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Impact of Mild and Moderate Aortic Stenosis in Acute Heart Failure: Insights From RELAX-AHF-2

CONSTANTIJN S. VENEMA, MD[1] MARCO METRA, MD[2] LAURA STAAL, PhD[1]
IRIS E. BELDHUIS, MD, PhD[1] GAD COTTER, MD[3] BETH A. DAVISON, PhD[3]
G. MICHAEL FELKER, MD[4] GERASIMOS FILIPPATOS, MD, PhD[5] BARRY H. GREENBERG, MD[6]
PETER S. PANG, MD[7] PIOTR PONIKOWSKI, MD[8] CLAUDIO GIMPELEWICZ, MD[9]
ERIK LIPSIC, MD, PhD[1] ADRIAAN A. VOORS, MD, PhD[1] JOHN R. TEERLINK, MD[10] and
JOANNA J. WYKRZYKOWSKA, MD, PhD[1]

Groningen, The Netherlands; Brescia, Italy; Durham, North Carolina, San Diego, California, Indianapolis, Indiana, and San Francisco, California, USA; Athens, Greece; Wroclaw, Poland; and Basel, Switzerland

ABSTRACT

Background: Aortic stenosis leads to increased afterload, which may be detrimental in a failing left ventricle and has been associated with an increased risk of hospitalizations due to heart failure and mortality in chronic heart failure. The prevalence and impact of aortic stenosis in acute heart failure are less well described. This post hoc analysis aimed to evaluate the prevalence and prognostic impact of aortic stenosis in a large cohort of patients hospitalized due to acute heart failure.

Methods and Results: All patients from the Relaxin in Acute Heart Failure 2 (RELAX-AHF-2) trial with data available on aortic stenosis severity were included in the present analysis (n = 6241). Patients with severe aortic stenosis were ineligible for RELAX-AHF-2. Baseline characteristics, in-hospital outcomes and 180-day clinical outcomes were compared between patients with and without aortic stenosis. Mild or moderate aortic stenosis was present in 454 (7.3%) patients. Patients with aortic stenosis were older, more commonly female, had more comorbidities, and had higher left ventricular ejection fractions compared to patients without aortic stenosis. Mild or moderate aortic stenosis was associated with a higher risk of cardiovascular mortality or readmission for heart or renal failure (unadjusted hazard ratio (HR) 1.32, 95% CI 1.11–1.57). This association was maintained when adjusting for age and sex, but not after comprehensive multivariable adjustment (adjusted HR 1.04, 95% CI 0.82–1.32).

Conclusion: The presence of mild or moderate aortic stenosis reflects an increased risk profile in patients with acute heart failure, but it is not an independent predictor of poor clinical outcomes. (*J Cardiac Fail 2026;32:419–429*)

Key words: Aortic stenosis, acute heart failure, clinical trial, valvular heart disease, structural heart disease.

From the [1]University of Groningen, University Medical Centre Groningen, Department of Cardiology and Cardiothoracic Surgery, Heart Centre, Groningen, The Netherlands; [2]Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [3]Momentum Research, Inc, Durham, NC, USA; [4]Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; [5]Department of Cardiology, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [6]Division of Cardiology, University of California, San Diego, CA, USA; [7]Department of Emergency Medicine, Indiana University School of Medicine and the Regenstrief Institute, Indianapolis, IN, USA; [8]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; [9]Novartis Pharma AG, Basel, Switzerland and [10]Section of Cardiology, San Francisco Veterans Affairs Medical Centre and School of Medicine, University of California San Francisco, San Francisco, CA, USA.

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Reprint requests: Joanna. J. Wykrzykowska, MD, PhD University of Groningen, University Medical Centre Groningen, Hanzeplein 1, 9700RB, Groningen, The Netherlands. Tel: 0031 503616161. E-mail: j.j.wykrzykowska@umcg.nl

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Introduction

Aortic stenosis is 1 of the most common forms of valvular heart disease worldwide, and the prevalence is growing with the aging of the population.[1,2] Aortic stenosis increases afterload on the heart, which can be detrimental in a failing left ventricle. Indeed, multiple studies have shown that a reduced left ventricular ejection fraction is associated with worse outcomes in patients with aortic stenosis, even when asymptomatic.[3–6] Therefore, guidelines recommend a class I indication for aortic valve replacement in asymptomatic severe aortic stenosis with reduced left ventricular function.[7,8]

Not only severe aortic stenosis, but even moderate aortic stenosis, has been associated with an increased risk hospitalization due to heart failure (HF) and mortality in patients with chronic HF with reduced left ventricular ejection fraction.[9–11] However, the prevalence and impact of aortic stenosis on outcomes in acute HF are less well described. Earlier studies report a prevalence of aortic stenosis of approximately 12%–19% in patients with acute HF.[12,13] In a large community-based study, mild or moderate aortic stenosis was independently associated with all-cause 1-year mortality in patients with acute decompensated HF with both reduced and preserved ejection fraction. However, this study did not include patients younger than 55 years, and follow-up data on readmission rates were lacking.

Therefore, we aimed to evaluate the prevalence and prognostic impact of aortic stenosis in a large cohort of patients who were hospitalized for acute HF across the full range of left ventricular ejection fraction.

