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ORIGINAL PAPER

Stroke volume index and transvalvular flow rate trajectories in severe aortic stenosis treated with TAVR

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Aims The prognostic impact of flow trajectories according to stroke volume index (SVi) and transvalvular flow rate (FR) in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) remains poorly assessed. We evaluated and compared SVi and FR prior and after TAVR for severe AS.

Methods and results Patients were categorized according to SVi (<35 mL/m^2) and FR (<200 mL/s). The association of pre- and post-TAVR SVi and FR with all-cause mortality up to 3 years was assessed with multivariable Cox regression models. Among 980 patients with pre-TAVR flow assessment, SVi was reduced in 41.3% and FR in 48.1%. Baseline flow status was not an independent mortality predictor [SVi: hazard ratio (HR) 1.22, 95% confidence interval (CI) 0.85–1.82, FR: HR 0.78, 95% CI 0.48–1.27]. Among 731 patients undergoing early (5 days, interquartile range 2–29) post-TAVR flow assessment, SVi recovered in 40.1% and FR in 49.0% patients with baseline low flow. Reduced FR following TAVR was an independent predictor of mortality (HR 1.67, 95% CI 1.02–2.74), whereas SVi was not (HR 0.97, 95% CI 0.53–1.78). Three-year estimated mortality in patients with recovered FR was lower than that in patients with reduced FR (13.3 vs. 37.7% vs, $P = 0.003$) and similar to that in patients with normal baseline FR ($P = 0.317$).

Conclusion Baseline flow status was not an independent predictor of mid-term mortality among all-comers with severe AS undergoing TAVR. Flow recovery early after TAVR was frequent. Post-TAVR FR, but not SVi, was independently associated with mid-term all-cause mortality. By impacting flow status, AV replacement modifies the association of flow status with outcomes.

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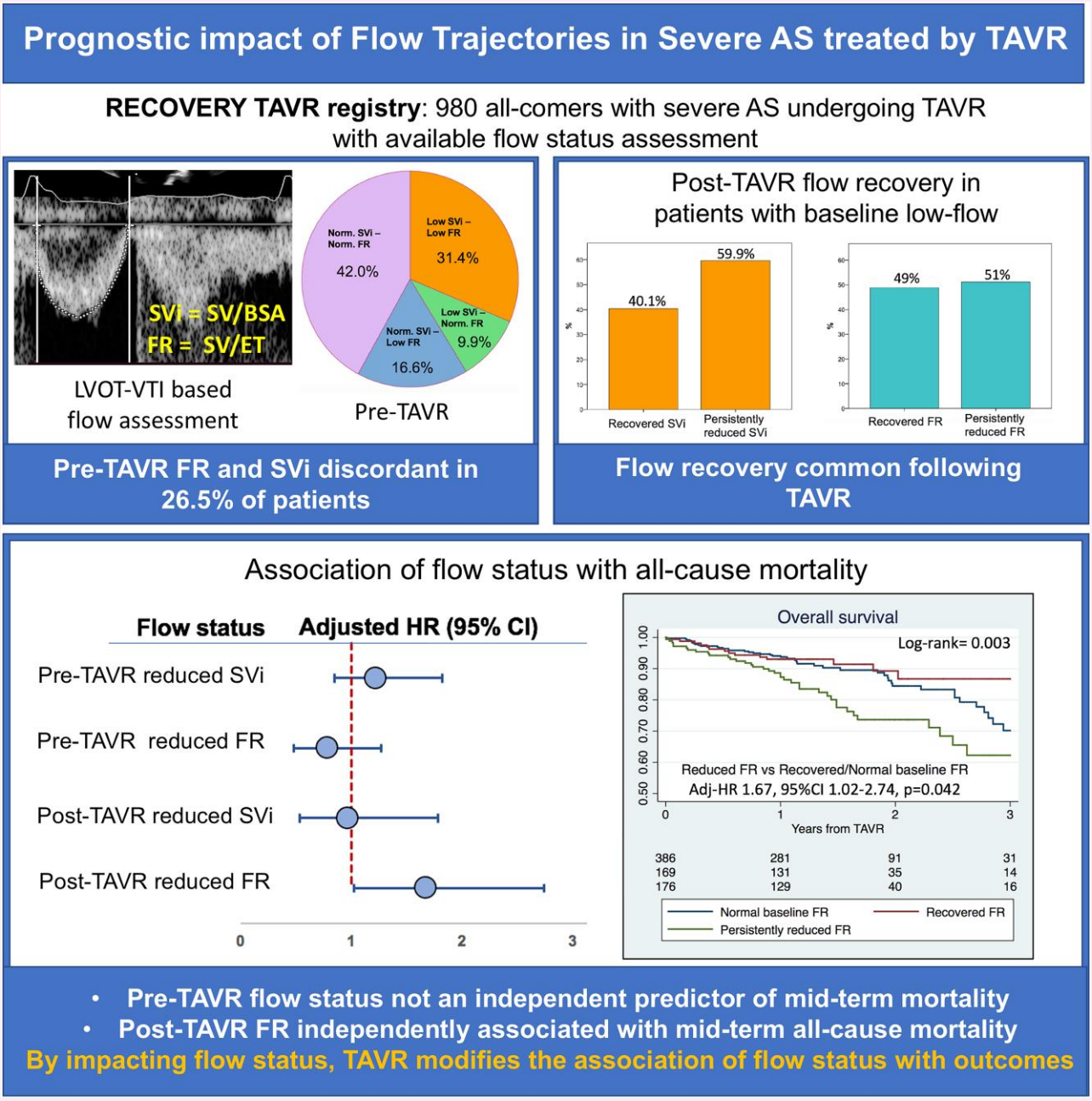
The full list of contributing authors is provided in the Supplementary data online, *Appendix*.

Graphical Abstract



Left top panel. Two parameters based on velocity-time integral calculation at the LV outflow tract have been proposed to assess flow status: (SVi, the ratio of stroke volume to BSA) and transvalvular flow rate (FR, the ratio of stroke volume to systolic ET). The pie chart describes the distribution of baseline FR and SVi in the study population. *Right top panel.* The bar graph depicts post-TAVR flow status according to SVi and FR in patients with pre-TAVR low flow. *Lower panel.* The Forest plot depicts the independent association (adjusted for demographics and in-study outcome predictors) of flow parameters pre- and post-TAVR with mid-term all-cause mortality. The Kaplan–Meier curve presents all-cause mortality stratified by post-TAVR flow status.

