Title

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ORIGINAL RESEARCH

Patient- and Process-Related Contributors to the Underuse of Aortic Valve Replacement and Subsequent Mortality in Ambulatory Patients With Severe Aortic Stenosis

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BACKGROUND: Many patients with severe aortic stenosis (AS) and an indication for aortic valve replacement (AVR) do not undergo treatment. The reasons for this have not been well studied in the transcatheter AVR era. We sought to determine how patient- and process-specific factors affected AVR use in patients with severe AS.

METHODS AND RESULTS: We identified ambulatory patients from 2016 to 2018 demonstrating severe AS, defined by aortic valve area ≤1.0 cm^2. Propensity scoring analysis with inverse probability of treatment weighting was used to evaluate associations between predictors and the odds of undergoing AVR at 365 days and subsequent mortality at 730 days. Of 324 patients with an indication for AVR (79.3±9.7 years, 57.4% men), 140 patients (43.2%) did not undergo AVR. The odds of AVR were reduced in patients aged >90 years (odds ratio [OR], 0.24 [95% CI, 0.08–0.69]; *P*=0.01), greater comorbid conditions (OR, 0.88 per 1-point increase in Combined Comorbidity Index [95% CI, 0.79–0.97]; *P*=0.01), low-flow, low-gradient AS with preserved left ventricular ejection fraction (OR, 0.11 [95% CI, 0.06–0.21]), and low-gradient AS with reduced left ventricular ejection fraction (OR, 0.18 [95% CI, 0.08–0.40]) and were increased if the transthoracic echocardiogram ordering provider was a cardiologist (OR, 2.46 [95% CI, 1.38–4.38]). Patients who underwent AVR gained an average of 85.8 days of life (95% CI, 40.9–130.6) at 730 days.

CONCLUSIONS: The proportion of ambulatory patients with severe AS and an indication for AVR who do not receive AVR remains significant. Efforts are needed to maximize the recognition of severe AS, especially low-gradient subtypes, and to encourage patient referral to multidisciplinary heart valve teams.

Key Words: aortic stenosis ■ aortic valve replacement ■ treatment predictors ■ survival

Calcific aortic stenosis (AS) is the most common cause of valvular heart disease in the Western world and is the most frequent indication for aortic valve replacement (AVR).[1–3] Current clinical practice guidelines recommend deferring AVR until symptom onset or overt left ventricular systolic dysfunction. Left untreated, 50% of patients with severe AS die within 1 to 2 years of symptom onset.[4–9] Although potentially lifesaving, past studies have estimated that up to a third of patients with an indication for AVR do not

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CLINICAL PERSPECTIVE

What Is New?

- A significant proportion of patients with severe aortic stenosis who have a likely indication for aortic valve replacement do not receive one despite the availability of transcatheter aortic valve replacement, and both patient- and process-related factors contribute to this.
- Patients with low-gradient phenotypes are less likely to receive an aortic valve replacement.
- Patients whose transthoracic echocardiogram was ordered by a cardiologist are more likely to receive aortic valve replacement; few patients who did not receive aortic valve replacement had an evaluation by a multidisciplinary heart valve team before the decision for no intervention.

What Are the Clinical Implications?

- Efforts are needed to maximize the recognition of severe aortic stenosis, especially low-gradient phenotypes, and to encourage patient referral to multidisciplinary heart valve teams.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVG	aortic valve gradient
AVR	aortic valve replacement
MGH	Massachusetts General Hospital
RMST	restricted mean survival time
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TTE	transthoracic echocardiogram

undergo treatment[10–12]; ultimately, these patients have a higher rate of hospitalization, are intensive users of health care resources, and cost the US Medicare program an estimated ≈$1.3 billion per year, all despite their limited long-term survival.[13]

Until recently, data on AVR use in patients with severe AS were primarily driven by surgical AVR (SAVR), because this was the sole treatment option for AS. With the advent of transcatheter AVR (TAVR), patients normally ineligible for SAVR because of high mortality risk, advanced age, or comorbid conditions can be eligible for a less-invasive treatment option for AS with lower procedural morbidity and mortality.[11,12,14–18] Because of this, TAVR was anticipated to improve adherence to guideline-based use of AVR in patients with symptomatic severe AS.[14,19–22] Nevertheless, recent studies suggest that a substantial number of patients with symptomatic severe AS still do not undergo AVR.[23,24]

The evaluation and management of patients with severe AS has become increasingly complex and heavily relies on provider referral upon detection of AS. The presence of discordant imaging measures of AS severity has been previously documented and is estimated to occur in up to 40% of patients with AS.[25,26] Moreover, the rapid evolution of TAVR devices and procedural techniques mandates an intimate knowledge of the field to inform the difficult risk–benefit analysis that surrounds treatment decisions. The American Heart Association/American College of Cardiology practice guidelines for the management of patients with valvular heart disease recommend that providers refer patients with severe valvular heart disease to a multidisciplinary heart valve team for further evaluation when intervention is being considered.[5] However, recent data suggest that medically managed patients with an indication for AVR are not consistently referred to a multidisciplinary heart valve team or valve specialist for evaluation.[23] Thus, factors beyond a patient's biology and more inherent to the patient referral process may affect AVR usage rates and, in turn, postprocedural outcomes in patients with severe AS.

We therefore sought to determine the extent to which patient characteristics and process-specific factors, including ordering provider specialty and whether the index transthoracic echocardiogram (TTE) report explicitly identified the presence of severe AS, affected AVR usage rates and, in turn, mortality rates in a retrospective cohort of ambulatory patients with severe AS. In this study, we identified and followed patients with severe AS for a 2-year period to determine predictors of undergoing AVR at 365 days and mortality at 730 days. Clinical implications and potential focus areas for future quality improvement initiatives to improve guideline-based use of AVR in patients with symptomatic severe AS are provided.

METHODS

This retrospective cohort study was approved by the Mass General Brigham Institutional Review Board before data collection and analysis. The data and analytic methods that support the findings of this study are available from the corresponding author upon request.

Patient Selection and Definitions

We queried the Massachusetts General Hospital (MGH) echocardiographic database to systematically identify any patient who underwent TTE between April 2016 and April 2018 and for whom an aortic valve area ≤ 1.0 cm^2 was reported (N=1432). For patients with multiple TTE reports during the study period, we used the first TTE report wherein an aortic valve area ≤1.0 cm^2

was reported as the index TTE. Our objective was to specifically examine AVR use among ambulatory patients within 1 year of being diagnosed with symptomatic severe native AS. Patients were therefore excluded if (1) their index TTE was performed in the inpatient setting, (2) they did not have a history of clinical care at MGH (defined as one or more clinical encounters between April 2016 and the date of their index TTE), (3) they had a prior history of AVR, or (4) they underwent AVR after the censoring threshold of 365 days and before the end of the study. Patients with index TTE occurring in the inpatient setting were excluded to facilitate investigation of a typical outpatient care pathway. We also excluded patients without a history of clinical care at MGH to identify a loyalty cohort likely to receive cardiac specialty care at MGH and to minimize the likelihood of missing AVR performed at another medical facility. Additionally, given our focus on evaluating predictors specific to the referral process for newly diagnosed AS, patients were also excluded if they were already undergoing AVR evaluation at the start of the study, defined by the presence of a clinical encounter with a cardiac surgeon. An encounter with a cardiac surgeon was used to define AVR evaluation given its commonality to both the SAVR and TAVR evaluation processes.

