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Impact of first-phase ejection fraction on clinical outcomes in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Background: First-phase left ventricular ejection fraction (LVEF1) is an early marker of left ventricular remodeling. Reduced LVEF1 has been associated with adverse prognosis in patients with aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF). It remains to be determined, whether reduced LVEF1 differentiates clinical outcomes after aortic valve replacement.
Objectives: We investigated the impact of LVEF1 on clinical outcomes in patients undergoing transcatheter aortic valve implantation (TAVI) for symptomatic severe AS with preserved LVEF (≥ 50%).
Methods: In the prospective Bern TAVI registry, we retrospectively categorized patients according to LVEF1 as assessed by transthoracic echocardiography. Clinical outcomes of interest were all-cause mortality and residual heart failure symptoms (New York Heart Association (NYHA) functional class III or IV) at 1 year after TAVI.
Results: A total of 644 patients undergoing TAVI between January 2014 and December 2019 were included in the present analysis. Patients with low LVEF1 had a lower LVEF (62.0 ± 6.89% vs. 64.3 ± 7.82%, $P < 0.001$) and a higher left ventricular mass index (129.3 ± 39.1 g/m^2 vs. 121.5 ± 38.0 g/m^2; $P = 0.027$) compared to patients with high LVEF1. At 1 year, the incidence of all-cause/cardiovascular death, and NYHA III or IV were comparable between patients with low and high LVEF1 (8.3% vs. 9.2%; $P = 0.773$, 3.9% vs. 6.0%; $P = 0.276$, 12.9% vs. 12.2%; $P = 0.892$, respectively).
Conclusions: Reduced LVEF1 was not associated with adverse clinical outcomes following TAVI in patients with symptomatic severe AS with preserved LVEF.
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1. Introduction

Timing of intervention in patients with aortic stenosis (AS) is challenging and requires the consideration of stenosis severity, symptom status, and evidence of downstream cardiac damage. The integration of structural and functional changes proofed effective in the categorization of AS into different stages associated with survival prognosis [1–3]. Beyond patients with symptomatic, severe AS and preserved left ventricular ejection fraction (LVEF), aortic valve replacement (AVR) is recommended in patients with reduced LVEF [4,5]. However, a reduction in LVEF in patients with AS is a rather late manifestation of LV remodeling preceded by LV hypertrophy and a compensatory increase in LVEF [6]. There is a need for sensitive markers of early LV remodeling to guide the optimal timing of intervention.

First-phase ejection fraction (LVEF1) is an echocardiographic marker reflecting the LVEF at the time of peak aortic jet velocity and has emerged as a novel marker of early LV systolic dysfunction. Recent studies suggested that LVEF1 is a powerful predictor of adverse events in patients with AS and preserved left ventricular function. There is, however, limited evidence on the prognostic importance of LVEF1 in patients undergoing AVR [7–11]. In particular, it remains to be determined whether decreased LVEF1 in patients with aortic stenosis and preserved left ventricular function translates into adverse clinical outcomes after AVR, or whether decreased LVEF1 is a reversible marker of LV remodeling without prognostic significance. In the present study, we aimed to evaluate the prognostic impact of LVEF1 in patients with AS and preserved left ventricular function undergoing transcatheter aortic valve implantation (TAVI).

Abbreviations: AS, aortic stenosis; LVEF, left ventricular ejection fraction; LVEF1, first-phase ejection fraction; TAVI, transcatheter aortic valve implantation.

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2. Methods

2.1. Study design and population

The study cohort for this retrospective analysis comprised consecutive patients undergoing TAVI at Bern University Hospital from January 2014 and December 2019, who were prospectively enrolled into the Bern TAVI registry, which forms part of the nationwide SwissTAVI registry (NCT01368250) [12]. For the purpose of the present study, patients with a reduced LV systolic function (LVEF < 50%) and those with inadequate echocardiographic images for the assessment of LVEF1 were excluded. The registry was approved by the Bern cantonal ethics committee, and patients provided written informed consent to participate.

