proprotein convertase substilisin/kexin type 9 inhibitor (10.9% versus 4.8%, $P<0.001$).

CONCLUSIONS: Lipoprotein (a) testing in patients with atherosclerotic cardiovascular disease is infrequent, with evidence of disparities among older or Black individuals. Testing for lipoprotein (a), regardless of level, is associated with greater initiation of any lipid-lowering therapy, while elevated lipoprotein (a) is associated with greater initiation of nonstatin lipid-lowering therapy. There is a critical need for multidisciplinary and inclusive approaches to raise awareness for lipoprotein (a) testing, and its implications on management.

Key Words: ASCVD ■ lipids ■ lipoprotein (a)

Despite advancements in treatment, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and death across the world.[1,2] Multiple societal guidelines recommend aggressive lowering of low-density lipoprotein cholesterol (LDL-C) in patients with ASCVD,[3,4] yet residual risk still remains. One major contributor to residual risk is elevated lipoprotein (a), an apolipoprotein

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with atherosclerotic cardiovascular disease across 5 US health systems, the prevalence of lipoprotein (a) testing was low at 0.4%.
- Disparities in lipoprotein (a) testing exists as older individuals and members of the Black race were less likely to get tested.
- Among those who were tested for lipoprotein (a), those with elevated levels had higher initiation of nonstatin therapies, though overall initiation of lipid-lowering therapies was low.

What Are the Clinical Implications?

- Despite multisocietal guidance on when to test for lipoprotein (a), testing patterns remain low, with significant disparities on who is being tested.
- There is a critical need for multidisciplinary and inclusive approaches to raise awareness of lipoprotein (a) testing and its implications for aggressive preventive management.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
FH	familial hypercholesterolemia
LLT	lipid lowering therapy
PCSK9i	proprotein convertase substilisin/kexin type 9 inhibitor

B100–containing lipoprotein bound with apolipoprotein (a), which has been shown to have an independent and causal effect on early-onset atherosclerosis.[5,6] lipoprotein (a) is primarily genetically determined[7,8] and elevated levels affect one in five individuals.[6]

Current guideline recommendations regarding lipoprotein (a) vary across societies. The American College of Cardiology/American Heart Association recommend testing for lipoprotein (a) in primary prevention individuals at borderline or intermediate risk in order to reclassify risk, and testing in all individuals (both primary and secondary prevention) with a premature family history of ASCVD.[3] The European Society of Cardiology/European Atherosclerosis Society guidelines recommend measurement of lipoprotein (a) once in a lifetime in all individuals to identify those with extremely elevated levels (>180 mg/dL or >430 nmol/L), which could serve as an equivalent lifetime ASCVD risk to those with heterozygous familial hypercholesterolemia (FH).[4] Additionally, the European Society of Cardiology/European Atherosclerosis Society recommend testing in all individuals with a premature family history of ASCVD and to reclassify risk in those at moderate and high risk.[4] Furthermore, the National Lipid Association[9] recommends testing for lipoprotein (a) in those with first-degree relatives with premature ASCVD, a personal history of premature ASCVD, or primary severe hypercholesterolemia.

Testing for patients with elevated lipoprotein (a) is important for many reasons. First, elevated lipoprotein (a) is considered a risk enhancer, which may warrant aggressive LDL-C–lowering therapy.[3,4,9] Second, given that lipoprotein (a) production is primarily genetically mediated, elevated levels in patients could have implications for cascade screening of first-degree relatives, who may benefit from earlier preventive interventions.[10,11] Third, knowing a lipoprotein (a) level can help determine how aggressive patients and clinicians need to be in optimizing modifiable cardiovascular risk factors in addition to LDL-C, such as diabetes, hypertension, and obesity.[10,12] Additionally, there may be a role for aspirin therapy in primary prevention for patients with elevated lipoprotein (a) if the bleeding risks are low.[13,14] Fourth, knowing a lipoprotein (a) level may identify eligibility in currently enrolling clinical trials for therapies targeting lipoprotein (a)[15,16] or may identify individuals who could benefit from future therapies, should they become available. Finally, in secondary prevention populations, higher lipoprotein (a) levels predict subsequent cardiovascular events and may warrant aggressive combination lipid-lowering therapy.[17]

However, it is unclear how often and what types of populations are being tested for lipoprotein (a) in contemporary real-world clinical practice. The literature also remains limited on whether knowing a lipoprotein (a) value has an impact on clinical management. To address these questions, we assessed data from 5 large health systems across the United States participating in the CardioHealth Alliance. The CardioHealth Alliance is a consortium established in 2021 with the goal of improving the implementation of evidence-based practices to improve the care and health of patients with cardiovascular, renal, and metabolic diseases (CardioHealthAlliance.org).

METHODS

A retrospective analysis was conducted using electronic health record data from 5 large health systems within the CardioHealth Alliance, including Allina Health, Duke University Medical Center, University of Pittsburgh Medical Center, Vanderbilt University Medical Center, and Ochsner Health System. Each health system participated in the Patient-Centered Clinical Research Network, and electronic health

record data were mapped into a common data model for analysis. Data elements include diagnosis and procedure codes, laboratory data, demographics, health system encounters, and medication data. The data used for analysis in this study are available from the corresponding author upon reasonable request.

