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Early Stroke Volume Variation After Transcatheter or Surgical Aortic Valve Replacement Predicts Clinical Outcomes in Low-Flow Aortic Stenosis

Giorgio Fiore[1] | Federico Biondi[1] | Paola Cunsolo[1] | Michele Morosato[1] | Marco Gamardella[1] | Giacomo Ingallina[1] | Stefano Stella[1] | Francesco Ancona[1] | Annamaria Tavernese[1] | Davide Margonato[1] | Margherita Fabris[1] | Alessandro Castiglioni[2] | Matteo Montorfano[3,4] | Francesco Maisano[2,3] | Eustachio Agricola[1,3]

[1]Unit of Cardiovascular Imaging, IRCCS Ospedale San Raffaele, Milan, Italy | [2]Department of Cardiac Surgery, IRCCS Ospedale San Raffaele, Milan, Italy | [3]Vita-Salute San Raffaele University, Milan, Italy | [4]Interventional Cardiology Unit, IRCCS Ospedale San Raffaele, Milan, Italy

Correspondence: Eustachio Agricola (agricola.eustachio@hsr.it)

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ABSTRACT

Background: Little is known about stroke volume index (SVi) change and its prognostic implication in patients with low-flow aortic stenosis (AS) undergoing aortic valve replacement (AVR) and conflicting results are present in literature. The aim of this study was to evaluate the postoperative change in SVi and its impact on outcomes in patients with low-flow severe AS undergoing AVR.

Methods: Retrospective observational study of a high-volume tertiary care center including consecutive patients with low-flow ($SVi \leq 35$ mL/m^2) severe AS who underwent AVR (either surgical or transcatheter) with available comprehensive pre- and post-AVR echocardiographic assessment. Post-AVR SVi improvement was defined as an increase $\geq 15\%$ from baseline, while SVi normalization was defined as post-AVR $SVi > 35$ mL/m^2. A up to 36-month follow-up was conducted and the study primary endpoint was the composite of all cause-mortality and hospitalizations for heart failure.

Results: One-hundred-fifty-one patients (mean age 80 ± 8 years, 53.6% female) were included. After AVR, SVi improved by > 15% in 51 (33.8%) and normalized in 51 (33.8%) patients. At a median follow-up of 17 (7−32) months, 62 (52.6%) patients reached the primary composite endpoint. SVi improvement, but not SVi normalization, was associated with better survival free from the primary endpoint (log rank $p = 0.02$ and 0.056, respectively). Multivariate analysis confirmed that both SVi improvement and its absolute change per mL/m^2 unit carried a better prognosis (adj. HR 0.51 [0.28–0.91, $p = 0.02$] and 0.97 (0.94–0.99), $p = 0.016$, respectively).

Conclusions: In patients with low-flow AS undergoing AVR, early post-procedural SVi increase has beneficial prognostic significance. These findings highlight the importance of post-AVR hemodynamic assessment and may help refine risk stratification in this vulnerable population.

1 | Introduction

Among the spectrum of aortic stenosis (AS), low-flow (LF) AS emerged as a distinct entity, marked by reduced stroke volume index (SVi) (≤ 35 mL/m^2) [1] and worse clinical outcomes [2–4]. LFAS patients are an heterogenous population characterized by reduced ledt ventricular ejection fraction (LVEF < 50%, "classical" LF), or preserved LVEF ($\geq$ 50%) bur reduced SVi ("paradoxical" LF) [5]. The mechanisms contributing to a reduced transvalvular flow in the presence of preserved LVEF are multifactorial and often interplay together to determinate the LF status (concentric remodeling with decreased LV cavity size, advanced diastolic dysfunction, infiltrative myocardial disease, severe atrioventricular valvular diseases, elevated arterial impedance, right ventricular dysfunction etc.) [6].

Aortic valve replacement (AVR) is a established therapeutic option that, by removing the hemodynamic load imposed by the stenotic aortic valve, may promote SVi normalization [7, 8]. While the impact of AVR on overall clinical outcomes has been extensively studied, there remains a knowledge gap concerning the stroke volume changes in the setting of patients with pre-procedural LF and whether these changes can impact on the prognosis.

Some studies reported that SVi recovery (post AVR SVi > 35 mL/m^2) may be associated with better clinical outcomes when compared with persistently LF [9, 10]. However, evidence is still conflicting [11], and it is unknown whether an improvement of SVi, rather than its normalization, can affect the outcome, especially in the population of patients with LF AS, characterized by advanced extravalvular damage [12, 13].

The aim of this study is to address this knowledge gap by examining the postoperative recovery of SVi and its impact on outcomes in a specific setting of patients with LF severe AS undergoing AVR.

2 | Methods

2.1 | Study Design and Patient Population

This is a retrospective cohort study including consecutive patients with echocardiographic diagnosis of LF severe AS who underwent AVR (both transcatheter—TAVR—and surgical—SAVR—) between February 1, 2017 to September 30, 2022. Exclusion criteria were AV endocarditis, previous AV or ascending aorta interventions and more than moderate pre- or post-AVR aortic regurgitation. Severe LF AS was defined as aortic valve area (AVA) ≤ 1 cm^2 (or $\leq$ 0.6 cm^2/m^2) and a SVi ≤ 35 mL/m^2 according to current guidelines [1]. Patients were classified as having "classical" severe LF AS with reduced LVEF (< 50%) or "paradoxical" severe LF-AS with preserved LVEF ($\geq$ 50%). After the index evaluation, therapeutic management (either conservative, SAVR, or TAVR) was determined by the Heart Team meeting at our Heart Valve Center, considering patient age, cardiac and extracardiac comorbidities, and surgical risk, as assessed by the EuroSCORE II and STS score, in accordance with the latest recommendations [1]. The study protocol was approved by the internal review board (MILDPVL-TAVI). The study was conducted according to institutional guidelines and legal requirements.

