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Moderate Aortic Stenosis in Patients With Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND The study investigators previously reported that moderate aortic stenosis (AS) is associated with a poor prognosis in patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) (HFrEF). However, the respective contribution of moderate AS versus HFrEF to the outcomes of these patients is unknown.

OBJECTIVES This study sought to determine the impact of moderate AS on outcomes in patients with HFrEF.

METHODS The study included 262 patients with moderate AS (aortic valve area >1.0 and <1.5 cm^2; and peak aortic jet velocity >2 and <4 m/s, at rest or after dobutamine stress echocardiography) and HFrEF (LVEF <50%). These patients were matched 1:1 for sex, age, estimated glomerular filtration rate, New York Heart Association functional class III to IV, presence of diabetes, LVEF, and body mass index with patients with HFrEF but no AS (i.e., peak aortic jet velocity <2 m/s). The endpoints were all-cause mortality and the composite of death and HF hospitalization.

RESULTS A total of 262 patients with HFrEF and moderate AS were matched with 262 patients with HFrEF and no AS. Mean follow-up was 2.9 ± 2.2 years. In the moderate AS group, mean aortic valve area was 1.2 ± 0.2 cm^2, and mean gradient was 14.5 ± 4.7 mm Hg. Moderate AS was associated with an increased risk of mortality (hazard ratio [HR]: 2.98; 95% confidence interval [CI]: 2.08 to 4.31; $p < 0.0001$) and of the composite of HF hospitalization and mortality (HR: 2.34; 95% CI: 1. 72 to 3.21; $p < 0.0001$). In the moderate AS group, aortic valve replacement (AVR) performed in 44 patients at a median follow-up time of 10.9 ± 16 months during follow-up was associated with improved survival (HR: 0.59; 95% CI: 0.35 to 0.98; $p = 0.04$). Notably, surgical AVR was not significantly associated with improved survival ($p = 0.92$), whereas transcatheter AVR was (HR: 0.43; 95% CI: 0.18 to 1.00; $p = 0.05$).

CONCLUSIONS In this series of patients with HFrEF, moderate AS was associated with a marked incremental risk of mortality. AVR, and especially transcatheter AVR during follow-up, was associated with improved survival in patients with HFrEF and moderate AS. These findings provide support to the realization of a randomized trial to assess the effect of early transcatheter AVR in patients with HFrEF and moderate AS. (J Am Coll Cardiol 2021;77:2796–803) © 2021 by the American College of Cardiology Foundation.

Approximately 10% of patients with aortic stenosis (AS) have heart failure (HF) with reduced ejection fraction (HFrEF) (1). In this subset, only patients with severe AS have a class I indication for aortic valve replacement (AVR) (2) because it is generally assumed that patients with moderate AS would not benefit from AVR. Previous studies reported that the outcome of patients with

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moderate AS is not benign and is close to being as unfavorable as in patients with severe AS (3). We previously reported that patients with HFrEF and moderate AS exhibit poor outcomes, with 61% dead, hospitalized for HF, or requiring AVR within a period of 4 years (4). Moreover, there are conflicting results regarding the outcome of pseudo-severe (i.e., nonsevere) AS in patients with reduced left ventricular ejection faction (LVEF) and low-flow, low-gradient AS. Some studies suggest that a proportion of patients with pseudo-severe (i.e., moderate) AS have worse outcomes compared with patients with no or mild AS and may benefit from AVR (5,6). Conversely, another study suggested no significant impact on outcome in HFrEF with pseudo-severe AS versus no AS (7).

Hence, the independent incremental contribution of moderate AS to the poor outcomes of patients is unclear. The objective of this study was thus to determine the impact of moderate AS on the outcomes of patients with HFrEF.

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METHODS

STUDY GROUP. We retrospectively included 262 patients with HFrEF (LVEF <50%) and moderate AS (aortic valve area [AVA] >1.0 and <1.5 cm^2 and peak aortic jet velocity >2 and <4 m/s) at rest or after dobutamine stress echocardiography between 2010 and 2015 in 3 academic centers, 1 in Canada (Québec, n = 181) and 2 in the Netherlands (Rotterdam, n = 58; and Leiden, n = 23) (4). Patients with previous aortic surgery, previous AVR, hypertrophic or noncompaction cardiomyopathy, congenital heart diseases, or previous heart transplantation were excluded.