For the current analysis we included adults aged ≥18 years with established ASCVD defined as acute coronary syndrome (myocardial infarction and unstable angina), stable angina, transient ischemic attack, ischemic heart disease, peripheral artery disease (PAD), or revascularization procedures (coronary revascularization such as percutaneous coronary interventions or coronary artery bypass grafting, peripheral and cerebrovascular revascularization procedures). The diagnosis and procedure codes used for the analysis can be seen in Tables S1 and S2, respectively.

Patients must have also had an ASCVD event within 5 years before an index date. For patients with a lipoprotein (a) test, the index date was defined as date of the first lipoprotein (a) test result in 2019 to 2021. Patients without any lipoprotein (a) test from 2015 to 2021 formed the non-lipoprotein (a) test group. To permit comparisons of change in lipid-lowering therapy (LLT) following lipoprotein (a) testing, the index date for this group was defined as the date of a randomly selected outpatient encounter in 2019 to 2021. Additionally, patients were required to have at least 2 encounters of any kind within the health system in the 2 years before the index date to capture patients who are active within the health system. The follow-up period ranged from the index date to 6 months after until the end of study period (June 30, 2022).

Variables collected for the study included age, sex, self-identified race, ethnicity, vitals, medical history, medications, and laboratory data (lipoprotein (a) level, LDL-C, total cholesterol, high density lipoprotein cholesterol, triglyceride levels, glycosylated hemoglobin, and creatinine). LLT was defined as either a statin at any dose, high-intensity statin (rosuvastatin 20–40 mg daily or atorvastatin 40–80 mg daily), monoclonal antibody–based proprotein convertase substilisin/kexin type 9 inhibitor (PCSK9i), ezetimibe, bempedoic acid, bile acid sequestrants, and fenofibrates. Medical history, medication prescriptions, laboratory tests, and vitals were assessed on the basis of electronic health records in the 12 months before the index date.

Baseline characteristics for the overall cohort, including demographics, medical history, lab values, and concomitant medications, were stratified by the presence and absence of a lipoprotein (a) test result. Continuous variables were summarized as median (25th–75th percentile), and categorical variables were presented as frequencies (percentages). A robust Poisson multivariable regression model was used to determine factors associated with obtaining a lipoprotein (a) test. Factors were prespecified for inclusion in the model on the basis of clinical relevance. The effects shown from the multivariable model included all the variables shown in Table S3 as well as site. All effects are adjusted for all the other variables in the model. Missing values for covariates that had ≤10% missingness were imputed via a single random draw from regression-based chained equations. Missingness >10% for important covariates resulted in the creation of a "Missing" category and categorization of the continuous covariate when applicable. Relative risks with 95% CIs and *P* values were presented for all variables in the model except for site to maintain site confidentiality. Continuous variables were checked for linearity with respect to the outcome; all relationships were linear.

Initiation of a medication was based on the presence of a prescription within 6 months following the index date and was assessed among patients without a corresponding prescription in the prior 12 months. Initiation of LLT within 6 months after the index date was described and compared for patients with versus without lipoprotein (a) testing and for those with lipoprotein (a) testing, elevated values (defined as lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L) versus nonelevated, as well as by lipoprotein (a) level (<50, 50–100, or >100 mg/dL, among those with lipoprotein (a) measured in mg/dL). *P* values for comparisons between groups were calculated using χ^2 or Fisher's exact tests, as appropriate.

A 2-sided *P* value of <0.05 was considered nominally statistically significant. All analyses were performed by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute, Inc., Cary, NC). The data were extracted through SAS queries that were distributed to health systems and executed against the most recent Patient-Centered Clinical Research Network Common Data Model. Limited data sets were delivered through site-approved secure file transfer methods. The study was approved by the Duke University Institutional Review Board under a waiver of Health Insurance Portability and Accountability Act authorization and informed consent, as no informed consent was required for this observational analysis.

RESULTS

Among 707 212 patients with ASCVD in the 5 health systems, 3437 (0.5%) had a lipoprotein (a) test between 2019 and 2021. Of the patients with a lipoprotein (a) test, 2781 had an ASCVD event or diagnosis in the 5 years before the lipoprotein (a) test and at least 2 encounters in the health system 2 years before the lipoprotein (a) test. After excluding patients with a prior lipoprotein (a)

test between 2015 and 2018, 2587 (0.4% of the study cohort) remained in the lipoprotein (a) testing cohort. For the cohort of patients without lipoprotein (a) testing, 670 138 had at least 1 outpatient encounter between 2019 and 2021. Among these patients without lipoprotein (a) testing, 593 097 had a diagnosis of ASCVD in 5 years before the outpatient encounter and at least 2 encounters in the health system in the 2 years before the outpatient encounter. This created an overall study cohort of 595 684 patients with ASCVD active in the health systems with and without a lipoprotein (a) test (Figure 1).

Baseline characteristics of the overall study cohort stratified by presence or absence of lipoprotein (a) testing are presented in Table 1. The median age of the overall cohort was 70 (quartiles 1–3:62–78) years. The cohort consisted of 45.0% women and 84.5%, 13.0%, and 1.4% White, Black, and Hispanic individuals, respectively. The majority of the study population had established coronary artery disease (75.4%), followed by PAD (31%), and stroke or transient ischemic attack (20.4%). In terms of risk factors, 84.0% had hypertension, 78.0% had hyperlipidemia (with 3.7% diagnosed with FH), and 35.9% had diabetes. The median LDL-C was 81 (quartiles 1–3:62–107) mg/dL, and only 48.9% of the study cohort were on any statin therapy. Furthermore, 3.0% were on ezetimibe, 0.9% were on PCSK9i, 1.8% were on fenofibrate, and <0.01% were on bempedoic acid.