2.2. Transthoracic echocardiography

Comprehensive transthoracic echocardiography using a Philips iE33 machine (Philips Healthcare, Andover, Massachusetts) was performed by a board-certified cardiologist before TAVI. Acquired images were transferred to a dedicated workstation (Tomtec Imaging Systems GmbH, Unterschleissheim, Germany) and re-evaluated by independent experienced imaging specialists blinded to clinical outcome in the Corelab. The LV dimensions and AS severity were determined by quantitative assessment as recommended by current guidelines [13,14]. Patients with mean gradient <40 mmHg and stroke volume index ≥35 ml/m^2 or mean gradient <40 mmHg and stroke volume index <35 ml/m^2 were defined as "high-flow low-gradient (HFLG) AS" and "low-flow low-gradient (LFLG) AS", respectively. LVEF1 was retrospectively measured by using Simpson's biplane method by measuring the volume change from end-diastole to the time of peak LV ejection time on continuous wave Doppler of aortic flow: (LV end-diastolic volume − LV volume at the time of peak aortic flow) / LV end-diastolic volume × 100 (%) [7] (Fig. 1). Patients were stratified into low and high LVEF1 group according to a cut-off value of 25%, as previously validated [8–10].

2.3. Data collection and clinical endpoints

All baseline clinical, procedural, and follow-up data were prospectively recorded in a dedicated database, held at the Clinical Trials Unit at the University of Bern, Switzerland. Clinical follow-up data at 30 days and at 1 year were obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee based on the Valve Academic Research Consortium criteria [15–17]. The outcomes of interest in the present study included all-cause and cardiovascular death, and residual heart failure symptoms (New York Heart Association (NYHA) functional class III or IV) at 30 days and 1 year after TAVI.

2.4. Statistical analysis

Categorical variables are represented as frequencies and percentages, and the differences between groups were evaluated with the chi-square test or Fisher's exact test. Continuous variables are presented as mean values ± standard deviation (SD) and compared between groups using a two-sample *t*-test. Time-to-event curves were constructed using the Kaplan-Meier method. Cox proportional hazards models were used to calculate adjusted hazard ratios and 95% confidence intervals. Baseline variables entered into the multivariable model for adjustment were predefined based on the presumed association with clinical outcomes of interest: age, gender, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), atrial fibrillation, and previous pacemaker implantation. All statistical tests were two-sided and *p*-values of <0.05 were considered significant. All statistical analyses were performed using R for Windows 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population and baseline characteristics

Between January 2014 and December 2019, 644 patients had adequate echocardiographic images for the evaluation of LVEF1 (Fig. 2). Mean LVEF1 was 29.4% in this study. The distribution of LVEF1 is shown in Fig. 3.

Table 1 shows baseline characteristics according to LVEF1. Patients with low LVEF1 were less likely to be female (47.4% vs. 56.5%; $P = 0.032$) and had a smaller body mass index (25.8 ± 5.41 kg/m^2 vs. 26.7 ± 5.43 kg/m^2; $P = 0.048$) and a higher prevalence of atrial fibrillation (39.6% vs 29.5%; $P = 0.011$). There were no significant differences between patients with low versus high LVEF1 in terms of age, STS-PROM, NYHA class III or IV, and past medical history.

Echocardiographic and computed tomographic measurements and procedural characteristics are summarized in Table 2. Patients with low LVEF1 had a larger LV systolic volume (34.5 ± 18.0 ml vs. 31.0 ± 15.3 ml; $P = 0.009$), a lower LVEF (62.0 ± 6.9% vs. 64.3 ± 7.8%, $P < 0.001$), a higher left ventricular mass index (129.3 ± 39.1 g/m^2 vs.

