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Trends in testing and prevalence of elevated Lp(a) among patients with aortic valve stenosis

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Abstract

Background and aims: Lipoprotein(a) [Lp(a)] is causally associated with aortic valve stenosis (AS) but Lp(a) testing among AS patients is not broadly incorporated into clinical practice. We evaluated trends in Lp(a) testing in an academic medical center.

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Declaration of competing interest

ST is a co-inventor and receives royalties from patents owned by UCSD and is a co-founder and has an equity interest in Oxitope, Inc and its affiliates, Kleanthi Diagnostics, LLC and Covicept Therapeutics, Inc. ST has a dual appointment at UCSD and Ionis Pharmaceuticals. Although these relationships have been identified for conflict-of-interest management based on the overall scope of the project, the research findings included in this particular publication may not necessarily relate to the interests of the above companies. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. ST has received research funding to UCSD from Novartis. The other co-authors have nothing to disclose.

CRedit authorship contribution statement

Harpreet S. Bhatia: conducted the study design, data collection, analysis and drafting of the manuscript. All other authors contributed significantly to the drafting and critical revision of the manuscript. **Gary S. Ma:** conducted the study design, data collection, analysis and drafting of the manuscript. All other authors contributed significantly to the drafting and critical revision of the manuscript.

Sotirios Tsimikas: conducted the study design, data collection, analysis and drafting of the manuscript. All other authors contributed significantly to the drafting and critical revision of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2022.01.022>.

Methods: Educational efforts and adding Lp(a) to the lipid panel on the electronic medical record (EMR) and preprocedure order sets were used to increase awareness of Lp(a) as a risk factor in AS. Medical records at University of California San Diego Health (UCSDH) were analyzed from 2010 to 2020 to define the yearly frequency of first time Lp(a) testing in patients with diagnosis codes for AS or undergoing transcatheter aortic valve replacement (TAVR).

Results: Lp(a) testing for any indication increased over 5-fold from 2010 to 2020. A total of 3808 patients had a diagnosis of AS and 417 patients had TAVR. Lp(a) levels >30 mg/dL were present in 37% of AS and 35% of TAVR patients. The rates of Lp(a) testing in AS and TAVR were 14.0% and 65.7%, respectively. In AS, Lp(a) testing increased over time from 8.5% in 2010, peaking at 24.2% in 2017, and declining to 13.9% in 2020 ($p < 0.001$ for trend). Following implementation of EMR order-sets in 2016, Lp(a) testing in TAVR cases increased to a peak of 88.5% in 2018.

Conclusions: Elevated Lp(a) is prevalent in AS and TAVR patients. Implementation of educational efforts and practice pathways resulted in increased Lp(a) testing in patients with AS. This study represents a paradigm that may allow increased global awareness of Lp(a) as a risk factor for AS.

Keywords

Lipoprotein(a); Lipids; Aortic stenosis; Testing

1. Introduction

The role of Lp(a) in the pathogenesis of AS is rapidly emerging. Elevated Lp(a) had been associated with AS in clinical studies since the 1990s [1–3]. However, it was not until 2013 that its role was elevated to a potential causal risk factor in up to one third of patients with AS by findings in genome wide association studies [4–6]. In conjunction with this, it has been documented that oxidized phospholipids on apolipoprotein B-100 and apolipoprotein(a) are also strongly and genetically associated with the presence and progression of AS [7–10]. Despite extensive evidence associating Lp(a) pathophysiologically with the prevalence and progression of AS and the potential of Lp(a) lowering therapy as a medical treatment for AS, incorporation of Lp(a) testing into clinical practice for AS is in its infancy.

There are no approved therapies specifically for the prevention or medical treatment of AS. Current therapy centers around valvular interventions at the advanced stage of severe stenosis when symptoms develop. Advances in novel RNA-targeted therapeutic agents, such as the antisense oligonucleotide pelacarsen that lowers mean Lp(a) levels over 80% [11], may provide tools to test the hypothesis that lowering Lp (a) may delay the progression of AS in the subset of patients with elevated Lp(a).

With these advances in the understanding of the potential role of Lp (a) in AS, we aimed to raise awareness of Lp(a) in AS through educational efforts and changes in practice patterns. We additionally aimed to evaluate the prevalence of elevated Lp(a) with increased testing rates. To gauge effectiveness, we evaluated the trends in testing for Lp(a) among all patients

diagnosed with AS and transcatheter aortic valve replacement (TAVR) in the University of California San Diego Health (UCSDH) system.