These patients with moderate AS were matched 1:1 within each center with 262 patients with HFrEF and no AS (peak aortic jet velocity <2 m/s and no evidence of valve thickening reducing leaflet mobility) for each of the following variables, in order of importance and with accepted differences between brackets: sex (exact match), age (within 2 years), estimated glomerular filtration rate (within 20 ml/min/1.73 m^2), New York Heart Association functional class III to IV (exact match), presence of diabetes (exact match), LVEF (within 5%), and body mass index (within 2 kg/m^2).

The study was carried out under the approval of all participating centers, which waived the requirement to obtain written consent forms because of the retrospective and anonymous nature of this research.

CLINICAL DATA. Patients' clinical characteristics, medication or treatment, and follow-up were collected from hospital records or requested from treating physicians and referring centers.

The presence of hypertension was defined by an antihypertensive medication or blood pressure ≥140/90 mm Hg; dyslipidemia by patients receiving cholesterol-lowering medication or, in the absence of such medication, having a total plasma cholesterol level >240 mg/dl; diabetes mellitus by patients receiving antidiabetic medication or, in the absence of such medication, having a fasting glucose level ≥126 mg/dl; and coronary artery disease by history of myocardial infarction or coronary artery stenosis on coronary angiography.

ECHOCARDIOGRAPHY. AVA was calculated by the continuity equation and indexed to the body surface area, mean gradient by the simplified Bernoulli equation, and LVEF by the biplane Simpson method following current guidelines (8). The Doppler velocity index was measured by dividing the time-integral velocity in the left ventricular outflow tract by the time-integral velocity in the aorta. The severity of aortic regurgitation and mitral regurgitation was assessed by a multiparametric approach and graded semiquantitatively on a scale from 1 to 4 by Doppler echocardiography according to the American Society of Echocardiography criteria (9).

The first qualifying echocardiography during the time of the study was considered as the beginning of the study.

STUDY ENDPOINTS. The primary endpoint of the study was all-cause mortality after diagnosis. Survival status was obtained from the respective national population registries. The secondary endpoints were the composite of HF hospitalization and all-cause mortality. HF hospitalization occurrences were collected from hospital records or requested from the treating physicians and referring centers. The end of study date was December 31, 2016, and all patients had at least 1-year follow-up completed.

STATISTICAL ANALYSIS. Continuous variables were tested for normality by the Shapiro-Wilk test. Results were expressed as mean ± SD or median (25th percentile to 75th percentile), and compared by Student's *t*-test or the Wilcoxon rank-sum test between patients with moderate AS versus without moderate AS. Categorical variables are presented as percentage and compared with the chi-square test or Fisher exact test, as appropriate. Cumulative

