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 $\leq 1.0$ 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). 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. Although potentially lifesaving, past studies have estimated that up to a third of patients with an indication for AVR do not...
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.

**Nonstandard Abbreviations and Acronyms**

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

undergo treatment10–12, 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.14,18–22 Nevertheless, recent studies
was specifically examined by Flannery et al. They reviewed a cohort of patients who underwent AVR within 1 year of their 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. 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. 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 $\phi$ coefficient was used to evaluate symmetry in distributions of categorical variables. For interpretation, magnitude of differences ($g/\phi$ values) are interpreted using the following ordinal scale: large ($g/\phi>0.80$); moderate-to-large ($g/\phi=0.60–0.79$); moderate ($g/\phi=0.40–0.59$); small-to-moderate ($g/\phi=0.20–0.39$); small ($g/\phi<0.20$); and negligible ($g/\phi<0.10$).

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 cm² 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 cm², $g=0.38$ [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 ($\phi=0.48$); 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 ($\phi<0.20$). 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
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 (χ²[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

![Flowchart](image)
### 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, cm²            | 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/m²        | 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.
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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 $\tau=730$ 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 $\tau=730$ days compared with patients who did not undergo AVR, after adjusting for covariates. RMST at $\tau=730$ 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 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
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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 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.

### Table 3. Survival Modifying Effects by Aortic Valve Replacement Status

| Parameter                        | 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) | 0.03       | 0.31         | −0.04        | 0.01         |
| 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.
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 valvular 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

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.
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 tract 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

| Table 4. Restricted Mean Survival Times |
|----------------------------------------|
| **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 (564.8–637.4) | 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 (549.3–581.2) | 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 (505.7–634.1) | 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.
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.\textsuperscript{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.

**REFERENCES**

1. Nkomo VT, Gardin JM, Skelton TN, Gottlieber JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8

2. Otto CM, Prendergast B. Aortic-valve stenosis—from patients at risk to severe valve obstruction. *N Engl J Med*. 2014;371:744–756. doi: 10.1056/NEJMr1313875

3. Osnbrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62:1002–1012. doi: 10.1016/j.jacc.2013.05.015

4. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Golstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography.

5. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e22–e627. doi: 10.1161/CIR.0000000000000923

6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O’Gara PT, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–e1195. doi: 10.1161/CIR.0000000000000503

7. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation*. 1968;38:61–67. doi: 10.1161/01.CIR.38.1.61

8. Braunwald E. On the natural history of severe aortic stenosis. *J Am Coll Cardiol*. 1990;15:1018–1020. doi: 10.1016/0735-1097(90)90235-H

9. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg*. 2006;82:2111–2115. doi: 10.1016/j.athoracsur.2006.07.048

10. Jung B, Baron G, Butchart EG, Delahaye F, Gohle-Bärwolf C, Levang CW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro heart survey on valvular heart disease. *Eur Heart J*. 2003;24:1231–1243. doi: 10.1016/S0195-668X(03)00201-X

11. Jung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohle-Bärwolf C, Boersma E, Flaude P, Vahanian A, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J*. 2005;26:2714–2720. doi: 10.1093/eurheartj/ehi471

12. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD Jr, Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement: the potential role of subjectively overestimated operative risk. *Circ Cardiovasc Qual Outcomes*. 2009;2:533–539. doi: 10.1161/CIRCOUTCOMES.108.848259

13. Clark MA, Arnold SV, Duhag FY, Thompson AK, Keyes MJ, Svensson LG, Bonow RO, Stockwell BT, Cohen DJ. Five-year clinical and economic outcomes among patients with medically managed severe aortic stenosis: results from a Medicare claims analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5:697–704. doi: 10.1161/CIRCOUTCOMES.112.966002

14. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana OP, Markar RR, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;362:1597–1607. doi: 10.1056/NEJMoa090232

15. Bouma BJ, van Den Brink BB, van Der Meulen JH, Verheul HA, Cheriex EC, Hamer HP, Dekker E, Lie KI, Tijssen JG. To operate or not on elderly patients with atrial fibrillation: the decision and its consequences. *Heart*. 1999;82:143–148. doi: 10.1136/hrt.82.2.143

16. Bach DS, Cinimo N, Deeb GM. Unoperated patients with severe aortic stenosis. *J Am Coll Cardiol*. 2007;50:2018–2019. doi: 10.1016/j.jacc.2007.08.011

17. Bach DS. Prevalence and characteristics of unoperated patients with severe aortic stenosis. *J Heart Valve Dis*. 2011;20:284–291.