Aortic Stenosis Phenotypes and AVR Class Indications

Patients who passed the initial screening were grouped into AS phenotypes on the basis of mean aortic valve gradient (AVG) and left ventricular ejection fraction (LVEF) reported in the index TTE, as per the European Association of Cardiovascular Imaging and the American Society of Echocardiography guidelines.[4] They were subsequently defined as having a likely indication for AVR by phenotype per the 2014 *American Heart Association/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease*.[4,5] Patients were subsequently categorized as having symptomatic high-gradient severe AS with preserved LVEF (mean AVG ≥40 mm Hg, LVEF ≥50%); high-gradient severe AS with reduced LVEF (mean AVG ≥40 mm Hg, LVEF <50%); symptomatic low-gradient AS with preserved LVEF (mean AVG <40 mm Hg, LVEF ≥50%, stroke volume index <35 mL/m^2); and symptomatic low-gradient severe AS with reduced LVEF (mean AVG <40 mm Hg, LVEF <50%). Patients who underwent AVR were presumed to have an appropriate indication for AVR.

Data Collection and Definitions

Symptom Status and Reasons for AVR Denial/Refusal

Medical records for patients who did not receive an AVR within 1 year of their index TTE were manually reviewed by 3 study physicians (L.F., M.E., R.L.) to determine symptom status and reasons for AVR denial or refusal. Patients were identified as symptomatic if an evaluating provider made direct mention of symptomatic AS in a patient's electronic health record or recorded the presence of heart failure, angina, or syncope in the time period spanning 2 months prior and 6 months after a patient's index TTE date. Reasons for not pursuing AVR were also identified within the same time period and collapsed into nominal categories: symptoms not attributed to AS, AS not considered severe, medical uncertainty/watchful waiting, AVR evaluation initiated but delayed, medical futility, patient/family refusal, or severe AS not discussed or mentioned in clinical records.

Comorbidities, Frailty, and Vital Status

Comorbidities were calculated from claims data using *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*) codes from 2011 to date of index TTE, allowing for a minimum of 5 years of available claims data. Three claims-based indices were chosen based on validation articles and/or application to the AVR literature, the Charlson Comorbidity Index, the Combined Comorbidity Index, and the Johns Hopkins Frailty Index, and were calculated in accordance with instructions provided by the original authors.[27–37] A Johns Hopkins Frailty Index cutoff of 0.20 or greater was defined as frail in accordance with guidance provided in the original article. The Combined Comorbidity Index was included in modeling out of the 3 calculated indices because it has been shown to correlate better with mortality and allowed for separate assessment of age, sex, and race.[27,28] Vital status and date of death were confirmed by internal electronic health record information or the social security death master file and was censored at 2 years after index TTE.

Process-Related Parameters

Natural language processing algorithms and structured database queries were used to extract the names and medical specialty of ordering providers; providers were subsequently categorized as a cardiologist or noncardiologist. Clinical encounters with heart valve team members and/or cardiac surgeons after the index TTE were verified by querying the names of valve specialists against a census of medical encounters for each patient. We used custom algorithms to extract references to the severity of AS from each index TTE report; mentions of AS severity were then classified into nominal categories. In our reporting structure, the mention of aortic stenosis as well as the severity is routinely found in the body of the report rather than in a summary statement.

Aortic Valve Replacement

AVR procedures were determined by querying *Current Procedural Terminology* (*CPT*) codes (TAVR *CPT* codes 33361–33366; SAVR *CPT* codes 33405, 33411) against our institutional SAVR and TAVR databases, which are used to populate the Society for Thoracic Surgery National Database and the Society for Thoracic Surgery/American College of Cardiology TVT Registry. Inconsistencies were settled by manual chart review.

Statistical Analysis

Patient demographics, clinical biomarkers, and echocardiogram data were summarized using scale-appropriate measures for categorical variables (eg, count, percentage) and interval variables (eg, mean±standard deviation). Hedge's *g* was used to estimate the magnitude of standardized mean differences between the patient groups; the φ coefficient was used to evaluate symmetry in distributions of categorical variables. For interpretation, magnitude of differences (*g*/φ values) are interpreted using the following ordinal scale: large (*g*/φ>0.80); moderate-to-large (*g*/φ=0.60–0.79); moderate (*g*/φ=0.40–0.59); small-to-moderate (*g*/φ=0.20–0.39); small (*g*/φ<0.20); and negligible (*g*/φ<0.10).

To account for imbalance in potential confounding factors between patients treated and not treated with AVR, a propensity score approach with inverse probability of treatment weighting was used to standardize populations. Weighted multivariable linear regression was then used to determine average treatment effects on survival. We estimated restricted mean survival times (RMSTs) for each group using a restricted cubic spline model with 4 knots. Briefly, RMST is a robust and more intuitive summary measure of survival than the traditional hazard ratio, especially in the presence of nonproportional hazards. RMST represents the area under the survival function for a specified time horizon $[0-\tau]$ from which an analogous measure of relative risk can be estimated using the ratio of RMST between groups (eg, AVR versus no AVR).

Probability thresholds for statistical significance were set at 0.05 using 2-sided tests; where possible, standard errors were calculated with bootstrapping using 99% CIs and 1000 subsamples. All analyses were conducted using Stata version 16.0 (StataCorp, College Station, TX).

RESULTS

Overall Patient Characteristics

During the study period, 1432 individuals with aortic valve area ≤1.0 cm^2 on TTE were identified (Figure 1). We excluded individuals who had not received additional clinical care at our institution (n=163) or had incomplete data (n=42). Of the 1227 remaining, 340 (27.7%) were inpatients at the time of the index TTE, and 92 (7.5%) were determined to already be in the process of an outpatient AVR evaluation by a valve specialist at the time of the index TTE and were therefore excluded (Table S1). Of the remaining 795 ambulatory patients in the base cohort, 350 (44%) had a likely indication for AVR. Twenty-six patients were excluded from further analysis for receiving an AVR after 1 year but before 2 years after index TTE, which is when survival was censored.

Baseline Clinical Characteristics of Patients With an Indication for AVR

Baseline patient- and process-related characteristics by AVR status are described in Table 1. Overall, 140 patients (43.2%) did not undergo AVR within 1 year of their index TTE, despite having a likely indication for AVR. Among the 184 patients who did undergo AVR, 74 patients (40.2%) underwent SAVR, and 110 patients (59.8%) underwent TAVR. Moderate and small-to-moderate differences were observed between patients in the AVR and no-AVR groups with regard to age (78±8 versus 81±10 years, *g*=0.26 [small-to-moderate difference]); the Combined Comorbidity Index (1.6±2.0 versus 2.7±2.9, *g*=−0.42 [moderate difference]); and the Johns Hopkins Frailty Score (0.16±0.15 versus 0.23±0.19, *g*=−0.41 [moderate difference]), respectively. Only small differences in the prior histories of congestive heart failure, renal failure, and metastatic cancer were observed.

Groups differed across imaging measures of AS severity and cardiac function. Patients who did not undergo AVR averaged lower mean AVG (48±13 versus 35±14 mm Hg, g=−0.87 [large difference]), larger aortic valve area (0.83±0.20 versus 0.77±0.20 cm^2, *g*=0.38 [small-to-moderate difference]), and lower LVEF (59±15 versus 65±12%, *g*=−0.44 [moderate difference]) than patients who did undergo treatment. Differences across these measures were associated with the distribution of AS phenotypes within each group (φ=0.46); we found a larger rate of low-gradient phenotypes among patients who did not undergo AVR (Figure 2).

