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ORIGINAL RESEARCH

Paradoxical Normal-Flow Aortic Stenosis Despite Reduced Left Ventricular Ejection Fraction: Insights From the Randomized COMPARE-TAVI 1 Trial

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BACKGROUND: The hemodynamic profile and remodeling patterns of paradoxical low-flow, low-gradient aortic stenosis are well understood. However, some patients with severe aortic stenosis exhibit eccentric remodeling with enlarged left ventricular cavities, enabling a normal flow, low ejection fraction (NF-LEF) phenotype. We assessed the prevalence, hemodynamic characteristics, and post-transcatheter aortic valve implantation outcomes of NF-LEF.

METHODS: In this substudy of the COMPARE-TAVI 1 trial, 979 patients undergoing transfemoral transcatheter aortic valve implantation were stratified by left ventricular ejection fraction (LVEF) (< or ≥50%) and stroke volume index (< or ≥35 mL/m^2) into 4 groups: normal flow, normal LVEF, NF-LEF, low flow, normal ejection fraction, and low flow, low ejection fraction.

RESULTS: NF-LEF was observed in 10.7% of patients. Reduced LVEF was associated with previous myocardial infarction, pacemakers, New York Heart Association class >2, atrial fibrillation, moderate or worse mitral regurgitation, and larger left ventricular cavities (P<0.001) with eccentric hypertrophy (P=0.004). Compared with low-flow, low-ejection fraction, patients with NF-LEF more frequently had moderate or worse aortic regurgitation (P=0.007), whereas low flow, low ejection fraction showed poorer diastolic indices, suggesting diastolic dysfunction with high left ventricular filling pressures. Patients with low flow, normal ejection fraction were the most symptomatic and showed less improvement in 6-minute walk distance at 1 year compared with normal flow, normal ejection fraction. During follow-up, both low-flow groups demonstrated significant increases in stroke volume index (P<0.001), whereas LVEF also improved among patients with reduced LVEF (P<0.001).

CONCLUSIONS: NF-LEF is a prevalent aortic stenosis phenotype characterized by preserved flow despite reduced LVEF, likely driven by eccentric remodeling with moderate or worse aortic regurgitation and more favorable diastolic properties, with similar survival and time-to-event outcomes across phenotypes after transcatheter aortic valve implantation at long-term follow-up. Despite higher comorbidity burdens, patients with NF-LEF showed functional and clinical improvements comparable with normal flow, normal ejection fraction, indicating a severe aortic stenosis phenotype.

Key Words: aortic stenosis ■ left ventricular ejection fraction ■ paradox normal-flow aortic stenosis ■ stroke volume ■ transcatheter aortic valve implantation

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CLINICAL PERSPECTIVE

What Is New?

- Paradoxical normal flow, low ejection fraction aortic stenosis (AS) represents a distinct and previously underrecognized AS phenotype, characterized by preserved stroke volume despite reduced left ventricular ejection fraction, possibly due to eccentric left ventricular remodeling resulting from a combined pressure and volume overload condition caused by severe AS with concomitant aortic regurgitation.

What Are the Clinical Implications?

- Normal flow, low ejection fraction occurs in approximately 11% of patients with severe AS referred for transcatheter aortic valve implantation and is frequently associated with prior myocardial infarction, pacemaker therapy, and concomitant valvular regurgitation.
- Despite a higher comorbidity burden, we observed comparable improvements in functional capacity and time-to-event outcomes between patients with normal flow, low ejection fraction and other AS phenotypes, despite a higher comorbidity burden, emphasizing that reduced left ventricular ejection fraction alone should not preclude intervention.

Nonstandard Abbreviations and Acronyms

6MWTD	6-minute walk test distance
LF-LEF	low flow, low ejection fraction
LF-NEF	low flow, normal ejection fraction
NF-LEF	normal flow, low ejection fraction
NF-NEF	normal flow, normal ejection fraction
NYHA	New York Heart Association
TAVI	transcatheter aortic valve implantation

Aortic stenosis (AS) associated left ventricular (LV) remodeling describes the complex myocardial changes in response to chronic pressure overload characterized by LV hypertrophy, altered LV geometry, and myocardial fibrosis. Although this myocardial response displays important individual and sex-related differences, the most common response is LV wall thickening with either normal (concentric hypertrophy) or reduced (concentric remodeling) cavities. Left ventricular remodeling poses significant challenges, because it may lead to alterations in systolic and diastolic function, potentially resulting in poor outcomes after aortic valve replacement, despite preserving end-systolic wall stress within the normal range.

The complex interplay between LV remodeling and AS hemodynamics has become evident in paradoxical low-flow low-gradient AS, a condition in which stroke volume is reduced despite preserved LV ejection fraction (LVEF) due to a reduced LV cavity. In this setting, reduced stroke volume may complicate graduation of AS severity, as transvalvular gradients may underestimate disease severity. This also applies to patients with LVEF <50%, for whom the guidelines accordingly recommend the use of dobutamine stress echocardiography to assess AS severity,[1] although this recommendation is regardless of stroke volume index (SVi). Because patients with AS also may present with increased LV cavities (ie, eccentric remodeling), it is possible that the other side of the spectrum, a paradoxically normal flow with reduced LVEF, also exists. However, there is a paucity of data describing the prevalence, echocardiographic characteristics, and outcomes of this condition following transcatheter aortic valve implantation (TAVI), which may have clinical implications on diagnostics and management of this patient group.

The purpose of this study was thus to assess the prevalence and describe the clinical characteristics of patients with normal flow despite reduced LVEF in patients referred for TAVI, and to investigate the interplay between different LVEF and SVi phenotypes on functional and clinical outcomes following TAVI.

METHODS

The COMPARE-TAVI 1 trial is a multicenter, prospective, randomized controlled trial, in which 1031 all-comer patients were randomized 1:1 to receive transfemoral TAVI with either the Sapien 3/Sapien 3 Ultra Transcatheter Heart Valve series (Edwards Lifesciences, Irvine, CA) or the Myval/Myval Octacor Transcatheter series (Meril Life Sciences, Vapi, Gujarat, India).[2] The study has received national ethical approval from the Central Denmark Region. Written and verbal informed consent was obtained from all screened participants at the time of enrollment. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was previously published.[3] All study-related documents will be made available on request. Individual data collected for the study will be made available for collaborative pooled analyses provided relevant contracts and data sharing agreements are made. Only anonymized data will be shared. Any requests for data access should be directed to the sponsor at Aarhus University via email: chriterk@rm.dk.