Methods

Study Design and Study Population

Patients from the Relaxin in Acute Heart Failure 2 (RELAX-AHF-2) trial with available data on aortic stenosis were included. The study design of the RELAX-AHF-2 trial has been described previously (ClinicalTrials.gov NCT01870778).[14,15] Briefly, this was a multicenter, randomized, double-blind, placebo-controlled phase III clinical trial including 6545 patients hospitalized with acute HF at 546 centers in 35 countries worldwide between October 2013 and February 2017. The trial complied with the Declaration of Helsinki, was approved in each participating center, and every participant provided written informed consent.

Patients were included in the trial if they met all of the following criteria: age $\geq$ 18 years; dyspnea, pulmonary congestion on chest radiograph, and elevated B-type natriuretic peptide (BNP) $\geq$ 500 pg/mL or N-terminal pro-BNP (NT-proBNP) $\geq$ 2000 pg/mL (BNP $\geq$ 750 pg/mL or NT-proBNP $\geq$ 3000 pg/mL for patients $\geq$ 75 years of age or with atrial fibrillation), systolic blood pressure $\geq$ 125 mmHg, mild-to-moderate renal impairment (estimated glomerular filtration rate [eGFR] $\geq$ 25 and $\leq$ 75 mL/min/1.73 m^2), and persistent HF symptoms after initial intravenous loop diuretic treatment (equivalent to $\geq$ 40 mg of furosemide). Importantly, patients with severe aortic stenosis were ineligible for participation. Detailed inclusion and exclusion criteria have been reported previously.[14,15]

Eligible patients were randomized to receive either intravenous serelaxin (30 mcg/kg/day) for 48 hours or placebo, on top of standard care, within 16 hours of admission. In the current analysis, both trial arms were pooled, because serelaxin had a neutral effect with regard to the coprimary and key secondary endpoints.[15]

Definition of Aortic Stenosis

In the RELAX-AHF-2 trial, the aortic stenosis severity grade was recorded by local investigators as none, mild, moderate, or severe, according to standard echocardiographic definitions.[7,16] Quantitative measurements of echocardiographic aortic valve parameters were not collected. Patients with an investigator-reported history of surgical correction of aortic stenosis were excluded from the current analysis; only patients with available data on aortic stenosis severity were included. To check for potential selection bias, baseline characteristics of patients with unknown aortic stenosis status were compared to the characteristics of those included in the analysis. Severe aortic stenosis was an exclusion criterion of the trial, so this analysis included patients with no, mild or moderate aortic stenosis.

Study Endpoints

Patients were assessed daily during hospitalization for 5 days or until discharge (whichever occurred first) and were followed for up to 180 days after randomization. All deaths and hospitalizations reported through day 180 were adjudicated by an independent Clinical Events Committee.

The primary endpoint of the current analysis was a composite of cardiovascular death or rehospitalization for HF or renal failure (RF) through day 180. Secondary endpoints were all-cause death, cardiovascular death, rehospitalization for HF or RF through day 180, and length of hospital stay.

Statistical Analysis

Continuous variables are reported as median and interquartile range (25th percentile; 75th percentile), and categorical variables are presented as number and percentage. Baseline characteristics, in-hospital outcomes and clinical outcomes were compared in patients with

mild or moderate aortic stenosis vs no aortic stenosis by using Mann-Whitney tests for continuous variables and χ^2 tests for categorical variables.

Event-free survival with regard to the various study endpoints, according to the presence of mild or moderate aortic stenosis, was estimated by using the Kaplan-Meier method, and groups were compared using Cox proportional hazards regression. First, we examined the crude association between mild or moderate aortic stenosis with each study endpoint and then in a model adjusted for age, sex and a composite of NT-proBNP or BNP Z-score. The composite of BNP or NT-proBNP Z-score was calculated by subtracting each value by its respective mean, dividing by the standard deviation and merging the standardized values. The BNP Z-score was used when the NT-proBNP Z-score was not available. Next, we adjusted the models for several confounders that were univariably associated with each respective endpoint at P value < 0.1 (Supplementary Tables S1−S4). In addition, all models were adjusted for sex, study treatment, edema, and baseline intravenous (IV) loop diuretic total dosage, as these were considered relevant by clinical judgment.[17] Furthermore, all models were adjusted for left ventricular ejection fraction based on its association with clinical outcomes.[17] The models for the composite endpoint at day 180 and HF/RF rehospitalization at day 180 were adjusted for creatinine (μmol/L), hemoglobin (g/L), sodium (mmol/L), blood urea nitrogen (mg/dL), cerebrovascular accident, depression, asthma/bronchitis/chronic obstructive pulmonary disease, atrial fibrillation/flutter, peripheral artery disease, heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg), edema, IV loop diuretics total dosage (in furosemide units) at baseline, history of diabetes mellitus, prior HF hospitalization, study treatment (serelaxin v. placebo), grouped geographical region, composite of NT-proBNP or BNP Z-score, sex, age (years), and left ventricular ejection fraction per 5% increase. The models for cardiovascular death and all-cause death at day 180 omitted 4 variables (atrial fibrillation/flutter, depression, geographical region, and heart rate) from the variable set described above and included body mass index. All models were analyzed by using a complete-case approach.

Subgroup analyses in patients with left ventricular ejection fraction $< 50\%$ and left ventricular ejection fraction $\geq 50\%$ were performed to assess the effect of mild or moderate aortic stenosis on the study endpoints by using Cox proportional hazard models with interaction between mild or moderate aortic stenosis and left ventricular ejection fraction as a binary variable (left ventricular ejection fraction $< 50\%$ or $\geq 50\%$). In addition, interaction with study treatment (serelaxin or placebo) was tested.