2. Patients and methods

2.1. Educational efforts and changes in practice pathways to raise awareness of Lp(a)

To raise awareness of Lp(a) as a risk factor for AS at UCSDH, educational efforts consisted of cardiology and internal medicine grand rounds, teaching conferences, fellow and resident lectures, didactic teaching and initiation of a dedicated “Lp(a) Clinic” in 2014 to evaluate and manage such patients and their affected relatives [12]. In August 2016, Lp(a) testing was incorporated as an optional test into the pre-procedure TAVR order set to understand the prevalence of elevated Lp(a) in such patients and to assess if elevated Lp(a) was associated with peri- and post-procedural complications through its potential to enhance calcification [4,10]. Starting in February 2018 in the hospital-wide order system, the “lipid panel” order set was modified to include 2 options: the traditional lipid panel (total cholesterol LDL-C, HDL-C, triglycerides) and “lipid panel with Lp(a).”

To define the rate of Lp(a) testing and prevalence of elevated Lp(a) (>30 mg/dL and >50 mg/dL), a retrospective cohort study of Lp(a) testing among patients with AS at UCSDH was designed. All patients with an Lp(a) level in the electronic medical record (EMR) from January 2010–December 2020 were identified. Additionally, data for patients with a diagnosis code for aortic stenosis (ICD-10 135.0 or 135.2) from 2010 to 2020 was extracted, including age and date of diagnosis, and cross-referenced against the Lp(a) database. Finally, a separate database of all patients who underwent TAVR at UCSDH (starting in 2013) was used to collect the frequency of Lp(a) testing in TAVR patients. The TAVR patients were a subset of the larger database collected based on diagnosis codes. The study protocol was approved by the UCSD Human Protections Program and conforms to the Declaration of Helsinki. Informed consent was not required due to the retrospective nature of this study.

2.2. Echocardiographic data

Echocardiographic data regarding severity of aortic stenosis (aortic valve area, peak velocity and mean gradient) was available starting in 2016 and was extracted for AS patients from 2016 to 2020 from our institutional echocardiographic database. For the analysis of Lp(a) testing among AS patients by severity, AS severity was defined based on echocardiographic data using the American Society of Echocardiography criteria [13]. By peak velocity, mild AS was defined as 2.6–2.9 m/s, moderate as 3.0–4.0 m/s, and severe as ≥ 4.0 m/s. By mean gradient, mild AS was defined as <20 mmHg, moderate as 20–40 mmHg, and severe as ≥ 40 mmHg. By aortic valve area (AVA), mild was defined as >1.5 cm², moderate as 1.0–1.5 cm², and severe as <1.0 cm². Cases of valve leaflet thickening/calcification or aortic sclerosis without a measurable gradient across the aortic valve were not included as having AS.

2.3. Lp(a) assays

Lp(a) measurements at UCSDH from 2010 to 2013 were performed using the Polymedco assay (Polymedco, Cortland Manor, NY) and from 2013 to 2018 using the Point Scientific assay (MedTest, Canton, MI) though ARUP laboratories (Salt Lake City,

UT); normal levels are <29 mg/dL [10,14]. Starting in 2018, UCSD began to perform Lp(a) testing internally using the Roche particle enhanced immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN). For patients with more than one Lp(a) level or echocardiography examination, we used the result closest to the ICD diagnosis of AS.

2.4. Statistical analysis

Lp(a) testing overall and testing among AS, severe AS and TAVR patients was compared by year. For the analysis of AS severity by echocardiography, Lp(a) testing was compared across strata (mild, moderate, severe) of peak velocity, mean gradient and AVA individually. We also evaluated the prevalence of elevated Lp(a) (>30 mg/dL) in AS and non-AS patients as well as across AS severity strata. Results were also stratified by sex and race/ethnicity.

Continuous variables were compared with independent sample t-tests or the Mann-Whitney *U* test for comparison among two groups, and analysis of variance (ANOVA) or Kruskal-Wallis tests for comparison among three or more groups. Categorical variables were compared using chi square tests. A two-tailed *p*-value of <0.05 was considered significant. Statistical analyses were performed using SPSS Statistics v28.0 (IBM, Armonk, New York, USA).

