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Impact of Moderate Aortic Stenosis in Patients With Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Afterload from moderate aortic stenosis (AS) may contribute to adverse outcomes in patients with heart failure with reduced ejection fraction (HFrEF).

OBJECTIVES The authors evaluated clinical outcomes in patients with HFrEF and moderate AS relative to those without AS and with severe AS.

METHODS Patients with HFrEF, defined by left ventricular ejection fraction (LVEF) <50% and no, moderate, or severe AS were retrospectively identified. The primary endpoint, defined as a composite of all-cause mortality and heart failure (HF) hospitalization, was compared across groups and within a propensity score–matched cohort.

RESULTS We included 9,133 patients with HFrEF, of whom 374 and 362 had moderate and severe AS, respectively. Over a median follow-up time of 3.1 years, the primary outcome occurred in 62.7% of patients with moderate AS vs 45.9% with no AS ($P < 0.0001$); rates were similar with severe and moderate AS (62.0% vs 62.7%; $P = 0.68$). Patients with severe AS had a lower incidence of HF hospitalization (36.2% vs 43.6%; $P < 0.05$) and were more likely to undergo AVR within the follow-up period. Within a propensity score–matched cohort, moderate AS was associated with an increased risk of HF hospitalization and mortality (HR: 1.24; 95% CI: 1.04-1.49; $P = 0.01$) and fewer days alive outside of the hospital ($P < 0.0001$). Aortic valve replacement (AVR) was associated with improved survival (HR: 0.60; CI: 0.36-0.99; $P < 0.05$).

CONCLUSIONS In patients with HFrEF, moderate AS is associated with increased rates of HF hospitalization and mortality. Further investigation is warranted to determine whether AVR in this population improves clinical outcomes. (J Am Coll Cardiol 2023;81:1235–1244) © 2023 by the American College of Cardiology Foundation.

Aortic stenosis (AS) is a common cardiac valve disease that affects 12.4% of individuals ≥75 years in age and is known to exert a fixed afterload on the left ventricle.[1] Current clinical management guidelines endorse aortic valve replacement (AVR) for patients with severe AS who experience reduced left ventricular ejection fraction (LVEF) even in the absence of clinical symptoms, owing to the adverse impact of increased afterload on the diseased left ventricle.[2,3] In heart failure with reduced ejection fraction (HFrEF), guideline-directed pharmacologic treatment focuses primarily on cardiac afterload reduction through inhibition of the renin-angiotensin-aldosterone system and

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

DAOH = days alive out of the hospital

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = international classification of disease

LVEF = left ventricular ejection fraction

sympathetic nervous systems. Moderate AS exerts a fixed afterload on the heart, and recent studies have identified adverse clinical outcomes in patients with concomitant HFrEF and moderate AS. However, clinical data regarding the full impact of moderate AS on heart failure (HF) outcomes remain limited.[4-7] In this investigation, we sought to quantify the incidence and burden of HF hospitalization and mortality in patients with moderate AS in comparison with patients with severe AS and HFrEF and those with HFrEF without AS by leveraging a large, longitudinal single-center cohort.

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METHODS

STUDY GROUP. Patients with HFrEF, defined by the presence of LVEF <50%, were retrospectively identified within the Massachusetts General Hospital echocardiographic database between January 1, 2016, and December 31, 2019. The study group included patients with HFrEF and moderate AS. Patients with severe AS and HFrEF and patients with no AS and HFrEF were included as positive and negative control groups, respectively. Study exclusion criteria included prior AVR, severe mitral valve disease, congenital heart disease, obstructive hypertrophic cardiomyopathy, end-stage renal disease, and liver cirrhosis at the time of the index echocardiogram. Patients with bicuspid aortic valves were included. The study protocol was approved by the Institutional Review Board at our institution. Patients were not required to provide written informed consent for this retrospective study.

CLINICAL AND ECHOCARDIOGRAPHIC DATA. Patient clinical data were obtained through electronic medical record review by using the Mass General Brigham Research Patient Data Registry. The study period extended from January 1, 2016, to September 30, 2021. Baseline clinical characteristics were determined by using the corresponding international classification of disease (ICD) codes within 5 years before the date of the index echocardiogram (Supplemental Table 1).

Echocardiographic parameters were collected from the first transthoracic echocardiogram that occurred during the study period and included an LVEF <50%. Severe AS was defined as an aortic valve area (AVA) <1.0 cm^2 and moderate AS as an AVA of 1.0 to 1.5 cm^2. AVA was used to categorize severity of AS rather than aortic valve mean gradient because of a concern about misclassifying low-flow, low-gradient severe AS as moderate AS in this cohort of patients with low LVEF. Dobutamine stress echocardiography was rarely performed; low-flow, low-gradient AS was therefore categorized as severe for the purposes of this analysis. Echocardiographic measurements were otherwise made according to the American Society of Echocardiography guidelines.[8]

STUDY OUTCOMES. The primary outcome was defined as a composite of HF hospitalization and mortality. Secondary outcomes included death, HF hospitalization, cumulative number of HF hospitalizations, and days alive out of the hospital (DAOH). HF hospitalization was defined as an admission with a primary diagnosis with ICD-9 code 428.xx, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 or ICD-10 code 150.xx, I11.0, I13.0, I13.2. If the patient was hospitalized at the time of the index echocardiogram, subsequent HF hospitalizations were considered outcome events. The primary outcome of HF hospitalization was censored at the time of surgical or transcatheter AVR, but patients were followed up after AVR for survival and cumulative HF hospitalizations.