All statistical analyses were performed in R version 4.4 (R Core Team, 2024) and 2-sided P values $< .05$ were considered statistically significant.

Results

Baseline Characteristics

Of 6545 patients enrolled in RELAX-AHF-2, 187 patients (2.9%) had histories of severe aortic stenosis with surgical correction of the aortic valve and were excluded from analysis. In 116 patients, information on aortic stenosis severity was not available. Compared to patients included in the analysis, patients with unknown aortic stenosis were older and had a higher proportion of de novo acute heart failure (Supplementary Table S5). Thus, 6241 patients were included in the current analysis, of whom 5787 patients (92.7%) had no aortic stenosis, 277 patients had mild aortic stenosis (4.4%), and 177 patients (2.8%) had moderate aortic stenosis. Patients with mild and moderate aortic stenosis were grouped for subsequent analyses to increase statistical power (n = 454, 7.3%), because both mild and moderate aortic stenoses have been associated with increased risks of mortality compared to the absence of aortic stenosis.[18]

Compared to patients without aortic stenosis, patients with mild or moderate aortic stenosis were older, more commonly female and white, and had more comorbidities (Table 1). Patients with mild or moderate aortic stenosis had higher baseline left ventricular ejection fractions, more commonly had HF with preserved ejection fraction, and more commonly had moderate or severe mitral regurgitation.

In-hospital Outcomes and Long-term Outcomes

Table 2 and Supplementary Fig. S1 show the in-hospital outcomes in patients with and without mild or moderate aortic stenosis. The median length of hospital stay was slightly longer in patients with mild or moderate aortic stenosis compared to patients without aortic stenosis (6.9 days vs 6.8 days; $P = 0.038$). In addition, patients with aortic stenosis had higher rates of residual orthopnea (58 vs 51%; $P = 0.019$). Changes in renal function during hospitalization, diuretic responses, and signs of congestion at discharge were similar.

Fig. 1 shows the cumulative incidence of all-cause mortality, HF/RF hospitalizations, cardiovascular mortality, and the composite endpoint through 180 days in patients with and without mild or moderate aortic stenosis. When further stratified by no, mild or moderate aortic stenosis, moderate aortic stenosis was associated with the highest event rates, followed by mild aortic stenosis (Supplementary Fig. S2).

The composite endpoint of cardiovascular death or HF/RF rehospitalization occurred in 30.2% (n = 137) of patients with mild or moderate aortic stenosis compared to 23.9% (n = 1384) of patients without aortic stenosis (unadjusted HR 1.32, 95% CI 1.11−1.57; $P = .003$) (Table 3). Mild or moderate aortic stenosis was

Table 1 Baseline characteristics of patients without aortic stenosis and patients with mild or moderate aortic stenosis

	No AS (n = 5787)	Mild or Moderate AS (n = 454)	*P* Value	% missing
Demographics				
Age	74 (65; 81)	79 (74; 84)	<0.001	0.00
Female sex	2298 (39.7)	227 (50)	<0.001	0.00
White	5288 (91.4)	443 (97.6)	<0.001	0.00
Geographic Region			<0.001	0.00
America/other	1292 (22.3)	55 (12.1)		
Eastern Europe	2554 (44.1)	196 (43.2)		
Western Europe	1941 (33.5)	203 (44.7)		
Medical History				
Hypertension	5183 (89.6)	416 (91.6)	0.188	0.00
Diabetes mellitus	2646 (45.7)	213 (46.9)	0.665	0.05
Atrial fibrillation	2899 (50.1)	263 (57.9)	0.002	0.00
Peripheral artery disease	741 (12.8)	81 (17.8)	0.003	0.00
COPD	901 (15.6)	74 (16.3)	0.730	0.00
CKD (baseline eGFR <60 mL/min/1.73m^2)	3978 (68.8)	321 (70.7)	0.434	0.11
Smoking History			0.021	0.50
Current	650 (11.3)	33 (7.3)		
Former	1982 (34.4)	152 (33.7)		
Never	3127 (54.3)	266 (59)		
Depression	539 (9.3)	39 (8.6)	0.669	0.00
Cerebrovascular accident	876 (15.1)	84 (18.5)	0.065	0.00
Hyperthyroidism	193 (3.3)	14 (3.1)	0.879	0.00
Hypothyroidism	606 (10.5)	61 (13.4)	0.059	0.00
Prior CABG	799 (13.8)	74 (16.3)	0.160	0.00
Prior PCI	1376 (23.8)	119 (26.2)	0.267	0.03
Prior history of HF	4270 (73.8)	353 (77.8)	0.075	0.06
Primary HF Etiology			0.052	26.04
Ischemic	2277 (53.4)	208 (58.9)		
Nonischemic	1986 (46.6)	145 (41.1)		
Prior HF hospitalization	2932 (54.3)	247 (57.2)	0.270	6.57
NYHA Class (1 month prior to index admission)			0.349	0.00
I	193 (3.3)	11 (2.4)		
II	1626 (28.1)	136 (30)		
III	1924 (33.2)	151 (33.3)		
IV	445 (7.7)	43 (9.5)		
Missing	1599 (27.6)	113 (24.9)		
Cardiac resynchronization therapy	229 (4)	12 (2.6)	0.203	0.00
Implantable cardioverter defibrillator	524 (9.1)	22 (4.8)	0.003	0.00
Aortic regurgitation	1124 (19.4)	214 (47.1)	<0.001	0.00
Physical Examination and Vital Signs				
Body mass index (kg/m^2)	29 (25.4; 33.3)	28.3 (25.1; 32.1)	0.014	1.94
Weight (kg)	82 (70; 96)	78 (67.6; 90)	<0.001	0.08
Systolic blood pressure (mmHg)	139 (130; 150)	140 (131; 150)	0.169	0.00
Diastolic blood pressure (mmHg)	80 (70; 89)	76 (67; 83)	<0.001	0.00
Heart rate (beats/min)	80 (70; 92)	76 (67; 88)	<0.001	1.41
Respiratory rate (breaths/min)	21 (18; 24)	20 (18; 24)	0.141	0.99
Composite congestion score	5 (3; 6)	5 (3; 6)	0.181	8.67
Any sign of congestion	5243 (99.1)	403 (98.8)	0.736	8.67
Dyspnea on Exertion			0.108	1.09
None	21 (0.4)	4 (0.9)		
Mild	210 (3.7)	24 (5.3)		
Moderate	2326 (40.7)	182 (40.4)		
Severe (including dyspnea at rest)	3165 (55.3)	241 (53.4)		
Edema			0.287	0.59
None	863 (15)	82 (18.1)		
1+	1724 (30)	136 (30)		
2+	2009 (34.9)	154 (34)		
3+	1155 (20.1)	81 (17.9)		
Jugular Venous Pulse			0.014	8.62
< 6 cm	1480 (28)	124 (30.4)		
6–10 cm	2524 (47.7)	165 (40.4)		
> 10 cm	1291 (24.4)	119 (29.2)		