3. Results

Between 2010 and 2020, there were 8,516 total Lp(a) tests performed on 6,049 patients at UCSDH for any indication (Supplemental Fig. 1). An increasing number of new patients were tested per year, starting with 236 patients in 2010 and peaking at 1458 patients in 2019, declining to 1329 patients in 2020 (Fig. 1). Overall, the total number of patients with an Lp(a) test increased over 5-fold from 2010 to 2020. Of these subjects with an Lp(a) level in the EMR, 535 (8.8%) had a diagnosis of AS from 2010 to 2020. Among all participants with Lp(a) testing, those with AS were older (76.1 ± 11.3 vs 58.6 ± 14.2 years, $p < 0.001$), but mean Lp(a), median Lp(a), and distribution of Lp(a) category were not significantly different from those without AS (Table 1).

Between 2010 and 2020, 3,808 patients were diagnosed with AS, of which 535 (14.0%) had an Lp(a) test (Supplemental Fig. 1). In this group, 465/535 (86.9%) had Lp(a) testing after the diagnosis of AS. Median absolute time between the diagnosis of AS and Lp(a) testing was 126 [36–780] days. Among those with AS, 197 (36.8%) had an Lp(a) level >30 mg/dL, and 150 (28.0%) had Lp(a) > 50 mg/dL. The prevalence of Lp(a) testing increased over time, starting with 8.5% in 2010, peaking at 24.2% in 2017, and declining to 13.9% in 2020 (Fig. 2, $p < 0.001$ for trend). The prevalence of Lp(a) testing among non-TAVR patients was 7.7%. Men with AS had more frequent Lp(a) testing than women (16.0 vs 12.8%, $p < 0.001$), but there was no difference in median Lp(a) levels (16.0 [6.0, 53.0] vs 18.0 [7.0, 60.0] mg/dL, $p = 0.220$, Table 2). There was no difference in the frequency of Lp(a) testing ($p = 0.574$) or median Lp(a) levels ($p = 0.120$) in AS patients stratified by race (Table 2).

Echocardiographic data of AS severity was available for 1453 participants starting in 2016. Of these, 517 had severe AS by at least one of three echo criteria. Among these patients, the prevalence of Lp(a) testing was 38.3%. The prevalence of testing was 20.3% in 2016,

peaking at 46.2% in 2017, and declining to 34.8% in 2020 ($p = 0.005$ for trend, Fig. 3). When evaluated by peak velocity, mean gradient, or AVA, those with severe AS ($n = 264, 233, 460$, respectively) had higher prevalence of Lp(a) testing with no difference in median Lp(a) (Supplemental Table 1). Among all those with severe AS by at least one echocardiographic criterion, there was a higher prevalence of Lp(a) testing (38.3% vs 18.4%, $p < 0.001$) with a non-significant difference in median Lp(a) (16.0, IQR 6.0–45.8 vs 29.0, IQR 8.0–79.0, $p = 0.054$) compared to non-severe AS. Those with severe AS had lower prevalence of Lp(a) > 30 mg/dL (32.3% vs 43.0%, $p = 0.034$) and Lp(a) > 50 mg/dL (22.7% vs 33.7%, $p = 0.019$) than those without severe AS (Supplemental Table 1). Lp(a) testing was more common for severe AS among both women (38.8 vs 15.5%, $p < 0.001$) and men (37.9 vs 20.7%, $p < 0.001$). Median Lp(a) did not differ for severe compared with non-severe AS among women ($p = 0.086$) or men ($p = 0.234$, Supplemental Table 2). When stratified by race, Lp(a) testing was significantly higher for severe compared with non-severe AS among White individuals (43.3 vs 18.7%, $p < 0.001$) and Asian individuals (34.8 vs 12.2%, $p = 0.024$) and borderline significantly higher among Hispanic individuals (32.0 vs 21.8%, $p = 0.054$) and individuals of other or mixed race (29.7 vs 13.3%, $p = 0.066$). Testing was not significantly different by AS severity among Black individuals, but the number of participants was low ($n = 40$, Supplemental Table 2).

A total of 417 patients underwent TAVR from 2013 to 2020, and 274 (65.7%) had Lp(a) testing. Among patients undergoing TAVR, the prevalence of Lp(a) testing increased from 2013 to 2020, starting at 0.0% in 2013, peaking at 88.5% in 2018, and declining to 68.4% in 2020 ($p < 0.001$ for trend, Fig. 4). Lp(a) levels >30 mg/dL were present in 34.7% of TAVR patients and levels >50 mg/dL were present in 25.9%.

