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The Mortality Burden of Untreated Aortic Stenosis

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ABSTRACT

BACKGROUND The American College of Cardiology/American Heart Association guidelines recommend the assessment and grading of severity of aortic stenosis (AS) as mild, moderate, or severe, per echocardiogram, and recommend aortic valve replacement (AVR) when the AS is severe.

OBJECTIVES The authors sought to describe mortality rates across the entire spectrum of untreated AS from a contemporary, large, real-world database.

METHODS We analyzed a deidentified real-world data set including 1,669,536 echocardiographic reports (1,085,850 patients) from 24 U.S. hospitals (egnite Database, egnite). Patients >18 years of age were classified by diagnosed AS severity. Untreated mortality and treatment rates were examined with Kaplan-Meier (KM) estimates, with results compared using the log-rank test. Multivariate hazards analysis was performed to assess associations with all-cause mortality.

RESULTS Among 595,120 patients with available AS severity assessment, the KM-estimated 4-year unadjusted, untreated, all-cause mortality associated with AS diagnosis of none, mild, mild-to-moderate, moderate, moderate-to-severe, or severe was 13.5% (95% CI: 13.3%-13.7%), 25.0% (95% CI: 23.8%-26.1%), 29.7% (95% CI: 26.8%-32.5%), 33.5% (95% CI: 31.0%-35.8%), 45.7% (95% CI: 37.4%-52.8%), and 44.9% (95% CI: 39.9%-49.6%), respectively. Results were similar when adjusted for informative censoring caused by treatment. KM-estimated 4-year observed treatment rates were 0.2% (95% CI: 0.2%-0.2%), 1.0% (95% CI: 0.7%-1.3%), 4.2% (95% CI: 2.0%-6.3%), 11.4% (95% CI: 9.5%-13.3%), 36.7% (95% CI: 31.8%-41.2%), and 60.7% (95% CI: 58.0%-63.3%), respectively. After adjustment, all degrees of AS severity were associated with increased mortality.

CONCLUSIONS Patients with AS have high mortality risk across all levels of untreated AS severity. Aortic valve replacement rates remain low for patients with severe AS, suggesting that more research is needed to understand barriers to diagnosis and appropriate approach and timing for aortic valve replacement. (J Am Coll Cardiol 2023;82:2101–2109)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

NLP = natural language processing

Aortic stenosis (AS) is a progressive disease associated with important morbidity and mortality.[1-4] Prior observational studies have demonstrated a significant decrease in survival with AS, especially when the aortic valve obstruction is deemed severe.[5] Recently, observational data have suggested that untreated moderate AS is also associated with poor prognosis.[6-9]

The American College of Cardiology/American Heart Association guidelines recommend the assessment and grading of severity of AS as mild, moderate, or severe, per echocardiogram, and recommend aortic valve replacement (AVR) when the AS is severe and when symptoms or decreased left ventricular function is present.[5] However, it is often challenging to determine the true severity of AS in real-world settings, especially when discordant data (ie, peak velocity, mean gradient, and aortic valve area) are obtained.[10-13] Underappreciation of the severity of AS may lead to undertreatment and potentially impact prognosis.[14,15] Data on how this translates to real-world outcomes and treatment rates are lacking. In the present study, we aim to assess mortality rates across the entire spectrum of untreated AS from a contemporary, large, real-world database.

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METHODS

The study population included 1,669,536 echocardiograms from 1,085,850 patients from 24 institutions with appropriate permissions (egnite Database, egnite, Inc). Exemption from Institutional Review Board review was obtained for this study from the WIRB-Copernicus Group. All deidentified data sets used were compliant with the Health Insurance Portability and Accountability Act. Data were prepared for the present study following initial data quality assessments by a clinical team and evaluated for study inclusion and exclusion criteria.

Inclusion criteria included the following: >18 years of age throughout analysis window; documented assessment of AS per a clinically reviewed and verified natural language processing (NLP) algorithm-based analysis of echocardiographic reports, with documented severity if a diagnosis of AS is present; and time from study index date (date of index event) to censoring date >0 days. Exclusion criteria included the following: patients with all documented echocardiograms dated before January 1, 2016 (for data quality purposes); patients with a record of AVR with missing date of procedure; and patients whose most severe AS diagnosis was recorded after their date of AVR.