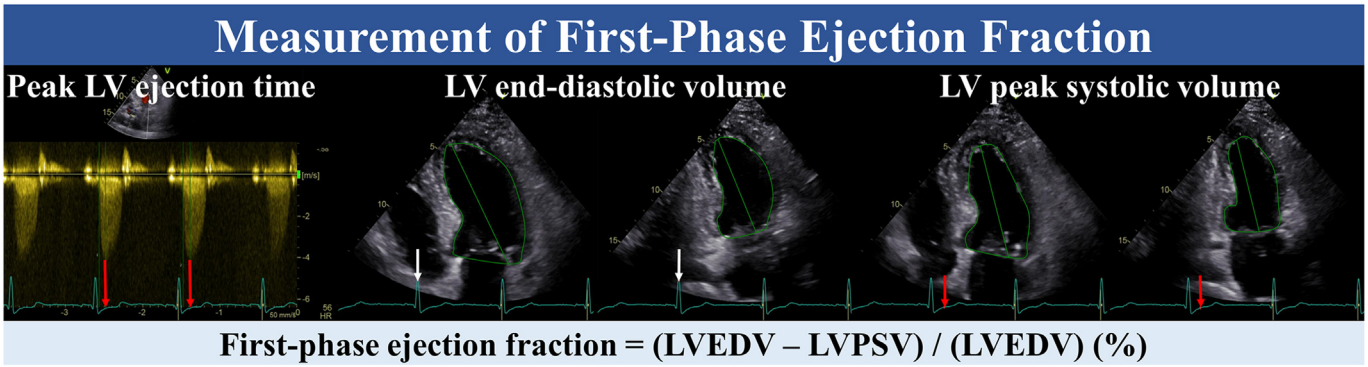

Fig. 1. Measurement of first-phase ejection fraction.
First-phase ejection fraction was measured by using Simpson's biplane method. (Left) Measurement of time peak LV ejection time on continuous wave Doppler of aortic flow. (Middle) Measurement of end-diastolic volume from 4-chamber and 2-chamber images. (Right) Measurement of LV peak systolic volume, using QRS peak time (left) as an anchor point, at peak LV ejection time. Red arrows indicate a time of peak LV ejection time. White arrows indicate a time of end-diastolic.
LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVPSV = left ventricular peak-systolic volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

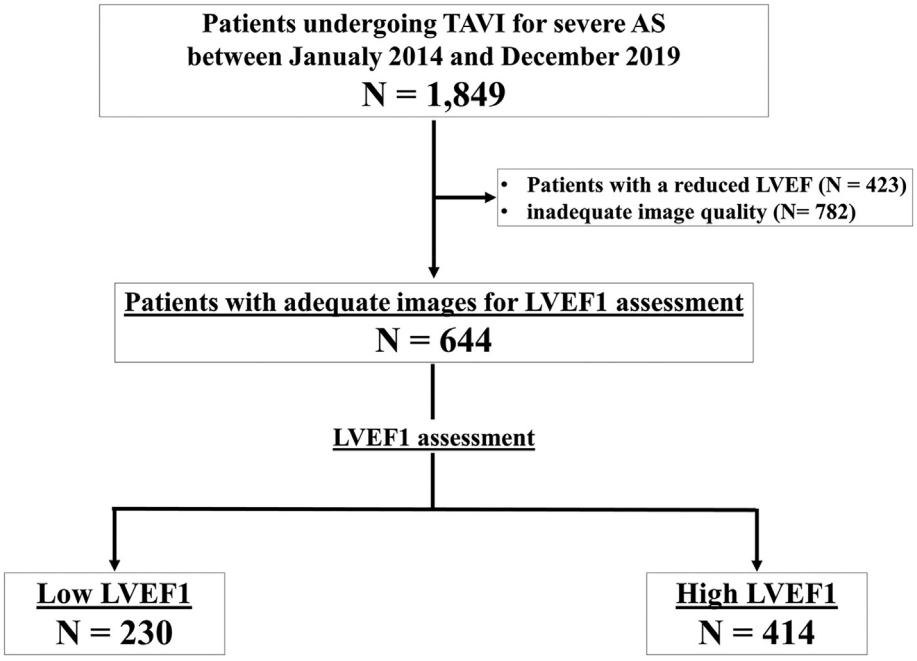

Fig. 2. Study flow chart.
AS = aortic stenosis; LVEF = left ventricular ejection fraction; LVEF1 = first-phase ejection fraction; TAVI = transcatheter aortic valve implantation.

121.5 ± 38.0 g/m^2; P = 0.027), and a larger aortic annulus area (447.9 ± 81.4 m^2 vs. 431.8 ± 75.4 m^2; P = 0.018) than those with high LVEF1. TAVI was performed by transfemoral access in 95.2% of patients without differences between groups. There were no significant differences in the valve types and valve sizes used.

3.2. Clinical outcomes according to LVEF1

At 30 days, there were no significant differences in the rates of all-cause death (1.7% vs. 2.9%; P = 0.439), cardiovascular death (1.3% vs. 2.7%; P = 0.398), and residual heart failure symptoms (NYHA III or IV: 7.0% vs. 8.5%; P = 0.636) between patients with low versus high LVEF1.