4. Discussion

This study demonstrates two clinically relevant observations in patients with AS: 1) Lp(a) > 30 mg/dL was present in over one-third of patients with AS and specifically in those undergoing TAVR, and 2) significant increases in Lp(a) testing occurred over the 10-year observation period. Educational efforts, practice pathway changes specifically linked to ordering Lp(a) levels, and a dedicated Lp(a) clinic for referrals likely contributed to the robust increase in the level of testing, particularly in patients undergoing TAVR.

This study of real-world data confirms that elevated Lp(a) is present in approximately one-third of patients with AS and in the subset of patients undergoing TAVR. There is now an extensive body of evidence demonstrating the relationship between elevated Lp(a) and AS. Genetic studies have demonstrated that single nucleotide polymorphisms of the *LPA* gene, which are also associated with elevated plasma levels of Lp(a), are associated with aortic valve calcification and incident AS [4–6, 15]. Additionally, clinical studies have demonstrated that elevated Lp(a) levels are associated with aortic valve calcification, incident AS, faster progression of AS and need for aortic valve replacement [3,5,8,9,16,17]. Taken together, these data create a rationale for a dedicated trial of Lp(a) lowering in subjects with AS and elevated Lp(a) to assess if the rate of progression and need for aortic valve replacement (AVR)/TAVR can be decreased.

The current study shows that Lp(a) testing at UCSDH, for any reason and specifically for AS, increased significantly over time, particularly after 2016. Although the current study design does not allow for determination of causal relationships, we believe a major reason for the increasing rates of testing was due to rising general awareness of Lp(a) as a risk factor for AS, along with the implementation of multi-pronged educational efforts and electronic medical record changes that facilitated ordering Lp(a) levels via preset orders. In particular, pre-procedure order sets for TAVR with the option to measure Lp(a) were highly effective in increasing the rates of Lp(a) testing in this group. However, they do not explain the entire effect as TAVR cases represent a minority of AS cases. A decline in Lp(a) testing for AS was noted starting in 2017. The explanation for this is not clear, but it may reflect the need for persistent educational efforts, particularly with yearly turnover of trainees that do a significant amount of the ordering of laboratories. A significant impact was likely also due to the COVID-19 global pandemic starting in 2019, resulting in an overall decrease in elective procedures and testing. Consistent with this, national US data demonstrates that compared to 2018–2019, outpatient visits declined significantly in 2020 [18].

Comprehensive data on clinical testing of elevated Lp(a) in AS/TAVR are generally lacking and measuring Lp(a) is not yet incorporated into clinical practice. In prior studies from UCSDH, Wilkinson et al. [14], observed a rate of testing of 4.6% in 2,710 AS patients from 2010 to 2016. The current data show that this increased further to 13.9% in all AS cases (peaking at 24.2%) and to almost 40% in those with severe AS. Ma et al. [10] previously observed that Lp(a) was elevated in 35% of TAVR patients. Lp(a) testing was integrated into the pre-TAVR order set in the electronic medical record in August 2016, which increased Lp(a) testing from 40% in 2016 to 86.5% in 2019. The clinical role of Lp(a) testing for management in TAVR cases is not yet defined, but it may predict procedural success. We have previously shown that patients undergoing TAVR with Lp(a) > 30 mg/dL had a statistically significant but modest association with para-valvular leak post-TAVR, which we postulated was due to increased calcification for the same valve area, leading to suboptimal apposition [10]. Although this is preliminary and hypothesis generating, as this database grows, these types of questions can be addressed with higher power and certainty. Identifying elevated Lp(a) in subjects undergoing TAVR also allows cascade screening of affected relatives, with a high yield of identifying subjects at risk of both AS and CVD [19].

Lp(a) testing is now incorporated in most international guidelines for managing blood cholesterol levels. The ACC/AHA recommends the use of Lp(a) as a risk-enhancing factor to guide intensity of therapies for people at intermediate risk for cardiovascular disease [20]. The ESC/EAS and CCS lipid/prevention guidelines recommend one-time testing for Lp(a) in all individuals [21,22]. The ACC/AHA valvular disease guidelines note that Lp(a) identifies those at risk for AS, but don't make a recommendation regarding testing, while the European and Canadian valvular guidelines do not specifically address Lp(a). The National Lipid Association endorses the use of Lp(a) testing in patients with AS [23], and given that levels are genetically determined and relatively stable throughout life, a one-time test may be a very cost-effective strategy to evaluate for risk of rapid progression of AS. Although country-wide data are not available for Lp(a) testing generally or specifically for AS, large single center studies are being reported. For example, Lp(a) levels were determined in 12,437 individuals in whom a lipid blood test was ordered between October 2018 and