Both the presence and severity of valve disease were derived from echocardiographic reports using a clinically reviewed and verified NLP algorithm with an overall accuracy of >99% (Supplemental Table 1). Patients with confirmed AS were classified according to AS severity (none, mild, mild-to-moderate, moderate, moderate-to-severe, severe) per the documented diagnosis of AS in echocardiographic reports generated in the context of usual clinical practice. All available echocardiogram types documented for a given patient were used to identify AS diagnosis, and in the event of more than 1 available diagnosis, the date of the report with the first most severe documented diagnosis was used as the study index date for consistency. The range of eligible index dates ranged from January 1, 2016, to December 22, 2022, in the study data set lock (although all true dates were eliminated at data set extraction for purposes of fully irreversible deidentification). Information on prespecified patient characteristics of interest was extracted as defined in Supplemental Table 2, with comorbidity history and treatment events identified according to relevant International Classification of Diseases-10th Revision/Current Procedural Terminology codes and/or echocardiographic report data preindex (all-time), with definitions adjudicated by a clinical reviewer as well as a medical coding expert where relevant. Outcomes were evaluated using Kaplan-Meier estimates through 4 years, with the index date as the date of relevant AS diagnosis specified in the previous text; the primary endpoint was all-cause untreated mortality, where patients were censored at time of treatment for AS or last documented clinical encounter. Information on patient deaths were extracted from medical records (ie, as documented by each site). The secondary endpoint was time to treatment with AVR for AS, where patients were censored on their date of death or last documented clinical encounter.

STATISTICAL ANALYSIS. Patient characteristics were reported either as n (%) for categorical variables or as mean ± SD or median (Q1-Q3) for continuous variables as appropriate. Kaplan-Meier estimates for all-cause mortality with untreated AS were reported per AS severity. In addition, an analysis with statistical adjustment for informative censoring caused by treatment, ie, inverse probability censoring weighting, was also performed. Kaplan-Meier estimates for treatment with AVR were also reported per AS severity. Statistical comparisons of findings across all cohorts were performed using log-rank tests.

TABLE 1 Aortic Stenosis Severity Among the Study Population of 595,120 Patients

No aortic stenosis	524,342 (88.1)
Mild aortic stenosis	34,614 (5.8)
Mild-to-moderate aortic stenosis	5,796 (1.0)
Moderate aortic stenosis	14,550 (2.4)
Moderate-to-severe aortic stenosis	3,689 (0.6)
Severe aortic stenosis	12,129 (2.0)

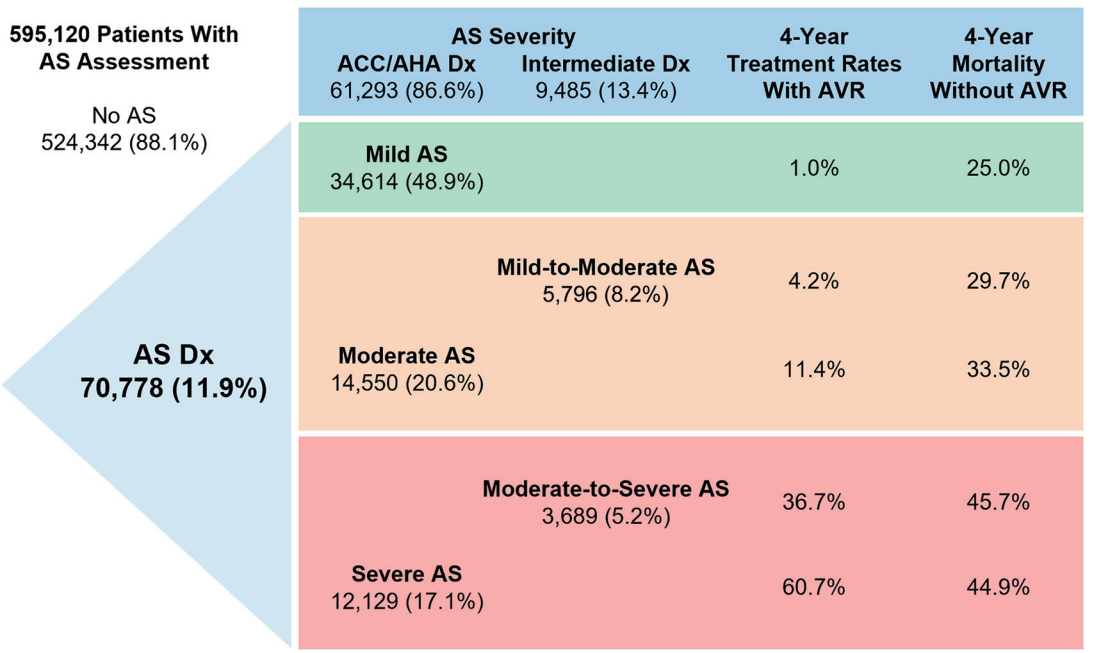
Values are n (%).