18. Herrmann HC, Thourani VH, Kodali SK, Makkar RR, Szeto WY, Anwaruddin S, Desai N, Lim S, Malaisrie SC, Kereiakes DJ, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. *Circulation*. 2016;134:130–140. doi: 10.1161/CIRCULATIONAHA.116.022797

19. Popma JJ, Deeb GM, Yakovub SJ, Muntaz M, Gada H, O’Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715. doi: 10.1056/NEJMoa1816885

20. Mack MJ, Leon MB, Tousari VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. doi: 10.1056/NEJMoa1814052

21. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana OP, Markar RR, et al. Transcatheter...
versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187–2198. doi: 10.1056/NEJMoa1103510
22. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609–1620. doi: 10.1056/NEJMoa1514816
23. Tang L, Gössl M, Ahmed A, Garberich R, Bradley SM, Nikura H, Witt D, Pedersen WR, Bae R, Lesser JR, et al. Contemporary reasons and clinical outcomes for patients with severe, symptomatic aortic stenosis not undergoing aortic valve replacement. Circ Cardiovasc Interv. 2018;11:e007220. doi: 10.1161/CIRCINTERVENTIONS.118.007220
24. Frey N, Steeds RP, Rudolph TK, Thambipillay J, Serra A, Schulz E, Maly J, Aiello M, Lloyd G, Bortone AS, et al. Symptoms, disease severity and treatment of adults with a new diagnosis of severe aortic stenosis. Heart. 2019;105:1709–1716. doi: 10.1136/heartjnl-2019-314940
25. Delgado V, Clavel MA, Hahn RT, Gillam L, Bax J, Sengupta PP, Pibarot P. How do we reconcile echocardiography, computed tomography, and hybrid imaging in assessing discordant grading of aortic stenosis severity? JACC Cardiovasc Imaging. 2018;12:267–282. doi: 10.1016/j.jcmg.2018.11.027
26. Clavel M-A, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Aracoza PA, Micheletta HI, Cuffe C, Larose E, Capoulade R, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62:2329–2338. doi: 10.1016/j.jacc.2013.08.1621
27. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64:749–759. doi: 10.1016/j.jclinepi.2010.10.004
28. Simard M, Sirois C, Candas B. Validation of the combined comorbidity index of Charlson and Elkhourieh to predict 30-day mortality across ICD-9 and ICD-10. Med Care. 2018;56:441–447. doi: 10.1097/MLR.0000000000000905
29. Kundu H, Valsodottir LR, Popma JJ, Cohen DJ, Strom JB, Cappola R, et al. The established frailty phenotype. J Am Heart Assoc. 2017;6:100072. doi: 10.1161/JAHA.117.000824
30. Martinez-BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and safety analysis. Circulation. 2018;138:483–493. doi: 10.1161/CIRCULATIONAHA.117.033432
31. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. J Am Coll Cardiol. 2012;60:1845–1853. doi: 10.1016/j.jacc.2012.06.051
32. Saybolt MD, Fiorilli PN, Gertz ZM, Herrmann HC. Low-flow severe aortic stenosis: evolving role of transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2017;10:e004838. doi: 10.1161/CIRCINTERVENTIONS.117.004838
33. Ribeiro HB, Lerakis S, Ghal SF, Cavalcante JL, Makkar R, Herrmann HC, Windecker S, Enriquez-Sarano M, Cheema AN, Nombela-Franco L, et al. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis: the TOPAS-TAVI registry. J Am Coll Cardiol. 2018;71:1297–1308. doi: 10.1016/j.jacc.2018.01.054
34. Herrmann HC, Pibarot P, Huetter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. Circulation. 2013;127:2316–2326. doi: 10.1161/CIRCULATIONAHA.112.012990
35. Dele-Michael AO, Fujikura K, Devereux RB, Islam F, Hriljac I, Wilson SR, Lin F, Weisnant JW. Left ventricular stroke volume quantification by contrast echocardiography - comparison of linear and flow-based methods to cardiac magnetic resonance. Echocardiography. 2013;30:880–888. doi: 10.1111/echo.12155
36. Sundararajan V, Romano PS, Quan H, Bursand B, Dösler SE, Brien S, Pincus HA, Ghali WA. Capturing diagnosis-fiming in ICD-coded hospital data: recommendations from the WHO ICD-11 topic advisory group on quality and safety. Int J Qual Health Care. 2015;27:328–333. doi: 10.1093/ijqhc/mzv037
37. Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muñibaier LH, Mark DB. Discordance of databases designed for claims payment versus clinical information systems. Implications for outcomes research. Ann Intern Med. 1993;119:844–850. doi: 10.7326/0003-4819-119-11-199310150-00011
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, cm²            | 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                    |
| Phenotype                                | Stroke Volume Index, mL/m² | 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.**

| Covariate                        | 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: ≥ 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, cm²         | 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/m²     | 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.