(*Continued*)

Table 1. (*Continued*)

	No AS (n = 5787)	Mild or Moderate AS (n = 454)	*P* Value	% missing
Orthopnea			0.179	0.64
None	213 (3.7)	26 (5.7)		
1 pillow (10 cm)	961 (16.7)	78 (17.2)		
2 pillows (20 cm)	2750 (47.8)	210 (46.4)		
> 30 degrees	1824 (31.7)	139 (30.7)		
Rales			0.417	0.63
No rales	344 (6)	29 (6.4)		
Rales < 1/3	2297 (40)	171 (37.7)		
Rales 1/3−2/3	2666 (46.4)	209 (46.1)		
Rales > 2/3	442 (7.7)	44 (9.7)		
Laboratory Values				
NT-proBNP (pg/mL)	6037 (3521; 9811)	6681 (3642; 11877)	0.094	19.92
BNP (pg/mL)	1130.4 (758.2; 1908.2)	1179.9 (759.3; 1507.9)	0.402	80.08
Blood urea nitrogen (mg/dL)	24.1 (18.7; 31.9)	25.8 (18.9; 35)	0.010	4.02
Creatinine μmol/L	113.2 (96; 138.8)	111 (91; 141.4)	0.141	0.18
eGFR (mL/min/1.73 m^2)	52 (40.9; 63.3)	48 (38.1; 63)	0.016	0.21
Urea/creatinine (ratio)	40.8 (33; 50)	43.2 (35.4; 52.7)	<0.001	25.11
Sodium (mmol/L)	140 (137.7; 142)	140 (137.7; 142)	0.959	0.91
Potassium (mmol/L)	4.3 (3.9; 4.7)	4.4 (4.0; 4.8)	0.008	1.73
Hemoglobin (g/L)	127 (113−141)	121.1 (109−135)	<0.001	0.56
Echocardiographic Data				
LVEF (%) at index hospitalization	37 (28-49.5)	42 (33-50)	<0.001	6.18
LVEF Categories			<0.001	6.18
LVEF <40%	2911 (53.6)	162 (38.6)		
LVEF 40%-49%	1166 (21.5)	117 (27.9)		
LVEF ≥50%	1358 (25)	141 (33.6)		
Moderate-severe MR	2934 (50.7)	338 (74.4)	<0.001	0.00
Baseline Medical Therapy				
ACEis or ARBs	3821 (66)	291 (64.1)	0.433	0.00
Beta-blockers	4104 (70.9)	337 (74.2)	0.148	0.00
MRAs	1662 (28.7)	123 (27.1)	0.493	0.00
Calcium channel blockers	1249 (21.6)	118 (26)	0.033	0.00
Digoxin	635 (11)	49 (10.8)	0.968	0.00
Oral loop diuretics	3519 (60.8)	294 (64.8)	0.107	0.00
Oral loop diuretics total daily (mg)	40 (40; 80)	40 (25; 80)	0.436	39.02

The composite congestion score ranges from 0−8 points and is calculated as the sum of scores for orthopnea (0−3), peripheral edema (0−3) and jugular venous pulse (0−2).

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aortic stenosis; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

significantly associated with the composite endpoint in multivariable analysis when adjusting for age, sex and natriuretic peptides (adjusted HR 1.25, 95% CI 1.05−1.50; *P* = .017) but not when adjusting for the full multivariable model (adjusted HR 1.04, 95% CI 0.82−1.32; *P* = .76).