STATISTICAL ANALYSIS. Data are presented as n (%) for categorical variables, mean ± SD for normally distributed variables, and median (IQR) for skewed distributions. Between-group differences were analyzed by a Student's *t*-test and a chi-square or Fisher exact test for categorical variables. Kaplan-Meier analysis was conducted to estimate the time to event for each outcome. Multivariable Cox proportional hazard analyses were conducted to determine independent associations of moderate AS with each outcome. Multivariable models included age, sex, history of diabetes, hypertension, hyperlipidemia, atrial fibrillation (AF), coronary artery disease (CAD), chronic lung disease (CLD), chronic kidney disease (CKD), peripheral artery disease (PAD), smoking, LVEF, and the severity of AS.

To account for imbalance in potential confounding factors between HFrEF patients with moderate AS and those with no AS, propensity score matching was used to standardize populations. Propensity matching was based on 1-to-1 nearest neighbor matching with a greedy matching algorithm and a caliper width of 0.5. Each of the 374 patients within the HFrEF and moderate AS was matched 1:1 to a patient within the HFrEF and no AS. The criteria used for propensity score matching were the clinical characteristics listed in **Table 1**, including sex (exact match), age ± 5 years, LVEF ± 5%, and major comorbidities including diabetes, hypertension, hyperlipidemia, coronary artery disease, and lung disease.

All statistical tests were 2-sided with P value <0.05 considered statistically significant. Analyses were performed with SAS 9.4 (SAS Institute).

RESULTS

BASELINE CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS. A total of 9,133 patients with HFrEF were included in the analysis, of whom 374 and 362 had moderate and severe AS, respectively. The median follow-up time was 3.1 years (IQR: 1.9-4.4 years). Baseline clinical and echocardiographic characteristics for the cohort are listed in **Table 1**. Patients with moderate or severe AS tended to be older (mean age 81.9 ± 10.1 years and 84.6 ± 10.2 years, respectively) compared with patients with no AS (mean age 70.8 ± 14.8 years). Patients with moderate and severe AS also more frequently possessed comorbidities, including diabetes, atrial fibrillation, coronary artery disease, chronic kidney disease, and concomitant aortic, mitral, and tricuspid regurgitation. The mean LVEF was similar for all 3 groups.

TABLE 1 Patient Baseline Characteristics and Echocardiographic Parameters

	No AS (n = 8,412)	Moderate AS (n = 374)	Severe AS (n = 362)	*P* Value
Demographic data				
Age, y	70.8 ± 14.8	81.9 ± 10.1	84.6 ± 10.2	<0.0001
Female	2,642 (41.4)	80 (21.4)	125 (34.5)	<0.0001
Diabetes	3,116 (37.0)	166 (44.4)	144 (39.8)	0.01
Hypertension	7,365 (87.6)	353 (94.4)	332 (91.7)	<0.0001
Hyperlipidemia	6,051 (71.9)	31.7 (84.8)	276 (76.2)	<0.0001
Atrial fibrillation	4,556 (54.2)	236 (63.1)	232 (64.1)	<0.0001
CAD	620 (7.4)	39 (10.4)	38 (10.5)	0.01
CLD	622 (7.4)	27 (7.2)	23 (6.4)	0.76
CKD	3,263 (38.8)	216 (57.8)	190 (52.5)	<0.0001
Smoking	4,472 (53.2)	231 (61.8)	180 (49.7)	0.002
PAD	2,010 (23.9)	147 (39.3)	147 (40.6)	<0.0001
Prior stroke	1,905 (22.7)	85 (22.7)	85 (23.5)	0.93
Index echocardiographic data				
LVEF, %	35.5 ± 10.0	35.8 ± 8.8	35.4 ± 8.9	0.807
AV mean gradient, mm Hg	8.0 [4.0-13.0]	16.0 [12.0-21.0]	31 [21.0-42.75]	<0.001
AR > mild	364 (4.4)	43 (11.5)	52 (14.4)	<0.0001
MR > mild	2,243 (26.7)	155 (41.4)	169 (46.7)	<0.0001
TR > mild	1,712 (20.4)	100 (26.7)	128 (35.4)	<0.0001

Values are n (%), mean ± SD, or median [IQR].

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CAD = coronary artery disease; CKD = chronic kidney disease; CLD = chronic lung disease; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; TR = tricuspid regurgitation.