Keywords aortic stenosis • transcatheter aortic valve replacement • low flow • stroke volume index • transvalvular flow rate

Introduction

Myocardial maladaptation to aortic valve stenosis (AS) with ensuing reduction in flow is associated with impaired prognosis. Stroke volume index (SVi), the ratio of stroke volume to body surface area (BSA), is currently recommended to evaluate flow status in the echocardiographic assessment of severe AS, and it has been associated with worse prognosis following transcatheter aortic valve replacement (TAVR) when low.[1,2]

Transvalvular flow rate (FR), the ratio of stroke volume to systolic ejection time (ET), is a parameter of flow state that may better reflect the haemodynamic load imposed by the stenotic aortic valve (AV) when compared with SVi.[3] Both parameters have been variably associated with severe AS outcomes, resulting in contradicting evidence on whether FR or SVi is a better prognostic gauge in this setting.[4,5]

Following TAVR, patients experiencing myocardial remodelling and haemodynamic improvement may have better prognosis and functional outcomes.[6–8] SVi normalization following TAVR has been previously associated with better clinical outcomes when compared with persistently low SVi.[7,8] Conversely, the evolution of FR following TAVR and its prognostic value remain unexplored. The aim of this study is to evaluate and compare the prognostic value of SVi and FR and their evolution following TAVR in patients with severe AS.

Methods

Study design

RECOVERY-TAVR (Myocardial recovery following transcatheter aortic valve replacement for severe aortic stenosis: an echocardiography multiparametric registry) is an bi-national multi-centre observational retrospective registry, including patients with symptomatic severe AS undergoing TAVR between January 2017 and January 2021 at nine institutions (full list available in the Supplementary data online, *Appendix*) with available pre-TAVR [median 1, interquartile range (IQR) 1–4 days prior to TAVR] and early post-TAVR (median 5, IQR 2–29 days after TAVR) echocardiographic assessment.

Of 1066 patients, 980 had available pre-TAVR SVi and FR assessment and were the population of interest for this analysis (*Figure 1*). The study cohort was categorized on the basis of previously defined cut-offs of low flow according to both SVi (<35 mL/m^2) and FR (<200 mL/s).[1,5,9] The change in flow status following TAVR according to SVi and FR was assessed. SVi recovery and FR recovery were defined as flow normalization after the procedure according to the previously reported cut-offs. A total of 731 patients had serial flow status assessment and were the cohort of interest for the serial flow analysis (*Figure 1*). Baseline clinical and echocardiographic characteristics were mostly similar among patients with available and patients without available serial flow status assessment (see Supplementary data online, *Tables S1 and S2* and *Appendix*). The association of pre- and post-TAVR SVi and FR with all-cause mortality at last available follow-up was assessed. The predictors of flow recovery following TAVR were further explored.

TAVR was performed according to local expertise and standard techniques. All patients provided written informed consent before the procedure. The registry was approved by the ethics committee and was conducted in accordance with the Declaration of Helsinki.

Echocardiographic assessment and data collection

Clinical, echocardiographic, and laboratory variables along with clinical follow-up data were recorded in a dedicated database.

Echocardiographic examinations were performed according to the recommendations of the European Association of Cardiovascular Imaging.[10] Left ventricle (LV) stroke volume was calculated multiplying the systolic velocity-time integral (VTI) at the LV outflow tract per its area and was indexed to BSA (SVi). FR was calculated as LV stroke volume divided by the LV ET. The ET was measured using the Doppler LV outflow signal as the time interval between the beginning and the end of the previously traced LV outflow tract VTI (see Supplementary data online, *Figure S1* and *Appendix*). When the patient was in atrial fibrillation, measurements were averaged over five cardiac cycles.

LV volumes were determined utilizing standard techniques. LV ejection fraction (EF) was measured using a biplane measurement from the apical views and the modified Simpson's method. The aortic valve area (AVA) was calculated by using the continuity equation, and the maximum pressure gradient across the restrictive orifice was estimated by using the modified Bernoulli equation. Mean transaortic pressure gradient was calculated by averaging the instantaneous gradients over the ejection period on the continuous-wave Doppler recordings.

The severity of valvular regurgitation was determined on a qualitative scale (mild, moderate, and severe) according to the current guidelines for the management of patients with valvular heart disease.[11]

Study outcomes

All-cause mortality up to 3 years was the primary study endpoint. Cardiovascular mortality up to 3 years was a secondary study endpoint. The association of flow status with 30-day outcomes (Valve Academic Research Consortium 2 definitions[12]) including all-cause mortality, cardiovascular mortality, coronary obstruction, major bleeding, major vascular complication, acute kidney disease stage 2–3, new pacemaker, and stroke was also assessed.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean ± standard deviation or median and IQR as appropriate. The unpaired *t*-test or non-parametric Mann–Whitney *U* test was used for making comparisons of continuous variables, and the χ^2 test was used for categorical variables.

Kaplan–Meier survival curves and log-rank *P* values were used to evaluate the impact of flow status variables on mortality.

Univariate and multivariate Cox regression analyses were performed to identify the outcome predictors. All clinical and echocardiographic variables were tested in univariate analysis. Two multivariable models were generated, taking into account the pre-TAVR and post-TAVR flow status, respectively. Age, sex, BSA, ≥moderate aortic regurgitation, SVi, FR, along with clinical and echocardiographic variables with $P < 0.1$ in the univariable analysis, were entered into the multivariable models. Multicollinearity among the variables included in the final multivariate models was assessed by calculating the variance inflation factor (VIF). VIFs are reported in Supplementary data online, *Table S3* and were below five for all the independent variables, suggesting no significant multicollinearity.

Logistic regression was used to determine the independent predictors of flow recovery.

Spline curves adjusted with the same covariates of the Cox multivariate models were performed to assess the relationship of pre-TAVR and post-TAVR SVi and FR as continuous variables with the primary outcome, using a restricted cubic spline function.

The results are presented as hazard ratio (HR)/odds ratio and 95% confidence intervals (CIs). A score of $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0, SPSS Inc., Chicago, IL, USA), R Statistical Software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and STATA (version 17, StataCorp, College Station, TX, USA).

Results

Baseline clinical and echocardiographic characteristics

Baseline clinical and echocardiographic characteristics of the study population stratified by flow status are described in *Tables 1* and *2*.