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

TABLE 1 Baseline Characteristics of the Patients

	Whole Cohort (N = 524)	HFrEF Without Aortic Stenosis (n = 262) (50%)	HFrEF With Moderate Aortic Stenosis (n = 262) (50%)	p Value
Clinical data				
Age, yrs	74.0 ± 10.2	74.6 ± 10.1	73.4 ± 10.4	0.20
Male	406 (77)	203 (77)	203 (77)	1.00
Diabetes	194 (37)	97 (37)	97 (37)	1.00
Body mass index, kg/m^2	28.1 ± 5.1	27.9 ± 4.9	28.3 ± 5.3	0.39
Coronary artery disease	382 (73)	189 (72)	193 (74)	0.69
Smoker	100 (19)	44 (17)	56 (21)	0.11
Peripheral artery disease	115 (22)	61 (23)	54 (21)	0.47
Hypertension	373 (71)	181 (69)	192 (73)	0.29
Dyslipidemia	369(70)	179 (68)	190 (73)	0.26
Ischemic cardiomyopathy	**232 (44)**	**128 (49)**	**104 (40)**	**0.05**
Previous coronary interventions	252 (48)	123 (47)	129 (49)	0.57
Previous PCI	**152 (29)**	**63 (24)**	**89 (34)**	**0.01**
Previous CABG	150 (29)	83 (32)	67 (26)	0.13
Cardiac resynchronization therapy	64 (12)	35 (13)	29 (11)	0.40
NYHA III–IV	168 (32)	84 (32)	84 (32)	1.00
Medications				
Acetylsalicylic acid	330 (63)	159 (61)	171 (65)	0.13
Beta-blockers	386 (74)	206 (79)	180 (69)	0.42
ACE inhibitors	264 (50)	140 (53)	124 (47)	0.31
ARBs	129 (25)	58 (22)	71 (27)	0.11
Other diuretics	332 (64)	163 (62)	169 (65)	0.33
Calcium antagonists	**150 (29)**	**64 (24)**	**86 (33)**	**0.01**
Statin	390 (74)	200 (76)	190 (73)	0.69
Spironolactone	106 (20)	50 (19)	56 (21)	0.39
P2Y12 inhibitors	118 (23)	58 (22)	60 (23)	0.76
Oral anticoagulants	250 (47)	135 (52)	115 (44)	0.16
Laboratory data				
Creatinine, µmol/l	94.5 (78–120)	95 (80–120)	92 (77–119.5)	0.33
eGFR, ml/min/1.73 m^2	69.4 ± 26.6	70.7 ± 28.3	68.1 ± 24.8	0.28
Echocardiographic data				
Aortic valve area, cm^2	**1.76 ± 0.75**	**2.51 ± 0.58**	**1.24 ± 0.17**	–
Indexed aortic valve area, cm^2/m^2	**0.86 ± 0.44**	**1.28 ± 0.32**	**0.65 ± 0.12**	–
Doppler velocity index	**0.54 ± 0.39**	**0.72 ± 0.28**	**0.30 ± 0.08**	–
Mean gradient, mm Hg	**10.5 ± 7.3**	**3.1 ± 1.5**	**15.2 ± 5.3**	–
Peak aortic jet velocity, m/s	**1.86 ± 0.76**	**1.16 ± 0.22**	**2.55 ± 0.39**	–
Aortic regurgitation > mild	11 (2)	1 (0.4)	10 (4)	0.003
Mitral regurgitation > mild	59 (11)	49 (19)	10 (4)	<0.0001
LVEF, %	**37.5 ± 6.7**	**36.6 ± 7 .5**	**38.5 ± 9.6**	**0.01**

Values are mean ± SD, n (%), or median (interquartile range). Values in **bold** highlight the statistically significant differences between the 2 groups.

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; eGFR = estimated glomerular filtration rate; CABG = coronary artery bypass grafting; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New-York Heart Association (functional class); PCI = percutaneous coronary intervention.

incidence functions for mortality and the composite of mortality and HF hospitalization were determined using the Kaplan-Meier method, with the date of the index echocardiogram as initial time of follow-up (t = 0).

Survival analyses were performed with the use of multivariate Cox proportional hazards analyses, adjusted for clinically relevant variables and variables with a p value <0.10 in univariate analysis, carefully avoiding collinearity. Variables used for adjustment were age, sex, body mass index, diabetes, hypertension, previous myocardial infarction, dyslipidemia, ischemic cardiomyopathy, New York Heart Association functional class III to IV, estimated glomerular filtration rate, and LVEF. AVR, either transcatheter or surgical, was analyzed as a time-dependent variable.

A p value <0.05 was considered statistically significant. Statistical analyses were performed with

TABLE 2 Univariate and Multivariate Analyses of All-Cause Mortality and the Composite of HF Hospitalization and All-Cause Mortality