2.2 | Echocardiographic Evaluation

A comprehensive transthoracic echocardiographic examination was performed according to current recommendations [14]. The grading of AS was based on the multiparametric approach suggested by current recommendations [15, 16], including the peak transaortic flow velocity, mean transvalvular pressure gradient, and AVA calculation by the continuity equation. SVi was calculated using left ventricular outflow tract diameter, obtained from the parasternal long-axis view, and left ventricular outflow tract

TABLE 1 | Patients' clinical data.

	Total population ($n = 151$)	Post SVi > 35 mL/m^2 ($n = 51$)	Post SVi $\leq$ 35 mL/m2 ($n = 100$)	OR	*p* value
Age (years)	80 ± 8	80 ± 9	80 ± 7		0.76
Female (*n*, %)	81 (53.64%)	26 (50.98%)	55 (55%)		0.64
BSA (m^2)	1.76 ± 0.2	1.72 ± 0.2	1.78 ± 0.2		0.07
Atrial fibrillation (*n*, %)	44 (29.14%)	3 (5.88%)	41 (41%)	0.1	**0.0005**
Smoking (*n*, %)	13 (8.61%)	6 (11.76%)	7 (7%)	1.52	0.49
Hypertension (*n*, %)	125 (82.78%)	42 (82.35%)	83 (83%)	1	1
Dyslipidemia (*n*, %)	85 (56.29%)	28 (54.90%)	57 (57%)	0.95	0.90
Diabetes (*n*, %)	54 (35.76%)	18 (35.29%)	36 (36%)	1.05	0.9
CAD (*n*, %)	76 (50.33%)	29 (56.86%)	47 (47%)	1.46	0.27
NYHA Class (I; II; III; IV) (%)	2.88%; 44.60%; 44.60%; 7.91%	2.13%; 46.81%; 46.81%; 4.25%	3.26%; 43.48%; 43.48%; 9.78%		0.7
CKD (*n*, %)	118 (78.15%)	37 (72.55%)	81 (81%)	0.63	0.26

Note: Data are expressed as mean ± standard deviation for continuous variables and as number (percentage) for categorical variables. Bold values indicate $p < 0.05$.
Abbreviations: BSA, body surface area according to Mosteller formula; CAD, coronary artery disease; CKD, chronic kidney disease defined as eGFR < 60 mL/min/1.73 m^2 according to Cockcroft-Gault formula; MI, myocardial infarction; OR, odds ratio.

velocity time integral (VTI). Valvular regurgitations were graded as absent/trivial (grade 0), mild (grade 1+), moderate (grade 2+), moderate-to-severe (grade 3+), and severe (grade 4+) according with current recommendations [17]. In case of atrial fibrillation, measurements were averaged over five cardiac cycles. Detailed echocardiographic protocol is reported in supporting material.

2.3 | Flow Status Assessment

We included only patient with preoperative LF ($SVi \leq 35\ mL/m^2$), irrespective of mean transvalvular gradient. The flow status was reassessed soon after AVR, commonly few days before hospital discharge and defined as follows:

TABLE 2 | Echocardiographic data.

	Total population ($n = 151$)	Post $SVi > 35\ mL/m^2$ ($n = 51$)	Post $SVi \leq 35\ mL/m^2$ ($n = 100$)	p value
• *Baseline (pre-AVR) ECHO*				
EF (%)	48 ± 13	51 ± 13	47 ± 12	0.054
LVEDVi (mL/m^2)	66 ± 29	65 ± 25	66 ± 31	0.78
LVESVi (mL/m^2)	38 ± 25	36 ± 21	39 ± 27	0.55
LAVi (mL/m^2)	51 ± 16	50 ± 14	51 ± 17	0.77
IVS diast (mm)	12 ± 2	13 ± 2	12 ± 2	**0.026**
LVPW diast (mm)	11 ± 2	11 ± 2	11 ± 2	0.41
RWT	0.50 ± 0.16	0.52 ± 0.14	0.49 ± 0.17	0.31
LV mass indexed (g/m^2)	118 ± 34	122 ± 35	117 ± 35	0.47
E/e' lat	14 ± 6	15 ± 6	13 ± 6	0.32
Aortic Mean Gradient (mmHg)	35 ± 13	39 ± 16	33 ± 11	**0.017**
Aortic Vmax	3.7 ± 0.6	3.8 ± 0.7	3.6 ± 0.6	**0.024**
AVA (cm^2)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.8
SVi (mL/m^2)	30 ± 4	30 ± 3	30 ± 5	0.32
AR grade > 1 (n, %)	40 (26.49%)	15 (29.41%)	25 (25%)	0.69
MR grad ≥ 3 (n, %)	35 (23.18%)	10 (19.60%)	25 (25%)	0.45
TR grade ≥ 3 (n, %)	22 (14.57%)	4 (7.84%)	18 (18%)	0.09
PASP (mmHg)	42 ± 13	45 ± 16	40 ± 12	0.09
TAPSE (mm)	19 ± 4	19 ± 4	19 ± 4	0.86
• *Predischarge (post-AVR) ECHO*				
EF	49 ± 13	51 ± 13	47 ± 12	0.054
Delta EF (absolute)	1 ± 7	4 ± 8	0 ± 6	**0.01**
Improved EF (n, %)	11 (7.28%)	8 (15.69%)	3 (3%)	**0.0046**
SVi	33 ± 10	43 ± 6	27 ± 5	**< 0.001**
Delta SVi (absolute)	2.7 ± 10	13 ± 8	−2.8 ± 6	**< 0.001**
Delta SVi (%)	11 ± 36	45 ± 31	−7 ± 23	**< 0.001**
Improved SVi (n, %)	51 (33.77%)	44 (86.27%)	7 (7%)	**< 0.001**
Aortic Mean Gradient (mmHg)	7 ± 3	8 ± 4	7 ± 3	0.24
Aortic Vmax	1.7 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	0.77
Self expanding valve (TAVR)	116 (76.82%)	42 (82.35%)	74 (74%)	0.34
Balloon expandable valve (TAVR)	11 (7.28%)	2 (3.92%)	9 (9%)	0.42