Modeled hazards analysis (Cox proportional hazards regression) was performed to simultaneously assess associations of risk factors of interest with all-cause mortality. Unless otherwise stated, $P < 0.05$ was considered statistically significant, but with Bonferroni corrections for multiple comparisons. All analyses were performed using Databricks Runtime version 13.2 (Apache Spark 3.4.0, Scala 2.12), R version 4.1.3 (R Foundation for Statistical Computing), survival package version 3.4.0.

RESULTS

STUDY POPULATION. A total of 595,120 patients met eligibility criteria and had documented AS severity by echocardiogram. Median time to patient treatment, last documented clinical encounter, or death was 421 days (Q1-Q3: 138-808 days). Table 1 shows the distribution of AS severity. A total of 70,778 (11.9%) patients were diagnosed with some degree of AS, and 524,342 (88.1%) had no AS. Among patients with AS, 61,293 (86.6%) patients were classified as mild, moderate, or severe, and 9,485 (13.4%) patients were identified as mild-to-moderate or moderate-to-severe (Central Illustration). Table 2 shows baseline characteristics per AS severity. In general, patients with AS and more severe AS were older and had more concomitant disease such as hypertension, atrial fibrillation, coronary artery disease, and low left ventricular ejection fraction. Similarly, prevalence of concomitant valve disease such as mitral regurgitation and tricuspid regurgitation increased with AS

CENTRAL ILLUSTRATION Mortality Associated With Untreated Aortic Stenosis



Généreux P, et al. J Am Coll Cardiol. 2023;82(22):2101-2109.

A total of 595,120 patients with documented AS assessment per echocardiogram were included in our study. Among them, 70,778 (11.9%) patients were diagnosed with some degree of AS, from whom 61,293 (86.6%) were classified as mild, moderate, or severe, and 9,485 (13.4%) were identified with "intermediate" severity (mild-to-moderate or moderate-to-severe AS). Treatment rates up to 4 years were low, with mortality increasing with AS severity increment. ACC = American College of Cardiology; AHA = American Heart Association; AS = aortic stenosis; AVR = aortic valve replacement; Dx = diagnosis.