	All-Cause Mortality		Composite of HF Hospitalization and All-Cause Mortality	
	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)
Age, yrs	1.03 (1.01-1.04) p = 0.0005	**1.03 (1.02-1.06) p < 0.0001**	1.02 (1.01-1.04) p = 0.0004	**1.02 (1.01-1.05) p = 0.0006**
Male	1.20 (0.85-1.72) p = 0.31	1.12 (0.75-1.75) p = 0.56	1.21 (0.90-1.66) p = 0.22	1.12 (0.79-1.62) p = 0.52
Body mass index, kg/m^2	0.98 (0.95-1.01) p = 0.09	1.00 (0.99-1.01) p = 0.50	0.98 (0.95-1.01) p = 0.38	1.0 (0.99-1.01) p = 0.52
Diabetes	1.14 (0.86-1.52) p = 0.34	1.340 (0.94-1.87) p = 0.11	1.19 (0.93-1.54) p = 0.16	1.22 (0.91-1.62) p = 0.19
Hypertension	0.99 (0.72-1.38) p = 0.95	**0.58 (0.37-0.94) p = 0.03**	1.28 (0.95-1.73) p = 0.10	0.98 (0.66-1.50) p = 0.93
Previous myocardial infarction	1.23 (0.92-1.65) p = 0.15	1.25 (0.85-1.85) p = 0.25	1.51 (1.17-1.95) p = 0.002	**1.63 (1.16-2.3) p = 0.005**
Ischemic cardiomyopathy	0.88 (0.66-1.18) p = 0.41	**0.65 (0.45-0.97) p = 0.03**	1.07 (0.83-1.39) p = 0.59	**0.62 (0.44-0.88) p = 0.008**
Dyslipidemia	1.09 (0.81-1.52) p = 0.56	1.54 (0.95-2.52) p = 0.08	1.31 (0.99-1.77) p = 0.06	1.31 (0.87-2.02) p = 0.19
NYHA III-IV	1.95 (1.46 -2.59) p < 0.0001	**2.08 (1.49 -2.93) p < 0.0001**	1.95 (1.51 -2.51) p < 0.0001	**1.93 (1.43 -2.60) p < 0.0001**
eGFR, ml/min/1.73 m^2	0.99 (0.98-0.99) p = 0.002	1.00 (0.99-1.01) p = 0.87	0.99 (0.98-0.99) p = 0.002	1.0 (0.99-1.00) p = 0.88
Aortic regurgitation > mild	0.78 (0.19 -2.05) p = 0.66	0.58 (0.09 -2.01) p = 0.43	0.78 (0.19 -2.05) p = 0.65	0.52(0.08 -1.74) p = 0.33
Mitral regurgitation > mild	1.44 (1.05 -2.02) p = 0.04	0.91 (0.52 -1.54) p = 0.75	1.45 (1.00 -2.02) p = 0.05	1.20 (0.76 -1.85) p = 0.42
LVEF, %	0.98 (0.97-1.00) p = 0.04	**0.98 (0.97-0.99) p = 0.04**	0.98 (0.96-0.99) p = 0.0009	**0.98 (0.97-0.99) p = 0.01**
Moderate aortic stenosis	2.31 (1.73-3.12) p < 0.0001	**2.98 (2.08-4.31) p < 0.0001**	1.87 (1.45-2.43) p < 0.0001	**2.34 (1. 72-3.21) p < 0.0001**

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

CI = confidence interval; HF = heart failure; HR = hazard ratio; other abbreviations as in Table 1.

JMP software version 14.0 (SAS Institute, Cary, North Carolina) and SPSS software version 26.0 (IBM Corp. Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. Among the 524 patients with HFrEF (262 with AS and 262 with no AS), mean age was 74.0 ± 10.2 years, and 33% were women. Diabetes was present in 37%, hypertension in 71%, and coronary artery disease in 73% of patients, all well matched between the 2 cohorts (p ≥ 0.29). LVEF was slightly higher in the AS group than in the no-AS group (38.5 ± 9.6% vs. 36.6 ± 7.5%; p = 0.01). In the moderate AS group, AVA was 1.24 ± 0.17 cm^2, mean gradient 15.2 ± 5.3 mm Hg, and peak aortic jet velocity 2.55 ± 0.39 m/s (Table 1). Medications were comparable between groups (all p ≥ 0.11), except for calcium antagonists, which were more often prescribed in the AS group (33% vs. 24%; p = 0 .01). Previous percutaneous coronary interventions appeared more frequent in the AS group (34% vs. 24%; p = 0.01); however, the occurrence of overall previous coronary intervention was comparable in both groups (p = 0.57).