Clinical outcomes at 1 year according to LVEF1 are summarized in Table 3. At 1 year, rates of all-cause death, cardiovascular death, and NYHA III or IV were comparable between patients with low and high LVEF1 (8.3% vs. 9.2%; P = 0.773, 3.9% vs. 6.0%; P = 0.276, 12.9% vs. 12.2%; P = 0.892, respectively). Kaplan-Meier curves and adjusted hazard ratios for the endpoints are shown in Fig. 4.

3.3. Clinical outcomes according to LVEF1 stratified by flow state

We performed exploratory analyses in subgroups of HFLG and LFLG. Consistent with the main analysis, rates of all-cause death (13.7% vs.

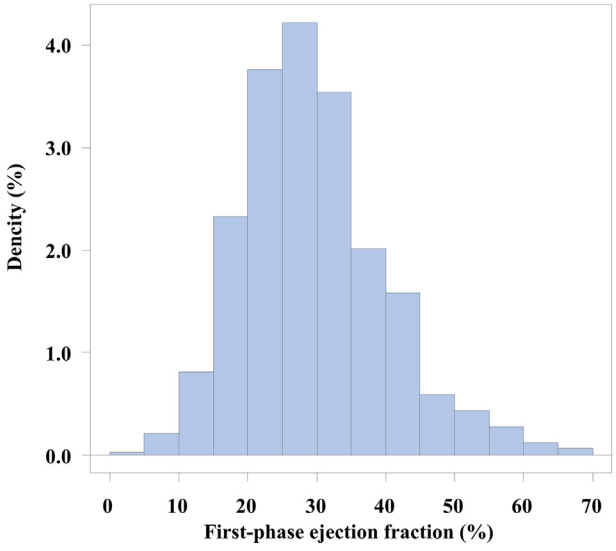

Fig. 3. Distribution of patients according to first-phase ejection fraction.
Histogram shows the distribution of patients according to first-phase ejection fraction.

Table 1
Baseline characteristics according to first-phase ejection fraction.

	Low LVEF1 (N = 230)	High LVEF1 (N = 414)	P value
Age, years	82.4 ± 5.78	81.7 ± 6.35	0.156
Female, n (%)	109 (47.4)	234 (56.5)	0.032
Body mass index, kg/m^2	25.8 ± 5.41	26.7 ± 5.43	0.048
STS-PROM, %	4.72 ± 3.22	4.36 ± 3.05	0.156
NYHA functional class III or IV, n (%)	160 (69.6)	265 (64.0)	0.165
Comorbidities			
Hypertension n (%)	205 (89.1)	356 (86.0)	0.272
Diabetes mellitus, n (%)	54 (23.5)	102 (24.6)	0.774
Renal failure (eGFR < 60 ml/min/1.73 m^2), n (%)	165 (71.7)	267 (64.5)	0.066
Coronary artery disease, n (%)	139 (60.4)	241 (58.2)	0.616
COPD, n (%)	31 (13.5)	37 (8.9)	0.082
Past medical history			
History of myocardial infarction, n (%)	28 (12.2)	36 (8.7)	0.170
History of cerebrovascular accident, n (%)	21 (9.1)	49 (11.8)	0.355
Peripheral artery disease, n (%)	21 (9.1)	55 (13.3)	0.127
Atrial fibrillation, n (%)	91 (39.6)	122 (29.5)	0.011
Previous permanent pacemaker, n (%)	12 (5.2)	31 (7.5)	0.324

Values are mean ± SD or n (%).
COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF1 = first-phase ejection fraction; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2
Baseline echocardiographic, computed tomographic, and procedural characteristics according to first-phase ejection fraction.