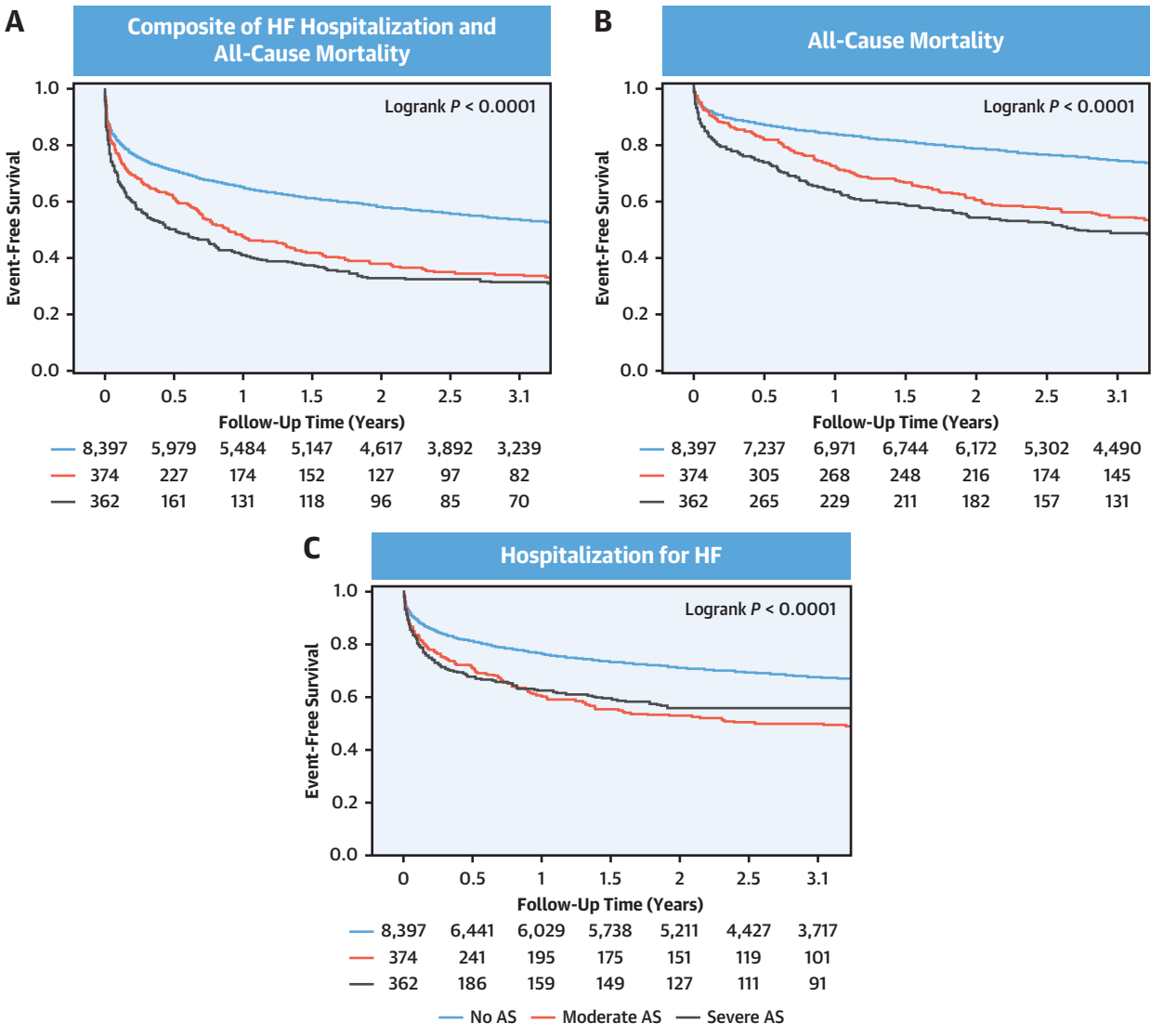
EFFECT OF AORTIC STENOSIS SEVERITY ON HF HOSPITALIZATION AND MORTALITY. Rates of the composite outcome of HF hospitalization and all-cause mortality were similar in HFrEF patients with moderate and severe AS (62.0% vs 62.7%; $P = 0.68$) but were greater than in patients with HFrEF and no AS (45.9%; $P < 0.0001$) (**Central Illustration A**). All-cause mortality occurred in 42.2% of patients with moderate AS and HFrEF compared with 45.9% with severe AS and HFrEF ($P = 0.37$) and 25.8% with HFrEF and no AS ($P < 0.0001$) (**Central Illustration B**). The relationship between AVA and mortality, and between AV mean gradient and mortality in patients with moderate AS were characterized by using spline curves (Supplemental Figures 1A and 1B). The spline curves did not suggest a threshold effect for the impact of AVA or AV mean gradient.

Hospitalization for HF occurred in 43.6% of those with moderate AS, more than in HFrEF patients with no AS (30.3%; $P < 0.0001$) and those with severe AS (36.2%; $P < 0.05$) (**Central Illustration C**). Without censoring for AVR, patients with moderate AS and HFrEF had the highest cumulative number of HF hospitalizations, continuing to rise beyond the 1-year follow-up period, whereas the rate of HF hospitalizations in the severe AS group plateaued (**Figure 1A**). Over the study period, those with moderate AS had 1.1 hospitalizations per patient, compared with 0.77 hospitalizations per patient in the severe AS group ($P < 0.0001$) and 0.75 in the no-AS group ($P < 0.0001$).