All-cause mortality occurred in 17.0% (n = 103) of patients with mild or moderate aortic stenosis compared to 10.8% (n = 1063) of patients without aortic stenosis (unadjusted HR 1.61, 95% CI 1.27−2.04; *P* < .001) (Table 3). Mild or moderate aortic stenosis was significantly associated with all-cause mortality in multivariable analysis when adjusting for age, sex and natriuretic peptides (adjusted HR 1.38, 95% CI 1.08−1.76; *P* = 0.013) but not when adjusting for the full model (adjusted HR 1.25, 95% CI 0.91−1.72; *P* = 0.19).

Table 4 shows the results of the subgroup analysis in patients with left ventricular ejection fraction < 50% and left ventricular ejection fraction ≥ 50%, which showed similar associations without significant interaction. However, we found a significant interaction between mild or moderate aortic stenosis and study treatment for the composite endpoint, all-cause mortality, and cardiovascular mortality, with the risk of events being higher in patients with aortic stenosis receiving serelaxin (Table 4). This is depicted in Supplementary Fig. S3.

Discussion

This analysis investigating the impact of mild and moderate aortic stenosis in a large cohort of patients admitted with acute HF showed that: (1) the prevalence of mild or moderate aortic stenosis was ~ 7%; (2) patients with aortic stenosis were older, more commonly female, and had more cardiovascular comorbidities; and (3) aortic stenosis

Table 2 In-hospital outcomes of patients without aortic stenosis and patients with mild or moderate aortic stenosis

	No AS (n = 5787)	Mild or Moderate AS (n = 454)	*P* Value	% missing
Diuretic Dosages and Length of Stay				
Total IV loop diuretics dosage through day 5 (mg)	220 (120; 375)	220 (120; 380)	0.981	0.00
Total oral loop diuretics dosage through day 5 (mg)	220 (120; 360)	200 (80; 280)	0.131	86.08
Length of ICU and/or CCU stay (days)	2 (0; 4)	2 (0; 5)	0.875	0.00
Length of hospital stay (days)	6.8 (5−9.9)	6.9 (5.1; 11.7)	0.038	0.00
Diuretic Response and Congestion Status at Day 5				
Weight loss at day 5 (% change)	−3.5 (-6.2;-1.5)	−3.5 (-5.8;-1.6)	0.698	8.03
Diuretic response through day 5 (kg of weight loss per 40 mg of furosemide)	−0.4 (-0.8;-0.1)	−0.4 (-0.8;-0.1)	0.697	44.91
Hemoconcentration (increase of hemoglobin) at day 5	2321 (48.4)	175 (46.4)	0.498	17.08
Dyspnea on Exertion at Day 5			0.245	3.56
None	1759 (31.5)	124 (28.6)		
Mild	2503 (44.8)	194 (44.7)		
Moderate	924 (16.5)	75 (17.3)		
Severe (including dyspnea at rest)	399 (7.1)	41 (9.4)		
Orthopnea at Day 5			0.019	3.41
None	3227 (57.7)	220 (50.6)		
1 pillow (10 cm)	1598 (28.6)	152 (34.9)		
2 pillows (20 cm)	401 (7.2)	30 (6.9)		
> 30 degrees	367 (6.6)	33 (7.6)		
Edema (any degree) at day 5	1795 (32.1)	141 (32.3)	0.96	3.41
Jugular Venous Pulse at Day 5			0.326	9.65
< 6 cm	4151 (79.2)	301 (76)		
6−10 cm	733 (14)	63 (15.9)		
> 10 cm	359 (6.8)	32 (8.1)		
Rales (any degree) at day 5	1266 (22.6)	108 (24.8)	0.337	3.43
Any sign of congestion at day 5	2963 (56.5)	241 (61)	0.093	9.69
Change in Vital Signs at Day 5 (% Change From Baseline)				
Systolic blood pressure at day 5 (% change)	−10.8 (-18; -3.6)	−10.7 (-18.3; -4.6)	0.552	5.37
Diastolic blood pressure at day 5 (% change)	−9 (-19.6; 1.6)	−7.9 (-20; 3)	0.463	5.38
Respiratory rate at day 5 (% change)	−16.7 (-28.6; -5.6)	−16.7 (-28.6; 0)	0.027	12.32
Change in Renal Function at Day 5 (% Change From Baseline) and WRF				
Creatinine (% change from baseline)	3.4 (-10.1; 19.2)	4.2 (-8.5; 19.4)	0.547	14.76
eGFR (% change from baseline)	−3.8 (-18.3; 13.1)	−4.4 (-19.5; 11.6)	0.524	15.54
Blood urea nitrogen (% change from baseline)	17.4 (-8.2; 50.9)	20.1 (9.8; 56.2)	0.612	18.96
Urea/Creatinine ratio (% change from baseline)	12.6 (-7.3; 36.7)	10.5 (-8.3; 41.9)	0.995	35.88
WRF through day 5, n and % of patients	982 (19.9)	74 (19)	0.72	14.76

AS, aortic stenosis; CCU, coronary care unit; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; WRF worsening renal function.

was associated with higher mortality rates and higher risk of hospitalizations due to HF or renal failure. However, this association was not statistically significant after comprehensive multivariable adjustment.