Note: Improved EF defined as ≥ 10% absolute increase. Bold values indicate $p < 0.05$.
Abbreviations: AVA, aortic valve area; EF, left ventricular ejection fraction; LAVi, left atrial volume index; LVEDVi/LVESVi, left ventricle end-diastolic/end-systolic volume index; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; SVi, left ventricular outflow tract stroke volume indexed per body surface area; TAPSE, tricuspid annular plane excursion; TR, tricuspid regurgitation.

- *SVi improvement*: ≥ 15% increase in SVi at the the post-AVR echocardiography.
- *SVi worsening*: ≥ 15% decrease in SVi at the the post-AVR echocardiography.
- *SVi unchanged*: SVi percentage change between −14% and +14% at the the post-AVR echocardiography.
- *SVi normalization*: achievement of post-AVR SVi > 35 mL/m^2 irrespective of percentage change.

The value of 15% change as the threshold to define improvement or worsening was chosen to take into account both a clinically meaningful difference and the intrinsic variability in left ventricultar outflow tract VTI (LVOT VTI) calculation [18] as underlined by the reproducibility analysis described below.

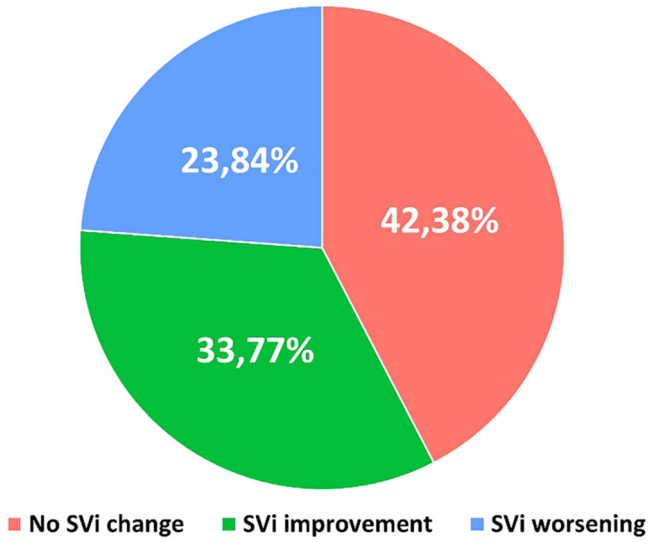


FIGURE 1 | Flow status after AVR. The majority of patients maintained ther SVi unchanged while in 34% SVi improved. [Color figure can be viewed at wileyonlinelibrary.com]

2.4 | Follow-Up and Clinical Outcome

Clinical follow-up was retrospectively obtained and data on event rate were collected through the revision of hospital medical software systems records and via phone-calls. In case of no response a second attempt was made with a time lag of at least 7 days. If no response was obtained and no data were retrieved from the institutional medical software records, the patient was considered lost to follow-up and excluded from the study.

The primary endpoint was the composite of all-cause death and hospitalizations for heart failure up to 36 months. The single secondary endpoints were hospitalizations for heart failure and all-cause death up to 36 months.

2.5 | Statistical Analysis

Continuous data are presented as either the mean ± standard deviation or median (interquartile range), depending on the normality of distribution, which was evaluated through the Shapiro–Wilk test. Categorical data were represented by number and percentage. For comparison purposes, the Student's *t*-test or the Wilcoxon rank sum test were used for continuous variables and the Chi-square test or Fisher exact test for categorical variables, as deemed appropriate. Univariate and multivariate Cox regression analyses were performed to identify the outcome predictors. Variables significantly associated with events at univariate analysis ($p < 0.05$) were entered into a multiple logistic regression model to determine independent parameters. Kaplan–Meier method with the log-rank test of the time-to-event data was employed to analyze survival free from the study endpoints; patients were censored at the time of last available follow-up. Logistic regression analysis was used to determine the predictors of stroke volume improvement among clinical, baseline and pre-discharge echocardiographic data. Inter-rater reproducibility of LVOT VTI measurement was assessed through percentage variability, the intraclass correlation coefficient (ICC) and Pearson's linear correlation coefficient. Two different raters, blinded to each other's results, retrospectively measured the