IMPACT OF MODERATE AS ON MORTALITY AND HF HOSPITALIZATION. During a mean follow-up of 2.9 ± 2.2 years, there were 198 deaths. In univariate analysis, moderate AS was associated with excess mortality (HR: 2.31; 95% confidence interval [CI]: 1.72 to 3.12; p < 0.0001) (Central Illustration). After adjustment for age, sex, body mass index, diabetes, hypertension, previous myocardial infarction, dyslipidemia, ischemic cardiomyopathy, New York Heart Association functional class III to IV, and LVEF, moderate AS was the strongest independent predictor of mortality (adjusted HR: 2.98; 95% CI: 2.08 to 4.31; p < 0.0001) (Table 2).

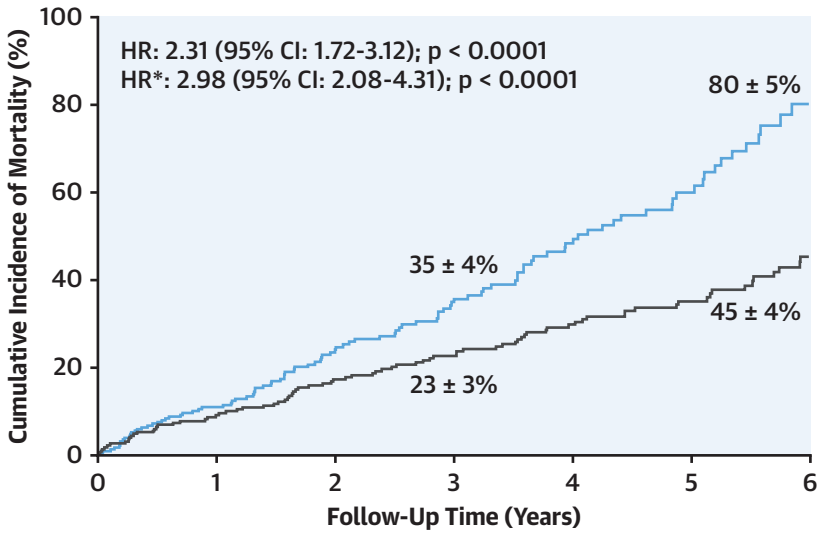
During a mean follow-up of 2.6 ± 2.15 years, there were 123 hospitalization for HF, for a total number of events of the composite of HF hospitalization or death of 270. Moderate AS was the strongest predictor of the composite of HF hospitalization and mortality (HR: 1.87; 95% CI: 1.45 to 2.43; p < 0.0001) in univariate analysis and after comprehensive adjustment (HR: 2.34; 95% CI: 1. 72 to 3.21; p < 0.0001) (Figure 1, Table 2).

IMPACT OF AVR IN PATIENTS WITH MODERATE AS AND HFrEF. When restricting the analysis to patients with AS who underwent AVR during follow-up (n = 44) and their corresponding matched HFrEF patients with no AS (n = 44), moderate AS remained associated with excess mortality (adjusted HR: 2.91; 95% CI: 2.05 to 4.16; p = 0.01).

In the moderate AS group (Supplemental Table 1), AVR performed at a median follow-up time of 10.9 ± 16 months was associated with improved survival (adjusted HR: 0.59; 95% CI: 0.35 to 0.98; p = 0.04). Transcatheter AVR (n = 15) (Supplemental Table 2) appeared to be associated with better survival (adjusted HR: 0.43; 95% CI: 0.18 to 1.00; p = 0.05), whereas surgical AVR (n = 29) was not (adjusted p = 0.92).