	Low LVEF1 (*N* = 230)	High LVEF1 (*N* = 414)	P value
Echocardiography			
Aortic valve area, cm^2	0.67 ± 0.24	0.68 ± 0.24	0.673
Mean aortic valve gradient, mmHg	40.1 ± 15.6	39.6 ± 16.9	0.672
Peak aortic valve gradient, mmHg	66.7 ± 23.1	63.5 ± 25.5	0.118
LV end-diastolic volume, mL	87.7 ± 36.2	84.1 ± 31.5	0.210
LV end-systolic volume, mL	34.5 ± 18.0	31.0 ± 15.3	0.009
LVEF, %	62.0 ± 6.89	64.3 ± 7.82	<0.001
First-phase ejection fraction, %	19.4 ± 4.32	35.0 ± 8.40	<0.001
Stroke volume index, mL/m^2	34.2 ± 11.7	34.2 ± 12.5	0.981
High-flow low-gradient AS, n (%)	117 (50.9)	225 (54.3)	0.411
Low-flow low-gradient AS, n (%)	64 (27.8)	132 (31.9)	0.199
Left ventricular mass index, g/m^2	129.3 ± 39.1	121.5 ± 38.0	0.027
E/e′	18.0 ± 7.88	18.5 ± 8.16	0.539
Left atrial volume index, mL/m^2	40.2 ± 14.7	40.0 ± 16.2	0.874
Pulmonary artery systolic pressure, mmHg	46.4 ± 14.2	44.0 ± 13.9	0.051
Moderate/severe AR, n (%)	31 (14.4)	35 (9.0)	0.056
Moderate/severe MR, n (%)	34 (15.4)	61 (15.5)	1.00
Moderate/severe TR, n (%)	37 (17.2)	68 (17.5)	1.00
Acceleration time, ms	100.3 ± 25.7	97.1 ± 23.7	0.112
Ejection time, ms	335.5 ± 201.6	316.0 ± 41.6	0.058
Acceleration/ejection time ratio	143.8 ± 31.6	139.4 ± 28.5	0.070
Computed tomography			
Annulus area, mm^2	447.9 ± 81.4	431.8 ± 75.4	0.018
Ascending aorta diameter, mm	33.0 ± 3.52	32.8 ± 3.32	0.489
Device landing zone calcium, mm^3	322.1 ± 300.3	284.0 ± 303.2	0.151
Procedure			
Femoral main access site, n (%)	223 (97.0)	390 (94.2)	0.129
Type of valve, n (%)			0.084
Balloon-expandable	123 (53.7)	192 (46.5)	
Self- or mechanically-expandable	106 (46.3)	221 (53.5)	
Valve size, mm	26.0 ± 2.73	25.9 ± 2.47	0.626

Values are mean ± SD or n (%).
AR = aortic regurgitation; AS = aortic stenosis; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEF1 = first-phase ejection fraction; MR = mitral regurgitation; TR = tricuspid regurgitation.

10.7%; $P = 0.478$ and 12.5% vs. 9.8%; $P = 0.625$, respectively), cardiovascular death (6.8% vs. 6.2%: $P = 0.820$ and 9.4% vs. 6.8%: $P = 0.571$, respectively), and NYHA III or IV (20.4% vs. 16.8%; $p = 0.507$ and 23.1% vs. 17.1%; $P = 0.394$, respectively) at 1 year after TAVI were comparable between patients with low and high LVEF1 (Table 3). Kaplan-Meier curves and adjusted hazard ratios for the endpoints in the entire cohort are provided in Fig. 5.

4. Discussion

In a prospective registry of consecutive patients with preserved LVEF undergoing TAVI for severe AS, clinical outcome and heart failure symptoms at one year were comparable in patients with low LVEF1 compared to those with high LVEF1.

Chronic pressure overload due to AS causes LV remodeling, which ultimately leads to LV systolic dysfunction. It has been shown that the relief from pressure overload by AVR improves LVEF in the majority of patients with LV systolic dysfunction, which is associated with improved clinical outcomes [18]. Preserved pressure overload may, however, cause irreversible myocardial damage in some patients, at which point in time LV function may not improve even after treatment of AS. Thus, early intervention prior to irreversible myocardial fibrosis may be crucial to obtain the optimal benefit from AVR [19,20]. Current guidelines allocate a Class I Level of evidence B recommendation for AVR in asymptomatic patients with severe AS and LV systolic dysfunction (LVEF < 50%) [4,5]. However, in the HAVEC registry including 1375 asymptomatic

Table 3
Clinical outcomes at 1 year after TAVI according to first-phase ejection fraction.