Over the study period, patients with moderate AS spent a median of 850.5 DAOH (IQR: 310.8-1,334.3 DAOH), similar to those with severe AS who had 732.5 DAOH (IQR: 139.8-1,356.3 DAOH) and significantly fewer than those with no AS with 1,162.0 DAOH (IQR: 703.0-1,606.0 DAOH). Compared with those with moderate and severe AS, those without AS had 26.8% and 37.0% more DAOH, respectively. The median overall follow-up time from date of index echocardiogram to death or study end date was longest in patients without AS at 1,219 days (IQR: 778.0-1,646.0 days), compared to 998.5 days (IQR: 423.5-1,424.5 days) in patients with moderate AS and 980.5 days (IQR: 252.0-1476.5 days; $P < 0.001$) in those with severe AS.

PROPENSITY-MATCHED STUDY COHORT. The baseline characteristics for propensity score-matched patients and the covariance balance plot before and after matching are listed in Supplemental Table 2 and Supplemental Figure 2, respectively. Before propensity score matching, age was the largest difference between the 2 groups (Supplemental Figure 2). With 1:1 matching between patients with moderate AS and those with no AS, the significant difference in the composite outcome (64.4% vs 59.9%; $P < 0.05$), mortality (45.2% vs 38.2%; $P < 0.05$), and HF hospitalization (45.2% vs 37.8%; $P < 0.05$) persisted (**Figures 2A, 2B, and 2C**). In multivariable analysis, moderate AS remained an independent predictor of the composite outcome (HR: 1.24; 95% CI: 1.04-1.49),

CENTRAL ILLUSTRATION **Kaplan-Meier Analysis for Patients With HFrEF Stratified by AS**



Khan KR, et al. J Am Coll Cardiol. 2023;81(13):1235-1244.

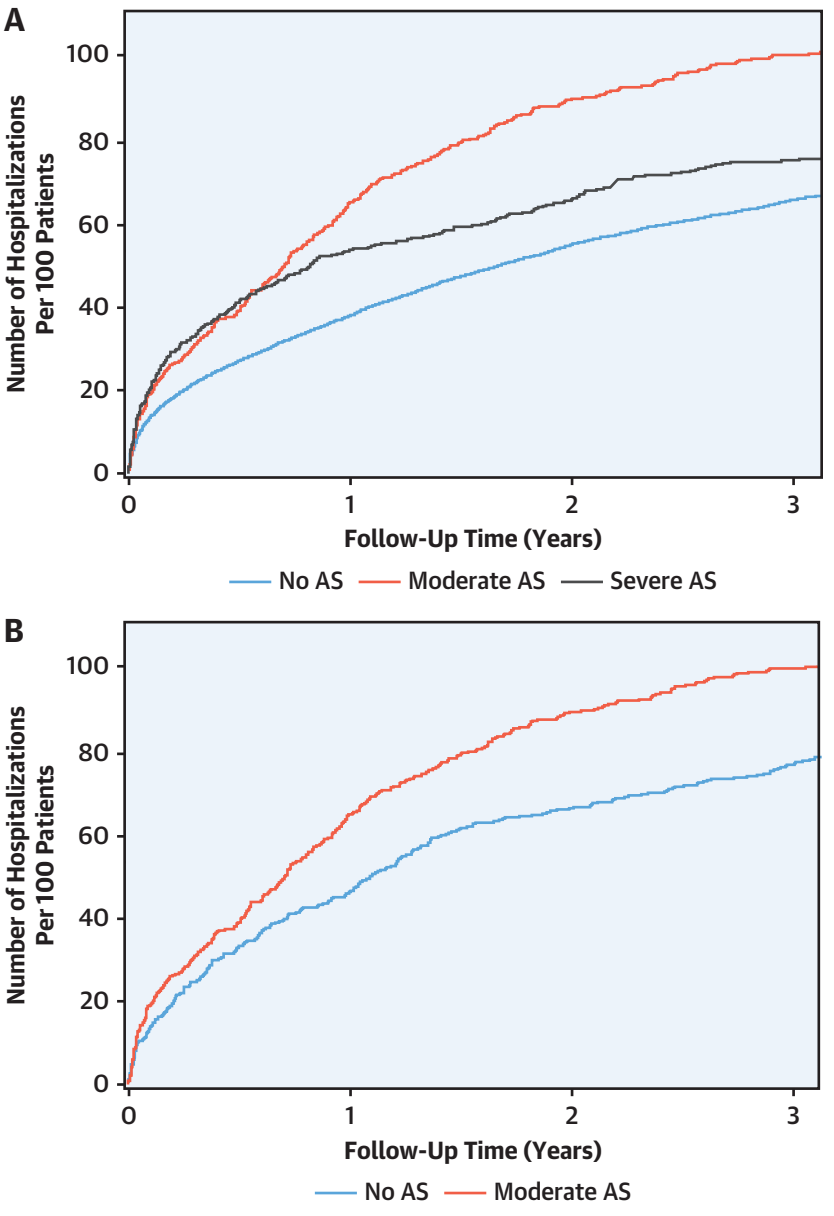
The primary outcome was a composite of first HF hospitalization and all-cause death. Kaplan-Meier analyses depict the time to event for **(A)** the composite outcome, **(B)** all-cause mortality, and **(C)** HF hospitalization. Patients with moderate AS and HFrEF had a higher rate of the primary outcome, death and HF hospitalization compared to patients with HFrEF and no AS ($P < 0.0001$). AS = aortic stenosis; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

HF hospitalization (HR: 1.27; 95% CI: 1.02-1.59), and mortality (HR: 1.32; 95% CI: 1.07-1.63) despite multivariable adjustment (Table 2).