In the COMPARE-TAVI 1 trial, patients underwent a clinical examination including assessment of New York Heart Association (NYHA) classification, a 6-minute walk test distance (6MWTD), echocardiogram, and echocardiography before TAVI (baseline), at discharge,

after 30 days, and after 1-year follow-up. In the present substudy, we excluded patients with missing LVEF and SVi at baseline and patients with concomitant moderate or worse aortic regurgitation or valve-in-valve procedure.

Echocardiography

A comprehensive transthoracic echocardiography was performed by board-certified cardiologists and sonographers using Vivid 9 (GE Healthcare, Horten, Norway) or EPIQ7 (Philips Professional Healthcare, the Netherlands) machines, digitally archived locally, deidentified, and transferred in raw format to a core laboratory. Echocardiograms were assigned to 5 readers, including highly experienced research fellows and a cardiologist with level III certification in echocardiography and were subsequently approved by the core laboratory director. Furthermore, interobserver analysis demonstrated acceptable variability between analysts, with a variance of ±12% to 15% for SVi and ±8% to 9% for LVEF. Echocardiograms were analyzed using Viewpoint 6 (GE Healthcare, Horten, Norway) and Intellispace Cardiovascular (Philips Healthcare, Best, the Netherlands) software.

Doppler values were calculated as the average of 3 cardiac cycles for patients with sinus rhythm and 5 cycles for atrial fibrillation with horizontal sweep of 100 cm/s and a frame rate of a minimum 60 per second. Left ventricular outflow tract diameter was measured in the parasternal long-axis view in early systole from the point of aortic cusp insertion into the interventricular septum to the point of aortic cusp insertion into the intervalvular fibrosis. Aortic valve area was estimated by quantitative Doppler ultrasound using the continuity equation. Dimensionless velocity index was calculated as the ratio of the LV outflow tract velocity-time integral to the aortic valve jet velocity-time integral. Peak and mean flow velocity across the valve were determined in the window where the highest velocity could be recorded using continuous wave Doppler with the cursor as parallel as possible with the flow across the valve. Peak and mean transvalvular gradients were estimated using the modified Bernoulli equation.[4] LVEF was calculated by the Simpson biplane method from the apical 4-chamber and 2-chamber views. SVi was calculated using pulsed-wave Doppler as the product of the LV outflow area and LV outflow tract velocity-time integral indexed to body surface area.

Left ventricular mass index was estimated using the Devereux formula.[5] Left ventricular mass index >115 g/m^2 in men and >95 g/m^2 in women were considered indicative of LV hypertrophy. Relative wall thickness was calculated for assessment of LV geometry using the formula 2*LV posterior wall thickness/LV internal diameter in diastole. Relative wall thickness was considered increased when >0.42. Patients were classified as normal geometry, concentric geometry, concentric LV hypertrophy, and eccentric LV hypertrophy based on LV mass index and relative wall thickness.[6] Indexed left atrial volume and diastolic dysfunction grade were evaluated according to guidelines.[7]

Patients were categorized according to SVi (< or ≥35 mL/m^2) and LVEF (< or ≥50%) into 4 flow-LVEF phenotypes: normal flow, normal ejection fraction (NF-NEF; LVEF ≥50% and SVi ≥35 mL/m^2); normal flow, low ejection fraction (NF-LEF; LVEF <50% and SVi ≥35 mL/m^2); low flow, normal ejection fraction (LF-NEF; LVEF ≥50% and SVi <35 mL/m^2); and low flow, low ejection fraction (LF-LEF; LVEF <50% and SVi <35 mL/m^2).

The primary outcome of this study was defined as changes in functional capacity stratified according to LVEF and SVi phenotypes from baseline to 1-year follow-up measured by changes in NYHA classifications and 6MWTD, respectively. Secondary outcomes included all-cause death and freedom from a composite end point comprising death, stroke, moderate or severe aortic regurgitation, or moderate or severe hemodynamic transcatheter heart valve deterioration at 1-year follow-up. No patients were lost to follow-up.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical variables as frequency (%). Comparisons across AS phenotypes were performed using ANOVA with Bonferroni-adjusted post hoc tests for continuous variables and Pearson χ^2 tests for categorical variables. ANOVA models were applied in their robust form to account for unequal variances where necessary, recognizing that these methods are robust to minor deviations from normality in large samples.

The distribution of NYHA classifications among the flow gradient phenotypes were compared using a χ^2 test at baseline, 1-month follow-up, and 1-year follow-up. The same method was used to compare changes in number of patients with improved unchanged and worsened NYHA classification between baseline to 1-month and 1-year follow-up, respectively, within each phenotype and between paired groups according to LVEF and SVi.

Mean changes in 6MWTD were analyzed using a mixed-effects linear regression model to evaluate the association with time, AS phenotype, and their interaction on changes in 6MWTD. Patients with NF-LEF were set as the reference group. A random intercept was included to account for repeated measures within individuals, and maximum likelihood estimation was used to estimate model parameters. Model fit was evaluated using log-likelihood. Adjusted predictions were generated using marginal analysis to visualize phenotype-specific performance at each time point.

Multivariable adjustments for sex, age, diabetes, previous myocardial infarction, atrial fibrillation, congestive heart failure, peripheral vascular disease, and pacemaker device along with a sensitivity analysis excluding all patients without complete follow-up for 6MWTD were performed to test robustness of our results. A missingness indicator was included in the model to account for potential selection bias due to nonrandom missing 6MWTD data. Bonferroni correction was used to account for multiple testing within the 4 groups. Associations between changes in LVEF and SVi and change in 6MWTD from baseline to 1-year follow-up were also evaluated using Pearson correlation and simple linear regression analyses.

Time-to-event was defined as from the TAVI procedure to the first occurrence of death, stroke, or moderate/severe valve dysfunction. Event-free survival was estimated using Kaplan-Meier curves and compared with log-rank tests. Cox proportional hazard models were applied for all-cause mortality, with univariable and multivariable analyses including a prespecified clinical and an echo-adjusted model. Results are reported as hazard ratios (HRs) with 95% CIs. The proportional hazards assumption was assessed using Schoenfeld residuals, and $P<0.05$ was considered statistically significant.