Process-Specific Factors

Approximately 3 out of every 4 index TTEs were ordered by cardiologists (N=251; 77.5%). We found that AS severity was explicitly qualified as severe in 1 out of every 5 index TTE reports (18.8%). Differences between groups in these 2 variables were small (φ<0.20). Although all patients who underwent AVR had a confirmed encounter with a valve specialist, we found that only 7 out of the 140 patients in the no-AVR group (5%) had such an encounter within a year of their index

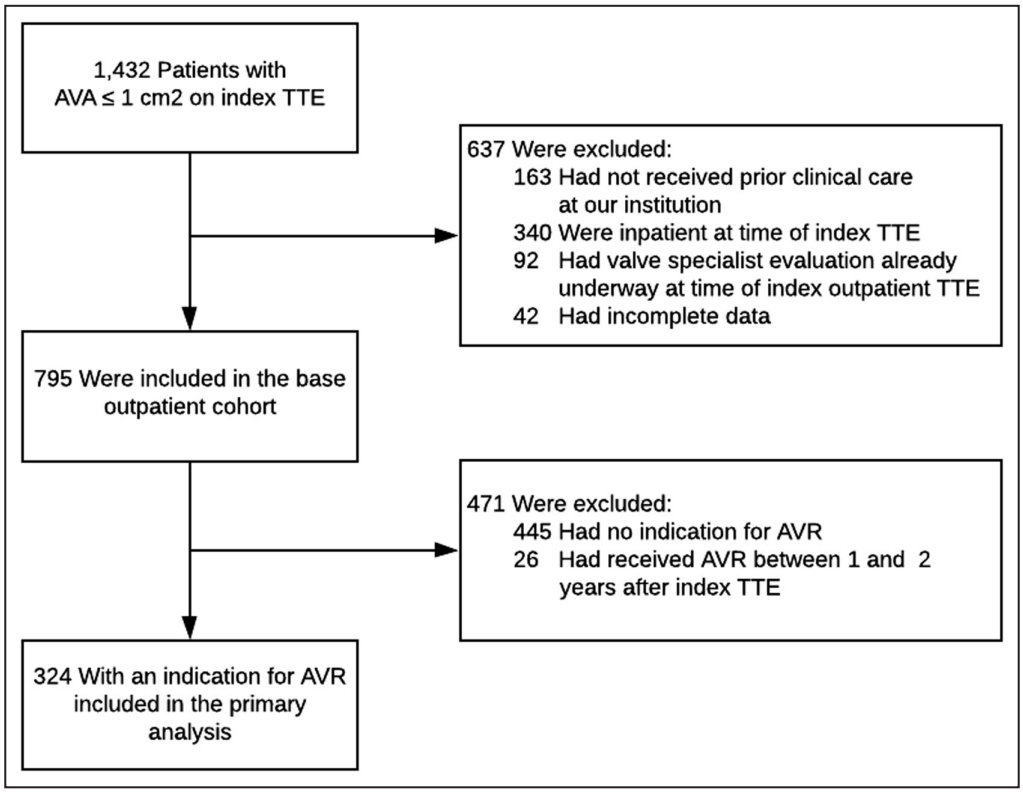

Figure 1. Study flowchart.
AVA indicates aortic valve area; AVR, aortic valve replacement; and TTE, transthoracic echocardiogram.

TTE (φ=0.95 [large difference]). On average, patients who underwent AVR met with a valve specialist within 70 days (95% CI, 59.6–80.4) of their index TTE; in contrast, the 7 patients with a confirmed encounter averaged 101 days from the date of their index TTE (95% CI, 94.6–143.4). For patients who did undergo treatment, the average time to AVR was 156.5 days (95% CI, 142.8–170.2) from the index TTE date.

Predictors of AVR

We found that the odds of undergoing AVR were primarily affected by patients' age, Combined Comorbidity Index score, AS phenotype, and the specialty of their ordering provider (Table 2). Specifically, the odds of undergoing AVR decreased by 76% for patients aged >90 years (OR, 0.24 [95% CI, 0.08–0.69]; *P*=0.01) and by 12% for every point increase on the Combined Comorbidity Index (OR, 0.88 [95% CI, 0.79–0.97]; *P*=0.01). Odds of undergoing AVR differed between low-gradient and high-gradient AS phenotypes; we found that the odds of undergoing treatment were 89% lower for patients with low-flow, low-gradient AS with preserved LVEF (OR, 0.11 [95% CI, 0.06–0.21]; *P*<0.001) and 82% lower for patients with low-gradient AS with reduced LVEF (OR, 0.18 [95% CI, 0.08–0.40]; *P*<0.001) when compared with patients with high-gradient AS with preserved LVEF. Nonetheless, the odds of undergoing AVR increased over 2-fold if the provider who ordered the index TTE was a cardiologist (OR, 2.46 [95% CI, 1.38–4.38]; *P*=0.001).

Mortality and Restricted Mean Survival Times

Inverse probability of treatment weighting balanced covariates between groups, as demonstrated by negligible standardized mean differences, variance ratios close to 1.0, and a nonsignificant result for overidentification (χ^2[13]=7.88, *P*=0.85; Table S2). AVR had a significant effect on mortality. Outcome means suggest an average 28.2% probability of mortality at 730 days had no one undergone AVR versus a 10.3% probability of mortality at 730 days had every patient undergone AVR (Table S3). Thus, the average treatment effect of AVR was a 17.9 percentage point reduction in the probability of mortality at 730 days after the index TTE date. In the untreated group, predictors that independently associated with increased probability of mortality at 730 days included a Combined Comorbidity Score of 3 points or higher. In contrast, the only predictor to associate with decreased probability of mortality was whether the patient had a cardiologist as their ordering provider (β=–1.06, *P*=0.03; Table 3). Predictors independently associated with increased probabilities of mortality in the treated group included a Combined