Patients with moderate AS and HFrEF had a higher cumulative rate of HF hospitalizations, with 1.1 hospitalizations per patient in comparison with 0.87 hospitalizations per patient in propensity score-matched patients without AS ($P < 0.0001$) (Figure 1B), and also significantly fewer DAOH compared with propensity-matched patients with no AS and HFrEF (850.5 days [IQR: 310.8-1,334.3 days] vs 1,078.5 days [IQR: 459.5-1,563.5 days], or 21.1% fewer) ($P = 0.002$).

In subgroup analysis, the propensity-matched groups were stratified by degree of LVEF reduction. Among both patients with LVEF <35% and those with LVEF 35% to 50%, moderate AS appeared to add risk to the composite outcome, although the difference was not significant. At the median follow-up time,

FIGURE 1 Cumulative Number of Heart Failure Hospitalizations

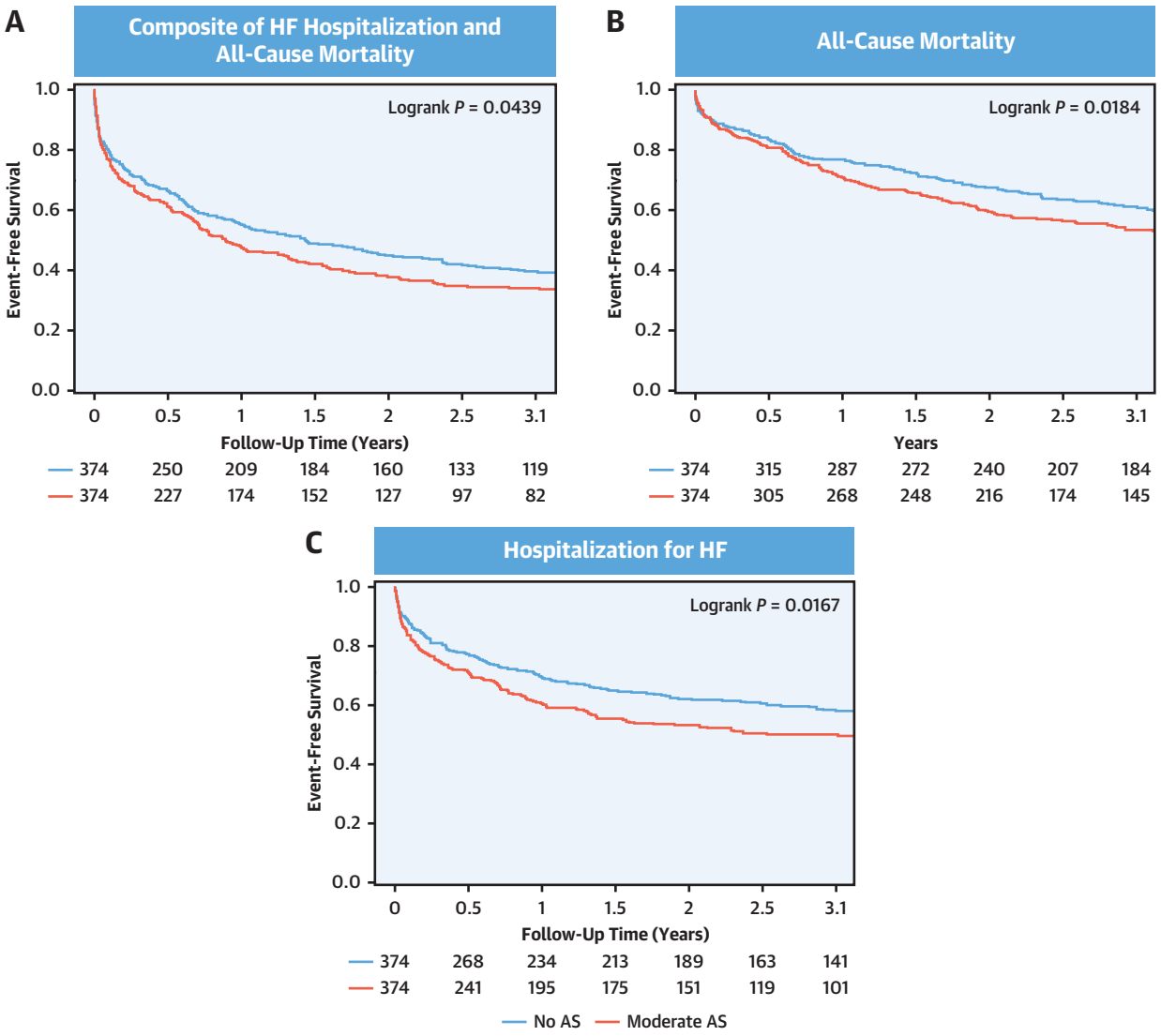


Cumulative number of recurrent heart failure hospitalizations per 100 patients among **(A)** the entire cohort and **(B)** propensity-matched HFrEF patients with moderate AS and no AS. Patients with moderate AS and HFrEF had the highest cumulative number of HF hospitalizations over the study period for the entire cohort ($P < 0.0001$) and the propensity-matched group ($P < 0.0001$). AS = aortic stenosis; HFrEF = heart failure with reduced ejection fraction.