All statistical analysis were conducted using Stata version 18.0 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

From June 2020 to November 2023, 1031 patients were included in the primary COMPARE-TAVI 1 trial. After excluding 52 participants according to the exclusion criteria, 979 participants remained in this substudy (NF-NEF [n=468, 47.8%], NF-LEF [n=105, 10.7%], LF-NEF [n=232, 23.7%], and LF-LEF [n=174, 17.8%]; Figure 1).

Patients with reduced LVEF were more likely to have a history of acute myocardial infarction (NF-NEF [8.8%] versus NF-LEF [15.2%] versus LF-NEF [8.2%] versus LF-LEF [14.4%], $P=0.042$) and a pacemaker (NF-NEF [7.9%] versus NF-LEF [14.3%] versus LF-NEF [8.2%] versus LF-LEF [16.7%], $P=0.004$). Pairwise comparisons showed that both groups with reduced LVEF differed significantly from NF-NEF and LF-NEF with respect to prior myocardial infarction, whereas no significant difference was observed between NF-LEF and LF-NEF in the prevalence of pacemaker implantation ($P=0.085$). Although sharing many characteristics with patients with LF-LEF, pairwise comparison revealed that those with NF-LEF were less likely to be men ($P=0.032$) and have a history of medical treatment for heart failure ($P=0.004$) and atrial fibrillation ($P=0.001$), whereas advanced NYHA class ($P=0.062$) and history with stroke ($P=0.072$) were borderline significant (Table 1). In the subset of patients with incomplete 6MWTD follow-up, differences in baseline characteristics between flow-LVEF phenotypes were largely comparable with those observed in the total population, although no differences were observed between groups in the prevalence of diabetes or peripheral vascular disease (Table S1).

Echocardiographic Characteristics

Although all patients had severe AS, 32 (3.3%) patients had concomitant moderate aortic regurgitation with no difference between the groups ($P=0.20$), but pairwise comparison between NF-LEF and LF-LEF revealed that NF-LEF more often had moderate aortic regurgitation ($P=0.007$). Additionally, 47 (4.8%) patients had concomitant moderate or worse mitral regurgitation, and 79 (8.1%) had moderate or worse tricuspid regurgitation. Moderate or worse mitral regurgitation was most common in patients with reduced LVEF (NF-NEF [3.4%] versus NF-LEF [9.5%] versus LF-NEF [3.9%] versus LF-LEF [6.9%], $P=0.027$), with no difference between NF-LEF and LF-LEF ($P=0.32$). On the contrary, moderate or worse tricuspid regurgitation was most common among patients with low flow (26.1% versus 28.6% versus 30.6% versus 37.9%, $P=0.032$), with no difference between LF-NEF and LF-LEF ($P=0.12$) (Table 2). Compared with patients with LVEF ≥50%, those with reduced LVEF were more likely to have larger LV cavities with higher LV end-diastolic diameter (50.0±7.3 versus 45.2±6.8 mm, $P<0.001$) and LV end-diastolic volume (140±44 versus 105±34 mL, $P<0.001$), but with no difference between NF-LEF and LF-LEF (Figure 2). These differences were reflected by a higher prevalence of eccentric hypertrophy among patients with low LVEF, irrespective of SVi (NF-NEF 7.9%, NF-LEF 13.3%, LF-NEF 10.8%, LF-LEF 17.8%; $P=0.004$), whereas the distribution of ventricular remodeling patterns did not differ significantly between NF-LEF and LF-LEF ($P=0.78$). Pairwise comparison between NF-NEF and the 2 groups with reduced LVEF revealed that concentric remodeling was more common among patients with NF-NEF. On the contrary, eccentric hypertrophy was more common among patients with LF-LEF (17.8% versus 7.9%, $P<0.001$), which was only borderline significant for patients with NF-LEF ($P=0.078$) (central illustration, middle). Additionally, in the subset of patients with reduced LVEF, those with LF-LEF had lower global longitudinal strain (11.2±2.9% versus 9.1±2.9%, $P<0.001$) and lower deceleration time (236±128 versus 191±105 ms, $P<0.001$) compared with patients with NF-LEF (Table 2).