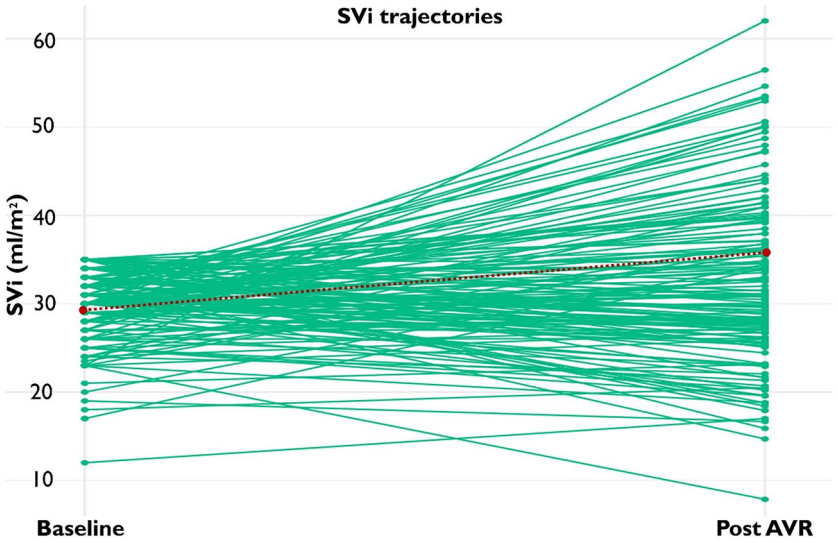


FIGURE 2 | SVi trajectories. The illustration shows the trajectory of SVi for each included patient. The red dots connected by the dashed line represent the mean value. [Color figure can be viewed at wileyonlinelibrary.com]

LVOT VTI in a subgroup of 70 patients by tracing the pulsed wave Doppler spectral curve at the LVOT level. A p-value of < 0.05 was considered statistically significant. Statistical analyses were carried out using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Patients Clinical and Echocardiographic Characteristics

One-hundred-fifty-one patients (mean age 80 ± 8 years, 53.6% female) were included in the study, after excluding 52 patients lost to follow-up. Patients clinical and echocardiographic characteristics are reported in Tables 1 and 2. The most common cause of LF was reduced LVEF ($n = 83$, 54%).

The majority of patients ($n = 127$, 84.1%) underwent TAVR while the remaining 24 (15.9%) SAVR. Self expanding valves were more commonly used in the TAVR group ($n = 116$) while biological valves were more commonly used in the surgical group ($n = 20$). At the post-AVR echocardiography (median 4 [2–7] days after AVR), 64 (42.4%) patients maintained their SVi unchanged, in 51 (33.8%) SVi improved $\geq 15\%$ and in 36 (23.8%) SVi worsened $\geq 15\%$ (Figure 1). Patients with post-procedural SVi normalization ($> 35\ mL/m^2$, $n = 51$, 33.8%) had higher pre-operative transvalvular gradients and a lower prevalence of atrial fibrillation compared to those who did not achieve SVi normalization. As

TABLE 3 | Predictors of the composite outcome at the univariate and multivariate analysis (adjusted for age, sex, and significant [$p < 0.05$] predictors at univariate analysis).

Determinants of primary endpoint	Univariate analysys		Multivariate model 1		Multivariate model 2	
	HR	*p* value	Adj. HR	*p* value	Adj. HR	*p* value
Age	1 (0.97–1.04)	0.8	1 (0.97–1.04)	0.8	1.02 (0.98–1.05)	0.35
Female sex	0.67 (0.41–1.11)	0.1	0.68 (0.41–1.14)	0.1	0.64 (0.38–1.08)	0.098
BMI	1.06 (0.9–1.12)	0.07				
Smoking	0.60 (0.22–1.67)	0.3				
Hypertension	1.67 (0.75–3.67)	0.2				
Dyslipidemia	1.08 (0.64–1.80)	0.8				
Diabetes	1.36 (0.80–2.28)	0.3				
CAD	1.6 (1.0–2.76)	**0.049**	1.59 (0.95–2.67)	0.05	1.56 (0.92–2.63)	0.096
NYHA Class > 2	0.94 (0.56–1.58)	0.8				
CKD	1.16 (0.61–2.18)	0.7				
AF	1.32 (0.68–2.56)	0.4				
Reduced EF	1.32 (0.79–2.21)	0.3				
Preserved EF	0.75 (0.45–1.26)	0.3				
MR > 2+	1.07 (0.60–1.92)	0.8				
TR > 2+	1.05 (0.47–1.94)	0.9				
RV dysfunction	1.10 (0.91–1.89)	0.7				
TAVR	1.13 (0.57–2.22)	0.7				
SAVR	0.89 (0.45–1.75)	0.7				
Balloon expandable valve (TAVR)	0.70 (0.57–3.57)	0.5				
Self expanding valve (TAVR)	1.03 (0.54–1.73)	0.9				
PRE-DISCHARGE ECHO						
SVi > 35 mL/m^2	0.58 (0.33–1.02)	0.05				
Svi improvement > 15%	0.51 (0.28–0.91)	**0.02**	**0.51 (0.28–0.91)**	**0.02**		
Delta SVi (absolute)	0.97 (0.94–0.99)	**0.02**			0.97 (0.94–0.99)	**0.016**
Delta SVi (%)	0.99 (0.98–0.99)	**0.04**				
Delta EF	0.98 (0.94–1.01)	0.2				
EF improvement > 10%	0.76 (0.28–2.10)	0.6				
Post EF preserved	0.75 (0.46–1.24)	0.3				

Note: Two multivariate models were reported, one with SVi improvement as categorical variable and one with SVi change as absolute continuous variable. Bold values indicate $p < 0.05$.

Abbreviations: AF, atrial fibrillation; AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney; EF, left ventricular ejection fraction; Gmed, mean transvalvular gradient; MR, mitral regurgitation; NYHA, new York heart association; RV, right ventricle; TR, tricuspid regurgitation.

expected, patients with normalized SVi exhibited a higher increase in LVEF. Figure 2 depicts the flow trajectories from baseline to post-AVR echocardiography of the included patients.