TABLE 2 Baseline Characteristics[a] of the Study Population per AS Severity

	Overall (N = 595,120)	No AS (n = 524,342)	Mild AS (n = 34,614)	Mild-to-Moderate AS (n = 5,796)	Moderate AS (n = 14,550)	Moderate-to-Severe AS (n = 3,689)	Severe AS (n = 12,129)	*P* Value
Age, y	66.7 ± 15.2	65.3 ± 15.2	76.1 ± 10.8	77.7 ± 10.1	77.8 ± 10.3	78.5 ± 10.0	78.4 ± 10.3	<0.001
Sex								<0.001
Female	308,056 (51.8)	274,247 (52.3)	17,413 (50.3)	2,744 (47.3)	6,612 (45.4)	1,640 (44.5)	5,400 (44.5)	
Male	286,870 (48.2)	249,930 (47.7)	17,186 (49.7)	3,052 (52.7)	7,933 (54.5)	2,048 (55.5)	6,721 (55.4)	
Other/unknown	194 (<0.1)	165 (<0.1)	15 (<0.1)	0 (0.0)	5 (<0.1)	1 (<0.1)	8 (0.1)	
Diabetes	136,243 (22.9)	115,751 (22.1)	10,370 (30.0)	1,806 (31.2)	4,253 (29.2)	1,011 (27.4)	3,052 (25.2)	<0.001
Hypertension	341,701 (57.4)	294,068 (56.1)	23,875 (69.0)	3,953 (68.2)	9,871 (67.8)	2,463 (66.8)	7,471 (61.6)	<0.001
Atrial fibrillation	106,444 (17.9)	88,348 (16.8)	8,754 (25.3)	1,589 (27.4)	3,856 (26.5)	999 (27.1)	2,898 (23.9)	<0.001
Prior stroke	53,292 (9.0)	45,928 (8.8)	3,794 (11.0)	649 (11.2)	1,488 (10.2)	370 (10.0)	1,063 (8.8)	<0.001
HFrEF	46,118 (7.7)	37,939 (7.2)	3,862 (11.2)	719 (12.4)	1,740 (12.0)	440 (11.9)	1,418 (11.7)	<0.001
LVEF, %	56.6 ± 11.0	56.5 ± 10.9	57.8 ± 11.0	56.2 ± 11.3	57.4 ± 11.6	56.0 ± 12.0	56.2 ± 13.1	<0.001
LVEF <50%	85,331 (14.3)	73,618 (14.0)	5,177 (15.0)	1,024 (17.7)	2,362 (16.2)	710 (19.2)	2,440 (20.1)	<0.001
CAD	165,468 (27.8)	138,774 (26.5)	12,966 (37.5)	2,326 (40.1)	5,662 (38.9)	1,417 (38.4)	4,323 (35.6)	<0.001
Prior MI	41,432 (7.0)	35,431 (6.8)	2,833 (8.2)	492 (8.5)	1,326 (9.1)	324 (8.8)	1,026 (8.5)	<0.001
Prior PCI	19,063 (3.2)	16,684 (3.2)	1,142 (3.3)	203 (3.5)	498 (3.4)	149 (4.0)	387 (3.2)	0.015
Prior CABG	3,911 (0.7)	3,325 (0.6)	337 (1.0)	62 (1.1)	110 (0.8)	23 (0.6)	54 (0.4)	<0.001
COPD	64,579 (10.9)	55,257 (10.5)	4,789 (13.8)	879 (15.2)	1,840 (12.6)	535 (14.5)	1,279 (10.5)	<0.001
COPD on O_2	9,057 (1.5)	7,389 (1.4)	879 (2.5)	185 (3.2)	335 (2.3)	84 (2.3)	185 (1.5)	<0.001
Chronic kidney disease	82,271 (13.8)	66,390 (12.7)	7,891 (22.8)	1,405 (24.2)	3,456 (23.8)	816 (22.1)	2,313 (19.1)	<0.001
Metastatic cancer	12,389 (2.1)	10,963 (2.1)	791 (2.3)	115 (2.0)	275 (1.9)	57 (1.5)	188 (1.6)	<0.001
Dementia	7,594 (1.3)	5,884 (1.1)	798 (2.3)	146 (2.5)	377 (2.6)	85 (2.3)	304 (2.5)	<0.001
Aortic valve area, cm^2	2.4 ± 0.8	2.6 ± 0.7	1.7 ± 0.5	1.4 ± 0.4	1.2 ± 0.3	0.9 ± 0.2	0.8 ± 0.3	<0.001
Peak velocity, m/s	1.6 ± 0.6	1.4 ± 0.3	2.2 ± 0.4	2.6 ± 0.5	2.9 ± 0.6	3.4 ± 0.6	3.9 ± 0.9	<0.001
Mean pressure gradient, mm Hg	6.4 ± 7.3	4.4 ± 2.2	11.0 ± 4.1	15.4 ± 5.2	20.1 ± 7.3	27.7 ± 8.7	38.6 ± 15.3	<0.001
Moderate or greater MR	36,617 (6.2)	28,557 (5.4)	3,235 (9.3)	653 (11.3)	1,781 (12.2)	532 (14.4)	1,859 (15.3)	<0.001
Moderate or greater TR	38,497 (6.5)	29,679 (5.7)	3,722 (10.8)	789 (13.6)	1,929 (13.3)	602 (16.3)	1,776 (14.6)	<0.001
Moderate or greater AR	13,520 (2.3)	8,538 (1.6)	1,889 (5.5)	348 (6.0)	1,172 (8.1)	353 (9.6)	1,220 (10.1)	<0.001
Moderate or greater MS	2,605 (0.4)	992 (0.2)	514 (1.5)	106 (1.8)	413 (2.8)	111 (3.0)	469 (3.9)	<0.001

Values are mean ± SD or n (%). [a]All characteristic definitions provided in Supplemental Table 2.

AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

and with increase in severity of AS. Supplemental Table 3 and Supplemental Figure 1 summarize the relative prevalence of cases where any/all of the 3 key severity criteria (aortic valve area, mean pressure gradient, peak velocity) were found to be in the severe range per guidelines within each diagnosed cohort. Some element of discordance in diagnosed severity of AS and presence of echocardiographic criteria for severe AS was present in at least 22.8% and 59.8% of the patients with moderate and moderate-to-severe AS, respectively.