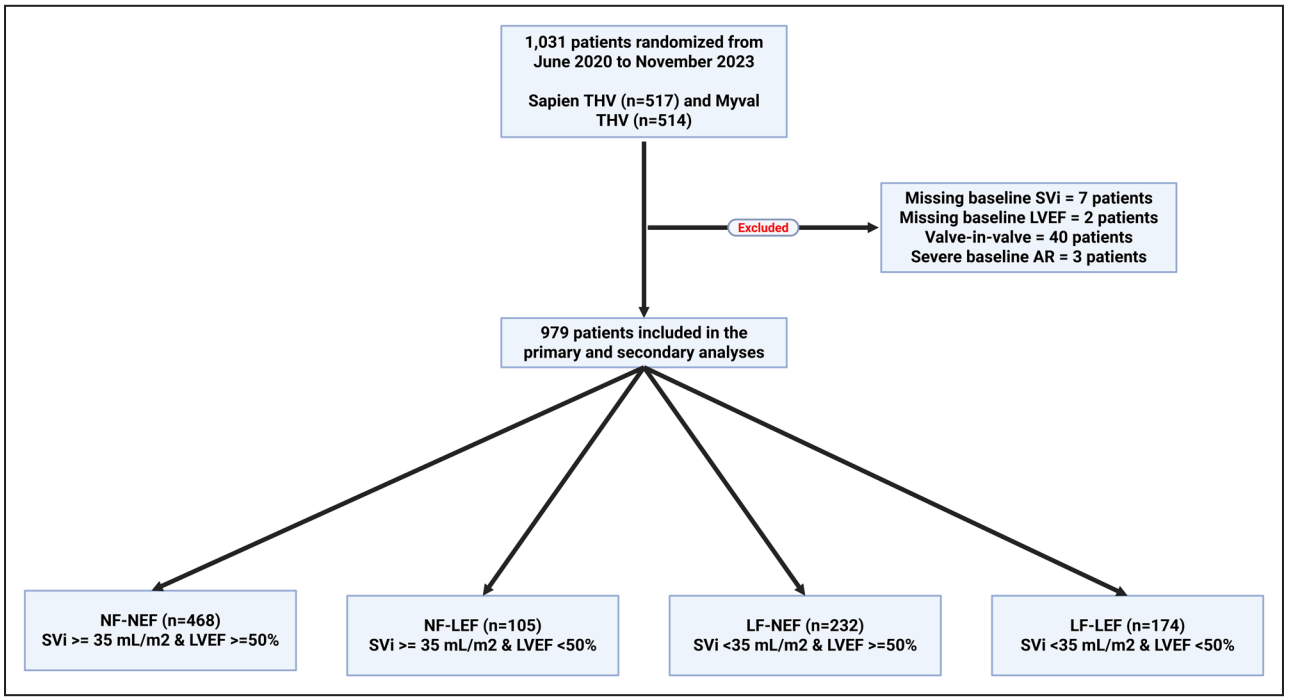

Figure 1. Flowchart describing the population included in this substudy with stratification according to flow-LVEF phenotypes.
This illustration was made with Biorender. AR indicates aortic regurgitation; LF-LEF, low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; SVi, stroke volume index; and THV, transcatheter heart valve.

Outcomes

During a total 1-year follow-up period after TAVI, 57 patients died (NF-NEF [n=20, 4.3%], NF-LEF [n=7, 6.7%], LF-NEF [n=17, 7.3%], LF-LEF [n=13, 7.5%]; *P*=0.26) with no difference in 1-year risk estimates of all-cause death rates among groups (*P*=0.25) (Figure 3). There was also no difference among groups in a composite end point of all-cause death, stroke, moderate or worse aortic regurgitation, or moderate or worse hemodynamic transcatheter heart valve deterioration (NF-NEF [n=58, 12.4%], NF-LEF [n=13, 12.4%], LF-NEF [n=38, 16.4%], and LF-LEF [n=21, 12.1%]; *P*=0.47).

In univariable analyses, none of the flow LVEF phenotypes were significantly associated with all-cause mortality (Table 3). However, higher NYHA class ≥3 (HR, 1.75 [95% CI, 1.04–2.94]; *P*=0.035), higher heart rate (HR, 1.02 per bpm [95% CI, 1.00–1.04]; *P*=0.034), and lower SVi (HR, 0.97 per mL/m^2 [95% CI, 0.95–1.00]; *P*=0.037) were associated with increased mortality risk. In the multivariable echo-adjusted models, these associations were attenuated, and no variable remained independently predictive of all-cause death, suggesting that these findings primarily reflect overall disease severity rather than independent effects.

NYHA classification was available for 977 patients at baseline (99.8%), 952 patients at 1-month follow-up (97.2%), and 906 patients at 1-year follow-up (92.5%). Patients with NF-LEF and LF-LEF were more symptomatic at baseline, with NYHA ≥3 occurring in 45.3% and 53.4%, respectively (*P*<0.001) (central illustration, middle). NYHA improved consistently after TAVI across all groups, but 26.1% still had NYHA ≥2 after 1 year. LF-NEF and LF-LEF more commonly had persistent symptoms 1 month following TAVI (NYHA ≥2, 36.2% and 40.8%; *P*=0.004), which was most common among patients with LF-NEF after 1 year (NYHA ≥2, NF-NEF 23.3% versus NF-LEF 21.9% versus LF-NEF 32.8% versus LF-LEF 27.0%; *P*=0.040) (central illustration, bottom right).

Baseline 6MWTD was available in 651 (66.4%) patients at baseline and in 551 (56.3%) and 505 (51.6%) at 1-month and 1-year follow-up, respectively. Overall, the baseline 6MWTD was 320±4 m, with significant differences between groups (NF-NEF 332±6 versus NF-LEF 289±13 versus LF-NEF 305±8 versus LF-LEF 292±11; *P*<0.001). The 6MWTD increased to 374±5 m at 1 month and 382±5 m at 1 year (*P*<0.001), with no difference in improvement between 1-month and 1-year follow-up (56±4 m versus 59±5 m, *P*=0.62), The increase was uniformly significant in all groups (*P*<0.001), but with significant heterogeneity between groups at both time points (*P*<0.001). Compared with patients with NF-NEF, patients with LF-NEF

Table 1. Baseline Characteristics

Variables	NF-NEF, n=468	NF-LEF, n=105	LF-NEF, n=232	LF-LEF, n=174	*P* value
Male sex, n (%)*	262 (58.7)	63 (60.0)	126 (54.3)	126 (72.4)	<0.001†
Age, y, mean±SD	81±5.8)	82±6.5)	81±6.4)	81±7.2)	0.33
Body surface area, m^2, mean±SD	1.87±0.20	1.89±0.23	1.93±0.24	1.91±0.22	0.003†
Systolic BP, mm Hg, mean±SD	144±20	136±22	151±32	129±21	<0.001†
Diastolic BP, mm Hg, mean±SD	74±12	72±12	89±14	76±12	0.061
Heart rate, mean±SD	69±13	73±11	77±14	77±15	<0.001†
Hypertension, n (%)	357 (76.3)	78 (75.0)	181 (78.0)	121 (69.5)	0.23
Diabetes, n (%)	82 (17.5)	25 (23.8)	59 (25.4)	45 (25.9)	0.032†
Previous AMI, n (%)‡	41 (8.8)	16 (15.2)	19 (8.2)	25 (14.4)	0.042†
Atrial fibrillation, n (%)*,‡	120 (25.6)	32 (30.5)	109 (47.0)	89 (51.1)	<0.001†
Congestive HF, n (%)*,‡	21 (4.5)	40 (38.1)	32 (13.8)	97 (55.7)	<0.001†
NYHA class ≥3, n (%)	143 (30.6)	44 (41.9)	105 (45.3)	93 (53.4)	<0.001†
PVD, n (%)	22 (4.7)	12 (11.5)	20 (8.7)	11 (6.3)	0.004†
Previous stroke, n (%)	81 (17.3)	18 (17.1)	35 (15.1)	17 (9.8)	0.12
COPD, n (%)	69 (14.9)	15 (14.3)	38 (16.5)	31 (18.0)	0.76
Pacemaker, n (%)‡	37 (7.9)	15 (14.3)	19 (8.2)	29 (16.7)	0.004†

AMI indicates acute myocardial infarction; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; LF-LEF, low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; NYHA, New York Heart Association; and PVD, peripheral vascular disease.