The population with a lipoprotein (a) test were younger (median age, 61 versus 70 years), more frequently men (45.0% versus 41.1%), and less frequently Black individuals (11.6% versus 13.0%) compared with patients without a lipoprotein (a) test. In terms of medical comorbidities, patients with a lipoprotein (a) test had higher rates of ischemic stroke (25.2% versus 20.3%), hyperlipidemia (87.0% versus 78%), and FH (7.7% versus 3.7%) compared with those without a lipoprotein (a) test. In contrast, patients with a lipoprotein (a) test had lower rates of atrial fibrillation (17.7% versus 23.0%), hypertension (75.1% versus 84.1%), and diabetes (30.2% versus 35.9%) compared with those without a lipoprotein (a) test. LDL-C was higher in those with lipoprotein (a) testing (87 versus 81 mg/dL), and a greater proportion were on statin therapy (70% versus 48.8%). Additionally, more patients with a lipoprotein (a) test were on ezetimibe (12.1% versus 2.9%) and PCSK9i (6.9% versus 0.8%) (Table 1).

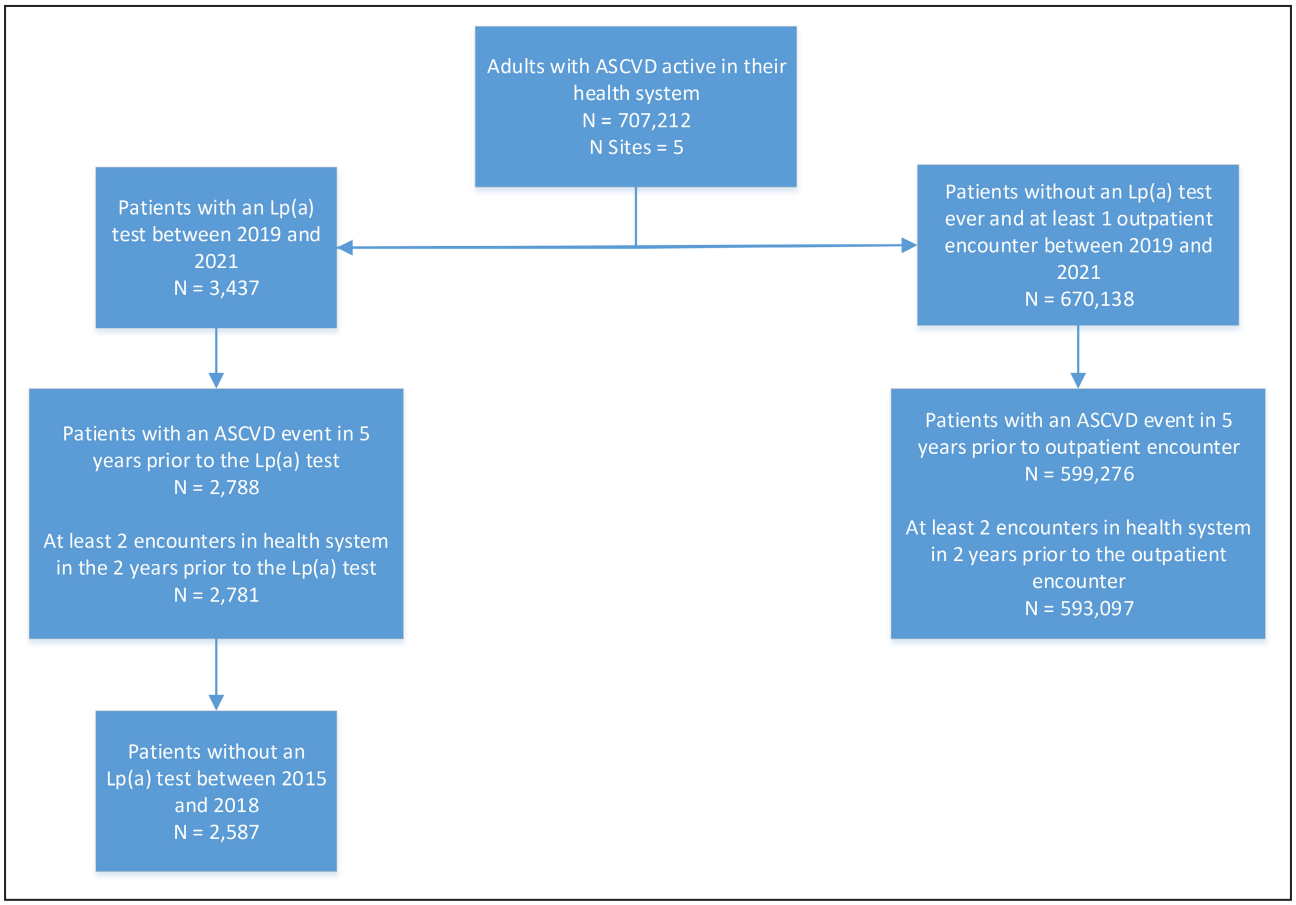

Figure 1. Consolidated Standards of Reporting Trials diagram describing study cohort.
sASCVD indicates atherosclerotic cardiovascular disease; and Lp(a), lipoprotein (a).