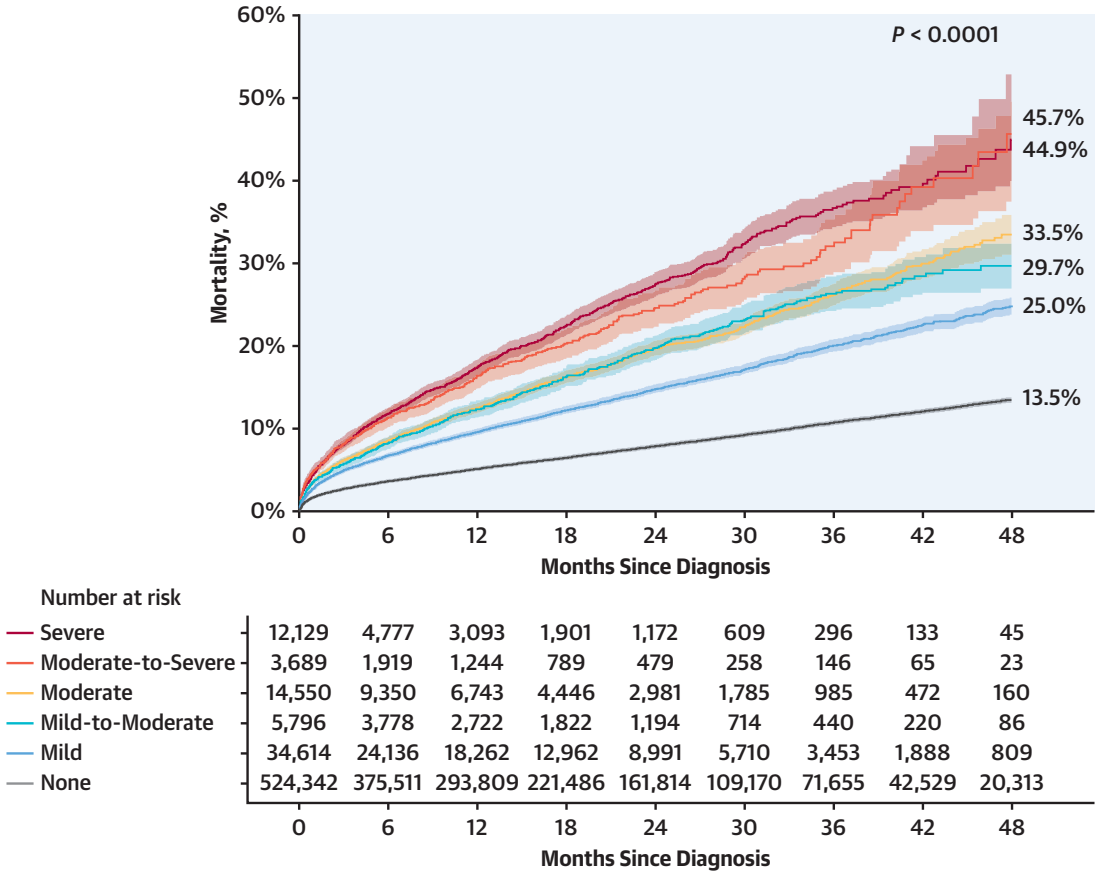
MORTALITY FOR PATIENTS WITH UNTREATED AS. Estimated 4-year all-cause untreated mortality associated with AS diagnosis of none, mild, mild-to-moderate, moderate, moderate-to-severe, or severe was 13.5% (95% CI: 13.3%-13.7%), 25.0% (95% CI: 23.8%-26.1%), 29.7% (95% CI: 26.8%-32.5%), 33.5% (95% CI: 31.0%-35.8%), 45.7% (95% CI: 37.4%-52.8%), and 44.9% (95% CI: 39.9%-49.6%), respectively (**Table 3**, **Figure 1**). Results were directionally similar when adjusted for informative censoring caused by treatment (**Table 3**, Supplemental Figure 2). Estimated 4-year observed treatment rates were 0.2% (95% CI: 0.2%-0.2%), 1.0% (95% CI: 0.7%-1.3%), 4.2% (95% CI: 2.0%-6.3%), 11.4% (95% CI: 9.5%-13.3%), 36.7% (95% CI: 31.8%-41.2%), and 60.7% (95% CI: 58.0%-63.3%), respectively (**Figure 2**).

MULTIVARIABLE ANALYSIS. Modeled hazards analysis demonstrated a trend of incremental increase in mortality per increase in AS severity (**Figure 3**). After adjustment, all degrees of AS severity were associated with increased untreated mortality risk.

DISCUSSION

To the best of our knowledge, the current study represents, by far, the largest cohort of patients with AS diagnosis to be presented. From a contemporary

FIGURE 1 Unadjusted Mortality by Aortic Stenosis Severity



Mortality with untreated aortic stenosis over up to 4 years of follow-up after the index documented diagnosis.

database using NLP to extract diagnosed severity of AS, the key findings are the following: 1) ranged/intermediate diagnoses (mild-to-moderate, moderate-to-severe) are common in real-world practice and are associated with mortality similar to the next-most-severe AS grade; 2) treatment of severe AS was low, and was performed in ~60% of patients up to 4 years after initial diagnosis; and 3) mortality risk with AS increased incrementally across the full spectrum of AS severity, suggesting the need for earlier diagnosis, closer follow-up, and potentially earlier intervention.