*Significant difference between patients with NF-LEF and patients with LF-LEF.

†Significant differences with $P<0.05$.

‡Significant difference between patients with normal LVEF and reduced LVEF.

showed less prominent improvements in 6MWTD at 1-year follow-up (59±6 m versus 40±8 m, $P=0.023$). Multivariable adjustment for sex, age, and clinically relevant covariates confirmed these results. The significant baseline differences in 6MWTD persisted (NF-NEF 326.3±5.6 versus NF-LEF 293.8±12.1 versus LF-NEF 314.5±8.0 versus LF-LEF 300.7±10.9, $P<0.001$). Pairwise comparisons with Bonferroni correction showed that NF-LEF ($P=0.016$) and LF-LEF ($P=0.044$) had significantly lower 6MWTD at baseline but demonstrated comparable improvement with NF-NEF during follow-up, with no statistically significant differences among groups at 1 year (Figure S1). A similar sensitivity analysis including 409 patients (41.8%) with 6MWTD available at all time points also showed consistent findings (Figure S2). Additionally, follow-up completeness was associated with a significantly higher 6MWTD (+41.2 m, $P<0.001$), but the trajectory of improvement over time did not differ from those with incomplete follow-up after 1 month ($P=0.65$) and after 1 year ($P=0.96$).

During follow-up, SVi increased from 39±0.4 mL/m^2 at baseline to 44±0.4 mL/m^2 at 1-year follow-up ($P<0.001$), whereas LVEF increased from 55.4±0.4% to 60.5±0.4% ($P<0.001$). The increase in SVi occurred primarily in patients with low flow, with a uniform increase in patients with LF-NEF (10±1 mL/m^2) and LF-LEF (14±1 mL/m^2) from baseline to 1-year follow-up ($P<0.001$), but with no changes in patients with NF-LEF (1±1 mL/m^2) and NF-NEF (1±1 mL/m^2) (Figure S3). In contrast, a significant increase in LVEF only occurred in patients with reduced LVEF, with an equal increase between patients with NF-LEF (15±1%) and LF-LEF (15±1%) from baseline to 1-year follow-up ($P<0.001$), whereas patients with NF-NEF (1±1%) and LF-NEF (0±1%) did not increase (Figure S3). Changes in LVEF were weakly correlated with increments in 6MWTD ($r=0.081$, $P=0.10$), which was also the case for changes in SVi ($r=-0.045$, $P=0.37$). In linear regression including both LVEF and SVi, changes in SVi ($P=0.27$) and LVEF ($P=0.06$) were still not independently associated with 6MWTD increments.

DISCUSSION

In this study including all-comers with severe AS undergoing TAVI, we found that: (1) More than one-third of patients with reduced LVEF are able to preserve stroke volume in the normal range, potentially due to eccentric remodeling with concomitant LV dilatation. (2) A paradoxically preserved stroke volume is more common among women and in patients with concomitant aortic regurgitation, mitral regurgitation, and those treated with a pacemaker device. (3) Although

Table 2. Baseline Echocardiographic Characteristics

Variables	NF-NEF, n=468	NF-LEF, n=105	LF-NEF, n=232	LF-LEF, n=174	*P* value
Aortic peak velocity, cm/s*	442 (60.1)	427 (64.6)	419 (57.5)	390 (64.2)	<0.001†
Aortic mean gradient, mm Hg‡	52.4 (20.9)	48.4 (14.4)	47.0 (13.7)	40.0 (12.6)	<0.001†
Aortic valve area, cm^{2}*	0.79 (0.20)	0.80 (0.19)	0.59 (0.14)	0.58 (0.15)	<0.001†
DVI*	0.24 (0.05)	0.23 (0.05)	0.19 (0.04)	0.17 (0.04)	<0.001†
LV mass index, g/m^{2}§	117 (31)	133 (32)	115 (28)	132 (30)	<0.001†
Relative wall thickness, %§	56 (18)	53 (15)	58 (19)	51 (16)	<0.001†
LV end-diastolic diameter, mm§	45 (7)	50 (8)	45 (7)	50 (7)	<0.001†
LV end-diastolic volume, mL§	107 (33.1)	144 (46.1)	101 (34.7)	137 (44.0)	<0.001†
LV ejection fraction, %§	63 (7.7)	41 (7)	61 (8)	37 (9)	<0.001†
Stroke volume index, mL/m^{2}*	46.3 (9.2)	43.3 (7.4)	29.6 (4.6)	26.7 (5.5)	<0.001†
Global longitudinal strain, %§	14.9 (2.8)	11.2 (2.9)	12.8 (2.9)	9.1 (2.9)	<0.001†
E velocity, cm/s	92 (31)	96 (29)	92 (31)	97 (32)	0.37
A velocity, cm/s‡	102 (33)	95 (34)	95 (42)	78 (40)	<0.001†
Deceleration time, ms‡	260 (97)	236 (128)	235 (113)	191 (105)	<0.001†
e′ lateral, cm/s, mean±SD	6.7±2.3	6.3±2.2	6.9±2.9	6.7±2.7	0.29
A′ lateral, cm/s, mean±SD‡	9.4±3.4	8.8±4.1	9.1±4.2	6.2±3.4	<0.001†
LA volume index, mL/m^{2}	44.5±16.9	50.5±14.9	45.5±20.3	49.5±19.1	0.027†
E/e′ lateral, mean±SD	15.2±7.5	17.2±9.2	15.9±9.4	17.9±12.2	0.036†
TR gradient, mm Hg, mean±SD‡	27.1±11.6	30.1±14.9	29.5±11.9	32.6±15.4	<0.001†
Aortic regurgitation grade, %					0.011†
None/trace	253±54.6	59±56.7	133±62.2	109±63.0	
Mild	193±41.7	36±34.6	73±34.1	61±35.3	
Moderate‖	17±3.7	6±5.7	7±3.3	2±1.2	
Mitral regurgitation grade, %§					<0.001†
None/trace	315±67.3	45±42.9	134±57.6	65±37.6	
Mild	130±27.8	45±42.7	86±37.1	91±52.6	
Moderate	13±2.8	9±8.6	8±3.5	10±5.8	
Severe	3±0.6	1±1.0	1±0.4	2±1.2	

a′, mitral annulus late tissue velocity; A, atrial filling; DVI indicates dimensionless velocity index; e′, mitral annulus early tissue velocity; E, early filling; E/e′, ratio of E and e′ velocities; LA, left atrial; LF-LEF, low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; and TR, tricuspidal regurgitation.