3.2 | Follow-Up and Outcomes

At a median follow-up time of 17 (IQR 7–32) months, 62 (52.6%) patients reached the primary composite endpoint, 37 patients died (35.8%) and 41 (30.8%) were hospitalized due to HF. Univariate and multivariate analysis is reported in Table 3. In the univariate analysis, predictors of the primary endpoint were coronary artery disease (CAD, HR: 1.80 [1.07–3.05], $p = 0.03$), absolute (HR 0.97 [0.94–0.99], $p = 0.02$) and percentage (HR 0.99 [0.98–0.99], $p = 0.04$) change (delta) of SVi. SVi improvement ≥ 15% was associated with a reduced occurrence of the primary endpoint (HR 0.52 [0.28–0.91], $p = 0.02$). A positive, albeit non-significant trend, was observed for SVi normalization to > 35 mL/m^2 ($p = 0.05$). In the two multivariate models, with SVi included as a categorical variable (delta > 15%) or continuous variable (absolute change) and corrected for age, sex, and significant predictors from the univariate analysis, both SVi delta > 15% and SVi absolute change maintained their independent association with the outcome (adj. HR: 0.51 [0.28–0.91, $p = 0.02$] and 0.97 (0.94–0.99), $p = 0.016$, respectively) while a positive, but non-significant trend was found for SVi normalization to > 35 mL/m^2 (adj. HR 0.6 [0.35–1.03, $p = 0.055$], Supporting Information S1: Figure 1). The spline curve analysis depicted in Figure 4 shows a progressive reduction in the risk of the primary endpoint with the increase in SVi after AVR.

Patients with SVi improvement showed better event free survival from primary endpoint compared to both patients with unchanged or worsened SVi (log rank $p < 0.05$) (Figure 3).

Patients with SVi improvement showed a reduced risk of HF hospitalization (log rank p 0.04) but not all-cause mortality (log rank p 0.4) (Supporting Information S1: Table 1).

3.3 | Predictors of Stroke Volume Improvement

Among multiple clinical and echocardiographic parameters, the only independent predictor of SVi improvement was an absolute delta EF > 10%. (Adj OR 1.55 [1.17–2.03, $p = 0.002$]). Atrial fibrillation nearly reached statistical significance. No other clinical or echocardiographic parameters, including the etiology of LF (i.e., preserved vs. paradoxical) were associated to SVi improvement in our analysis (Table 4).

3.4 | Longer Term Follow-Up

Longer-term echocardiographic data were available for 82 patients (Supporting Information S1: Table 2). The median time

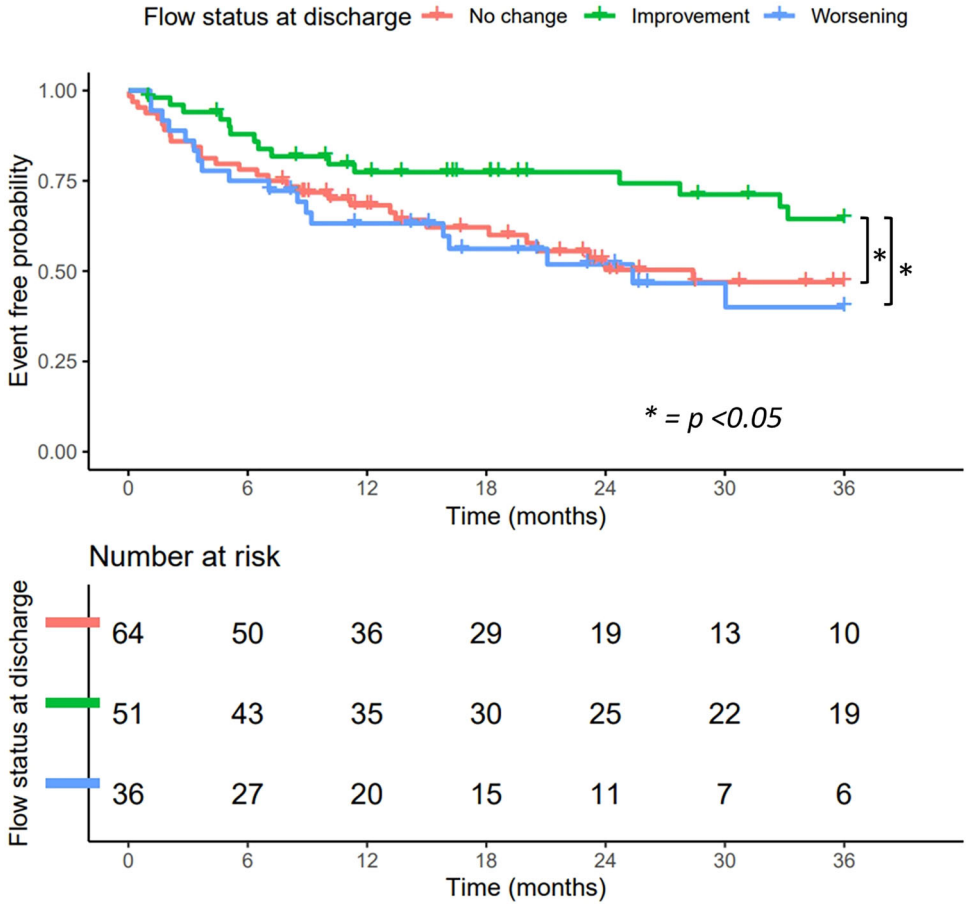


FIGURE 3 | Impact of SVi change on outcomes. As depicted by the Kaplan–Meier curves, patients with SVi improvement had a reduced risk of the primary outcome against both patients with SVi unchanged and worsening ($p < 0.05$). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 | Univariate and multivariate predictors of stroke volume index improvement.