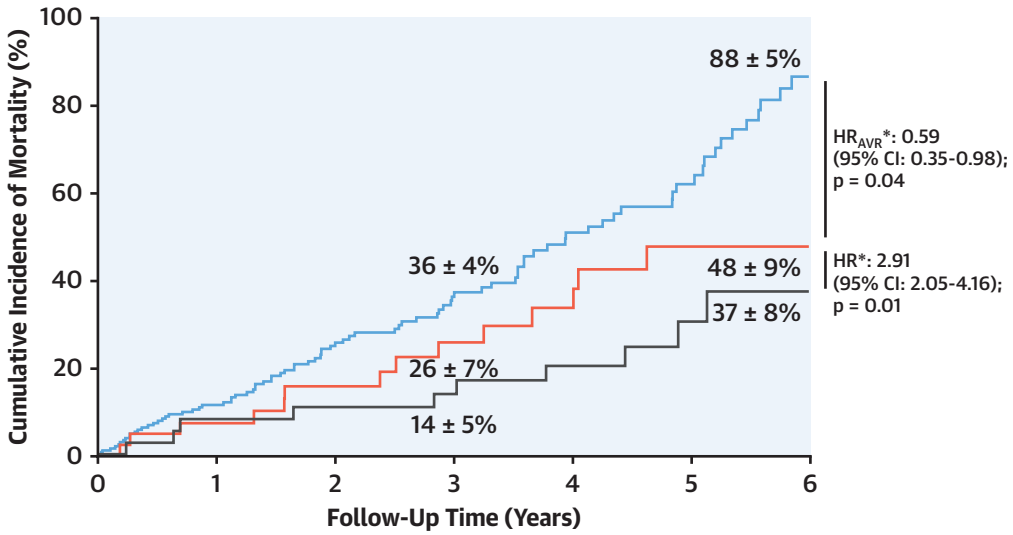
CENTRAL ILLUSTRATION **Incidence of Mortality in Patients With Heart Failure With Reduced Ejection Fraction According to Moderate Aortic Stenosis**

A



Patients at risk:				
— HFrEF	262	178	117	44
— HFrEF + Moderate AS	262	129	51	9

B



Patients at risk:				
— HFrEF + Moderate AS without Intervention	219	103	36	5
— HFrEF + Moderate AS with Intervention	43	26	15	4
— HFrEF	43	32	22	7

Matched Patients

Jean, G. et al. J Am Coll Cardiol. 2021;77(22):2796–803.

Continued on the next page

DISCUSSION

The main findings of this study are that: 1) in patients with HFrEF, the presence of moderate AS has an incremental independent impact on outcomes; 2) moderate AS is indeed independently associated with a ~3-fold increase in mortality; and 3) AVR, and particularly transcatheter AVR, during follow-up was associated with improved survival in patients with HFrEF and moderate AS.

In the general population, the presence of moderate AS has been shown to be associated with a 2.3-fold increase in mortality compared with the absence of AS and a 1.3-fold mortality increase compared with mild AS (3). A previous report with a small number of patients and short follow-up did not find any impact of moderate AS in patients with low LVEF, low-flow, low-gradient, pseudo-severe (i.e., moderate) AS compared with patients with HFrEF and no AS (7). In our series of patients with HFrEF, the presence of moderate AS confirmed by rest or dobutamine stress echocardiography was associated with a 3-fold increase in mortality after comprehensive adjustment for baseline characteristics. These findings provide strong support to the concept that the pressure overload imposed by a moderate AS on the left ventricle may have an important detrimental impact, especially in patients with HFrEF. These findings also raise the hypothesis that early transcatheter AVR may improve survival in patients with HFrEF and moderate AS. This hypothesis is currently being tested in the context of the TAVR-UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure; NCT02661451) trial (10).

The detrimental impact of moderate AS observed in our series of patients with HFrEF may also be related to the progression of AS from moderate to severe during follow-up. However, in the group of patients with moderate AS at baseline included in this study, only 44 had evidence of progression to severe AS and required AVR, and even in patients who underwent AVR during follow-up, moderate AS remained associated with an increased risk of mortality. AVR performed during follow-up was associated with improved survival in patients with HFrEF and moderate AS at baseline. In this subgroup, only transcatheter AVR seems to be associated with survival benefit; this may be related to a less invasive procedure and less prosthesis-patient mismatch, which has been shown to be highly detrimental in patients with HFrEF (11–14). However, given the small number of patients who underwent AVR, this finding is solely hypothesis generating.

STUDY LIMITATIONS. The retrospective nature of the study does not exclude that other potential confounding variables not included in the models could have affected the results. Moreover, the use of surgical or transcatheter AVR was at the discretion of the treating physician. Only a limited number of patients underwent transcatheter AVR, and they had worse baseline characteristics than other patients with AS (data not shown). Hence, the potential survival benefit of transcatheter AVR in the context of patients with HFrEF and moderate AS needs to be validated in randomized controlled trials.

CONCLUSIONS

In patients with HFrEF, moderate AS is independently associated with a ~3-fold increase in mortality. AVR, and especially transcatheter AVR during follow-up, was associated with improved survival in patients with HFrEF and moderate AS. These findings provide support to the concept that early transcatheter AVR may improve outcomes of patients with HFrEF and moderate AS.