*Significant difference between patients with normal flow and reduced flow.

†Significant differences with $P<0.05$.

‡LF-LEF is significantly different from all other groups.

§Significant difference between patients with normal LVEF and reduced LVEF.

‖Significant difference between patients with NF-LEF and patients with LF-LEF.

patients with NF-LEF share a high prevalence of heart failure and atrial fibrillation, they exhibit better systolic and diastolic function compared with patients with LF-LEF, yet both phenotypes equally improved in LVEF following TAVI. (4) Irrespective of LVEF, patients with low flow uniformly increased in SVi and improved in functional capacity following TAVI, and an NF-LEF phenotype did not affect all-cause mortality or the composite end point of all-cause death, stroke, moderate or severe aortic regurgitation, or moderate or severe hemodynamic transcatheter heart valve deterioration after 1 year. Finally, NF-LEF showed improvement in functional capacity after TAVI, comparable with that observed in other groups.

Over the past decades, great effort has been put in research dealing with the evaluation of patients with low-flow AS, particularly those with preserved LVEF.[8] This entity presents diagnostic challenges in assessing AS severity, because it may lead to discordance between pressure gradients and Aortic Valve Area (AVA).[1] The conundrum of the paradoxically low flow with preserved LVEF has been dismantled and solved, revealing that the low-flow state is the result of a distinct LV remodeling pattern, which leads to a smaller cavity with diastolic dysfunction, and despite preserved LVEF, ultimately a reduced SVi.[9] Although this entity clearly has emphasized that stroke volume is the product of LVEF and LV end-diastolic volume, most guidelines still only

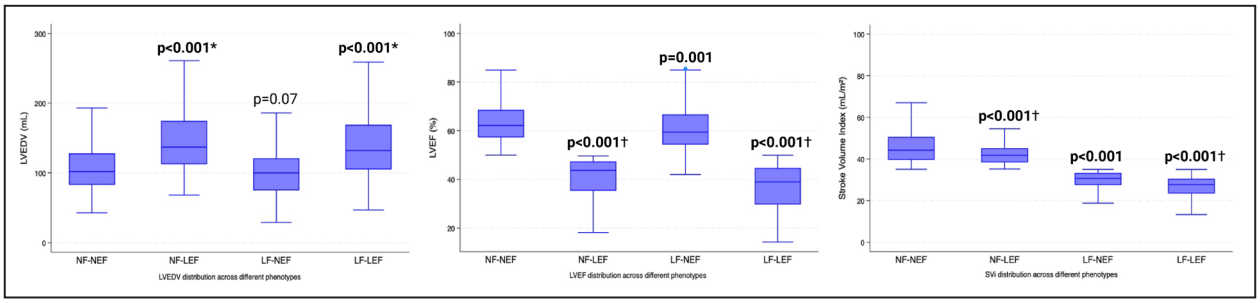

Figure 2. Box plot illustrating intergroup differences in LV end-diastolic volume, LVEF, and SVi between flow-LVEF phenotypes.

This illustration was partially made with Biorender. Comparison of LVEDV (left), LVEF (middle), and stroke volume index (right) across groups. *P* values show pairwise comparison between NF-NEF and each of the other flow-LVEF phenotypes. Significant *P* values are highlighted in bold. *Pairwise comparison between NF-LEF and LF-LEF was nonsignificant, with a *P* value of 0.26. †Pairwise comparison was significant between NF-LEF and LF-LEF (*P*<0.001). LF-LEF indicates low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; and SVi, stroke volume index.

recommend the use of SVi when LVEF is preserved.[10] It is therefore important that we demonstrate that more than one-third of patients with low LVEF have a normal SVi, emphasizing the existence of an inverse paradoxical condition in which flow may be preserved despite reduced LVEF. We hypothesize that the possible mechanism enabling this preservation is LV dilatation. Interestingly, we observed that patients with NF-LEF were more likely to have concomitant moderate or worse aortic regurgitation compared with patients with low flow and reduced LVEF (ie, LF-LEF), suggesting that the volume-overload conditions imposed by this entity may drive LV dilatation. Although patients with LF-LEF exhibited similar structural changes as patients with NF-LEF, despite differences in sex,[11–14] it is noteworthy that those with NF-LEF had significantly better diastolic properties and reduced markers of increased filling pressures compared with LF-LEF.

Our finding that preserved flow is common in the subset of reduced LVEF may have important implications for the diagnosing of severe discordant AS. According to the most recent American Heart Association/American College of Cardiology guidelines,[10] patients with LVEF <50%, AVA <1.0 cm^2, and mean gradient <40 mm Hg should be evaluated with a dobutamine stress test, because an increase in mean

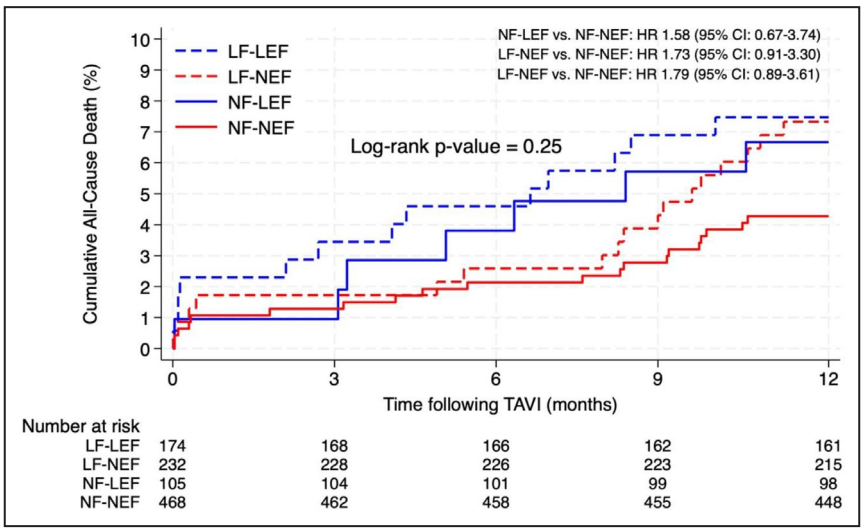

Figure 3. Kaplan-Meier plot illustrating the cumulative rate of all-cause death at 1-year follow-up according to flow-LVEF phenotypes.