	Univariate analysis		Multivariate analysis	
Predictors of SVi improvement	**OR**	***p* value**	**Adj. OR**	***p* value**
Age	0.98 (0.93−1.02)	0.53	0.96 (0.91−1.01)	0.09
Female sex	1.08 (0.55−2.14)	0.82	1.38 (0.66−2.97)	0.40
BMI	0.98 (0.94−1.02)	0.11		
Smoking	1.04 (0.26−3.59)	1		
Hypertension	0.95 (0.38−2.57)	1		
Dyslipidemia	0.70 (0.34−1.42)	0.41		
Diabetes	1.10 (0.52−2.29)	0.94		
CAD	0.88 (0.43−1.80)	0.86		
NYHA Class > 2	1.50 (0.74−3.09)	0.34		
CKD	0.86 (0.37−2.05)	0.89		
AF	0.38 (0.12−1)	0.05	0.40 (0.14 – 1.12)	0.08
Preserved LVEF	1.01 (0.51−1.98)	1		
EF < 50%	0.99 (0.50−1.98)	1		
TR > 2+	0.71 (0.24−1.88)	0.65		
TR 4+	0.52 (0.11−1.79)	0.45		
MR > 2+	0.74 (0.31−1.66)	0.59		
MR 4+	1.11 (0.32−3.48)	1		
RV dysfunction	1.52 (0.74−3.13)	0.33		
TAVR	0.82 (0.33−2.12)	0.85		
Baloon expandable valve (TAVR)	0.43 (0.06−1.83)	0.33		
Self expanding valve (TAVR)	1.62 (0.71−3.99)	0.25		
Delta EF > 10%	5.76 (1.54−28.83)	**0.005**	7.56 (1.19−37.72)	**0.006**
EF change (absolute)	1.54 (0.72−3.34)	0.26		

Note: Bold values indicate $p < 0.05$.
Abbreviations: AF, atrial fibrillation; AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney; EF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, new York heart association; RV, right ventricle; TR, tricuspid regurgitation.

from the index echocardiography was 12 months (IQR 2–30 months). SVi remained substantially stable compared to the pre-discharge echocardiogram (32 vs. 33 mL/m^2, $p = 0.7$; mean change +2%) and was significantly higher than the pre-procedural value (32 vs. 30 mL/m^2, $p < 0.05$). Additionally, 39% of patients showed an increase in SVi of at least 15% from baseline (mean change +12%). Similarly, EF improved compared to the index echocardiogram (50% vs. 48%, $p < 0.05$), and the proportion of patients with reduced EF (< 50%) decreased from 55% (83/151) to 40% (33/82).

3.5 | Reproducibility Analysis

After AVR, LVOT area can be assumed constant allowing the use of LVOT VTI alone to assess changes in stroke volume and transvalvular flow rate. In a random sample of 70 patients, the reproducibility analysis of LVOT VTI measurement showed an excellent level of inter-rater agreement with a percentage variability of 4.4%, an ICC of 0.95 and a Pearsons's *r* coefficient of 0.95, all $p < 0.001$ (Supporting Information S1: Table 3, Supporting Information S1: Figure 2).

4 | Discussion

The main findings of our study can be summarized as follows:

1. almost one-third of patients with reduced SVi experience SVi normalization early after AVR.
2. SVi improvement above 15% is associated with a reduced incidence of the composite outcome of death for any cause and HF hospitalizations.
3. Any increase in SVi after AVR protects from the risk of the primary outcome.
4. LVEF improvement is associated with SVi improvement.

4.1 | Prognostic Role of SVi Improvement after AVR

Conflicting findings exist in literature regarding the role of SVi improvement after AVR. Gallone et al. investigated the impact of SVi normalization to > 35 mL/m^2 and flow rate improvement as predictors of mortality following TAVR. They found that flow