Table 1. Baseline Characteristics of Patients With ASCVD With and Without a Lipoprotein (a) Test

Characteristic	Overall (N=595 684 [100%])	No lipoprotein (a) test (N=593 097 [99.6%])	Lipoprotein (a) test (N=2587 [0.4%])
Median age (quartiles 1–3)	70 (62–78)	70 (62–78)	61 (52–69)
Female sex, n (%)	268 251 (45.0)	267 188 (45.0)	1063 (41.1)
Race or ethnicity, n (%)			
White	499 875 (84.5)	497 712 (84.5)	2163 (84.5)
Black	76 639 (13.0)	76 341 (13.0)	298 (11.6)
Other*	15 129 (2.6)	15 029 (2.6)	100 (3.9)
Hispanic	7913 (1.4)	7876 (1.4)	37 (1.5)
Medical history, n (%)			
Coronary artery disease	449 367 (75.4)	447 310 (75.4)	2057 (79.5)
Ischemic heart disease	442 753 (74.3)	440 710 (74.3)	2043 (79.0)
Myocardial infarction	149 079 (25.0)	148 312 (25.0)	767 (29.6)
Stable angina	48 251 (8.1)	47 994 (8.1)	257 (9.9)
Unstable angina	18 935 (3.2)	18 782 (3.2)	153 (5.9)
Percutaneous coronary intervention	137 393 (23.1)	136 612 (23.0)	781 (30.2)
Coronary artery bypass grafting	78 826 (13.2)	78 430 (13.2)	396 (15.3)
Ischemic stroke or transient ischemic attack	121 228 (20.4)	120 575 (20.3)	653 (25.2)
Ischemic stroke	85 942 (14.4)	85 424 (14.4)	518 (20.0)
Transient ischemic attack	49 803 (8.4)	49 551 (8.4)	252 (9.7)
Peripheral artery disease	184 582 (31.0)	183 826 (31.0)	756 (29.2)
Aortic valve stenosis	39 539 (6.6)	39 440 (6.6)	99 (3.8)
Heart failure	151 534 (25.4)	150 882 (25.4)	652 (25.2)
Atrial fibrillation	137 133 (23.0)	136 675 (23.0)	458 (17.7)
Hypertension	500 650 (84.0)	498 707 (84.1)	1943 (75.1)
Hyperlipidemia	464 866 (78.0)	462 616 (78.0)	2250 (87.0)
Diabetes	213 859 (35.9)	213 078 (35.9)	781 (30.2)
Hypertriglyceridemia	16 063 (2.7)	15 930 (2.7)	133 (5.1)
Familial hypercholesterolemia	22 308 (3.7)	22 108 (3.7)	200 (7.7)
Chronic kidney disease	149 861 (25.2)	149 320 (25.2)	541 (20.9)
Vitals and laboratory tests			
Median systolic blood pressure (quartiles 1–3)	129 (118–141)	129 (118–141)	126 (116–137)
Median diastolic blood pressure (quartiles 1–3))	74 (67–80)	74 (67–80)	76 (68–82)
Median body mass index (quartiles 1–3)	29 (25–33)	29 (25–33)	29 (26–33)
Current or former smoker	69 350 (13.0)	69 157 (13.0)	193 (8.1)
Median creatinine (quartiles 1–3)	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Median eGFR (quartiles 1–3)	67 (50–83)	67 (50–83)	76 (61–89)
Mean glycosylated hemoglobin (quartiles 1–3)	6.2 (5.6–7.2)	6.2 (5.6–7.2)	5.8 (5.4–6.6)
Median total cholesterol (quartiles 1–3)	156 (131–187)	156 (131–187)	162 (132–201)
Median HDL (quartiles 1–3)	46 (37–57)	46 (37–57)	46 (38–57)
Median triglycerides (quartiles 1–3)	111 (80–159)	111 (80–159)	110 (77–169)
Median LDL (quartiles 1–3)	81 (62–107)	81 (62–107)	87 (63–120)
Medications quartiles			
ACE or ARB	225 003 (37.8)	223 839 (37.7)	1164 (45.0)
β blocker	239 708 (40.2)	238 572 (40.2)	1136 (43.9)
Statin	291 313 (48.9)	289 502 (48.8)	1811 (70.0)
PCSK9i	5156 (0.9)	4978 (0.8)	178 (6.9)
Ezetimibe	17 592 (3.0)	17 279 (2.9)	313 (12.1)
Bempedoic acid	80 (0.0)	77 (0.0)	3 (0.1)

(*Continued*)

Table 1. Continued

Characteristic	Overall (N=595 684 [100%])	No lipoprotein (a) test (N=593 097 [99.6%])	Lipoprotein (a) test (N=2587 [0.4%])
Fenofibrates	10 600 (1.8)	10 528 (1.8)	72 (2.8)
SGLT2i	12 479 (2.1)	12 377 (2.1)	102 (3.9)
GLP1 RA	15 769 (2.6)	15 675 (2.6)	94 (3.6)
Any LLT	299 624 (50.3)	297 685 (50.2)	1939 (75.0)
Unit of lipoprotein (a) test			
mg/dL	1925 (74.4)	…	1925 (74.4)
nmol/L	662 (25.6)	…	662 (25.6)
Elevated lipoprotein (a)	…	…	821 (33.4)

Units: blood pressure, mm Hg; body mass index, kg/m^2; creatinine, mg/dL; eGFR, mL/min per 1.73 m^2; total cholesterol, mg/dL; HDL, mg/dL; triglycerides: mg/dL; LDL, mg/dL. Elevated lipoprotein (a) is defined as lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L. ACE/ARB indicates angiotensin-converting enzyme/angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; GLP1 RA, glucagon-like peptide 1 receptor agonist; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, monoclonal antibody based proprotein convertase subtilisin/kexin type 9 inhibitor; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

*Other indicates those who do not self-identify as White or Black.