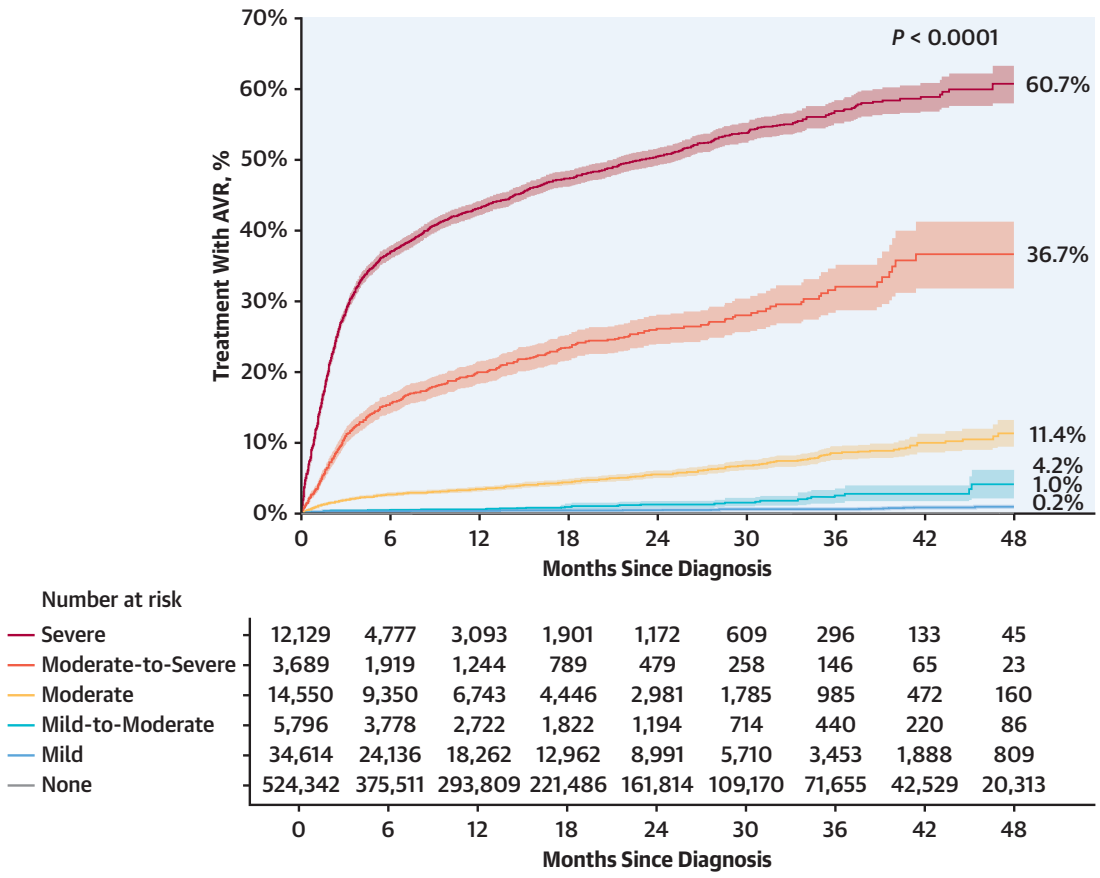
TABLE 3 4-Year Mortality per Aortic Stenosis Severity

Aortic Stenosis Diagnosis	Unadjusted 4-Year Mortality (%)	Adjusted[a] 4-Year Mortality (%)
None	13.5	13.5
Mild	25.0	25.0
Mild-to-moderate	29.7	29.7
Moderate	33.5	33.3
Moderate-to-severe	45.7	44.2
Severe	44.9	42.0

[a]Adjustment for informative censoring because of treatment applied using inverse probability censoring weighting methodology.

The current study, based on approximately 600,000 patients who received an echocardiogram, is the largest study related to untreated AS and its associated mortality. The recent study published by Strange et al[6] in 2019 from ~240,000 patients from a national registry demonstrated similar findings. Indeed, mortality seems to increase proportionally to AS severity. Whether the observed increase in mortality within these 2 observational studies is truly related to AS or rather an association remains to be determined in a prospective fashion. More importantly, whether earlier intervention on lower AS severity could result in improved survival among these patients also needs to be proven. Multiple prospective randomized trials are currently ongoing