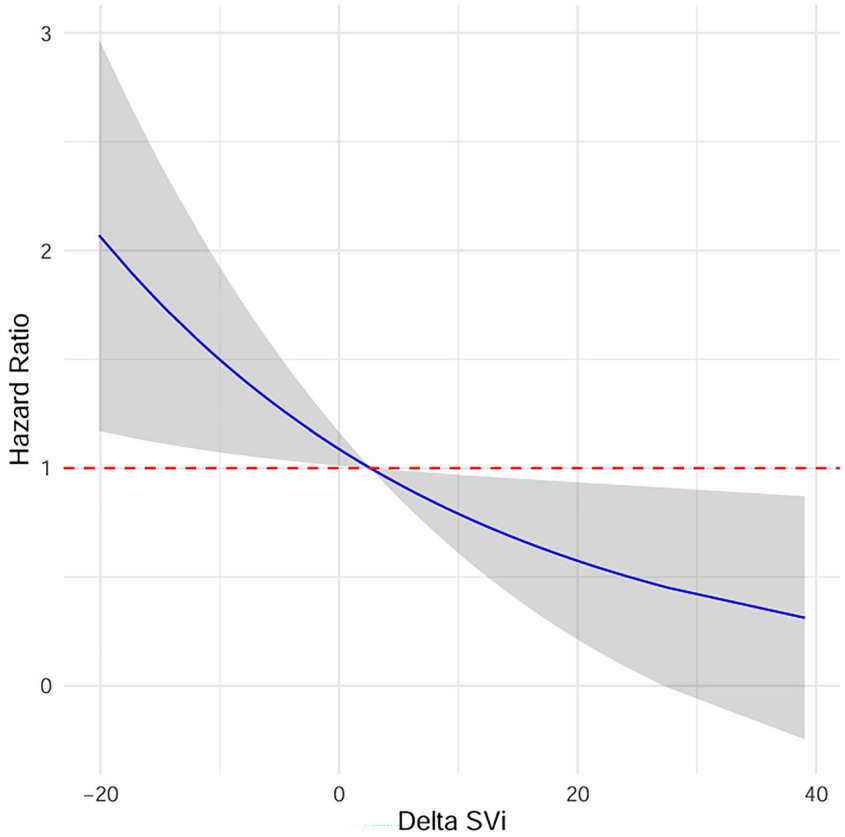


FIGURE 4 | Spline curve analysis. The illustration depicts the inverse relationship between SVi variation after AVR and the occurrence of the primary endpoint. An increase in SVi is associated with a reduced risk of the occurrence of the primary endpoint. SVi, stroke volume index. [Color figure can be viewed at wileyonlinelibrary.com]

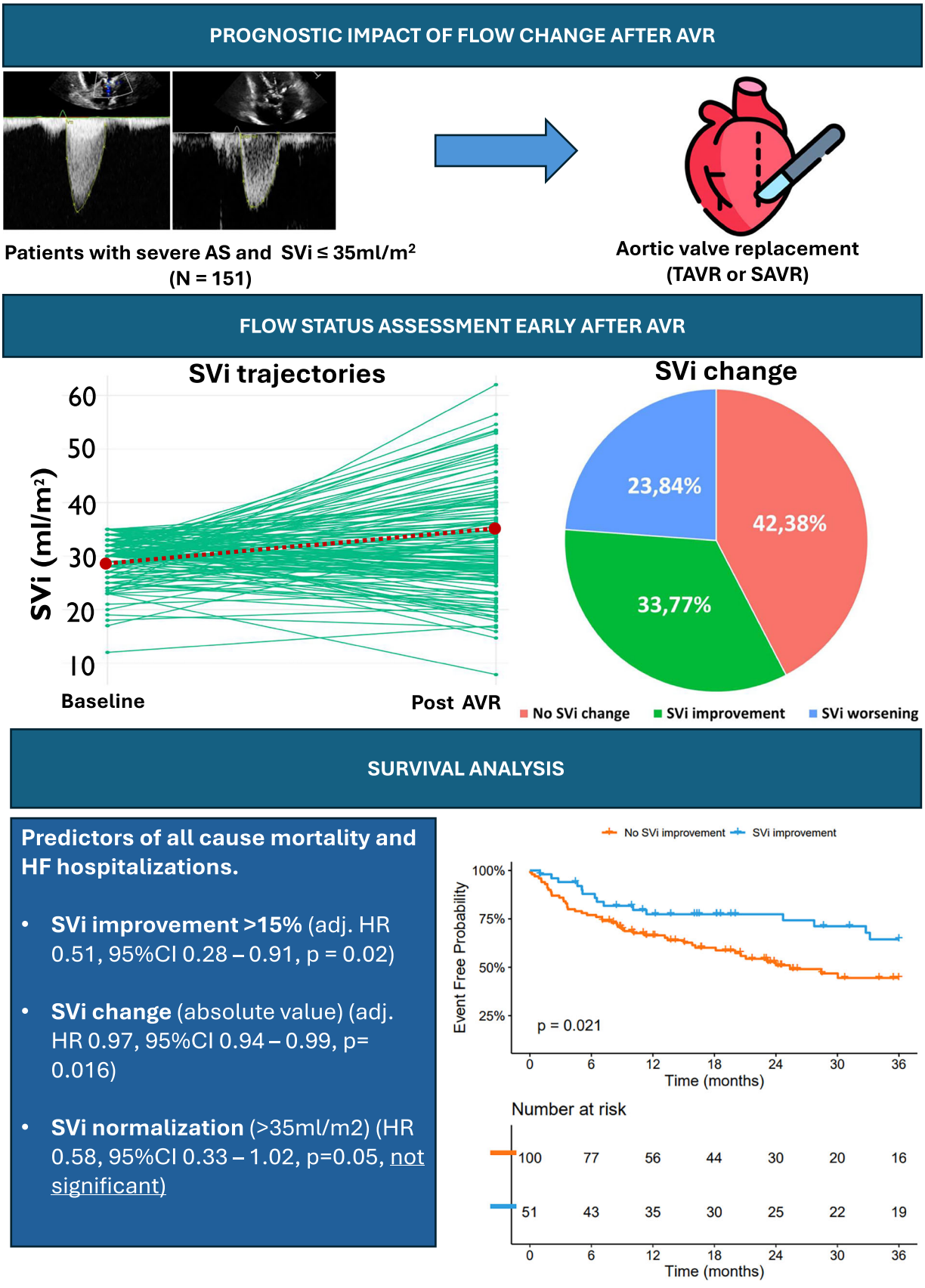
rate improvement, but not SVi normalization, was associated with a reduced risk of death for any cause [11]. In the present study, we obtained similar results, finding that SVi normalization to $> 35\,mL/m^2$ did not significantly reduce the risk of the composite outcome of hospitalization for heart failure and all-cause mportality, although a positive trend was observed ($p = 0.05$). However, our analysis introduced a novel perspective by evaluating not only SVi normalization but also its improvement, defined as post-AVR SVi increase of $\geq 15\%$. We observed a reduced risk of the primary endpoint in patients who achieved SVi improvement. A possible explication for the apparent discrepancy between the prognostic role of SVi normalization and SVi improvement $\geq 15\%$ is that the cut-off of $35\,mL/m^2$, originally suggested for diagnosing LF low-gradient AS, may not necessarily predict worse outcomes after AVR. Instead, the inability to improve flow status appears to be more strongly associated with poorer prognosis. In summary, our findings suggest that early improvement in SVi after AVR, even if normalization to $> 35\,mL/m^2$ is not achieved, is a predictor of better prognosis.