70.0% of patients with moderate AS and LVEF <35% reached the composite outcome vs 65.3% of patients with no AS and LVEF <35% ($P = 0.13$). For patients with LVEF 35% to 50%, 61.0% of those with moderate AS reached the composite outcome vs 56.5% of those with no AS ($P = 0.16$). Patients with LVEF <35%, regardless of the presence of AS, had an increased risk of the composite outcome compared with those with an LVEF of 35% to 50% ($P < 0.05$) (Figure 3).

EFFECT OF AVR ON CLINICAL OUTCOMES. Over the course of the study, 46 (12.2%) patients within the moderate AS group underwent surgical or transcatheter AVR, whereas a total of 112 (33.7%) patients

FIGURE 2 Kaplan-Meier Analysis for Propensity Score-Matched Patients



Propensity score matching was used to account for potential confounding factors between HFrEF patients with moderate AS and with no AS. Kaplan-Meier analyses depict the time to event for **(A)** the composite outcome of HF hospitalization and all-cause mortality, **(B)** all-cause mortality, and **(C)** HF hospitalization. Patients with moderate AS and HFrEF had a higher rate of the primary outcome, death and HF hospitalization compared to patients with HFrEF and no AS ($P<0.05$). HF = heart failure; other abbreviations as in Figure 1.

in the severe AS group underwent surgical or transcatheter AVR. The median time to AVR was 313 days (IQR: 106-432 days) for patients with moderate AS and 74 days (IQR: 17.5-263 days) for patients with severe AS. Among patients with severe AS who underwent AVR, 76% (n = 93) were alive at the median follow-up time of 3.1 years, compared with only 35% (n = 85) with severe AS who did not undergo AVR. For those with moderate AS who underwent AVR, 72% (n = 33) were alive at the median follow-up time compared with 52% (n = 172) of those who did not undergo AVR. Age, AVA, and AV mean gradient were the only baseline characteristics that were found to be significantly different in patients with moderate AS who underwent AVR compared with those who did not undergo AVR (Supplemental Table 3).

At the time of AVR, 80.0% of those who initially had moderate AS had experienced progression to severe AS. The remainder of patients with moderate AS

TABLE 2 Multivariate Analysis of Outcomes in Propensity-Matched Patients With HFrEF and No AS vs Moderate AS

	Composite Outcome		HF Hospitalization		All-Cause Mortality	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, y	1.01 (0.99-1.02)	0.073	1.01 (0.99-1.02)	0.255	**1.02 (1.01-1.03)**	**0.003**
Female	**1.25 (1.01-1.56)**	**0.042**	1.28 (0.98-1.67)	0.076	1.08 (0.83-1.40)	0.564
Diabetes	**1.22 (1.01-1.48)**	**0.038**	**1.41 (1.11-1.79)**	**0.005**	1.15 (0.92-1.44)	0.209
HTN	1.27 (0.86-1.89)	0.236	0.96 (0.58-1.58)	0.875	1.31 (0.81-2.12)	0.273
HLD	0.91 (0.66-1.24)	0.536	0.95 (0.64-1.42)	0.807	0.92 (0.64-1.32)	0.643
AF	1.13 (0.94-1.36)	0.209	0.95 (0.75-1.19)	0.639	1.15 (0.92-1.42)	0.225
CAD	1.11 (0.90-1.37)	0.335	1.14 (0.88-1.48)	0.308	1.20 (0.93-1.53)	0.157
CLD	**1.45 (1.18-1.79)**	**0.001**	1.18 (0.92-1.52)	0.190	**1.37 (1.07-1.75)**	**0.011**
CKD	**1.48 (1.22-1.79)**	**<0.001**	**1.56 (1.24-1.96)**	**<0.001**	**1.45 (1.16-1.81)**	**0.001**
Smoking	1.09 (0.90-1.31)	0.379	1.05 (0.83-1.32)	0.709	1.08 (0.87-1.34)	0.497
PAD	1.26 (1.03-1.55)	0.022	0.95 (0.75-1.22)	0.695	1.18 (0.93-1.49)	0.175
LVEF, %	**0.98 (0.97-0.99)**	**<0.001**	**0.98 (0.97-0.99)**	**<0.001**	0.99 (0.98-1.01)	0.295
Moderate AS (vs no AS)	**1.24 (1.04-1.49)**	**0.019**	**1.27 (1.02-1.59)**	**0.035**	**1.32 (1.07-1.63)**	**0.011**

Values in **bold** indicate statistically significant multivariate predictors.

AF = atrial fibrillation; AS = aortic stenosis; CAD = coronary artery disease; CKD = chronic kidney disease; CLD = chronic lung disease; HFrEF = heart failure with reduced ejection fraction; HLD = hyperlipidemia; HTN = hypertension; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease.