FIGURE 2 Treatment Rates by Aortic Stenosis Severity

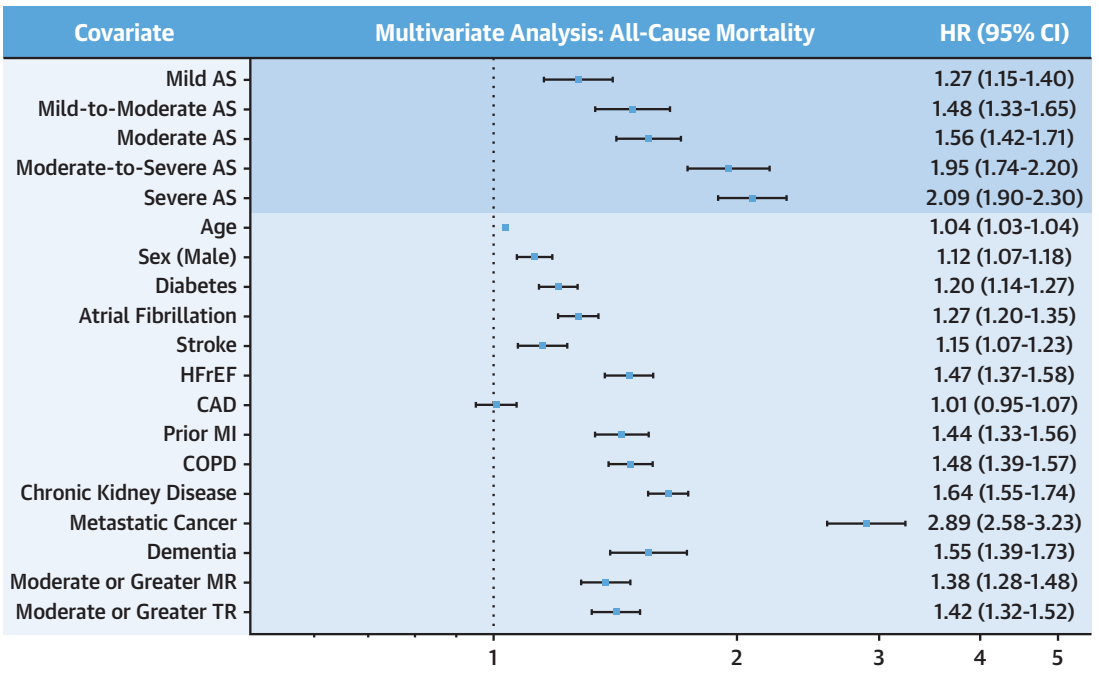


Rates of aortic valve replacement over up to 4 years of follow-up after the index documented diagnosis.

and are expected to bring meaningful information on whether preemptive AVR may be beneficial (EARLY TAVR [Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104], the EVoLVeD [Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143] and the EASY-AS [Early Valve Replacement in Severe ASYmptomatic Aortic Stenosis Study; NCT04204915] trials; PROGRESS [Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement; trial; NCT04889872], and the Evolut [Medtronic] EXPAND TAVR II Pivotal Trial; NCT05149755).

Importantly, our study using NLP on echocardiographic reports identified a significant proportion of patients with "intermediate" diagnoses (mild-to-moderate and moderate-to-severe). Although 86.6% of patients with AS received a diagnosis of mild, moderate, or severe AS, which conforms to American College of Cardiology/American Heart Association guideline recommendations, 13.4% received a diagnosis of mild-to-moderate or moderate-to-severe AS. This finding illustrated the challenges of precise AS severity diagnosis in a real-world setting and in the community. This is most likely caused by multiple factors such as difficult image acquisition, patient echogenicity, variability in image quality, and challenging clinical situations such as discordant AS with or without low flow states.[10-16] This finding is even more important because it may lead physicians to underappreciate the true severity of AS and may lead to delayed referral and delayed treatment. Our study also demonstrated that the mortality of patients receiving those "intermediate" diagnoses exhibit similar mortality as the next-most-severe grade of AS, meaning moderate for patients identified as "mild-to-

FIGURE 3 Mortality Modeled Hazards Analysis



Mortality adjusted for patient age, sex, and comorbidities. AS = aortic stenosis; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; TR = tricuspid regurgitation.

moderate," and severe for patients identified as "moderate-to-severe." Although the guidelines recommend 3 grades of severity of AS (mild, moderate, severe) with specific criteria for each grade, it might be appropriate and more practical to "upgrade" patients to a higher severity of AS when one severity criterion coexists with a less severe one (discordance). Echocardiographic assessment remains an imperfect tool with many caveats, and such an approach might mitigate those limitations and avoid scenarios where patients effectively fall between 2 diagnoses, with subsequent suboptimal follow-up or treatment.