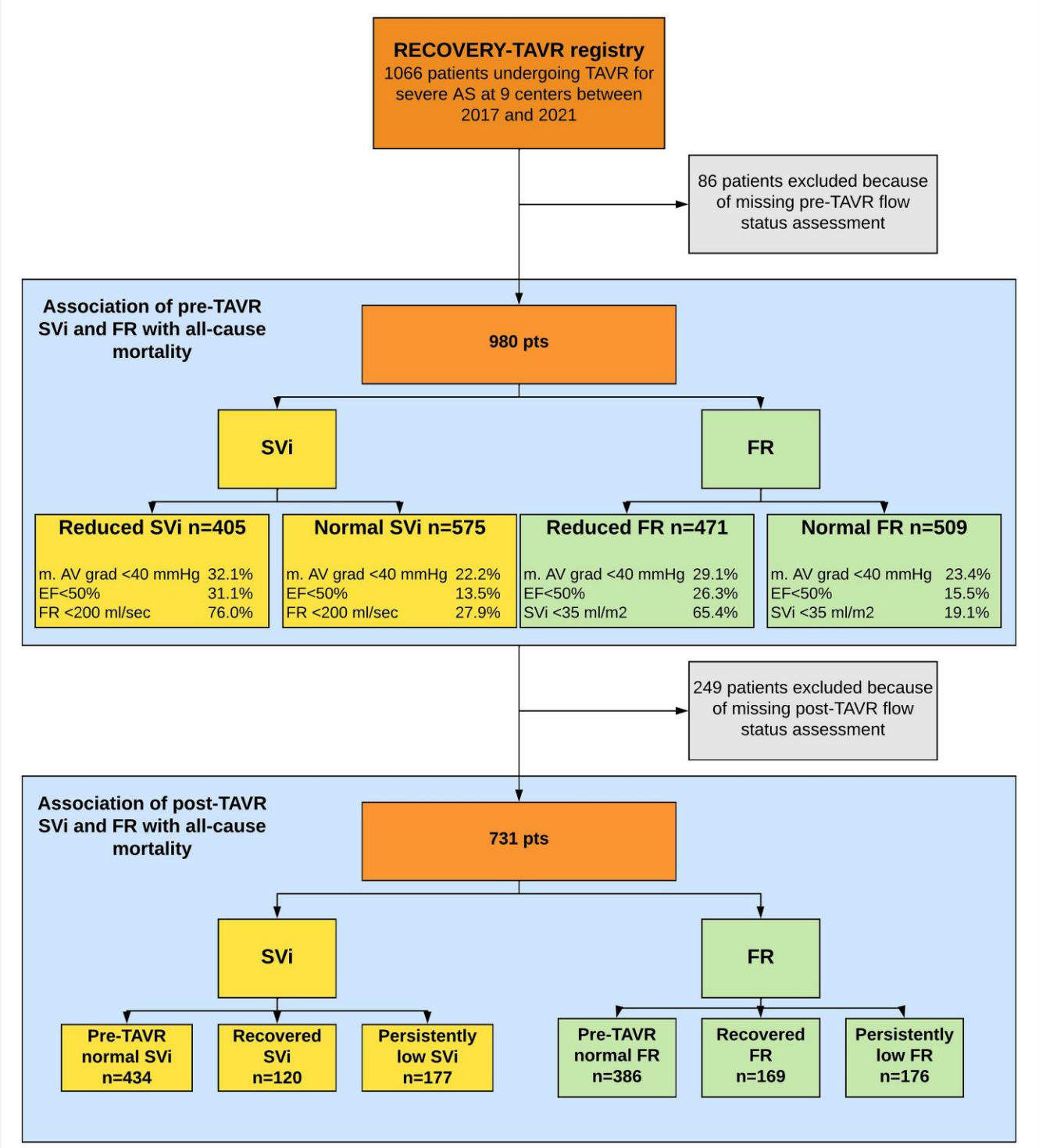


Figure 1 Study flow chart.
Abbreviations as in *Tables 1* and *2*.

The mean age was 82 ± 6 years and 46.3% patients were female. TAVR was performed with self-expanding devices in 52.5% and balloon-expandable devices in 47.5% of patients.

Of 980 patients, 405 (41.3%) had reduced SVi and 471 (48.1%) had reduced FR. Patients with discordant FR and SVi flow status numbered 260 (26.5%), of whom 62.7% had reduced FR and 37.3% had reduced SVi. SVi and FR were reduced in 61.5 and 60.5% of patients with LVEF < 50%, in 36.4 and 44.5% of patients with LVEF ≥ 50%, and in 50.8 and 53.5% of patients with low gradient (mean AV gradient <40 mmHg) AS.

Reduced SVi was associated with higher weight and BSA, more frequent history of atrial fibrillation, and low systolic blood pressure at presentation (*Table 1*). Among echocardiographic features, reduced SVi was associated