Table 1. Baseline Patient and Process Related Characteristics

Variable	Overall n=324	Aortic valve replacement n=184	No aortic valve replacement n=140	Standardized mean differences	
				g (interval) φ (categorical)	Magnitude
Demographics					
Age, y	79.3±9.7	78.2±8.7	80.7±10.7	−0.26	Small-to-moderate
Male sex	57.4%	56.5%	58.6%	−0.02	Negligible
White	92.3%	92.4%	92.1%	0.01	Negligible
Married	61.1%	62.0%	60.%	0.02	Negligible
Veteran	27.5%	25.0%	30.7%	−0.06	Negligible
Comorbidities					
Coronary artery disease	79.9%	82.6%	76.4%	0.08	Negligible
Previous myocardial infarction	6.5%	6.5%	6.4%	0.01	Negligible
Peripheral vascular disease	17.9%	17.9%	17.9%	0.01	Negligible
Congestive heart failure	28.4%	21.2%	37.9%	−0.18	Small
Atrial fibrillation	56.8%	59.2%	53.6%	0.06	Negligible
Chronic pulmonary disease	11.1%	9.2%	13.6%	−0.09	Negligible
Renal failure	14.5%	11.4%	18.6%	−0.10	Small
Liver disease	3.7%	2.2%	5.7%	−0.09	Negligible
Metastatic cancer	3.4%	1.1%	6.4%	−0.14	Small
Charlson Comorbidity Index	1.3±1.8	1.1±1.8	1.5±2.0	−0.26	Small-to-moderate
Combined Comorbidity Index	2.1±2.6	1.6±2.0	2.7±2.9	−0.42	Moderate
Johns Hopkins Frailty Index	0.19±0.17	0.16±0.15	0.23±0.19	−0.41	Moderate
Frail, ≥0.2	65.7%	72.3%	57.1%	0.16	Small
Serum laboratory data					
Hematocrit, %	38.2±5.4	38.8±5.4	37.1±5.2	0.31	Small-to-moderate
Albumin, g/dL	4.1±0.5	4.2±0.5	4.0±0.5	0.40	moderate
Creatinine, mg/dL	1.3±1.0	1.2±0.9	1.4±1.2	−0.20	Small-to-moderate
Echocardiographic findings					
Aortic valve area, cm^2	0.80±0.2	0.77±0.2	0.83±0 .2	−0.38	Small-to-moderate
Mean aortic valve gradient, mm Hg	42.5±15.1	48.2±13.4	35.1±13.9	0.87	Large
Mean LVEF, %	61.9±13.9	64.6±12.2	58.5±15.1	0.44	Moderate
Stroke volume index, mL/m^2	35.8±9.6	37.1±9.6	34.2±9.4	0.30	Small-to-moderate
Bicuspid	5.6%	8.2%	2.1%	0.20	Small-to-moderate
Phenotype				0.46	Moderate
High gradient with preserved LVEF	59.9%	78.3%	35.7%		
High gradient with reduced LVEF	3.1%	3.8%	2.1%		
Low gradient with reduced LVEF	14.2%	7.6%	22.9%		
Low gradient with preserved LVEF	22.8%	10.3%	39.3%		
Process characteristics					
TTE ordering provider is cardiologist	77.5%	81.0%	72.9%	0.10	Small
TTE report qualification of aortic stenosis				0.11	Small
Severe	18.8%	22.3%	14.3%		
Nonsevere	4.9%	3.8%	6.4%		
No qualification provided	76.2%	73.9%	79.3%		
Valve specialist evaluation	59.0%	100.0%	5.0%	0.95	Large
Days between TTE and valve specialist encounter	78±82	70±71	101±103	−0.38	Small-to-moderate

LVEF indicates left ventricular ejection fraction; and TTE, transthoracic echocardiogram.

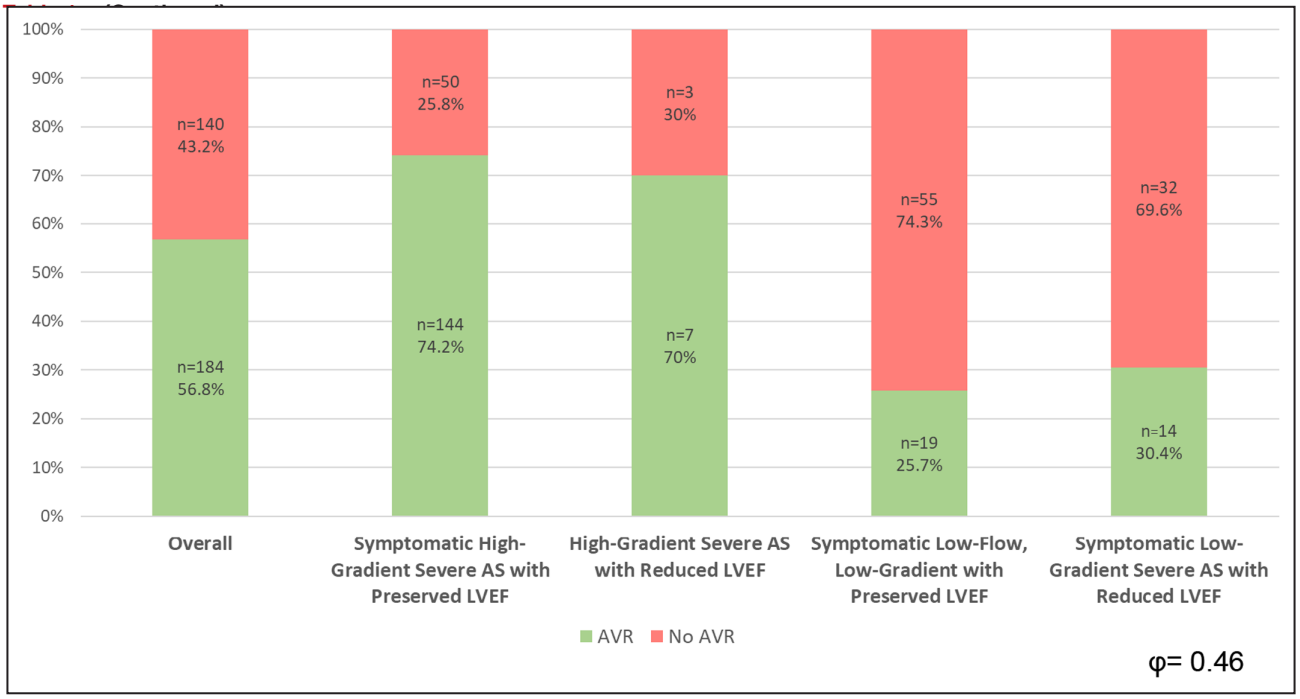

Figure 2. Percentage of patients with indication for aortic valve replacement who received aortic valve replacement, by phenotype.
AS indicates aortic stenosis; AVR, aortic valve replacement; and LVEF, left ventricular ejection fraction.

Comorbidity Score of 3 to 6 points; a score of 7 points or higher had an inverse effect (Table 3).

To better characterize the treatment effect of AVR on mortality, we calculated unadjusted and adjusted RMST at τ=730 days for both groups (Table 3; Figure 3). Patients who underwent AVR within 1 year of their index TTE gained an average of 85.8 days of life (95% CI, 40.9–130.6; *P*<0.001) at τ=730 days compared with patients who did not undergo AVR, after adjusting for covariates. RMST at τ=730 days differed between AS phenotypes and ranged from a gain of 67.5 days of life (95% CI, 30.4–104.5; *P*<0.001) in patients with low-flow, low-gradient AS with preserved LVEF to a gain of 103.8 days of life (95% CI, 45.1–162.6; *P*=0.001; Table 4) in patients with low-gradient AS with reduced LVEF (Figure 4).

Reasons for No AVR in Patients With an Indication for AVR

Among the 140 patients with a likely indication for AVR who did not receive one, 108 (77.1%) had heart failure symptoms, 36 (25.7%) had angina, and 24 (17.1%) had syncope/presyncope.

Thirty-one patients (22%) did not undergo AVR because the provider was concerned for symptomatic, severe AS but deferred further evaluation (watchful waiting); 21 patients (15%) did not undergo AVR because the provider did not think AS was severe, 18 patients (12.8%) did not undergo AVR because the provider did not attribute symptoms to AS, 15 patients (11%) did not undergo AVR because the patient declined treatment, and 10 patients (7%) did not undergo AVR because the provider determined that AVR was futile. No cases of provider determination of futility or patient declining AVR occurred in conjunction with a valve specialist evaluation. We did not find evidence of an assessment for AS for 14 patients (10%) before or after their index TTE, 28 patients (20%) had an AS evaluation listed as underway but had not yet been completed at the end of the study period, and 3 patients (2%) were lost to follow up.