Data describing the prevalence of aortic stenosis in acute HF are limited. In the Atherosclerosis Risk in Communities (ARIC) study, a community surveillance study in the United States, the overall prevalence of any degree of aortic stenosis in patients with acute HF was 15.4%, and mild or moderate aortic stenosis was present in 11.8% of patients.[12] In the current analysis, we found that mild or moderate aortic stenosis was present in 7.3% of patients admitted with acute HF. It should be noted that severe aortic stenosis was an exclusion criterion in the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) trial, which may have resulted in a relative underrepresentation of aortic stenosis in that trial. In addition, the RELAX-AHF-2 trial included primarily patients from Europe. Nonetheless, the characteristics of the ARIC study cohort were strongly similar in terms of demographics and comorbidities, suggesting that the overall prevalence of mild to moderate aortic stenosis in patients with acute HF is approximately 7%−12%.

With respect to demographics, we observed that patients with aortic stenosis were older compared to patients without aortic stenosis. It is well known that the risk of aortic stenosis increases with age, and the prevalence is particularly high in elderly individuals.[19] In addition, the older age in patients with aortic stenosis could be attributed partly to the higher proportion of females in this group, who tend to present at an older age.[20] The higher proportion of females in patients with aortic stenosis could also be related to the observation that females respond with less concentric remodeling to similar degrees of aortic stenosis compared to males.[21,22] This results in higher wall stress and filling pressures, which might make women with aortic stenosis more prone to develop acute HF.

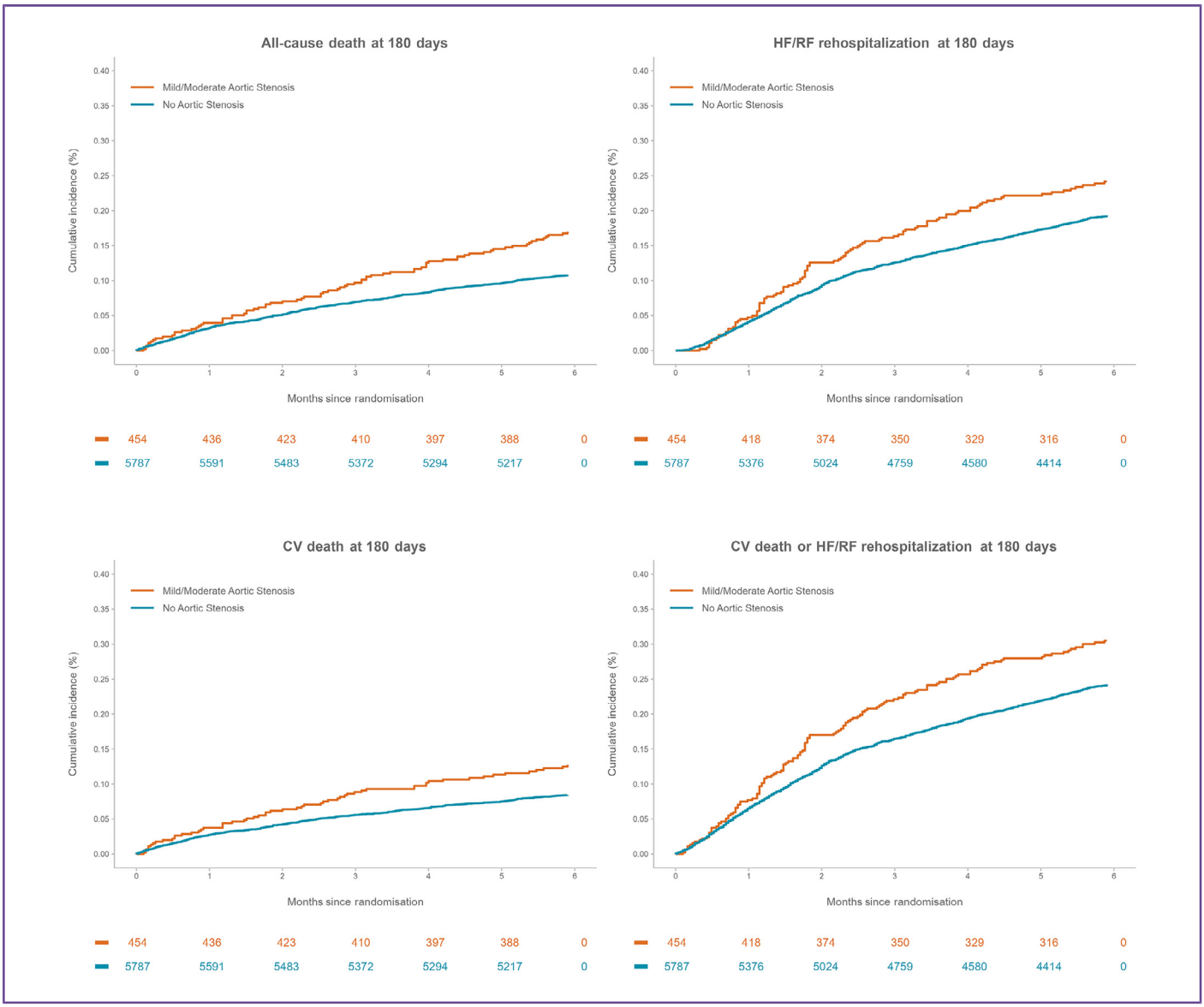

Fig. 1. Event-free survival through 180 days (1-Kaplan Meier curves) of patients without aortic stenosis and patients with mild or moderate aortic stenosis for all-cause mortality (upper left); heart failure or renal failure rehospitalization (upper right); cardiovascular mortality (lower left); and the composite of cardiovascular mortality and heart failure or renal failure rehospitalization (lower right). CV, death: cardiovascular death; HF,heart failure; RF, renal failure.