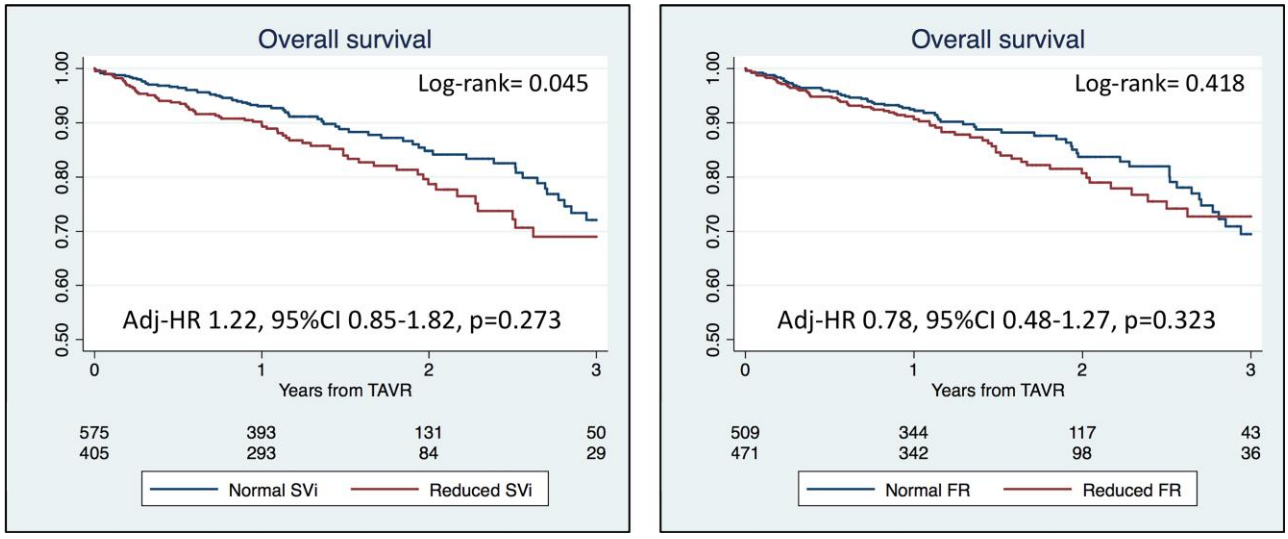


Figure 2 Kaplan–Meier curves for all-cause mortality stratified by pre-TAVR flow status. (*Left*) SVi stratification. (*Right*) FR stratification. HRs are derived from adjusted Cox proportional hazard models.
Abbreviations as in *Tables 1* and *2*.

with lower AV gradients, smaller AVA, lower LVEF, larger left atrial volume index, and lower tricuspid annular plane systolic excursion (*Table 2*).

Reduced FR was associated with male sex, lower weight, height, BSA, and systolic blood pressure at presentation (*Table 1*). Among echocardiographic features, reduced FR was associated with lower maximum AV gradient and smaller AVA, lower LVEF, and tricuspid annular plane systolic excursion.

The clinical and echocardiographic characteristics associated with FR-SVi discordance are reported in Supplementary data online, *Tables S4 and S5* (see Supplementary data online, *Appendix*).

Association of pre-TAVR flow status with all-cause mortality

After a median 13 months (IQR 12–22 months) of follow-up, 130 (13.3%) patients died. Overall, the 3-year all-cause mortality estimate was 29.4%. Dead patients when compared with surviving ones had lower SVi (35 mL/m^2, IQR 27–43 vs. 38 mL/m^2, IQR 30–46, $P = 0.007$) and similar FR (198 mL/s, IQR 150–244 vs. 203 mL/s, IQR 167–248, $P = 0.077$).

Patients with reduced SVi had higher 3-year mortality estimates (31 vs. 27.9%, log-rank = 0.045) than those with normal SVi. Conversely, 3-year mortality was similar between patients with reduced and normal FR (28.3 vs. 30.5%, log-rank = 0.418) (*Figure 2*).

Significant univariable predictors of all-cause mortality and the multivariable models are presented in *Table 3*. Following multivariable adjustment, pre-TAVR flow status was not an independent mortality predictor (SVi: HR 1.24, 95% CI 0.85–1.82, $P = 0.273$; FR: HR 0.78, 95% CI 0.48–1.27, $P = 0.323$). Spline curves for pre-TAVR SVi and FR are reported in Supplementary data online, *Figures S2 and S3*.

Flow recovery following TAVR

A total of 731 patients had available post-TAVR flow assessment with SVi and FR. Clinical and echocardiographic characteristics were mostly similar between patients undergoing post-TAVR echocardiographic assessment within 5 days vs. between 6 and 29 days post-TAVR (see Supplementary data online, *Tables S6–S8*) Among 299 patients with reduced baseline SVi, 120 (40.1%) normalized the SVi following TAVR. Univariate clinical predictors of SVi recovery were lower diastolic blood pressure and the absence of a pacemaker at presentation (see Supplementary data online, *Table S9* and *Appendix*). Echocardiographic predictors of SVi recovery were higher AV gradients, lower dimensionless valve index, smaller AVA, higher FR and lower ET, and lower estimated central venous pressure (see Supplementary data online, *Table S10* and *Appendix*). At multivariate analysis, no baseline pacemaker and lower AVA were associated with a higher likelihood of SVi recovery (see Supplementary data online, *Table S11* and *Appendix*). No statistically significant difference in estimated 3-year mortality was observed among patients with SVi recovery when compared with patients with persistently low SVi (24.4 vs. 32.3%, log-rank = 0.444), and between patients with SVi recovery vs. those with normal baseline SVi (24.4 vs. 28.1%, log-rank = 0.499), whereas a trend was observed for patients with persistently low SVi vs. those with normal baseline SVi (log-rank = 0.053). (*Figure 3*). Reduced SVi following TAVR was not associated with mortality (HR 1.22, 95% CI 0.83–1.79, $P = 0.311$) also after multivariable adjustment (HR 0.97, 95% CI 0.53–1.78, $P = 0.909$) (*Table 3*).

Of 345 patients with reduced baseline FR, 176 (49.0%) normalized the FR following TAVR. Patients of male sex, taller, with heavier weight, and higher BSA were more likely to experience FR recovery (see Supplementary data online, *Table S9* and *Appendix*). Echocardiographic predictors of FR recovery were higher SVi and FR, smaller left atrial volume index, absence of more than mild aortic regurgitation, and presence of more than mild tricuspid regurgitation (see Supplementary data online, *Table S10* and *Appendix*). At multivariate analysis, higher BSA, higher baseline FR, and higher max aortic valve gradient were associated with a higher likelihood of FR recovery (see Supplementary data online, *Table S12* and *Appendix*). Patients with persistently reduced FR had significantly higher 3-year estimated mortality when compared with patients with recovered FR (37.7 vs. 13.3%, log-rank = 0.003) and to patients with normal baseline FR (37.7 vs. 29.8%, log-rank = 0.006). Patients with recovered FR had similar 3-year estimated mortality to patients with normal baseline FR (log-rank = 0.317) (*Figure 3*). Reduced FR following TAVR was associated with mortality (HR 1.83, 95% CI 1.22–2.74, $P = 0.003$). At multivariable analysis, reduced FR following TAVR was an independent predictor of mortality (HR 1.67, 95% CI 1.02–2.74; $P = 0.042$) (*Table 3*). Spline curves for post-TAVR SVi and FR are

Table 1 Distribution of baseline clinical characteristics in the overall study population and stratified by flow status