Of the patients who did not receive AVR, 33 (23.6%) died within 1 year of index TTE. The patients who died were frailer with a higher comorbidity index (Table S4). None of these patients were evaluated by a valve specialist. Seven (21%) of these patients did not have any assessment of their AS in the chart before or after the index TTE. In 6 (18%) of these patients, the provider was concerned for symptomatic, severe AS but deferred further evaluation (watchful waiting); in total, the entire "watchful waiting" subset had a 19% 1-year mortality. Only 5 (15%) of the 33 who died within 1 year without AVR did not receive AVR for futility reasons.

DISCUSSION

Within a contemporary cohort of ambulatory patients treated at a large academic medical center with

Table 2. Clinical Parameters Associated With Undergoing Aortic Valve Replacement

Parameter	Odds ratio	Significance	95% CI lower	95% CI upper
Sex: women	1.21	0.42	0.76	1.94
Race: non-Hispanic White	1.44	0.33	0.69	3.00
Age: <70 y	(Reference group)			
Age: 70–74 y	0.95	0.91	0.39	2.35
Age: 75–79 y	1.66	0.27	0.68	4.04
Age: 80–84 y	1.20	0.68	0.50	2.87
Age: 85–89 y	0.96	0.91	0.45	2.02
Age: >90 y	0.24	0.01*	0.08	0.69
Combined Comorbidity Index score	0.88	0.01*	0.79	0.97
High gradient, preserved LVEF	(Reference group)			
High gradient, reduced LVEF	1.03	0.97	0.21	4.90
Low gradient, preserved LVEF	0.18	<0.01*	0.08	0.40
Low gradient, reduced LVEF	0.11	<0.01*	0.06	0.21
Ordering provider: cardiologist	2.46	<0.01*	1.38	4.38
TTE report: severe AS	1.30	0.48	0.63	2.67

AS indicates aortic stenosis; LVEF, left ventricular ejection fraction; and TTE, transthoracic echocardiogram.
*$P<0.05$.

high-volume surgical and transcatheter AVR programs, we report a series of key observations on the management of symptomatic severe AS. Specifically, we found the following: (1) Forty-three percent of patients with a likely indication for AVR, who had not yet been referred to a valve specialist, did not receive AVR. (2) Patients with low-gradient severe AS are markedly less likely to undergo AVR. (3) The likelihood of AVR was 2-fold higher in patients in whom the index TTE was ordered by a cardiologist. (4) A myriad of diverse reasons for no AVR were observed without a sole dominant reason or explanation. (5) In patients not receiving AVR within 12 months of an index TTE showing severe AS, only a small fraction (5%) were seen by a heart valve team

Table 3. Survival Modifying Effects by Aortic Valve Replacement Status

	β	Significance	95% CI Lower	95% CI Upper
Survival modifying effects among non–aortic valve replacement recipients				
Sex: women	−0.30	0.49	−1.16	0.56
Race: non-Hispanic White	0.27	0.73	−1.32	1.87
Age	−0.01	0.45	−0.02	0.01
Combined Comorbidity Index score: 0 points	(Reference group)			
Combined Comorbidity Index score: 1–2 points	−0.43	0.59	−2.03	1.16
Combined Comorbidity Index score: 3–4 points	1.40	0.02*	0.20	2.59
Combined Comorbidity Index score: 5–6 points	2.12	<0.01*	0.62	3.63
Combined Comorbidity Index score: ≥7 points	2.01	<0.01*	0.74	3.28
Ordering provider: cardiologist	−1.06	0.03*	−2.08	−0.05
Survival modifying effects among aortic valve replacement recipients				
Sex: women	−1.18	0.07	−2.44	0.09
Race: non-Hispanic White	−0.33	0.75	−2.37	1.70
Age	−0.01	0.31	−0.04	0.01
Combined Comorbidity Index score: 0 points	(Reference group)			
Combined Comorbidity Index score: 1–2 points	0.36	0.66	−1.26	1.98
Combined Comorbidity Index score: 3–4 points	2.72	<0.01*	1.23	4.21
Combined Comorbidity Index score: 5–6 points	2.12	0.02*	0.28	3.95
Combined Comorbidity Index score: ≥7 points	−5.03	<0.01*	−6.23	−3.82
Ordering provider: cardiologist	−0.09	0.91	−1.77	1.58

*$P<0.05$.