Multivariable analysis suggested that several factors were independently associated with the likelihood of lipoprotein (a) testing, including diagnosis of coronary artery disease, ischemic stroke/transient ischemic attack, PAD, or heart failure (Figure 2, Table S3). A diagnosis of FH or hyperlipidemia, along with use of any prior LLT, were also positively associated with lipoprotein (a) testing. Of note, LDL-C level appeared to be associated with lipoprotein (a) testing in a graded relationship, such that lower levels <130 mg/dL were not associated with lipoprotein (a) testing, but higher levels were increasingly associated with higher likelihood of receiving a lipoprotein (a) test (Figure 2). In contrast, older age, Black race, higher body mass index, current smoking status, and diagnosis of hypertension or diabetes were associated with a lower likelihood of lipoprotein (a) testing. Missing glycosylated hemoglobin and lipid laboratory values in the 12 months before the index date were also associated with lower likelihood of lipoprotein (a) testing.

The majority of lipoprotein (a) testing was reported in mg/dL (74.4%) compared with nmol/L (25.6%). Those with elevated values, defined as lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L, (n=821, 31.7%) were more frequently Black individuals (18.2% versus 8.6%), with higher LDL-C values (91 versus 85 mg/dL) and higher rates of LLT use (78.1% versus 73.5%) than those without elevated lipoprotein (a) (Table S4). Specifically, ezetimibe (16.3% versus 10.1%) and PCSK9i (8.5% versus 6.1%) were used at index more frequently in those with elevated lipoprotein (a).

With regard to initiation of LLT, those with a lipoprotein (a) test, regardless of the lipoprotein (a) value, more often initiated LTT within 6 months of the index date (Table 2). Specifically, patients with a lipoprotein (a) test were more frequently initiated on any statin therapy (30.3% versus 10.6%, $P<0.001$), or high-intensity statin therapy (14.6% versus 5.1%, $P<0.001$) compared with those without a test. Initiation of PCSK9i (6.7% versus 0.3%, $P<0.001$) and ezetimibe (7.65 versus 0.8%, $P<0.001$) were more often in the group with lipoprotein (a) testing as well.

The lipoprotein (a) value itself was associated with initiation of nonstatin LLT (Figure 3). Among patients with lipoprotein (a) values, there was no difference in the initiation of any statin (32.1% versus 29.7%, $P=0.51$), high-intensity statin (16.2% versus 14.0%, $P=0.29$), or in up-titration from regular- to high-intensity statin dosing (49.3% versus 41.1%, $P=0.27$) in those with elevated versus nonelevated lipoprotein (a) levels (Table 3). However, initiation rates of PCSK9i (10.9% versus 4.8%, $P<0.001$) and ezetimibe (11.5% versus 5.9%, $P<0.001$) were significantly higher in those with elevated lipoprotein (a) levels. Of note, there appeared to be a graded relationship such that those with highly elevated lipoprotein (a) levels (≥100 mg/dL) were more likely to initiate PCSK9i or ezetimibe than those with lipoprotein (a) 50–100 mg/dL or <50 mg/dL, respectively (PCSK9i: 15.5% versus 7.4% versus 5.5%, $P<0.001$; ezetimibe: 15.6% versus 12.8% versus 7.3%, $P<0.001$) (Table S5). This trend was not present for statin initiation.

DISCUSSION

Across 5 large US health systems within the CardioHealth Alliance, the frequency of lipoprotein (a) testing was low (0.4%) among patients with ASCVD. Disparities in lipoprotein (a) testing were apparent, as older age, Black race, higher body mass index, current smoking status, and diagnosis of hypertension or diabetes were associated with a lower likelihood of lipoprotein (a) testing. Testing for lipoprotein (a), regardless of lipoprotein (a) level, was associated with greater initiation of LLT, including statin, ezetimibe, and PCSK9i.