	Overall population ($n = 980$)	SVi < 35 mL/m^2 ($n = 405$)	SVi ≥ 35 mL/m^2 ($n = 575$)	*P*-value	FR < 200 mL/s ($n = 471$)	FR ≥ 200 mL/s ($n = 509$)	*P*-value
Age (years)	82 ± 6	81 ± 6	82 ± 6	0.291	82 ± 6	81 ± 7	0.451
Weight (kg)	72 ± 15	74 ± 14	70 ± 15	**<0.001**	70 ± 14	73 ± 16	**0.012**
Height (cm)	162 ± 10	163 ± 9	161 ± 10	0.056	161 ± 9	163 ± 11	**0.024**
Male sex (%)	53.7 (526)	52.3 (212)	54.6 (314)	0.515	59 (278)	48.7 (248)	**0.001**
BSA (m^2)	2 (2-2)	1.8 (1.7–2)	1.8 (1.6–1.9)	**<0.001**	1.8 (1.6–1.9)	1.8 (1.7–2)	**0.002**
Cardiovascular risk factors							
Smoke (%)	3.8 (31)	2.6 (9)	4.8 (22)	0.229	3.9 (15)	3.8 (16)	0.052
Hypertension (%)	84 (810)	84.1 (339)	84 (471)	1.000	83.3 (388)	84.7 (422)	0.539
Diabetes (%)	30.7 (296)	32.3 (130)	29.5 (166)	0.396	29.6 (138)	31.7 (158)	0.530
Dyslipidaemia (%)	61.7 (529)	64.3 (225)	60 (304)	0.224	59.9 (243)	63.4 (286)	0.292
Medical history							
Known CAD (%)	39.1 (370)	38 (149)	39.9 (221)	0.589	38.9 (177)	39.3 (193)	0.947
Prior MI (%)	13.2 (125)	12.1 (48)	14 (77)	0.437	11.1 (51)	15.2 (74)	0.068
Prior coronary revasc. (%)	27.6 (286)	26.1 (105)	30.4 (171)	0.079	27.8 (130)	29.3 (146)	0.331
Prior stroke (%)	9.2 (89)	7.4 (30)	10.5 (59)	0.115	8.8 (41)	9.6 (48)	0.739
Known PAD (%)	17.7 (171)	15.6 (63)	19.2 (108)	0.171	18.6 (87)	16.8 (84)	0.500
Known AF (%)	29.2 (282)	33.3 (134)	26.3 (148)	**0.022**	31.5 (147)	27.1 (135)	0.137
Clinical characteristics							
Sistolic BP (mmHg)	128 ± 17	126 ± 17	130 ± 18	**0.002**	127 ± 18	130 ± 17	**0.011**
Diastolic BP (mmHg)	71 ± 10	70 ± 10	72 ± 10	0.143	71 ± 10	71 ± 10	0.678
Heart rate (bpm)	67 ± 12	67 ± 13	67 ± 11	0.900	68 ± 13	66 ± 11	0.290
NYHA class (%)							
1	3.1 (29)	1.2 (11)	1.9 (18)	0.295	3.1 (14)	3.1 (15)	0.872
2	41.6 (394)	44.9 (179)	39.2 (215)		41.8 (192)	41.3 (202)	
3	50.5 (479)	47.4 (189)	52.8 (290)		49.7 (228)	51.3 (251)	
4	4.9 (46)	5 (20)	4.7 (26)		5.4 (25)	4.3 (21)	
COPD (%)	20.1 (194)	20.8 (84)	19.6 (110)	0.626	19.1 (89)	21.1 (105)	0.470
LBBB (%)	8.4 (48)	10.4 (21)	7.3 (27)	0.208	9.4 (25)	7.6 (23)	0.454
PM at baseline (%)	12.6 (84)	15.2 (38)	11 (46)	0.118	14.1 (45)	11.1 (39)	0.293
eGFR <60 mL/min/1.73 m^2	42.9 (370)	44.1 (162)	42 (208)	0.578	46.4 (192)	39.7 (178)	0.054
Dialysis (%)	1.7 (16)	0.7 (7)	0.9 (9)	1.000	1.8 (8)	1.6 (8)	1.000

Values are expressed as % (*n*) of patients or mean ± standard deviation or median and IQR. *P*-values <0.05 highlighted in bold.
Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PM, pacemaker.

reported in Supplementary data online, *Figures S4* and *S5*, supporting risk inflection around the FR cut point adopted in this analysis.

Secondary outcomes

The association of pre-TAVR and post-TAVR flow status with 3-year cardiovascular mortality and 30-day outcomes is reported in Supplementary data online, *Tables S13–S15* (see Supplementary data online, *Appendix*).

Sensitivity analyses

Subgroup analysis according to the presence of ≥ moderate aortic regurgitation pre-and post-TAVR is reported in the Supplementary data online, *Appendix* (see Supplementary data online, *Results*). A sensitivity analysis assessing the primary outcomes among patients with baseline low flow according to tertiles of post-TAVR flow is reported in the Supplementary data online, *Appendix* (see Supplementary data online, *Results*).

Discussion

This is the first study to assess the prognostic value of flow status pre- and post-TAVR according to SVi and FR in a large population of patients with severe AS.

Our main findings can be summarized as follows (*Graphical Abstract*):

(1) Pre-TAVR adjusted flow status was not associated with mid-term all-cause mortality.

Table 2 Distribution of baseline echocardiographic characteristics in the overall study population and stratified by flow status