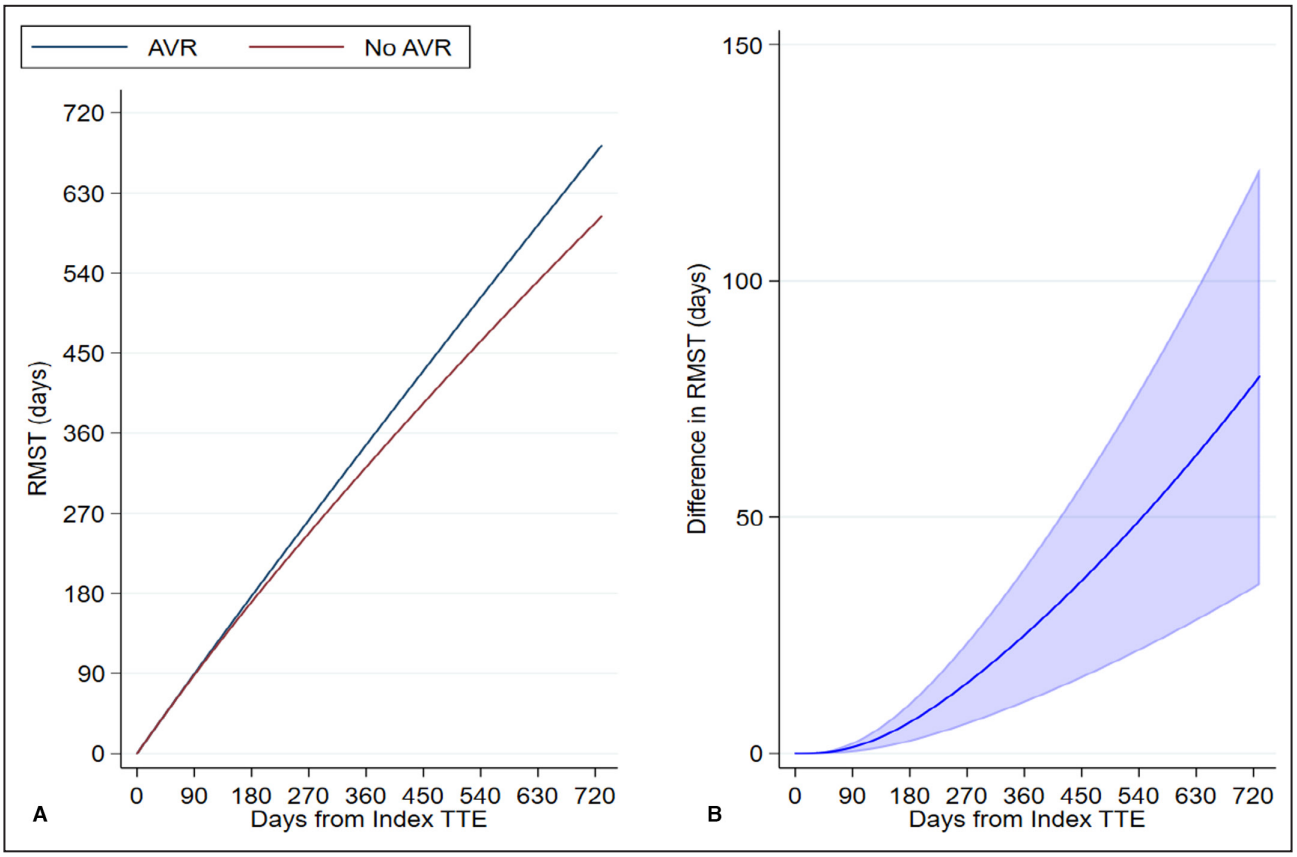

Figure 3. Restricted mean survival times by AVR status.
A, Adjusted RMST is shown for patients by AVR status over time from the index TTE. **B**, Difference in RMST between the AVR and no-AVR groups is depicted over time from index TTE. At τ=730 days, patients who underwent AVR within 1 year of their index TTE gained an average of 85.8 days of life (95% CI, 40.9–130.6; P<0.001) compared with patients who did not undergo AVR, after adjusting for covariates. Shaded area represents 95% CI. AVR indicates aortic valve replacement; RMST, restricted mean survival time; and TTE, transthoracic echocardiogram.

member. (6) In patients with an indication for AVR, AVR has a strong effect on mortality, resulting in ≈3 months of life gained at 730 days. (7) AVR resulted in a survival benefit in those with low and high gradients and also preserved or reduced LVEF.

In 2003, the Euro Heart Survey on vaulvular heart disease described the management of patients with valvular heart disease and demonstrated that 72 out of 216 (33%) of patients aged ≥75 years followed in an outpatient setting with severe, symptomatic AS did not receive AVR.[11] Our study reveals that over 15 years later and after the introduction of TAVR, ≈40% of patients with severe AS and an indication for AVR do not receive AVR within a 12-month period. It is notable that we excluded patients in whom the index TTE was performed as part of the AVR evaluation to specifically characterize the management of newly recognized severe AS. This observation is meaningful given the known dismal survival associated with medical management of symptomatic severe AS and also with delays to AVR.[7,14,38] Here, receiving AVR within 12 months of index TTE was associated with 69% lower risk of death within 2 years and an average of 3 months of life gained.

We found that patients with low-gradient AS phenotypes were 80% to 90% less likely to receive an AVR than those with the quintessential high-gradient, preserved ejection fraction phenotype, despite adjusting for age, comorbidities, and process-related variables. Clinical decision making for low-gradient AS phenotypes is challenging, with the integration of multimodality imaging, invasive diagnostic testing, and multidisciplinary clinical assessment often necessary to identify who may truly benefit from AVR.[39] In part, this complexity justifies the need for heart team evaluation for patients with a potential indication for AVR.[5] Although in our analysis it is possible that a proportion of included patients with low-gradient phenotypes may have had pseudo-severe AS and therefore may not have had a true indication for AVR, AVR was associated with robust improvements in survival across all AS phenotypes, including low-gradient subtypes. The low-gradient, reduced LVEF phenotype gained the greatest survival time from AVR. Several studies have similarly demonstrated that patients with low-gradient severe AS, whether classical low-gradient AS with reduced LVEF or paradoxical low-flow, low-gradient AS

Table 4. Restricted Mean Survival Times

	No AVR	AVR	Difference, τ=730 days	
			Estimate	*P* value
Overall				
Unadjusted RMST	577.0 days (536.3–617.7)	695.6 days (677.6–713.6)	118.6 days (73.6–163.6)	<0.001
Adjusted RMST†	600.9 days (564.6–637.4)	686.7 days (664.1–709.4)	85.8 days (40.9–130.6)	<0.001
By AS phenotype				
High gradient, preserved LVEF	600.2 days (549.3–651.2)	686.9 days (663.5–710.5)	86.7 days (35.5–137.9)	0.001
High gradient, reduced LVEF	*	*	*	*
Low gradient, preserved LVEF	630.9 days (585.8–676.1)	698.5 days (673.4–723.6)	67.5 days (30.5–104.5)	<0.001
Low gradient, reduced LVEF	571.4 days (508.7–634.1)	675.3 days (636.9–713.6)	103.8 days (45.1–162.6)	0.001

AS indicates aortic stenosis; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; and RMST, restricted mean survival times.
*Values not shown because of insufficient number of cases.
†Adjusted for sex, race, age group, Combined Comorbidity Index score range, AS phenotype, and type of provider.

with preserved LVEF, benefit from AVR.[40–42] Together, these observations emphasize the need for meticulous evaluation of patients with low-gradient severe AS and highlight the adverse clinical consequences of underestimating AS severity in such patients.

We evaluated the impact of several process-related factors on the likelihood of undergoing AVR and identified several potential targets for quality improvement initiatives. We found that the medical specialty of the provider ordering the TTE was impactful. Patients with an indication for AVR were twice as likely to receive an AVR if the ordering provider was a cardiologist. Efforts to bolster referral of patients with severe AS to cardiovascular specialists are therefore needed. Improved provider education and use of an electronic health record and echocardiography report alerts to highlight severe AS, and other actionable echocardiographic findings serve as potential interventions. We also found that of patients who did not get AVR, only 5% had an encounter with a heart valve team member. Whether earlier referral to a valve team member, especially in the complex low-gradient severe AS subgroup, would result in higher rates of appropriate AVR use is unclear, but such a practice is supported by clinical practice guidelines and by our study results and should be encouraged.[5] Furthermore, considering that over half of those who did not receive AVR have low-gradient phenotypes, and given the previously stated complexity of determining an indication for AVR in the low-gradient population, the need for multidisciplinary valve team involvement in decisions to not offer AVR is extremely relevant. Finally, determinations of AVR futility and patient refusal of AVR did not occur in conjunction with valve specialist evaluation for any patient in this study. It is therefore unclear whether patients were presented with and understood the natural history of severe AS, appreciated the associated morbidity and mortality risk of untreated symptomatic severe AS, or were informed of the risks, benefits, and alternatives to SAVR and TAVR. As endorsed by clinical practice guidelines, the choice of valve intervention, arguably also including the refusal of intervention, for severe valvular heart disease requires patient and family education by the heart valve team and should incorporate a shared decision-making process that accounts for the patient's values and preferences.[5] Education of primary care providers is therefore needed to encourage erring on the side of referral for patients with an indication for AVR to heart valve teams, even in cases when a patient appears disinterested in intervention or when the medical benefits are in question.