Interestingly, baseline left ventricular ejection fraction was higher in patients with aortic stenosis; hence, the proportion of patients with HFpEF. This may be a consequence of the pressure overload's initially leading to left ventricular hypertrophy and myocardial fibrosis, resulting in diastolic dysfunction. As aortic stenosis progresses to a severe stage, left ventricular function may decline, and a reduced ejection fraction can develop.[23] Patients with severe aortic stenosis were excluded from the current study, so that might explain why we did not find an association with reduced ejection fraction.

Furthermore, natriuretic peptide levels were similar in patients with and without aortic stenosis. Previous studies have shown that natriuretic peptide levels show correlation with aortic stenosis severity, which is related to increasing levels of left ventricular wall stress.[24,25] However, NT-proBNP levels are normal in most patients with mild or moderate aortic stenosis.[26] It is likely that the severity of aortic stenosis in this study was inadequate to have a significant effect on natriuretic peptide levels in patients with acute HF. In addition, patients without aortic stenosis more often had HFrEF, which is associated with higher natriuretic peptide levels than HFpEF. On the other hand, patients with aortic stenosis more often had atrial fibrillation and mitral regurgitation, which are associated with higher natriuretic peptide levels. These differences may, therefore, be responsible for similar levels, on average.

The presence of aortic stenosis was associated with higher rates of rehospitalization and mortality in

Table 3 Associations of mild or moderate aortic stenosis with study endpoints at 180 days, with no aortic stenosis as the reference group

	Hazard Ratio (95% CI)	N	*P* Value
Univariable Analysis			
CV death or HF/RF rehospitalization at 180 days	1.32 (1.11−1.57)	6241	0.003
CV death at 180 days	1.54 (1.17−2.03)	6241	0.004
All-cause death at 180 days	1.61 (1.27−2.04)	6241	<0.001
HF/RF rehospitalization at 180 days	1.30 (1.06−1.59)	6241	0.015
Adjusted for Age, Sex and the Composite of BNP/NT-proBNP			
CV death or HF/RF rehospitalization at 180 days	1.25 (1.05−1.50)	6210	0.017
CV death at 180 days	1.37 (1.03−1.81)	6210	0.037
All-cause death at 180 days	1.38 (1.08−1.76)	6210	0.013
HF/RF rehospitalization at 180 days	1.26 (1.03−1.55)	6210	0.033
Full Model			
CV death or HF/RF rehospitalization at 180 days	1.04 (0.82−1.32)	4186	0.755
CV death at 180 days	1.14 (0.78−1.67)	4159	0.492
All-cause death at 180 days	1.25 (0.91−1.72)	4159	0.186
HF/RF rehospitalization at 180 days	1.00 (0.76−1.31)	4186	0.981

Hazard ratios depict the effect of mild or moderate aortic stenosis on each respective clinical outcome relative to no aortic stenosis.
CV death, cardiovascular death; HF, heart failure; RF, renal failure.

univariable analysis. This association remained present after adjusting for age, sex and natriuretic peptides and is, therefore, not confounded by patients' with aortic stenosis being older. However, aortic stenosis did not remain independently associated with outcomes after multivariable adjustment. These models have previously been used to adjust for clinically relevant confounders in this trial.[17,27] The lack of independent association between aortic stenosis and mortality is different from the findings of the ARIC study, which showed that mild or moderate aortic stenosis was independently associated with all-cause mortality at 1 year across the spectrum of left ventricular ejection. We performed a more extensive adjustment for potential confounders and evaluated outcomes at 6 months compared to 1 year, which might explain the difference, as more events would have accrued at 1 year. Furthermore, patients in the RELAX-AHF-2 trial were required to have a systolic blood pressure above 125 mmHg at inclusion, which excludes patients with cardiogenic shock and may have resulted in more patients' having low-risk acute HF. However, the point estimates of the hazard and odds ratios were similar between this study

Table 4 Subgroup analysis in patients with LVEF < 50% and LVEF ≥ 50%, and patients receiving placebo or serelaxin

	Subgroup	Number of Patients	HR (95% CI)	*P* Value Interaction
Composite Endpoint				0.855
LVEF subgroup	LVEF < 50%	4720	1.30 (1.05. 1.60)	
	LVEF ≥ 50%	1135	1.25 (0.85. 1.83)	
Study Treatment				0.025
	Placebo	3123	1.08 (0.83; 1.40)	
	Serelaxin	3118	1.61 (1.27; 2.05)	
CV Death				0.833
LVEF subgroup	LVEF < 50%	4720	1.42 (1.01. 1.99)	
	LVEF ≥ 50%	1135	1.54 (0.82. 2.90)	
Study Treatment				0.003
	Placebo	3123	0.96 (0.61; 1.52)	
	Serelaxin	3118	2.26 (1.60; 3.20)	
All-Cause Death				0.414
LVEF subgroup	LVEF < 50%	4720	1.62 (1.21. 2.16)	
	LVEF ≥ 50%	1135	1.25 (0.72. 2.18)	
Study Treatment				0.002
	Placebo	3123	1.09 (0.75; 1.58)	
	Serelaxin	3118	2.29 (1.69; 3.12)	
HF/RF Rehospitalization				0.802
LVEF subgroup	LVEF < 50%	4720	1.33 (1.05. 1.69)	
	LVEF ≥ 50%	1135	1.25 (0.80. 1.95)	
Study Treatment				0.345
	Placebo	3123	1.18 (0.89; 1.56)	
	Serelaxin	3118	1.43 (1.07; 1.92)	