October 2019 at UMC Amsterdam, of whom 30.7% had a history of ASCVD. Although the prevalence rates at various cutoffs were not included, subjects with Lp(a) > 99th percentile (>387.8 nmol/L) had an OR of 2.64 for ASCVD and 3.39 for MI compared to those

20th percentile (< 7 nmol/L). Addition of Lp(a) to ASCVD risk algorithms led to 31–63% being reclassified into higher risk categories by several accepted metrics, suggesting the measurement of Lp(a) levels can make a significant difference in clinical care [24]. Lp(a) testing costs ~\$30–100 in the US, and 10–25 euros per sample in the EU. It is important to note that given the genetic nature of Lp(a), it only needs to be checked once in most patients. Commercial insurance may not always cover Lp(a) testing; however, this may be improved by the development of ICD-10 codes for Lp(a), as well as the evolution of major cardiovascular society guidelines to include Lp(a) testing [25]. The availability of LPA isoform measurements in clinical practice is not available, but the data to date suggests they do not add appreciably to risk prediction or management decisions once Lp(a) levels are known [26,27]. In addition, use of an isoform-insensitive assay for the measurement of Lp(a) is recommended by the American Heart Association, as this reduces the impact of apolipoprotein(a) size variability and results in high precision [28].

These findings have several clinical implications. The clinical relevance of elevated Lp(a) in patients with AS is reflected in the fact that such patients with concomitant mild-severe AS, including those individuals with bicuspid aortic valves, have significantly higher rates of echocardiographically-documented progression of AS and need for AVR [8,9,17]. Lp(a) testing among AS patients also provides an opportunity to identify individuals at risk for ischemic cardiovascular events. Thus, measuring an Lp(a) level may provide prognostic information, help tailor careful clinical assessment and surveillance imaging to determine the optimal timing for AVR/TAVR, and prompt aggressive risk factor modification for the prevention of coronary artery disease. Additionally, there have been continued advances towards therapies to lower plasma Lp(a) levels. Modest Lp(a) lowering with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors improves cardiovascular outcomes independent of lowering low-density lipoprotein (LDL) [29]. A phase 2 trial of antisense therapy demonstrated significant Lp(a) lowering, and is now the subject of a large phase 3 trial to evaluate the impact of Lp(a) lowering on cardiovascular outcomes [11]. Finally, the increase in Lp(a) testing observed after the institution of clinical changes and educational campaigns provides a feasible model for improving Lp(a) testing at other institutions.

Our study has limitations. First, the data reflect an academic, single center experience in an environment with broad institutional expertise and interest in Lp(a) among clinicians in several cardiology subspecialties. Further study is needed to assess whether similar results can be achieved at other institutions. Second, the study relies on diagnosis codes for the diagnosis of AS – as such, there may be missing or incorrectly classified cases of AS. Third, the study used 3 different Lp(a) assays which may have led to some variability around the 30 mg/dL threshold and influence prevalence rates, but all of these are approved for clinical use. Finally, these data could not be linked to long-term outcomes to assess if measuring Lp(a) impacted how patients were evaluated and managed or was associated with a change in outcomes.