Our study must be interpreted in the context of several limitations. First, this study is a retrospective analysis. Symptom status was completed by manual chart review and was subject to accurate and complete clinical documentation. Parameters used to define severe AS were exclusive to the index TTE, and the potential for changes in measures of AS severity in subsequent diagnostic tests, including subsequent TTEs, was not evaluated. Stroke volume index calculations by Doppler left ventricular outflow track measurements were not available, so stroke volume index was calculated at the time of data acquisition by the Teichholtz method, which has been shown to correlate well with cardiac magnetic resonance volumetric stroke volume in the presence of aortic valve abnormalities.[43] Patients requiring cardiac surgery who have moderate AS have an indication for AVR, but this indication was not considered in our study given the focus on AVR use for symptomatic severe AS. Patients who had an AVR were presumed to have an appropriate indication, which may have included additional

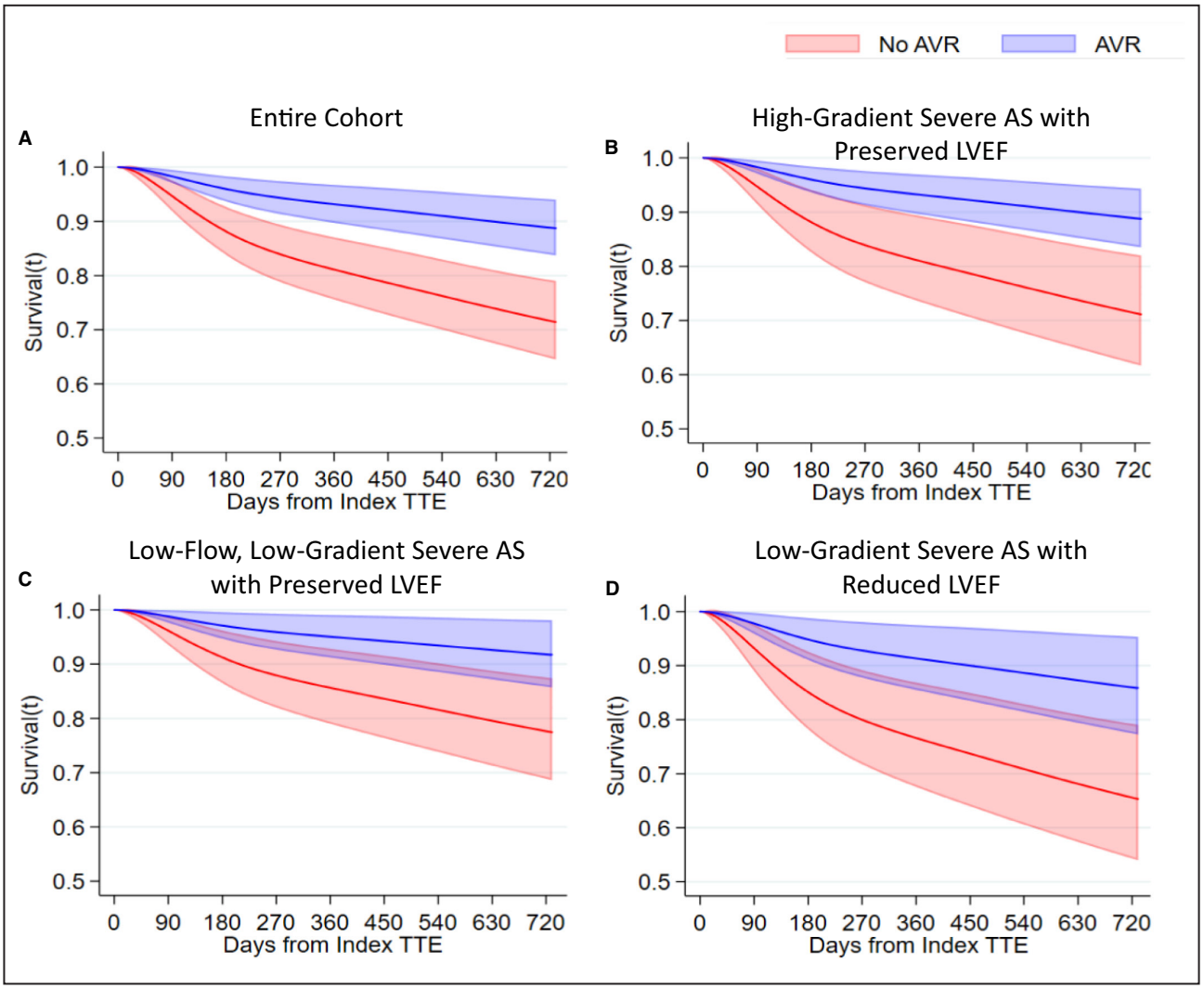

Figure 4. Survival with and without AVR across AS phenotypes.
Adjusted time-to-event survival curves are shown for (**A**) the entire cohort, (**B**) high-gradient severe AS with preserved LVEF, (**C**) low-flow, low-gradient severe AS with preserved LVEF, and (**D**) low-gradient severe AS with reduced LVEF by AVR status. In each AS phenotype, AVR resulted in significantly improved survival. High-gradient severe AS with reduced LVEF is not shown because of insufficient sample size. Shaded area represents 95% CI. AS indicates aortic stenosis; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; and TTE, transthoracic echocardiogram.

indications outside of the scope of the ones considered for this study. Comorbidities and indices were calculated using claims-based data, which are subject to misclassification bias and diagnosis-timing limitations, although the Combined Comorbidity Index was chosen in particular because of its validation in predicting mortality.[27,28,44,45] Patients who were already in the process of AVR referral were excluded, and this was defined by the presence of a clinical encounter with a cardiac surgeon within 60 days of the index TTE date. Patients with urgent clinical conditions may have been referred within a shorter time period, which would have led to an underestimation of AVR use. Additionally, AVR occurrence was determined by billing codes within the Partners HealthCare System, and valve replacements at outside facilities were not considered. However, we excluded patients who did not previously receive care at MGH in the hopes of mitigating this limitation. Lastly, this study was performed at a single high-volume major academic center, and the findings may not be generalizable to all practice settings. AVR use may be less in practice settings that do not have internal valve specialists.

CONCLUSIONS

Within a large academic medical center, the proportion of ambulatory patients with severe AS and a likely indication for AVR who do not receive AVR remains significant despite the advent and expansion of TAVR.

The likelihood of undergoing AVR was strongly associated with mean aortic valve gradient, with AVR less likely to occur in those with low-gradient severe AS phenotypes, and also by the medical specialty of the provider who ordered the TTE. Given the considerable reduction in mortality conferred by AVR in patients with symptomatic severe AS, efforts are needed to maximize the recognition of severe AS, especially low-gradient subtypes, and to encourage patient referral to multidisciplinary heart valve teams to ensure that treatment decisions are made using a shared decision-making process. These observations should serve as a foundation to inform future efforts to optimize processes surrounding the recognition and management of severe AS with the aim to improve patient outcomes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Patient and Process Related Characteristics of Patients already in Process of Valve Specialist Outpatient Evaluation.

Variable	**Overall n=92**	**Aortic Valve Replacement n=74**	**No Aortic Valve Replacement n=18**	**Standardized Mean Differences**	
				g(interval) φ(categorical)	Magnitude
Demographics					
Age, year	75.3 (±11.1)	76.4 (±10.3)	70.9 (±13.4)	.50	Moderate
Male sex	57.6%	58.1%	55.6%	.20	Small-to-moderate
Caucasian	90.2%	91.9%	83.3%	.11	Small
Comorbidities					
Coronary Artery Disease	75%	82.4%	44.4%	.35	Small-to-moderate
Previous Myocardial Infarction	15.2%	14.9%	16.7%	-.02	Negligible
Peripheral Vascular Disease	54.3%	55.4%	50.0%	.04	Negligible
Congestive Heart Failure	76.1%	81.1%	55.7%	.24	Small-to-moderate
Atrial Fibrillation	56.5%	62.2%	33.3%	.23	Small-to-moderate
Chronic Pulmonary Disease	32.6%	31.1%	38.9%	-.07	Negligible
Renal Failure	34.8%	37.8%	22.2%	.13	Small
Liver Disease	7.6%	9.5%	0	.14	Small
Metastatic Cancer	3.3%	4.1%	0	.09	Negligible
Charlson Comorbidity Index	4.5 (±2.4)	4.9 (±2.2)	2.6 (±2.3)	1.04	Large
Combined Comorbidity Index	5.8 (±3.2)	6.4 (±2.9)	3.5 (±3.5)	.95	Large
Serum Laboratory Data					
Hematocrit, %	38.9 (±5.5)	39.3 (±5.2)	36.7 (±7.1)	.48	Moderate
Albumin, g/dL	4.2 (±0.4)	4.2 (±0.4)	3.6 (±0.5)	1.60	Large
Creatinine, mg/dL	1.1 (±0.4)	1.1 (±0.3)	1.2 (±0.5)	.16	Small
Echocardiographic Findings					
Aortic Valve Area, cm^2	0.78 (±0.15)	0.77 (±0.15)	0.8 (±0.16)	.18	Small
Mean Aortic Valve Gradient, mmHg	48.9 (±17.5)	50.2 (± 16.9)	43.8 (±19.5)	.37	Small-to-moderate
Mean LVEF, %	63.7 (±13.6)	64.5 (±13.1)	60.2 (±15.2)	.32	Small-to-moderate