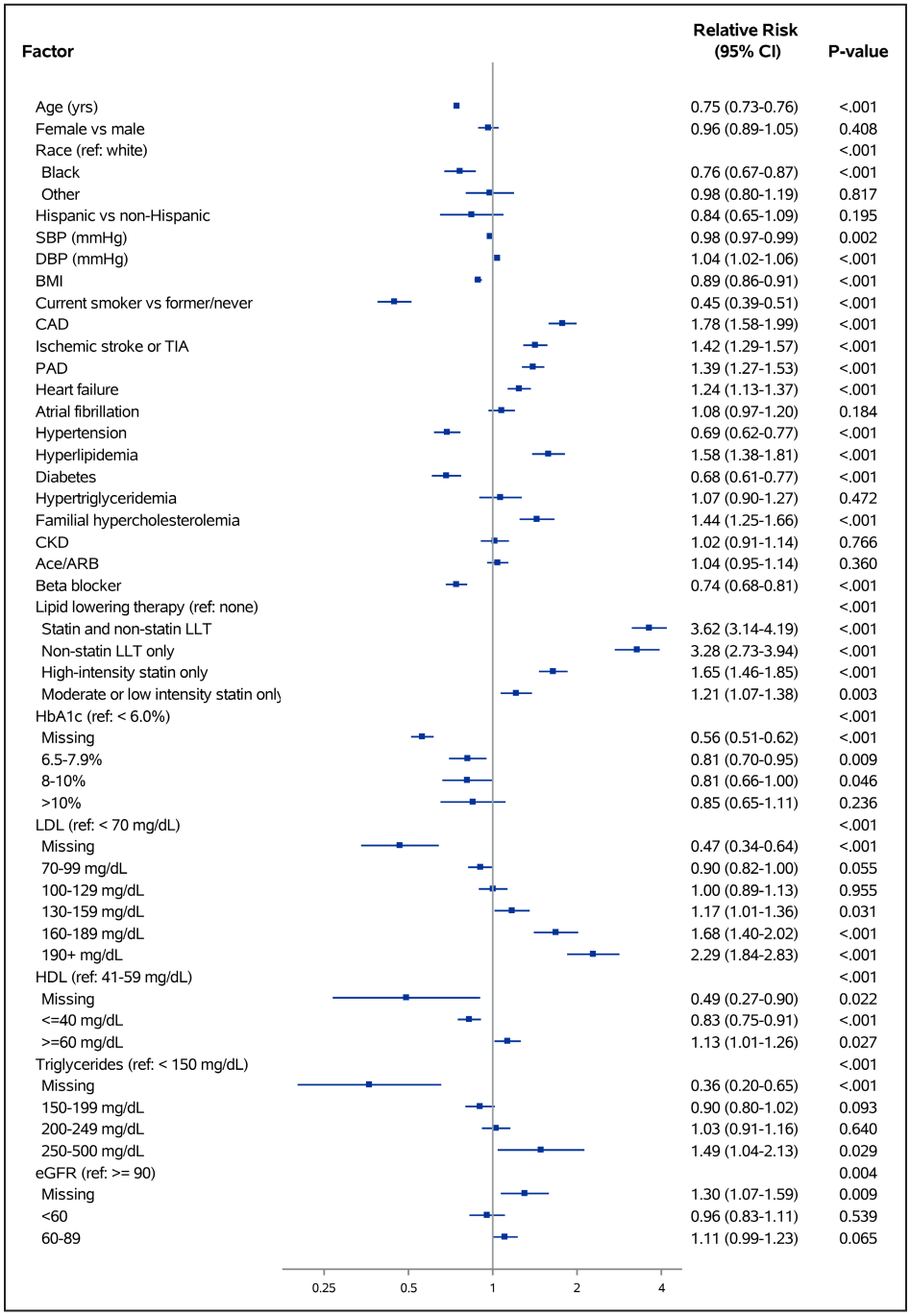

Figure 2. Forest plot of multivariable regression model describing factors associated with likelihood of testing for lipoprotein (a).

Units: blood pressure, mm Hg; BMI, kg/m^2; creatinine, mg/dL; eGFR, mL/min per 1.73 m^2; total cholesterol, mg/dL; HDL, mg/dL; triglycerides, mg/dL; LDL, mg/dL. ACE/ARB indicates angiotensin-converting enzyme/angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; HbA_{1c}, glycosylated hemoglobin; LDL, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PAD, peripheral artery disease; SBP, systolic blood pressure; and TIA, transient ischemic attack.

Interestingly, an elevated lipoprotein (a) result was associated with ezetimibe and PCSK9i initiation but not statin initiation or up-titration.

The low observed rate of lipoprotein (a) testing among a secondary prevention population is consistent with previous reports. In a large claims data

Table 2. Initiation of LLT Within 6 Months After Index Date

LLT	Overall, n (%)	No lipoprotein (a) test, n (%)	Lipoprotein (a) test, n (%)	*P* value
Initiated statins	32 493/304 371 (10.7)	32 258/303 595 (10.6)	235/776 (30.3)	<0.001
Initiated high intensity statins	22 631/441 969 (5.1)	22 422/440 536 (5.1)	209/1433 (14.6)	<0.001
Initiated PCSK9i	1810/590 528 (0.3)	1648/588 119 (0.3)	162/2409 (6.7)	<0.001
Initiated ezetimibe	4530/578 092 (0.8)	4357/575 818 (0.8)	173/2274 (7.6)	<0.001
Initiated bempedoic acid	57/595 604 (0.0)	53/593 020 (0.0)	4/2584 (0.2)	<0.001
Initiated any LLT	33 279/296 060 (11.2)	33 028/295 412 (11.2)	251/648 (38.7)	<0.001

Initiation defined by no prescription in the year before index date, but a prescription is present in the 6 mo following index date. For patients with lipoprotein (a) test, the index date was the date of the earliest lipoprotein (a) test in 2021. For patients without a lipoprotein (a) test, the index date was the date of a randomly selected outpatient visit in 2021. Any LLT indicates a patient was initiated on ≥1 of the following prescriptions: statins, PCSK9i, ezetimibe, or bempedoic acid. LLT indicates lipid-lowering therapy; and PCSK9i, monoclonal antibody based proprotein convertase subtilisin/kexin type 9 inhibitor.