HR indicates hazard ratio; LF-LEF, low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; and TAVI, transcatheter aortic valve implantation.

Table 3. Association Between Patient Characteristics and All-Cause Death During Follow-Up

Patient characteristics	Univariable analyses		Multivariable analysis		Multivariable echo-adjusted analysis	
	Hazard ratio±95% CI	*P* value	Hazard ratio±95% CI	*P* value	Hazard ratio±95% CI	*P* value
NF-LEF, yes	1.58±0.70–3.74	0.30	1.60±0.68–3.80	0.28	1.35±0.51–3.58	0.54
LF-NEF, yes	1.73±0.91–3.30	0.10	1.66±0.86–3.21	0.13	1.40±0.58–3.40	0.45
LF-LEF, yes	1.79±0.89–3.61	0.10	1.72±0.85–3.48	0.14	0.97±0.31–3.10	0.97
Male sex, yes	0.96±0.57–1.62	0.87	1.03±0.59–1.80	0.92	1.15±0.62–2.12	0.65
Age, y	1.01±0.97–1.07	0.59	1.01±0.96–1.05	0.82	1.01±0.96–1.06	0.72
Body surface area, m^2	0.67±0.20–2.28	0.52	…	…	…	…
Systolic BP, mm Hg	0.99±0.98–1.00	0.06	…	…	…	…
Diastolic BP, mm Hg	1.00±0.98–1.02	0.77	…	…	…	…
Heart rate, bpm	1.02±1.00–1.04	0.034†	…	…	…	…
Hypertension, yes	1.54±0.78–3.05	0.22	…	…	…	…
Diabetes, yes	0.77±0.39–1.51	0.44	…	…	…	…
Previous AMI, yes	0.65±0.24–1.80	0.41	0.62±0.22–1.72	0.36		
Atrial fibrillation, yes	1.32±0.78–2.22	0.31	…	…	…	…
Congestive HF, yes	0.99±0.52–1.92	0.99	…	…	…	…
NYHA class ≥3, yes	1.75±1.04–2.94	0.035†	1.70±1.00–2.88	0.049†	1.44±0.83–2.48	0.19
PVD, yes	1.38±0.55–3.46	0.49	…	…	…	…
Previous stroke, yes	0.89±0.42–1.87	0.75	…	…	…	…
COPD, yes	1.02±0.50–2.08	0.75	…	…	…	…
Pacemaker, yes	0.48±0.15–1.54	0.22	…	…	…	…
Aortic peak velocity, cm/s	1.00±1.00–1.01	0.84	…	…	…	…
Aortic mean gradient, mm Hg	1.00±0.99–1.02	0.98	…	…	…	…
Aortic valve area, cm^2	0.20±0.05–0.85	0.06	…	…	0.94±0.74–1.20	0.64
LV mass index, g/m^2	1.01±1.00–1.01	0.26	…	…	1.05±0.94–1.17	0.41
LV ejection fraction, %*	0.99±0.97–1.01	0.40	…	…	…	…
Stroke volume index, mL/m^2	0.97±0.95–1.00	0.036†	…	…	0.95±0.74–1.22	0.69
Global longitudinal strain, %	0.99±0.90–1.08	0.77	…	…	…	…
Aortic valve regurgitation, mild or worse	1.12±0.55–2.28	0.76	…	…	…	…
Mitral valve regurgitation, mild or worse	0.88±0.40–1.94	0.75	…	…	…	…

AMI indicates acute myocardial infarction; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; LF-LEF, low flow, low ejection fraction; LF-NEF, low flow, normal ejection fraction; LV, left ventricular; NF-LEF, normal flow, low ejection fraction; NYHA, New York Heart Association; and PVD, peripheral vascular disease.

*Proportional hazards assumption was not met.

†Significant differences with $P<0.05$.

gradient >40 mm Hg at any flow rate during the test in the setting of an AVA <1 cm^2 would be indicative of severe AS. This recommendation differs significantly from that for patients with preserved LVEF, where only AVA <1.0 cm^2 combined with a mean gradient <40 mm Hg and a SVi <35 mL/m^2 may be interpreted as indicative of severe AS. It is thus likely that a large proportion of patients referred for dobutamine stress tests, based on current guidelines, already have a normal-flow condition at baseline despite a reduced LVEF. Increasing the state of contractility with dobutamine among these patients may thus lead to a high-flow condition in which transvalvular pressure gradients may overestimate disease severity. However, dobutamine stress echocardiography should not rely on gradient changes alone; careful assessment of AVA and dimensionless velocity index throughout the test also remains central to differentiating true-severe from pseudo-severe AS (for visual summary, please see Figure 4). Future studies should thus be conducted to establish if the use of dobutamine provides additional information in this setting.

LV systolic dysfunction is recognized to be an adverse result of the pressure overload that occurs in severe AS. The increased LV wall stress in AS leads to