4.2 | Any Ml of Stroke Volume Matters

The results of our analysis underscore a simple yet crucial message: any improvement (or, by contrary, worsening) of stroke volume plays a central role in the prognosis of patients with severe valvular diseases causing a LF status. Looking at the survival analysis, beyond the improvement of SVi, we found a significant relationship between any delta in SVi, both as percentage delta or absolute delta, with the primary outcome. The same relationship is depicted in the spline curve analysis in Figure 4. In other words, according to our results, any little change in SVi can improve patient prognosis in the context of severe LF AS. These findings have important clinical implications. Indeed, while AVR represents a crucial step toward enhancing SVi, by reducing the transvalvular afterload, the identification of those patients who do not benefit from AVR can help to detect a population of subjects requiring a stricter follow-up and optimization of HF therapy to reduce the risk of rehospitalization and mortality. Similarly, those with persistently significant atrioventricular valves regurgitation, whose SVi failed to improve after AVR, represent a population with poorer prognosis, often excluded from randomized clinical trial, who may benefit from a tailored approach addressing these valves [19]. These findings pave the way for future studies aimed at evaluating the prognostic role of anterograde flow assessment in valvular heart disease, in addition to the standard grading approach [1], with the aim of identifying those patients in which the restoration of adequate flow can positively impact the prognosis.

4.3 | Predictors of SVi Improvement

In such population of high-risk patients with an advanced stage of the disease [12], it is important to identify those patients who are likely to benefit from AVR. Unfortunately, among several



CENTRAL ILLUSTRATION 1 | In patients with severe low-flow aortic stenosis, defined as a stroke volume index (SVi) ≤ 35 mL/m², who underwent either surgical or transcatheter aortic valve replacement, the early post-intervention variation of stroke volume was assessed. In about one-third of patients (33.8%), the stroke volume improved by more than 35% compared to the baseline evaluation. This early improvement in stroke volume was associated with a better outcome compared to patients who did not experience SVi improvement. [Color figure can be viewed at wileyonlinelibrary.com]

clinical and echocardiographic parameters (Table 3), no single pre-AVR predictor was associated with a higher likelihood of SVi improvement, while post-AVR LVEF improvement > 10% was. The etiology of LF (classic vs. paradoxical) and pre-AVR significant atrioventricular valve regurgitation were not associated with SVi improvement, although subgroup analysis is impaired by sample size and statistical power. Similarly, the type of AV intervention (TAVR vs. SAVR) did not influence the post-AVR flow-status. These findings suggest a complex and widely ununderstood interplay between ventricular function and afterload. Indeed, from a pathophysiological point of view, it is expectable a significant increase of stroke volume with the reduction of afterload following AVR, especially in patients with reduced LVEF. However, our results underline that this pathophysiological hypothesis is not uniformly applicable, as patients with reduced LVEF did not exhibit a higher rate of flow recovery compared to those with preserved LVEF. An explanation for this discrepancy is the heterogeneous nature of the reduced LVEF category, encompassing patients with varying degrees of LV dysfunction, ranging from more impaired, end-stage, LV dysfunction (including a proportion of patients with infiltrative disease [20]) to those where LV dysfunction is primarily the result of the high afterload imposed by the valvular stenosis. The dobutamine stress test before AVR could aid in further stratifying patients according to flow reserve status. However, it is noteworthy that even patients without demonstrated flow reserve at the dobutamine test could still experience flow recovery due to the reduction in the afterload imposed by the stenotic valve and can benefit from AVR [8, 21]. Moreover, the etiology of atrioventricular valve regurgitation may be a determinant of flow recovery after TAVR in patients with preserved LVEF. Indeed, secondary mitral and tricuspid regurgitation are sensitive to afterload and can significantly improve after AVR, leading to an increase in the forward stroke volume [22, 23]. However, the timing of SVi increment can vary considerably, and some patients may require ventricular reverse remodeling to experience a stable increase in SVi. Our results pave the way for larger studies investigating the association among LF cause and the likelihood of SVi improvement after AVR.

4.4 | Limitations

Some limitations should be acknowledged when interpreting the results of our study. First, this is a retrospective study of a single third level center for valve disease (i.e., population and selection bias). Furthermore, although the severity of AS was carefully assessed according to current recommendations, we lacked access to data regarding dobutamine test for a significant proportion of patients (that could have aided in further stratifying patients according to flow reserve status), as a proportion of them underwent these tests in other centers. Only the first echocardiographic assessment following AVR was considered and, as ventricular remodeling requires longer times, the observed changes in flow status reflect the direct impact of afterload reduction and do not take into account further changes in flow occurring later in time, that were beyond the scope of this study. Finally, the relatively small sample size reduced the power of our statistical analysis.

5 | Conclusion

In patients with LF AS undergoing AVR, any increase of SVi is associated to a reduced risk of the composite outcome of hospitalizations for heart failure and all-cause death. No single pre-AVR predictor, including the specific etiology of LF, predict flow increase after AVR. Central illustration 1.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available from the corresponding author upon reasonable request.

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Supporting Information

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