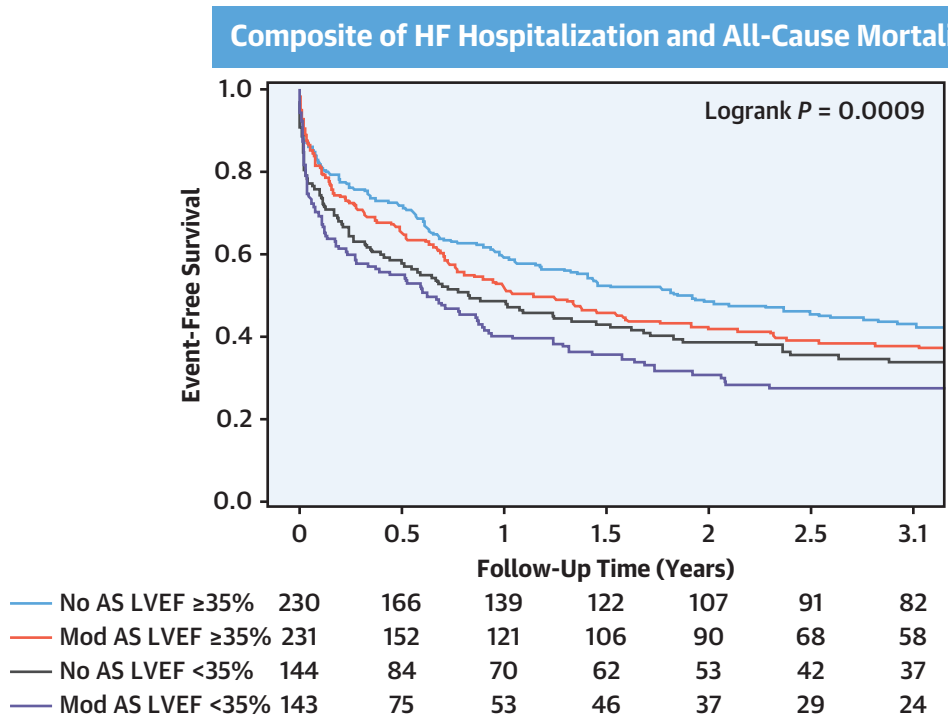
who underwent AVR had another reason to undergo valve replacement, such as coronary artery bypass surgery. Among the 46 patients with the moderate AS group who underwent AVR, 32.6% also underwent coronary artery revascularization at that time, by either bypass graft surgery or percutaneous coronary intervention. For patients with moderate AS, AVR was found in multivariate analysis to be independently associated with reduced risk of all-cause mortality (HR: 0.60; 95% CI: 0.36-0.99; $P < 0.05$), but not predictive of the composite outcome (HR: 0.8; 95% CI: 0.5-1.3; $P = 0.35$) or HF hospitalization (HR: 0.9; 95% CI: 0.6-1.4; P=0.74).

DISCUSSION

In this large longitudinal cohort study including 9,133 patients with reduced left ventricular systolic function and varying severity of AS, we present several key findings which add evidence that moderate AS adversely impacts clinical outcomes. First, patients with moderate AS and HFrEF have a higher rate of HF hospitalization, mortality, total burden of HF hospitalizations, and fewer DAOH compared to those with HFrEF and no AS. These observations held true despite robust statistical multivariable adjustment for comorbid conditions within a propensity score-matched cohort. Second, among patients with HFrEF, mortality was similar in patients with moderate AS compared to those with severe AS. Third, the incidence and total burden of HF hospitalizations was greater in those with moderate AS and HFrEF as compared with those patients with severe AS and HFrEF, likely due to the modifying effect of AVR in those with severe AS. Fourth, moderate AS appeared to have consistent adverse clinical impact regardless of the severity of HFrEF. Finally, among patients with moderate AS and HFrEF, AVR was performed in a minority of patients during the follow-up period and was associated with improved survival.

The increased afterload imposed by moderate AS in patients with low LVEF has been found to induce cardiac remodeling. Ito et al[9] noted progressive decline in LVEF in patients with HFrEF before AS becomes severe, accelerating after AVA reaches 1.2 cm^2. Similarly, moderate AS results in progressive changes in left atrial and ventricular size, systolic and diastolic dysfunction, and increased late gadolinium enhancement.[10,11] It is therefore not surprising that recent evidence also implicates moderate AS in driving adverse clinical events. Jean et al[6] found that among patients with HFrEF, moderate AS is associated with a 3-fold increased incidence in mortality, with improved survival for those who underwent AVR during the follow-up period. Another recent study found an increased incidence in HF hospitalization with 26% of patients with moderate AS and HFrEF hospitalized at 3 years, compared to 20% in previously reported studies of patients with HFrEF alone.[5,12] Here, we further expand these observations to include robust statistical adjustment, detailed quantification of HF hospitalization risk, comparisons to HFrEF patients with no AS (negative control) and with severe AS (positive control), and with the inclusion of patient-centered clinical outcomes including DAOH and total burden of HF hospitalization.