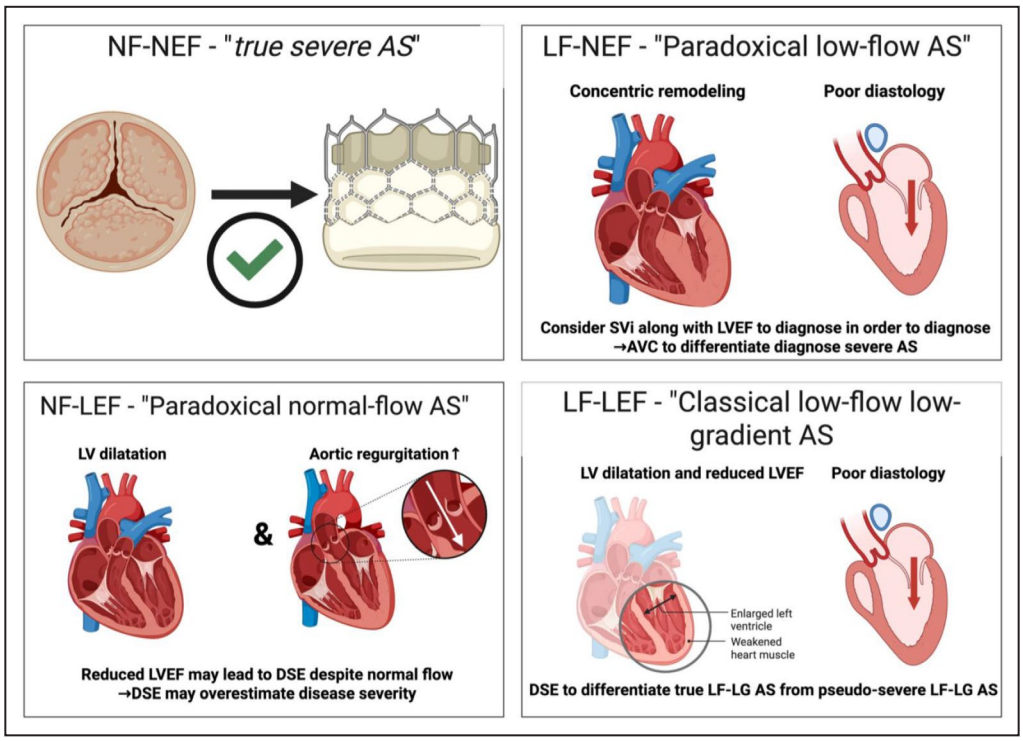

Figure 4. Schematic illustration of the 4 flow-LVEF AS phenotypes.
This illustration was made with Biorender. AS indicates aortic stenosis; AVC, aortic valve calcium; DSE, dobutamine stress echocardiography; LF-LEF, low flow, low ejection fraction; LF-LG, low flow, low gradient; LF-NEF, low flow, normal ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NF-LEF, normal flow, low ejection fraction; NF-NEF, normal flow, normal ejection fraction; and SVi, stroke volume index.

LV hypertrophy, concentric remodeling, compromised coronary flow reserve[15] and eventually reduced LV systolic function that commonly leads to a symptomatic state.[16] Although LVEF is the most routinely used parameter, it is well established that LVEF is highly load-dependent[17,18] and may remain normal despite reduced myocardial contractility by use of preload reserve[19] or changes in LV geometry.[20] In contrast, a decreased LVEF may occur in the setting of preserved contractility due to afterload mismatch,[19,21–23] but could also represent a failing left ventricle.[22] It is thus interesting that we observed that although patients with NF-LEF shared a reduced global longitudinal strain with patients with LF-LEF, they had less advanced diastolic dysfunction (ie, higher transvalvular deceleration times) and better atrial function (ie, higher a-wave and a' velocities), because this suggests that these mechanisms may help preserve SVi in the normal range. We demonstrate that despite presenting with larger AVAs, patients with paradoxical NF-LEF share the same improvement in NYHA functional class and 6MWTD following TAVI than other patients, emphasizing that these patients have a severe valvular condition that benefits from afterload reduction. In line with this, LVEF improved in patients with NF-LEF following TAVI.

From a clinical perspective, these findings emphasize the importance of recognizing the NF-LEF phenotype as a distinct subset of patients with severe AS who may present with reduced LVEF but preserved flow. In practice, identifying this AS phenotype can help avoid unnecessary diagnostic procedures such as dobutamine stress testing in patients who already demonstrate adequate flow at baseline. Moreover, clinicians should be aware that despite a reduced LVEF, these patients can derive substantial symptomatic and functional benefit from TAVI, similar to patients with true severe AS who are established candidates for intervention. Integrating flow assessment with LVEF in preprocedural evaluation of patients with low-gradient AS and reduced LVEF may therefore improve risk stratification and optimize decision-making among potential candidates for aortic valve replacement with TAVI.

Limitations

Several limitations warrant consideration. First and most important, although the COMPARE-TAVI 1 trial was an all-comer study including all patients referred for TAVI, we do not have data on patients not referred for TAVI. It is thus possible that the proportion of patients with LF-NEF

is different in outpatient clinics evaluating AS before TAVI. Second, our data represent a multicenter single-country setting, which may limit the external validity of our results on NF-LEF in other countries, although tertiary centers in Denmark follow the same guidelines as European and American countries. Third, we did not have a comparison group of patients undergoing a sham procedure. This may imply that improvement in functional capacity partially may reflect a placebo effect. It is thus important that we also demonstrate a difference in 6MWTD, because these changes are less likely to be placebo related. Fourth, nearly 50% of the data for 6MWTD were missing at 1-year follow-up. Given that missing data are likely associated with adverse outcomes such as death or significant functional decline, the data may not be missing at random. This introduces the potential for bias, because patients with the worst functional trajectories may be underrepresented. Furthermore, complete follow-up for 6MWTD was associated with significantly higher baseline 6MWTD, which could suggest that patients with incomplete follow-up were more frail and less willing to perform the 6-minute walk test. However, both multivariable adjustments for clinically relevant parameters and missing data along with a sensitivity analysis excluding all patients with incomplete follow-up confirmed the robustness of our results, supporting the overall findings in our study. Baseline characteristics of patients with an incomplete 6MWTD follow-up were largely comparable with those of the total population. Fifth, our estimation of LV mass relies on echocardiographic measurement, which has its known limitations compared with cardiac magnetic resonance imaging, particularly in patients with complex remodeling or prior myocardial infarction, of which the latter was significantly more prevalent among patients with NF-LEF.

CONCLUSIONS

Paradoxical NF-LEF is common among patients with severe AS referred for transfemoral TAVI and is most common in patients with previous myocardial infarction, pacemaker device, atrial fibrillation, and concomitant aortic and mitral valve regurgitation. This subgroup may preserve stroke volume despite reduced LVEF due to eccentric remodeling with LV dilatation, while demonstrating comparable improvements in functional capacity and time-to-event outcomes after TAVI to other AS phenotypes, indicating a severe AS phenotype.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figures S1–S3

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