	Overall population ($n = 980$)	SVi < 35 mL/m^2 ($n = 405$)	SVi ≥ 35 mL/m^2 ($n = 575$)	*P*-value	FR < 200 mL/s ($n = 471$)	FR ≥ 200 mL/s ($n = 509$)	*P*-value
Aortic valve							
Max AV gradient (mmHg)	74 ± 21	71 ± 23	75 ± 20	**0.004**	72 ± 22	75 ± 20	**0.019**
Mean AV gradient (mmHg)	46 ± 13	45 ± 14	47 ± 12	**0.012**	45 ± 14	47 ± 12	0.157
AVA (cm^2)	0.7 (0.6–0.8)	0.7 (0.5–0.8)	0.8 (0.6–0.9)	**<0.001**	0.7 (0.5–0.8)	0.8 (0.7–0.9)	**<0.001**
DVI	0.23 ± 0.08	0.21 ± 0.08	0.25 ± 0.08	**<0.001**	0.22 ± 0.07	0.24 ± 0.09	**<0.001**
SVi (mL/m^2)	38 ± 12	27 ± 6	46 ± 10	**<0.001**	32 ± 11	44 ± 11	**<0.001**
Trans-aortic FR (mL/s)	208 ± 62	172 ± 54	232 ± 55	**<0.001**	157 ± 31	255 ± 44	**<0.001**
Ejection time (ms)	331 ± 92	299 ± 68	354 ± 99	**<0.001**	356 ± 110	308 ± 61	**<0.001**
LVOT diameter (mm)	20 ± 2	20 ± 2	21 ± 2	**0.002**	20.0 ± 2	21 ± 2	**<0.001**
AS phenotype (%)							
HG	73.4 (719)	67.4 (273)	77.6 (446)	**0.020**	70.3 (331)	76.2 (388)	0.480
LFLG-C	5.9 (58)	14.3 (58)	0 (0)		9.8 (46)	2.4 (12)	
LFLG-P	7.6 (74)	18.3 (74)	0 (0)		11.7 (55)	3.7 (19)	
NF-LG	13.2 (129)	0 (0)	22.5 (129)		8.3 (39)	17.7 (90)	
Left ventricle							
LVEF (%)	57 ± 12	54 ± 14	59 ± 10	**<0.001**	55 ± 13	59 ± 11	**0.001**
EDD (mm)	46 ± 8	47 ± 8	45 ± 7	0.095	46 ± 8	46 ± 7	0.270
IVS thickness (mm)	14 ± 2	14 ± 2	14 ± 2	0.886	13 ± 2	134 ± 2	0.076
PW thickness (mm)	12 ± 3	12 ± 5	12 ± 2	0.918	12 ± 4	12 ± 2	0.332
LV mass index (g/m^2)	130 ± 58	132 ± 76	129 ± 39	0.681	131 ± 73	129 ± 38	0.941
Valves							
AR ≥ moderate (%)	27.7 (261)	29.5 (116)	26.4 (145)	0.302	26.9 (121)	28.4 (140)	0.662
MR ≥ moderate (%)	29.5 (275)	29.3 (114)	29.7 (161)	0.942	28.3 (126)	30.6 (149)	0.472
TR ≥ moderate (%)	30.3 (275)	32.5 (123)	28.7 (152)	0.214	33.4 (144)	27.5 (131)	0.060
Others							
E/*e*′ ratio	15 ± 7	16 ± 8	15 ± 7	0.296	15 ± 7	15 ± 7	0.673
LAVi (mL/m^2)	50 (39–70)	54 (40–77)	49 (38–66)	**0.001**	52 (40–74)	50 (39–68)	0.068
sPAP (mmHg)	39 ± 14	40 ± 16	39 ± 13	0.993	39 ± 14	40 ± 14	0.169
TAPSE (mm)	21 ± 4.3	20 ± 5	21 ± 4	**0.001**	20 ± 4	21 ± 4	**<0.001**
CVP (mmHg)	5 (3–5)	3 (3–8)	5 (3–5)	0.076	5 (3–5)	5 (3–5)	0.333

Values are expressed as % (*n*) of patients or mean ± standard deviation or median and IQR. *P*-values <0.05 highlighted in bold.
Abbreviations: AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; CVP, central venous pressure; DVI, dimensionless valve index; EDD, end-diastolic diameter; FR, transvalvular flow rate; HG, high gradient; IVS, interventricular septum; LAVi, left atrial volume indexed; LFLG-C, low-flow low-gradient classic; LFLG-P, low-flow low-gradient paradoxical; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; LVOT, left ventricular outflow tract; NFLG, normal-flow low gradient; sPAP, systolic pulmonary artery pressure; PW, posterior wall; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; SVi, stroke volume index.

(2) Reduced FR early after TAVR (but not reduced SVi) predicted mid-term all-cause mortality, an association that remained significant after multivariable adjustment.
(3) Among patients with reduced FR prior to TAVR, 49% had FR recovery. These patients had the same mid-term all-cause mortality of patients with normal FR prior to TAVR.

Prognostic value of FR in AS: reconciling the inconsistencies

The prognostic value of FR in patients with AS remains unclear. Among asymptomatic patients with mild to moderate AS from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, FR was reduced in 28% of patients with normal SVi, and reduced FR was a strong predictor of all-cause and cardiovascular mortality at long-term follow-up.[4] In a cohort of 218 patients with severe low-gradient AS undergoing AV replacement, baseline FR was associated with mid-term all-cause mortality.[5] In a community group of patients with severe AS in which only a minority eventually underwent AV intervention, FR was associated with the net composite outcome of all-cause mortality, heart failure hospitalization, and AV intervention.[9] Finally, in a wide cohort of patients with moderate or severe AS, FR determined the prognostic value of AVA. In this cohort, only about one-third of AS patients eventually underwent AV replacement.[3]

Our study, by offering information on flow trajectories in patients with severe AS following AV replacement, provides insights into the

Table 3 Univariable and multivariable models of pre- and post-TAVR flow status according to SVi and FR for all-cause mortality

	All-cause mortality					
	Univariate models		Pre-TAVR flow status multivariate model		Post-TAVR flow status multivariate model	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.00 (0.93–1.03)	0.933	0.99 (0.96–1.02)	0.655	0.99 (0.94–1.04)	0.826
Sex (M)	1.26 (0.89–1.77)	0.192	1.69 (1.11–2.56)	**0.014**	1.88 (1.08–3.27)	**0.006**
BSA (m^2)	0.99 (0.44–2.28)	0.993	0.35 (0.13–0.97)	**0.043**	0.19 (0.05–0.76)	**0.019**
Known atrial fibrillation	1.62 (1.14–2.31)	**0.007**	1.52 (1.03–2.24)	**0.034**	1.84 (1.11–3.04)	**0.019**
NYHA functional Class III and IV	1.29 (0.99–1.68)	0.063	1.25 (0.84–1.85)	0.268	1.27 (0.61–2.69)	0.365
COPD	1.71 (1.17–2.50	**0.005**	2.08 (1.38–3.14)	**<0.001**	2.54 (1.51–4.27)	**<0.001**
eGFR <60 mL/min/1.73 m^2	2.13 (1.48–3.08)	**<0.001**	2.23 (1.52–3.28)	**<0.001**	2.07 (1.23–3.45)	**0.006**
Pre-TAVR AR ≥ moderate	1.01 (0.68–1.50)	0.958	1.03 (0.67–1.57)	0.719	—	—
Pre-TAVR SVi <35 mL/m^2	1.42 (1.01–2.00)	**0.046**	1.24 (0.85–1.82)	0.273	—	—
Pre-TAVR FR <200 (mL/s)	1.15 (0.82–1.63)	0.418	0.78 (0.48–1.27)	0.323	—	—
Post-TAVR AR ≥ moderate	1.52 (0.83–2.79)	0.173	—	—	1.28 (0.61–2.69)	0.523
Post-TAVR SVi <35 mL/m^2	1.22 (0.83–1.79)	0.311	—	—	0.97 (0.53–1.78)	0.909
Post-TAVR FR <200 (mL/s)	1.83 (1.22–2.74)	**0.003**	—	—	1.67 (1.02–2.74)	**0.042**

Multivariate models included age, sex, BSA, aortic regurgitation ≥ moderate, and in-study univariate outcome predictors of all-cause mortality with $P < 0.10$, evaluated at a median follow-up of 1.1 years (IQR 1.0–1.8 years). *P*-values <0.05 highlighted in bold.
Abbreviations: CI, confidence interval; HR, hazard ratio. Other abbreviations as in *Tables 1* and *2*.