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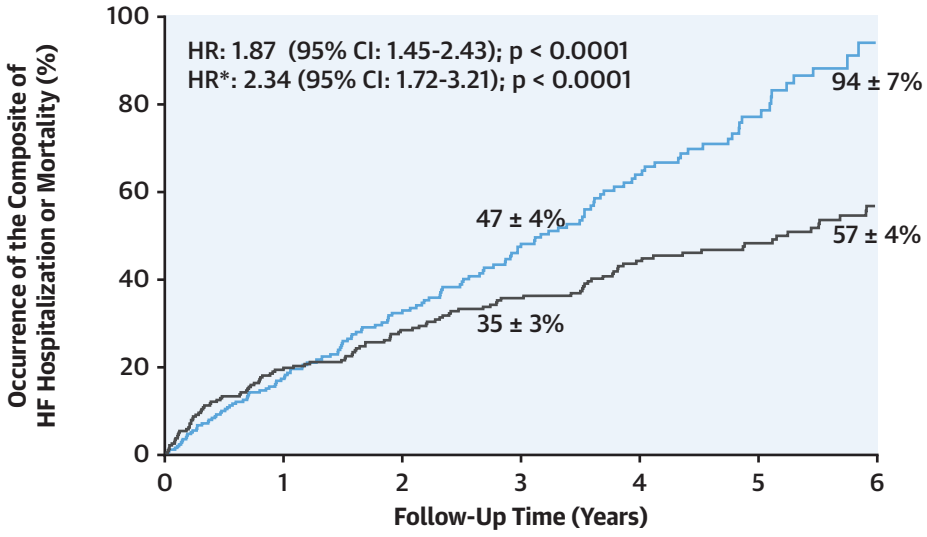
CENTRAL ILLUSTRATION Continued

(A) Excess mortality shown by cumulative incidence curves of patients with (**blue line**) versus without (**black line**) moderate aortic stenosis (AS). **(B)** Excess mortality shown by cumulative incidence curves of patients with moderate AS treated conservatively (**blue line**), patients with moderate AS who underwent aortic valve replacement during follow-up (**red line**), and patients without moderate AS (**black line**). Patients with heart failure with reduced ejection fraction (HFrEF) and moderate AS were matched 1:1 for the following variables, in order of importance: sex, age, estimated glomerular filtration rate, New York Heart Association functional class III to IV, presence of diabetes, left ventricular ejection fraction, and body mass index, with patients with HFrEF but without AS. *Adjusted for were age, sex, body mass index, diabetes, hypertension, prior myocardial infarction, dyslipidemia, ischemic cardiomyopathy, New York Heart Association functional class III to IV, estimated glomerular filtration rate, aortic regurgitation greater than mild, mitral regurgitation greater than mild, and left ventricular ejection fraction. CI = confidence interval; HR = hazard ratio; HR_{AVR} = hazard ratio for aortic valve replacement.

FIGURE 1 Cumulative Incidence of the Composite of HF Hospitalization or Mortality



Patients at risk:

— HFrEF	262	154	92	40
— HFrEF + Moderate AS	262	119	39	3

The cumulative incidence curves show the occurrence of the composite of heart failure (HF) hospitalization or mortality according to the presence **(blue line)** or absence **(black line)** of moderate aortic stenosis (AS) in patients with heart failure with reduced ejection fraction (HFrEF). *Adjusted for were age, sex, body mass index, diabetes, hypertension, previous myocardial infarction, dyslipidemia, ischemic cardiomyopathy, New York Heart Association functional class III to IV, estimated glomerular filtration rate, aortic regurgitation greater than mild, mitral regurgitation greater than mild, and left ventricular ejection fraction. CI = confidence interval; HR = hazard ratio.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients with HFrEF, moderate AS has an adverse impact on survival that can be ameliorated by aortic valve replacement, especially when performed by a transcatheter approach (TAVR).

TRANSLATIONAL OUTLOOK: Ongoing randomized trials will help clarify the role of TAVR in patients with HFrEF and moderate AS.

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KEY WORDS aortic stenosis, heart failure with reduced ejection fraction, hospitalization, survival

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