analysis performed on 4 million patient records in Germany, the frequency of lipoprotein (a) testing was similarly low at 0.34%.[18] An analysis of US claims data revealed that only 0.7% of secondary prevention patients were tested for lipoprotein (a).[19] Additionally, an analysis across 6 academic health systems in the University of California health system found an overall prevalence of lipoprotein (a) testing to be 0.3% in patients with ASCVD or at risk of ASCVD.[20] Reasons behind the consistently low testing rates for lipoprotein (a) in patients with ASCVD are likely multifactorial and may include lack of clinician understanding or awareness of lipoprotein (a) as a prevalent and causal risk factor for ASCVD.[21] Further, current clinical guidelines are inconsistent about recommendations for lipoprotein (a) testing, though most recommend testing in high-risk patients,[3,9] if not all patients at least once in a lifetime.[4] In addition, there are no available therapies that are currently indicated to lower lipoprotein (a), though several are in clinical trials (NCT04023552; NCT05581303).[22,23] Furthermore, health systems may not have resources internally to test for lipoprotein (a) and may have to send laboratory tests out, which could add to the cost of the test and therefore less motivation by providers

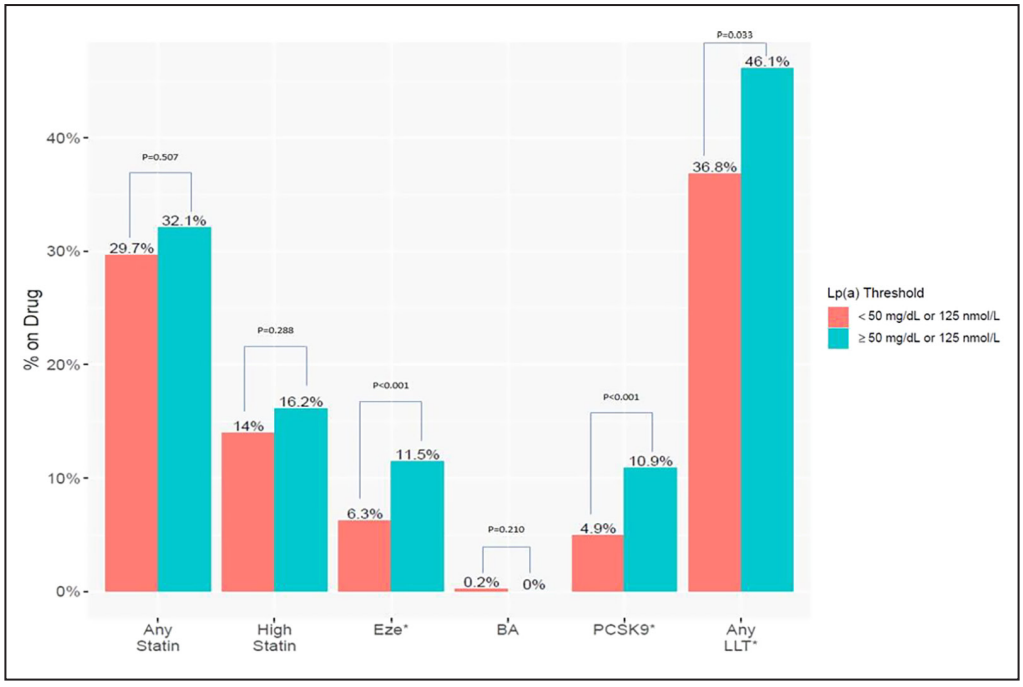

Figure 3. Initiation of therapy during follow up among patients with atherosclerotic cardiovascular disease with a lipoprotein (a) test.
Initiation defined by no prescription in the year before index date, but a prescription is present in the 6 mo following a lipoprotein (a) test. Above lipoprotein (a) threshold is defined as lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L). Any LLT indicates a patient was initiated on ≥1 of the following prescriptions: statins, PCSK9i, ezetimibe, or bempedoic acid. BA indicates bempedoic acid; Eze, ezetimibe; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); and PCSK9, monoclonal antibody-based proprotein convertase subtilisin/kexin type 9 inhibitor.

Table 3. Initiation of LLT Within 6 Months After Index Date by Elevated Lipoprotein (a)

LLT	Overall, n (%)	Elevated lipoprotein (a)		*P* value
		No, n (%)	Yes, n (%)	
Initiated statins	221/726 (30.4)	145/489 (29.7)	76/237 (32.1)	0.507
Initiated high intensity statins	198/1351 (14.7)	129/924 (14.0)	69/427 (16.2)	0.288
Initiated PCSK9i	158/2289 (6.9)	76/1538 (4.9)	82/751 (10.9)	<0.001
Initiated ezetimibe	171/2153 (7.9)	92/1466 (6.3)	79/687 (11.5)	<0.001
Initiated bempedoic acid	4/2454 (0.2)	4/1634 (0.2)	0/820 (0.0)	0.210
Initiated any LLT	238/601 (39.6)	155/421 (36.8)	83/180 (46.1)	0.033

Initiation defined by no prescription in the yearbefore index date, but a prescription is present in the 6 mo following a lipoprotein (a) test. Elevated lipoprotein (a) threshold is defined as lipoprotein (a) ≥50 mg/dL or ≥125 nmol/L. Any LLT indicates a patient was initiated on ≥1 of the following prescriptions: statins, PCSK9i, ezetimibe, or bempedoic acid. LLT indicates lipid-lowering therapy; and PCSK9i, monoclonal antibody based proprotein convertase subtilisin/kexin type 9 inhibitor.

to order the test. Additionally, providers may be unaware of local laboratories outside the health system that could test lipoprotein (a) for lower cost if cost is a concern. However, even in the absence of lipoprotein (a)–lowering therapies, testing for lipoprotein (a) is still clinically relevant for risk stratification, aggressive preventive management such as early use of statins, and testing of first-degree relatives.[6,11]