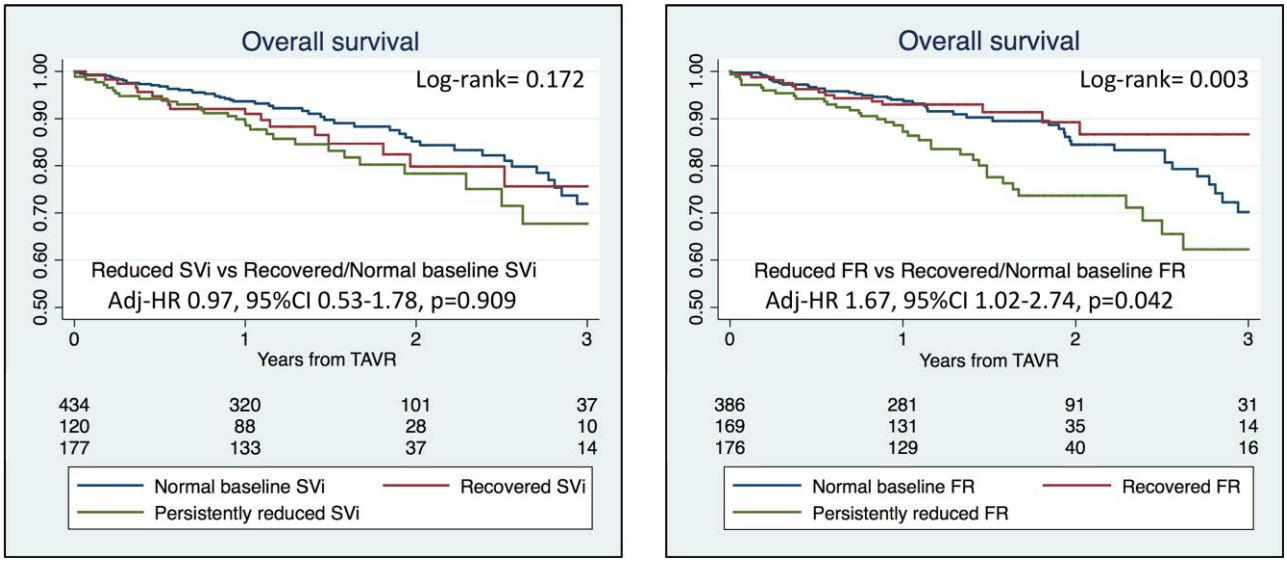


Figure 3 Kaplan–Meier curves for all-cause mortality stratified by post-TAVR flow status. (*Left*) SVi stratification. (*Right*) FR stratification. HRs are derived from adjusted Cox proportional hazard models.
Abbreviations as in *Tables 1* and *2*.

reasons for discrepancies from prior literature and allows to propose a unifying hypothesis on the prognostic value of FR in AS. Specifically, the results of our study reconcile with previous works by suggesting that AV replacement has a significant impact on flow status, modifying the association of baseline flow parameters with outcomes in patients with severe AS. In our cohort, 49% of patients with reduced baseline FR had FR recovery following TAVR and these patients had similar prognosis to patients with baseline normal flow. Most prior studies evaluating the prognostic value of FR comprised patients with different AS severities and overall low rates of AV replacement.[3,4,9] Accordingly, FR represented the flow status affecting the patient during the whole study period and thus conditioning prognosis. AV replacement, strongly

modifying the afterload status by removing the valvular component, will impact flow dynamics in a substantial proportion of severe AS patients, whose prognosis will depend on post-TAVR flow status.

Of note, in the study by Vamvakidou *et al.*, baseline FR predicted mortality following AV replacement among patient with low-gradient AS. This is likely due to the lower probability of flow recovery following AV replacement in a cohort exclusively comprising low-gradient AS (i.e. with more impaired LV function and/or less severe AS).[5]

Transvalvular FR vs. SVi

Even if SVi is the currently recommended parameter to evaluate flow status in the echocardiographic assessment of severe AS,[1] pre-clinical and clinical evidence suggest that FR may be a better parameter of haemodynamic adequacy to assess AS severity. In a bench model of severe AS, AVA severity significantly varied with transvalvular flow at reduced FRs but remained unchanged at FR above 200 mL/s.[13] Consistently, resting AVA at FR ≥200 mL/s reflects true valve area in patients with low-flow (SVi < 35 mL/m^2) low-gradient AS, avoiding the need for dobutamine stress echocardiography.[14] However, whether FR may be a better prognostic gauge in AS remains controversial. In the SEAS study and in the study from Vamvakidou *et al.*, only reduced FR (but not reduced SVi) predicted all-cause mortality.[4,5] Similarly, FR but not SVi determined the prognostic value of AVA.[3] Conversely, in the aforementioned community study, although both baseline FR and SVi were outcome predictors, only SVi improved risk reclassification compared with other conventional clinical and echocardiographic predictors.[9] These discrepancies may derive from differences in baseline characteristics. Specifically, the different prevalence of obesity, a major determinant of SVi/FR mismatch and a mortality predictor in low-flow AS,[15] may play a relevant role in SVi/FR discrepant prognostic value across studies.[5,16] In our cohort, patients with reduced baseline SVi had higher all-cause mortality, but this association was lost following multivariable adjustment. As discussed, our study is different from the mentioned works by including an all-comer population of severe AS patients undergoing AV replacement. Accordingly, the absence of independent association between baseline flow status and mortality, regardless of the adopted parameter, may relate to the high prevalence of patients experiencing flow recovery following TAVR. This may also explain the inconsistent evidence associating baseline SVi with mid-term mortality in TAVR patients across the literature.[2,8,17]