Stroke Volume Index, mL/ m^2	28.3 (±8.1)	27.8 (±7.7)	30.1 (±9.8)	.27	Small-to-moderate
Bicuspid	10.9%	10.8%	11.1%	-.004	Negligible
Phenotype				.18	Small
High-Gradient with Preserved LVEF	62%	66.2%	44.4%		
High-Gradient with Reduced LVEF	5.4%	5.4%	5.6%		
Low-Gradient with Reduced LVEF	7.6%	6.8%	11.1%		
Low-Gradient with Preserved LVEF	25%	21.6%	38.9%		

LVEF = left ventricular ejection fraction.

Table S2. Covariate Balancing after Inverse Probability of Treatment Weighting.

	Standardized Differences		Variance Ratio	
	Raw	Weighted	Raw	Weighted
Sex: Female	-0.04	-0.02	1.01	1.00
Race: non-Hispanic White	0.01	-0.03	0.97	1.12
Age: 70-74 years	-0.01	-0.04	0.98	0.93
Age: 75-79 years	0.21	-0.04	1.41	0.94
Age: 80-84 years	0.17	-0.01	1.34	0.98
Age: 85-89 years	-0.05	-0.03	0.93	0.96
Age: $\geq$ 90 years	-0.46	0.06	0.33	1.14
Combined Comorbidity Index Score	-0.45	-0.09	0.48	0.64
High-Gradient, Reduced LVEF	0.10	-0.05	1.74	0.77
Low-Gradient, Preserved LVEF	-0.43	0.02	0.40	1.03
Low-Gradient, Reduced LVEF	-0.71	-0.01	0.39	0.99
Ordering Provider: Cardiologist	0.19	0.03	0.78	0.96
TTE Report: Severe AS	0.21	-0.07	1.41	0.90

Overidentification Test: $(\chi^2(13) = 7.88; P = 0.85)$. LVEF = left ventricular ejection fraction; TTE = transthoracic echocardiogram; AS = aortic stenosis.

Table S3. Probability of mortality by 730 days after index TTE.

	β	Sig.	95% CI Lower	95% CI Upper
Probability of Mortality by 730 days				
No AVR	0.28	<0.001	**0.21**	**0.35**
AVR	0.10	<0.001	**0.06**	**0.17**

TTE = transthoracic echocardiogram; AVR = aortic valve replacement.

Table S4. Baseline Patient and Process Related Characteristics of Patients Who Did Not Receive AVR within 1 year of index TTE.

Variable	**Overall n=140**	**Deceased at 1 year n=33 (24%)**	**Alive at 1 year n=107 (76%)**	**Standardized Mean Differences**	
				g(interval) φ(categorical)	Magnitude
Demographics					
Age, year	80.7 (±10.7)	82.8 (±10.5)	80 (±10.8)	.26	Small-to-Moderate
Male sex	58.6%	66.7%	56.1%	-.09	Negligible
Caucasian	92.1%	90.9%	92.5%	.07	Negligible
Married	60.0%	66.7%	57.9%	.08	Negligible
Veteran	30.7%	39.4%	28%	-.10	Small
Comorbidities					
Coronary Artery Disease	76.4%	78.8%	75.7%	-.03	Negligible
Previous Myocardial Infarction	12.1%	12.1%	12.1%	.00	Negligible
Peripheral Vascular Disease	17.9%	15.1%	18.7%	.04	Negligible
Congestive Heart Failure	37.9%	54.5%	32.7%	-.19	Small
Atrial Fibrillation	53.6%	69.7%	48.6%	-.18	Small
Chronic Pulmonary Disease	13.6%	15.1%	13.1%	-.03	Negligible
Renal Failure	18.6%	24.2%	16.8%	-.08	Negligible
Liver Disease	5.7%	6.1%	5.6%	-.01	Negligible
Metastatic Cancer	6.4%	15.1%	3.7%	-.19	Small
Charlson Comorbidity Index	1.45 (±2.0)	1.7 (±2.3)	1.4 (±1.9)	.18	Small
Combined Comorbidity Index	2.7 (±2.9)	4.1 (±2.9)	2.3 (±2.9)	.60	Moderate-to-Large
John Hopkins Frailty Index	0.23 (±0.19)	0.29 (±0.25)	0.21 (±0.17)	.43	Moderate
Frail (≥ 0.2)	42.9%	54.5%	39.2%	-.13	Small
Serum Laboratory Data					
Hematocrit, %	37.1 (±5.2)	36.3 (±5.5)	37.4 (±5.1)	.21	Small-to-Moderate
Albumin, g/dL	4.0 (±.5)	3.7 (±0.6)	4 (±0.4)	.56	Moderate
Creatinine, mg/dL	1.4 (±1.2)	1.9 (±1.7)	1.2 (±0.9)	.58	Moderate
Echocardiographic Findings					

Aortic Valve Area, cm^2	0.83 (±0.2)	0.83 (±0.2)	0.83 (±0.2)	.02	Negligible
Mean Aortic Valve Gradient, mmHg	35.1 (±13.9)	37.2 (±14.4)	34.4 (±13.7)	.20	Small-to-Moderate
Mean LVEF, %	58.5 (±15.1)	55.1 (±14.3)	59.5 (±15.3)	.29	Small-to-Moderate
Stroke Volume Index, mL/ m^2	34.2 (±9.4)	36.9 (±11.2)	33.3 (±8.7)	.39	Small-to-Moderate
Bicuspid	2.1%	0	2.8%		
Phenotype					
High-Gradient with Preserved LVEF	35.7%	48.5%	31.7%		
High-Gradient with Reduced LVEF	2.1%	0	2.8%		
Low-Gradient with Reduced LVEF	22.9%	30.3%	20.5%		
Low-Gradient with Preserved LVEF	39.3%	21.2%	44.9%		
Process Characteristics					
TTE Ordering Provider is Cardiologist	72.9%	54.5%	78.5%	.23	Small-to-Moderate
TTE Report Qualification of Aortic Stenosis				.11	Small
Severe	14.3%	21.2%	12.1%		
Non-Severe	6.4%	6.1%	6.5%		
No Qualification Provided	79.3%	72.7%	81.3%		
Valve Specialist Evaluation	5.0%	0	6.5%	-.13	Small

AVR = aortic valve replacement; TTE = transthoracic echocardiogram; LVEF = left ventricular ejection fraction.