FIGURE 3 Outcomes in Propensity-Matched Patients Stratified by LVEF



Among propensity-matched patients with LVEF <35% and those with LVEF 35%-50%, moderate AS appeared to add risk to the composite outcome of HF hospitalization and mortality, although the difference was not significant ($P = 0.13$ and $P = 0.16$, respectively) in this subgroup analysis. LVEF = left ventricular ejection fraction; mod = moderate; other abbreviations as in Figures 1 and 2.

Within a propensity score-matched cohort, we found that patients with moderate AS and HFrEF have a higher incidence of HF hospitalization and mortality in comparison with patients with HFrEF and no AS. We are also the first to demonstrate a burden of mortality and HF hospitalization events in the moderate AS group that is comparable or in excess to those seen with severe AS and HFrEF. We found that HF hospitalizations accumulated over the duration of the study period in patients with moderate AS and HFrEF; whereas hospitalizations plateaued in the severe AS group in an analysis that was not censored after AVR. We hypothesized that the higher incidence of HF hospitalizations in the moderate AS group compared to the severe AS group is likely due to the performance of AVR, which occurred at a median time of 74 days in patients with severe AS and therefore could have mitigated further HF hospitalizations during the follow-up period.

We are also the first to evaluate days alive out of the hospital (DAOH) in this population, an important patient-centered outcome. DAOH is a measure that has been used in multiple prior cardiovascular studies to effectively quantify days spent in good health.[13-15] Within a propensity-score matched cohort, we found that patients with moderate AS and HFrEF have significantly fewer DAOH compared to those with HFrEF and no AS. DAOH was similar between patients with moderate and severe AS and concomitant HFrEF. In this study, there was a 21.1% difference in DAOH when comparing propensity-matched patients with moderate AS and no AS. Notable prior clinical trials that have utilized DAOH in patients with HFrEF include CHARM and PARADIGM-HF, which showed a relatively smaller percent change in DAOH of 1.64% and 1.79% with the medications candesartan and sacubitril/valsartan, respectively.[15] DAOH demonstrates the burden and morbidity of aortic valve disease in patients with HFrEF and will be a key measure to investigate in prospective studies evaluating the potential benefit of AVR.

In this study, only a small minority of patients in the moderate AS group underwent AVR during the study period with the median time to AVR of nearly 1

year. Nearly all patients had progressed to severe AS at the time of AVR, with exceptions primarily in those undergoing cardiac surgery for another indication such as coronary artery bypass surgery. In multivariate analysis of our propensity score-matched cohort, AVR was found to be associated with improved survival. This finding implicates AS as a potential causal mediator of the adverse clinical outcomes.

Patients with severe AS and HFrEF represent a high-risk population that benefit greatly from AVR.[3,16] Whether early AVR for moderate AS in the setting of HFrEF similarly interrupts maladaptive cardiac remodeling and improves clinical outcomes is of critical clinical importance and the focus of the ongoing TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure; NCT02661451) clinical trial. The PROGRESS (PROGRESS: Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR; NCT04889872) trial and the Evolut EXPAND TAVR II Pivotal Trial (NCT05149755) will also provide prospective data on the moderate AS population.[17] We eagerly await results from ongoing randomized clinical trials evaluating the impact of early AVR in the moderate AS population to definitively address this point.

STUDY LIMITATIONS. First, the study is subject to the inherent limitations of a retrospective analysis. Second, clinical comorbid conditions and heart failure hospitalization were determined using administrative claims-based data and are reliant on the accuracy and completeness of clinical documentation and subject to misclassification bias. Third, severity of AS was defined based solely on aortic valve area without consideration of dobutamine stress echocardiography or aortic valve calcium score, and other nuanced echocardiographic parameters to differentiate low-flow, low-gradient severe AS from pseudo-severe, moderate AS. However, we would expect that any patient with pseudo-severe AS would be categorized as severe AS in this study, so would not impact outcomes in the moderate AS group. Fourth, the total follow-up time was longer in patients without AS, primarily due to lower mortality rate, which limits our interpretation of DAOH. Fifth, AVR was treated as a binary variable rather than a time-dependent variable due to the relatively small sample size. Finally, despite robust statistical adjustment using propensity score-matched and multivariable analyses, residual confounders not considered within our analyses may have affected results.

CONCLUSIONS

In patients with HFrEF, we found that moderate AS portends poor clinical outcomes with high rates of HF hospitalization and mortality when compared to those without AS and even severe AS. Patients with moderate AS experience a greater burden of HF hospitalizations and fewer DAOH than those with HFrEF and no AS and comparable rates to those with HFrEF and severe AS. Alleviation of moderate AS with AVR was associated with improved survival in this retrospective analysis. These results suggest that moderate AS is clinically detrimental in patients with HFrEF and that early AVR may improve clinical outcomes in patients with moderate AS and HFrEF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HFrEF, even moderate AS is associated with increases in hospitalization for heart failure and mortality, and AVR improves survival in these patients.

TRANSLATIONAL OUTLOOK: Ongoing clinical trials will help clarify the role of transcatheter AVR in patients with HFrEF and moderate AS.

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KEY WORDS aortic stenosis, days alive out of hospital, heart failure hospitalization, heart failure with reduced ejection fraction, mortality

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