The prognostic value of post-TAVR flow status is poorly explored. Among 255 patients undergoing TAVR, mid-term mortality in patients with early SVi recovery was lower than in patients with persistent low SVi and similar to patients with baseline normal SVi.[8] However, among 984 patients with low-flow AS undergoing TAVR from the Placement of Aortic Transcatheter Valves (PARTNER) randomized trial, only persistently severe SVi (mean 23.1 ± 3.5 mL/m^2) but not mildly reduced SVi (31.7 ± 2.2 mL/m^2) at discharge was associated with mid-term mortality.[7] In our cohort, despite a trend for higher mortality in patients with persistently reduced SVi when compared with patients with normal SVi, reduced SVi following TAVR was not an independent mortality predictor. These partially discrepant results across studies might reflect differences in the study population (higher baseline reduced SVi rates of 51.0 vs. 41.3% and lower SVi recovery rates of 31.5 vs. 40.1% in Le Ven *et al.*[8] vs. our cohort) and study design (inclusion of patients with baseline low flow exclusively in Anjan *et al.*[7]).

Conversely, no data on the clinical significance of FR trajectory following TAVR is currently available. Our study is the first to characterize the prognostic value of post-TAVR FR and to compare it with that of SVi. We report several novel findings that provide a framework to shape the clinical adoption of non-invasive flow parameters to follow the prognostic trajectory of patients with severe AS undergoing TAVR.

First, baseline low flow according to FR was more common than baseline low flow according to SVi (48.1 vs. 41.3%), suggesting that FR may be a more sensitive marker of low flow in severe AS. Secondly, flow recovery according to FR was more common than flow recovery according to SVi (49 vs. 40.1%, respectively), suggesting that FR may better reflect the valvular component of the haemodynamic load compared with the overall valvulo-arterial afterload. Mechanistically, this may be due to the inherent myocardial adaptation process to the increased valvular afterload that occurs by increasing the ET to maintain stroke volume. Accordingly, FR, which is inversely proportional to ET, may capture the initial (mal)adaptation process to the valvular afterload prior that reduction in stroke volume (and thus in SVi) ensues.[4,18] This process may thus partly account for SVi-FR discordance in severe AS and may have relevant implications in terms of likelihood of flow recovery. Specifically, reduced FR in the context of normal SVi may identify a subset of patients where afterload mismatch, rather than truly impaired contractility, is the leading mechanism of low flow. Our findings suggest that, when afterload mismatch is the mechanism of decreased flow, no prognostic implication ensues.[19,20] Conversely, in more advanced AS disease, maladaptive mechanisms may underlie the flow impairment entailing worse outcome despite valve replacement.[21,22] In this framework, the adoption of FR to indicate early intervention in asymptomatic severe AS is a hypothesis requiring consideration in future studies. Thirdly, reduced FR following TAVR was an independent strong prognostic predictor, associated with a 1.7-fold risk of mid-term mortality.

Overall, our observations suggest that, beyond a better reflection of valvular haemodynamic load, FR may better represent flow status than SVi, also following AV replacement, advocating its use during early post-TAVR assessment in order to optimize medical therapy, assess reversible causes, and tailor follow-up. This approach may provide a substantial clinical advantage to track the patient's trajectory following TAVR when compared with other markers of myocardial remodelling such as LV mass and EF, which recover throughout a longer time course.[23]

Predictors of FR improvement

Finally, a better understanding of the structural and functional markers of irreversible maladaptive remodelling among patients with severe AS candidates to AV replacement may have important implications, including potential earlier valve intervention and futility prediction. As TAVR is associated with better haemodynamics performance compared with surgical AV replacement,[24] it also holds the potential to guide treatment selection. In our cohort, patients of male sex and larger body dimensions were more likely to undergo FR recovery. Also, less impaired flow status and echocardiographic markers of milder degree of adverse myocardial remodelling were associated with a higher likelihood of FR recovery. Finally, the association of more than mild aortic regurgitation with persistent low flow highlights the dismal consequences of low flow in the setting of LV volume overload. To conclude, whether the presence of cardiac amyloidosis, increasingly recognized among patients with AS,[25] might impact flow recovery and what are the implications for clinical outcomes remain to be explored.

Limitations

The findings of this study should be interpreted in the light of several limitations. First, this was a retrospective registry of clinical practice data. In front of the inherent limitations of study design, our findings have the advantage of generalizability to the real-world clinical setting. Of note, 13.2% of the study population underwent TAVR for normal-flow low-gradient AS (AVA <1 cmq), an entity not classified as severe AS according to societal guidelines, but for whom a prognostic benefit with TAVR is reported in the literature.[26] Secondly, as data were retrospectively collected, we could not assess inter-observer variability in flow assessment. Previous studies suggest moderate to good reliability across operators for Doppler-based flow assessment.[5] Thirdly, we did

not collected data on factors that might have affected Doppler-based flow assessment. Whether our results are fully applicable to patients with turbulent LV outflow tract or poor acoustic window is beyond the scope of this investigation. Fourth, flow status following TAVR was not available for all patients. Although we cannot exclude selection bias, the reasons for missing values are likely mostly related to practice heterogeneity in flow status assessment rather than for clinical reasons, reducing the implications of this limitation. Fifth, the study was designed to assess the value of early changes in flows following TAVR. Accordingly, only the early echocardiographic assessment following TAVR was considered. The timing of changes in haemodynamics following TAVR has specific pathophysiological implications. As myocardial remodelling requires longer times, the observed changes rather reflect the direct impact of afterload reduction on flow dynamics. Whether further changes in flow occurred later in time, reflecting reverse myocardial remodelling, and the related clinical implications, was beyond the scope of the current investigation.

Conclusions

In an unselected contemporary cohort of patients with severe AS undergoing TAVR, baseline flow status was not an independent predictor of mid-term mortality. A substantial proportion of patients with baseline low-flow experienced flow recovery early after TAVR. Patients with FR-defined persistent low-flow had increased mid-term all-cause mortality, whereas those with FR recovery had the same prognosis of patients with normal baseline FR. Post-TAVR FR, but not SVi, was independently associated with mid-term all-cause mortality. By impacting flow status, AV replacement modifies the association of flow status with outcomes among patients with severe AS.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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