In conclusion, Lp(a) is highly prevalent among AS and TAVR patients, and Lp(a) testing among AS patients can be increased significantly with institutional and clinician interest and support. Our results present a methodology that can be applied broadly in all clinical care settings to increase awareness of the role of Lp(a) in patients with AS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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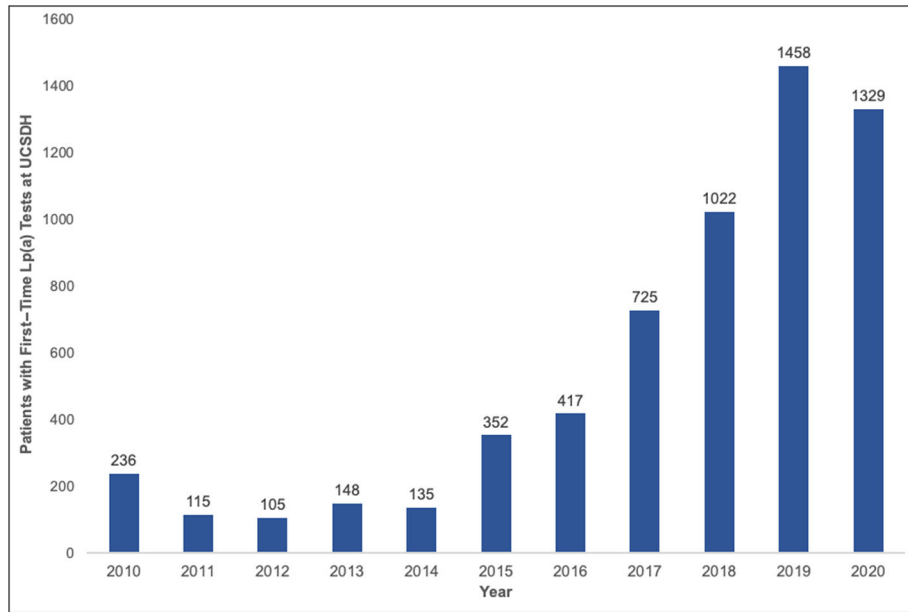


Fig. 1. Lp(a) testing at UCSD Health 2010–2020.

The graph represents the yearly volume of unique Lp(a) testing for all indications at UCSD Health from 2010 to 2020. Unique tests per year increased over time, starting with 236 patients in 2010 and peaking at 1458 patients in 2019.

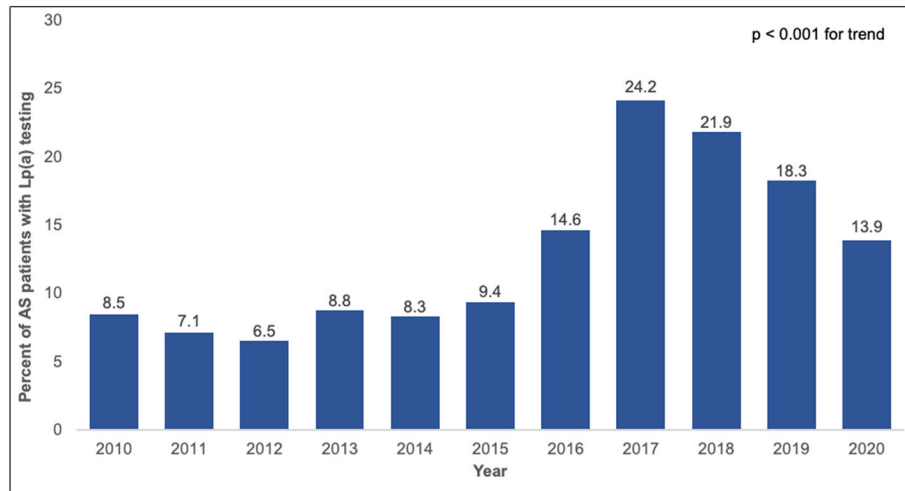


Fig. 2.

Frequency of Lp(a) testing among patients with AS by year.

The graph represents the prevalence of Lp(a) testing among patients diagnosed with aortic stenosis by year. Prevalence of Lp(a) testing increased over time from 8.5% in 2010 to a peak of 24.2% in 2017 ($p < 0.001$ for trend by chi square testing).

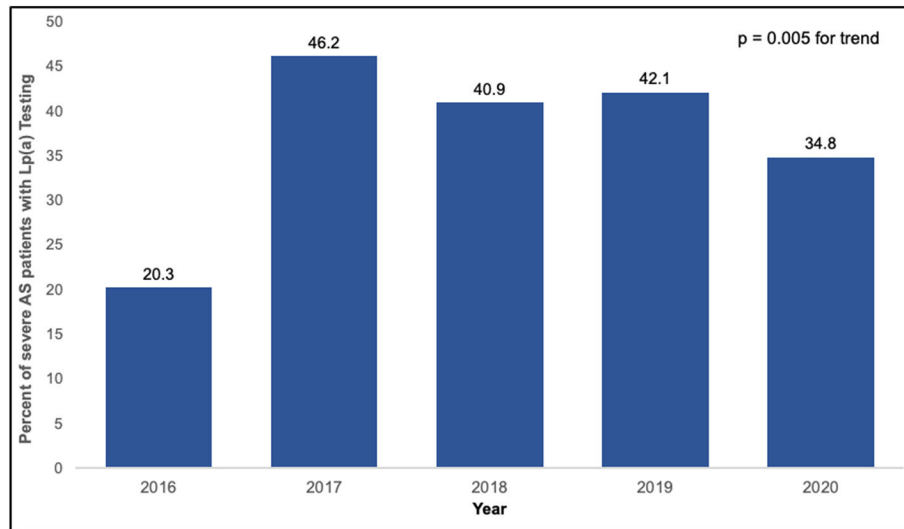


Fig. 3.