Those who did undergo lipoprotein (a) testing in our study population were different in important ways from those who did not undergo testing, revealing potential disparities in testing patterns. Older age was associated with a lower likelihood of lipoprotein (a) testing; this may be related to the National Lipid Association guidelines, which specifically recommend lipoprotein (a) testing for individuals with premature ASCVD and who are therefore young by definition.[9] Black race was also associated with a 24% lower likelihood of lipoprotein (a) testing; this likely represents a disparity in care, as Black individuals are known to have generally higher lipoprotein (a) levels than White individuals, with correspondingly higher lipoprotein (a)–related ASCVD risk.[19,24] Access to health care, socioeconomic status, patient comfort, and lack of provider awareness of high-risk subgroups are possible explanations in general for lipid screening and management disparities in underrepresented minorities.[25] As far as we are aware, this disparity in lipoprotein (a) testing across health systems has not been shown before and is important for addressing health equity in ASCVD prevention and management. Unsurprisingly, individuals with missing glycosylated hemoglobin and lipid levels were less likely to undergo lipoprotein (a) testing, potentially because they were not receiving routine preventive care.

In contrast, several factors were associated with greater likelihood of lipoprotein (a) testing, including prior coronary artery disease, ischemic stroke/transient ischemic attack, PAD, or heart failure. This pattern is consistent with prior studies[18,26] likely because of guideline recommendations for testing in high-risk populations.[3,9] Similarly, those with hyperlipidemia or FH were more likely to undergo testing, which also has been seen in prior studies and is consistent with guideline recommendations and the observation that elevated lipoprotein (a) is more common in individuals with elevated LDL-C or FH.[27,28] Interestingly, LDL-C level appeared to have a graded relationship with lipoprotein (a) testing, with increasing levels beyond 130 mg/dL being associated with greater likelihood of lipoprotein (a) testing. Alternatively, patients with higher body mass index, active smoking, hypertension, and diabetes were less likely to be tested. One possible explanation for this observation could be that these factors alone either represented competing markers of risk to providers or were very prevalent across the population to justify lipoprotein (a) testing on the basis of these markers alone.

We also found that lipoprotein (a) testing regardless of lipoprotein (a) level, along with the level itself, are both associated with changes in LLT in the 6 months after testing. Lipoprotein (a) testing (compared with no testing) was associated with initiation of both statin and nonstatin therapies, while an elevated lipoprotein (a) level (compared with a nonelevated level) was associated only with initiation of PCSK9i and ezetimibe. These results suggest that clinicians may be acting on lipoprotein (a) results with more aggressive therapies, indicating that testing may have an impact on clinical management (though causality cannot be established in this observational analysis). This is consistent with a prior study from Germany, which showed increased treatment intensity after lipoprotein (a) testing[18]; our study extends these results to the United States. Further, our finding that statins were initiated regardless of lipoprotein (a) result may reflect overall clinician concern and/or better care in those with an lipoprotein (a) result, given that all of these individuals have a clear indication for statin therapy. Notably, however, only 30% of individuals with a lipoprotein (a) test were initiated on a statin after testing,

compared with 11% in those without testing, reflective of a continued gap in guideline-based care. In contrast with statins, PCSK9i and ezetimibe were more likely to be initiated in those with lipoprotein (a) testing than in those without, but among those with testing, were only more likely to be initiated in those with an elevated lipoprotein (a) level. This may indicate that clinicians are responding to the level itself by initiating more advanced LLT, which is consistent with guidelines that recommend more aggressive LDL-C lowering in those with elevated lipoprotein (a).[3,9] Again, however, the overall rate of initiation of these therapies was relatively low, with 11% and 12% of individuals with elevated lipoprotein (a) initiating PCSK9i and ezetimibe, respectively.

Our study has several limitations that are important to note. First, this was a retrospective analysis that evaluated electronic health record data, so there is the potential for missing data, especially data generated outside the studied health systems; we attempted to minimize this risk by ensuring that all individuals in the study received regular care within these systems. Second, our study period overlapped with the advent of the COVID-19 pandemic period, which could have decreased the frequency of encounters and laboratory values. Third, adherence patterns and intolerance to LLT could not be captured, which could have influenced the distribution of various LLT medications. Fourth, it is possible that patients with a lipoprotein (a) test before 2019 were not captured; however, we aimed to capture testing patterns and influences on lipid management over a contemporary guideline period.

CONCLUSIONS

Across 5 large US health systems, the frequency of lipoprotein (a) testing among patients with ASCVD remains low, at 0.4%. Additionally, disparities exist as older and Black individuals were particularly unlikely to have a lipoprotein (a) test. Those with lipoprotein (a) testing were more likely to initiate any LLT regardless of lipoprotein (a) level, including statins, compared with those without lipoprotein (a) testing. Initiation of LLT was higher among those with a lipoprotein (a) test and elevated levels, though driven mostly by nonstatin therapies like ezetimibe and PCSK9i. In general, the overall initiation of LLT remained low in this population, despite clear guideline indications for LLT in patients with ASCVD. Thus, there is a critical need for multidisciplinary and inclusive approaches to raise awareness of lipoprotein (a) testing and its implications for aggressive preventive management. Such awareness may increase if lipoprotein (a)–lowering therapies, which are currently being tested, are shown to provide clinical benefit.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5

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