Hazard ratios depict the effect of mild or moderate aortic stenosis on each respective clinical outcome relative to no aortic stenosis.
CV death, cardiovascular death; HF, heart failure; LVEF, left ventricular ejection fraction; RF, renal failure.

and the ARIC study, respectively. In addition, the 1-year overall mortality rate in patients with mild or moderate aortic stenosis in the ARIC cohort was 35%, which is approximately twice the 180-day all-cause mortality rate of 17% in the current analysis. Therefore, our results signify that the presence of aortic stenosis reflects a higher risk of poor outcome after admission for acute HF. Moderate aortic stenosis was shown to be associated with increased mortality rates, compared with mild or no aortic stenosis, also in a recent meta-analysis of 25 studies including 12,143 patients with 3.7 years of follow-up.[28] The results of our study may, thus, support recent randomized trials investigating the effects on outcomes of transcatheter aortic valve replacement in patients with HF and moderate aortic stenosis.[29]

Remarkably, there was a significant interaction between aortic stenosis and the effects of serelaxin on the primary endpoint. Patients with mild or moderate aortic stenosis taking serelaxin had a higher risk of cardiovascular mortality than patients taking placebo, whereas in patients without aortic stenosis, there was no difference in cardiovascular mortality rates between those taking serelaxin or placebo. No previous data showed adverse effects of serelaxin in patients with aortic stenosis, and this was a post hoc subgroup analysis that was not prespecified, so this finding should be interpreted with caution. Also, this study included patients with mild or moderate aortic stenosis, which makes a direct biological effect less plausible, and this association may be influenced by confounding. Further studies are required to assess the effects of relaxin-2 analogues in aortic stenosis.

Strengths and Limitations

This study has several strengths. We used data from 1 of the largest cohorts of patients with acute HF across the range of left ventricular ejection fraction, which makes it representative of a broad population with acute HF. In addition, all clinical events were adjudicated in this trial. However, several limitations need to be addressed. Aortic stenosis severity was investigator-reported and not centrally validated, which is less accurate than extensive central core laboratory echocardiographic characterization. Accurate diagnosis of aortic stenosis can be particularly challenging in patients with HF, because it often results in a low-flow phenotype.[30] In a large proportion of patients with aortic stenosis (25%−35%), this concerns a paradoxical low-flow, low-gradient phenotype with a preserved ejection fraction, which may develop in patients with HFpEF and aortic stenosis and is difficult to diagnose.[31−33] This entity requires additional work-up by means of dobutamine stress echocardiography or aortic valve calcification by computed tomography, which were not available in this trial. Also, several additional echocardiographic parameters, such as global longitudinal strain, have been demonstrated to provide additional information that would thoroughly characterize left ventricular function as well as the degree of aortic stenosis severity.[7] Importantly, severe aortic stenosis was an exclusion criterion in this trial, which prevented our assessing the impact of incrementing degrees of aortic stenosis severity in acute HF.

Conclusion

Mild or moderate aortic stenosis was present in 7.3% of patients with acute HF enrolled in RELAX-AHF-2, and it was associated with older age, female gender, and preserved ejection fraction. In a multivariable analysis adjusted for age and sex, mild or moderate aortic stenosis was associated with a higher risk of all-cause mortality and readmission for HF or RF at 180 days. The presence of mild or moderate aortic stenosis, therefore, reflects an increased risk for poor outcomes in patients with acute HF. Future trials will provide more data on the benefit of preemptive intervention in patients with HF and moderate aortic stenosis (Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR [NCT04889872] and Evolut EXPAND TAVR II Pivotal Trial [NCT05149755]).

Brief Lay Summary

Some people admitted to the hospital with sudden breathlessness due to heart failure also have a narrowing of a heart valve (called the aortic valve). We were interested in whether this makes outcomes worse, as this narrowing makes it harder for the heart to pump blood. We found that 7% of patients had at least a mild or moderate narrowing of the aortic valve, and those who did were more likely to die or be readmitted. This shows that even mild valve narrowing in patients with heart failure is important and may guide better care.

Constantijn S. Venema

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CRediT authorship contribution statement

CONSTANTIJN S. VENEMA: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **MARCO METRA:** Writing – review & editing, Investigation. **LAURA STAAL:** Visualization, Methodology, Formal analysis, Data curation. **IRIS E. BELDHUIS:** Formal analysis, Investigation, Methodology, Validation. **GAD COTTER:** Writing – review & editing, Investigation. **BETH A. DAVISON:** Writing – review & editing, Investigation. **G. MICHAEL FELKER:** Writing – review & editing, Investigation. **GERASIMOS FILIPPATOS:** Writing – review & editing, Investigation. **BARRY H. GREENBERG:** Writing – review & editing, Investigation. **PETER S. PANG:** Writing – review & editing, Investigation. **PIOTR PONIKOWSKI:** Writing – review & editing, Investigation. **CLAUDIO GIMPELEWICZ:** Writing – review & editing, Project administration, Investigation. **ERIK LIPSIC:** Writing – review & editing, Supervision, Investigation, Conceptualization. **ADRIAAN A. VOORS:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **JOHN R. TEERLINK:** Writing – review & editing, Investigation. **JOANNA J. WYKRZYKOWSKA:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2025.07.017.

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