Frequency of Lp(a) testing among patients with severe AS by year.

The graph represents the prevalence of Lp(a) testing among patients diagnosed with severe aortic stenosis by at least one of three echo criteria. Prevalence of Lp(a) testing increased over time from 20.3% in 2016 to a peak of 46.2% in 2017 ($p = 0.005$ for trend by chi square testing).

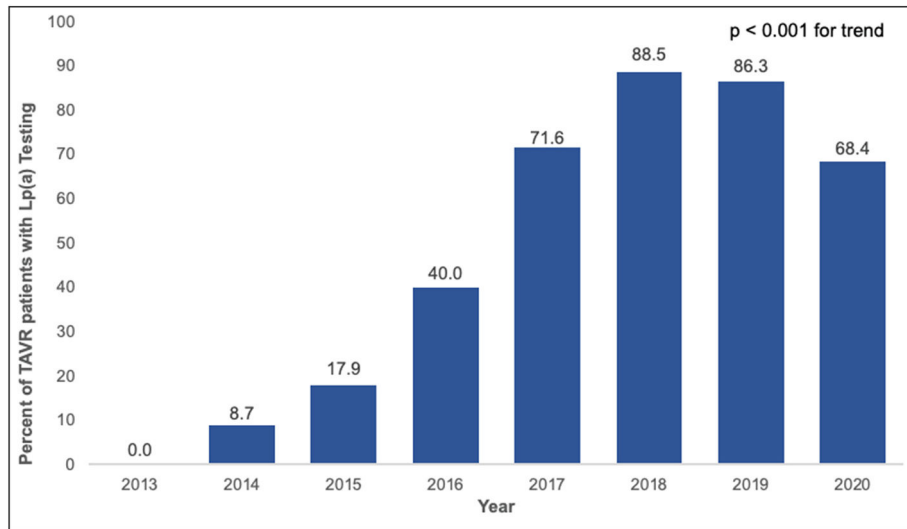


Fig. 4.

Frequency of Lp(a) testing among TAVR patients by year.

The graph represents the prevalence of Lp(a) testing among patients undergoing transcatheter aortic valve replacement. Prevalence of Lp(a) testing increased over time from 0.0% in 2013 to a peak of 88.5% in 2018 ($p < 0.001$ for trend by chi square testing).

Table 1

Characteristics of patients with Lp(a) tests 2010–2020 (n = 6049).

	Without AS (n = 5514)	With AS (n = 535)	<i>p</i>
Age at time of Lp(a), years	58.6 (14.2)	76.1 (11.3)	<0.001
Mean Lp(a), mg/dL	35.4 (45.8)	38.5 (48.4)	0.079
Median Lp(a), mg/dL	15.0 (6.0, 51.0)	17.0 (6.0, 56.0)	0.246
Lp(a) > 30 mg/dL, n(%)	1918 (34.8)	197 (36.8)	0.345

Values are presented as mean (SD), median (IQR), or n (%).

Frequency of unique Lp(a) testing among AS patients, stratified by sex and race/ethnicity 2010–2020.

Table 2

By sex			
	Female (n = 1715)	Male (n = 2079)	<i>P</i>
Lp(a) tests, n(%)	219 (12.8)	310 (14.9)	<0.001
Median Lp(a), mg/dL	18.0 [7.0, 60.0]	16.0 [6.0, 53.0]	0.220
By race/ethnicity			
	Non-Hispanic White (n = 2474)	Hispanic (n = 681)	Black (n = 106)
			Asian (n = 241)
			Other (n = 306)
<i>P</i>			
Lp(a) tests, n(%)	354 (14.3)	103 (15.1)	12 (11.3)
Median Lp(a), mg/dL	16.0 [6.0, 55.0]	15.0 [6.0, 53.0]	43.5 [33.3, 134.8]
			29 (12.0)
			37 (12.4)
			33.0 [7.0, 71.5]
			20.0 [3.5, 61.0]
			0.574
			0.120

Values are presented as median (IQR) or n (%).