The AVR rate was low in our study cohort, with only ~60% of patients with severe AS undergoing AVR within 4 years. Undertreatment of AS has been described previously,[14,15] and multiple initiatives have been implemented to solve this problem.[17] That being said, many factors could explain the appropriate choice of delaying treatment or of a conservative approach for severe AS: 1) some patients might have been truly asymptomatic (ie, negative stress test) and with a preserved left ventricular ejection fraction, where clinical surveillance every 6 to 12 months is recommended; 2) patients might have been too sick (ie, suffering from dementia or terminal disease such as advanced metastatic cancer) with multiple comorbidities making AVR futile; and 3) patients might have refused treatment for logistical reasons or fear of the procedures. Although our database does not allow for such granular details regarding the reasons for the lack of treatment, those situations most likely do not fully explain the magnitude of the observed undertreatment. Better understanding of the reasons driving this undertreatment is needed.

STUDY LIMITATIONS. First, we used an NLP algorithm to extract data from the echocardiographic report provided from each site. We did not reassess raw images or use independent core laboratory methodology for AS assessment. Second, our population consisted of patients undergoing echocardiographic assessment during an office or hospital visit, where AS might not have been the principal issue. The mortality observed in our study might not be fully explained by the AS itself. Third, these data originate from a subset of the many health systems that exist in the United States, although data from

both teaching and nonteaching institutions were included. Results from different types of institutions might have differed. Fourth, the index date selection methodology could theoretically result in a patient being assigned to one cohort while a subsequent echocardiogram reported a lower severity, but this would be expected to bias our findings toward the null. Fifth, it is possible that information on patient deaths as extracted from medical records (ie, as documented by each site) could be incomplete. Finally, a more granular assessment of each echocardiogram, including stroke volume index or the use of a dobutamine stress echocardiogram, may have improved the grading of AS in some instances. Despite these limitations, this study reflects real-world practice, provides meaningful information regarding challenges in applying guidelines in the community, and identifies potential areas for diagnosis and therapeutic improvement.

CONCLUSIONS

The high mortality observed across the full spectrum of untreated AS severity and the low treatment rate among patients with severe AS suggest that a call for action is necessary regarding the diagnosis and treatment of AS. Earlier diagnosis, intensification of follow-up, and potentially earlier intervention may be needed among patients with AS.

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Dr Généreux has served as a consultant for, an advisor for, and received speaker fees from Abbott Vascular, Abiomed, Edwards Lifesciences, and Medtronic; has served as a consultant for Boston Scientific, GE Healthcare, iRhythm Technologies, OpSens, Siemens, and Teleflex; has served as a consultant for and PI of the Eclipse Trial for Cardiovascular System Inc; has served as a proctor for, received research grants from, and served as PI for the EARLY-TAVR and PROGRESS trials for Edwards Lifesciences; has equity in and served as a consultant for Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc; has served as a consultant for and received speaker fees from Shockwave; has served as a consultant for and PI of the ALTA Valve Feasibility study for 4C Medical; and has served as a consultant and advisor for egnite, Inc. Dr Sharma has served as a consultant and advisor for Edwards Lifesciences, Boston Scientific, Abbott, Philips, Siemens, and egnite, Inc. Dr Cubeddu has served on the Speakers Bureau for Abbott Laboratories, Edwards Lifesciences, and Gore Medical. Dr Thourani has served on the advisory board for Edwards Lifesciences, Abbott Vascular, Atricure, Cryolife, JenaValve, Shockwave, and Boston Scientific. Dr Makkar has received grant support/research contracts from Edwards Lifesciences and St Jude Medical; and has received consultant fees/honoraria and served on the Speakers Bureaus of Abbott Vascular, Cordis Corporation, and Medtronic. Dr Cohen has received research grant support from Edwards Lifesciences, Boston Scientific, Abbott, Medtronic, Philips, Zoll Medical, iRhythm, and Corvia; and has served as a consultant for Edwards Lifesciences, Boston Scientific, Abbott, Medtronic, and Corvia. Mr Dobbles and Dr Kwon have equity, stock(s), and/or options in and are employees of egnite, Inc. Dr Barnhart has equity, stock(s), and/or options in and was employed at egnite, Inc at the time of the study. Dr Pibarot has received institutional funding from Edwards Lifesciences, Medtronic, Pi-Cardia, Cardiac Success, and Roche Diagnostics for echocardiography core laboratory analyses, blood biomarker analyses, and research studies in the field of interventional and pharmacologic treatment of valvular heart diseases, for which he received no personal compensation. Dr Leon has received institutional clinical research grants from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Gillam has served as a consultant for Medtronic, Philips, Edwards Lifesciences, and egnite, Inc; and has core laboratory contracts (no direct compensation) with Edwards Lifesciences, Medtronic, and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although mortality increases incrementally across the spectrum of hemodynamic severity in patients with AS, only 60% of patients with severe AS undergo aortic valve replacement.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to determine whether global initiatives targeting earlier detection and treatment can improve outcomes in patients with AS.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.