	Entire cohort					HFLG cohort					LFLG cohort				
	Low LVEF1 (N = 230)	High LVEF1 (N = 414)	*P* value	Adjusted HR (95% CI)[a]	Adjusted P value	Low LVEF1 (*N* = 117)	High LVEF1 (*N* = 225)	*P* value	Adjusted HR (95% CI)[a]	Adjusted P value	Low LVEF1 (*N* = 64)	High LVEF1 (*N* = 132)	*P* value	Adjusted HR (95% CI)[a]	Adjusted P value
At 1 year															
All-cause death, n (%)	19 (8.3)	38 (9.2)	0.773	1.27 (0.73–2.21)	0.405	16 (13.7)	24 (10.7)	0.478	0.84 (0.44–1.58)	0.582	8 (12.5)	13 (9.8)	0.625	1.06 (0.42–2.69)	0.906
Cardiovascular death, n (%)	9 (3.9)	25 (6.0)	0.276	1.99 (0.92–4.34)	0.081	8 (6.8)	14 (6.2)	0.820	1.03 (0.43–2.50)	0.946	6 (9.4)	9 (6.8)	0.571	1.16 (0.38–3.50)	0.794
NYHA III or IV[†], n (%)	25 (12.9)	42 (12.2)	0.892	0.87 (0.51–1.50)	0.618	19 (20.4)	30 (16.8)	0.507	0.75 (0.39–1.46)	0.402	12 (23.1)	18 (17.1)	0.394	0.51 (0.21–1.25)	0.142

Values are n (%), unless otherwise indicated.
Adjusted for age, gender, Society of Thoracic Surgeons Predicted Risk of Mortality, atrial fibrillation, and previous pacemaker implantation.
CI = confidence interval; HFLG = high-flow low-gradient; HR = hazard ratio; LFLG = low-flow low-gradient; LVEF1 = first-phase ejection fraction; NYHA = New York Heart Association.
[a] Comparison between high vs. low LVEF1.
[†] Described risk ratios (95% CIs) from robustified Poisson regression are reported, with corresponding *P* values.

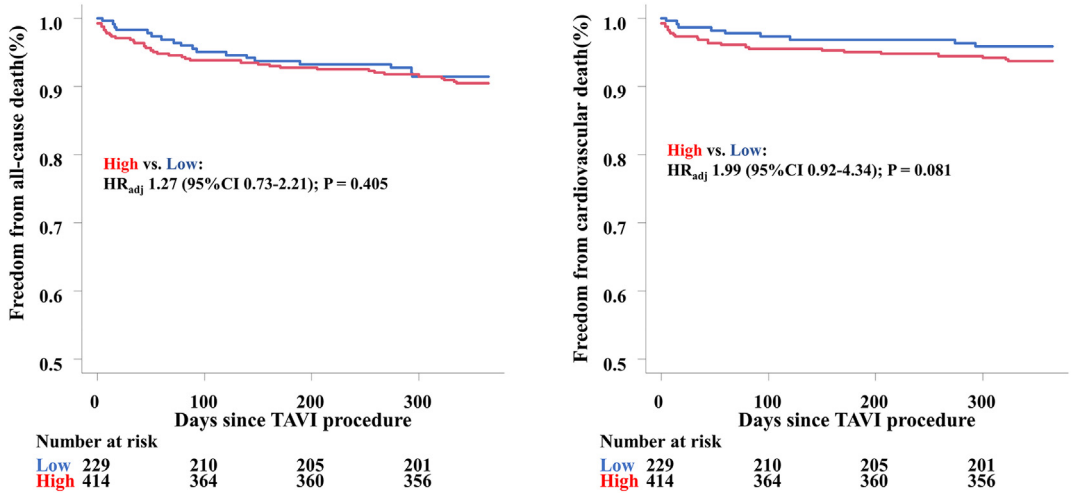

Fig. 4. Kaplan-Meier curves for clinical outcomes.
Kaplan-Meier curves for all-cause death (left) and cardiovascular death (right) comparing high vs. low LVEF1. Hazard ratios and *p*-values were calculated with the use of Cox proportional hazards models. CI = confidence interval; HR_{adj} = adjusted hazard ratio; LVEF1 = first-phase ejection fraction; TAVI = transcatheter aortic valve implantation.

patients with moderate or severe AS, even patients with LVEF between 50% and 59% had worse outcomes and a higher rate of heart failure-related death than those with LVEF > 60% [21], which suggests that reduced LVEF may be a late and sometimes irreversible manifestation of LV remodeling. LV reduction may therefore be a suboptimal marker to guide timing of intervention [22,23].

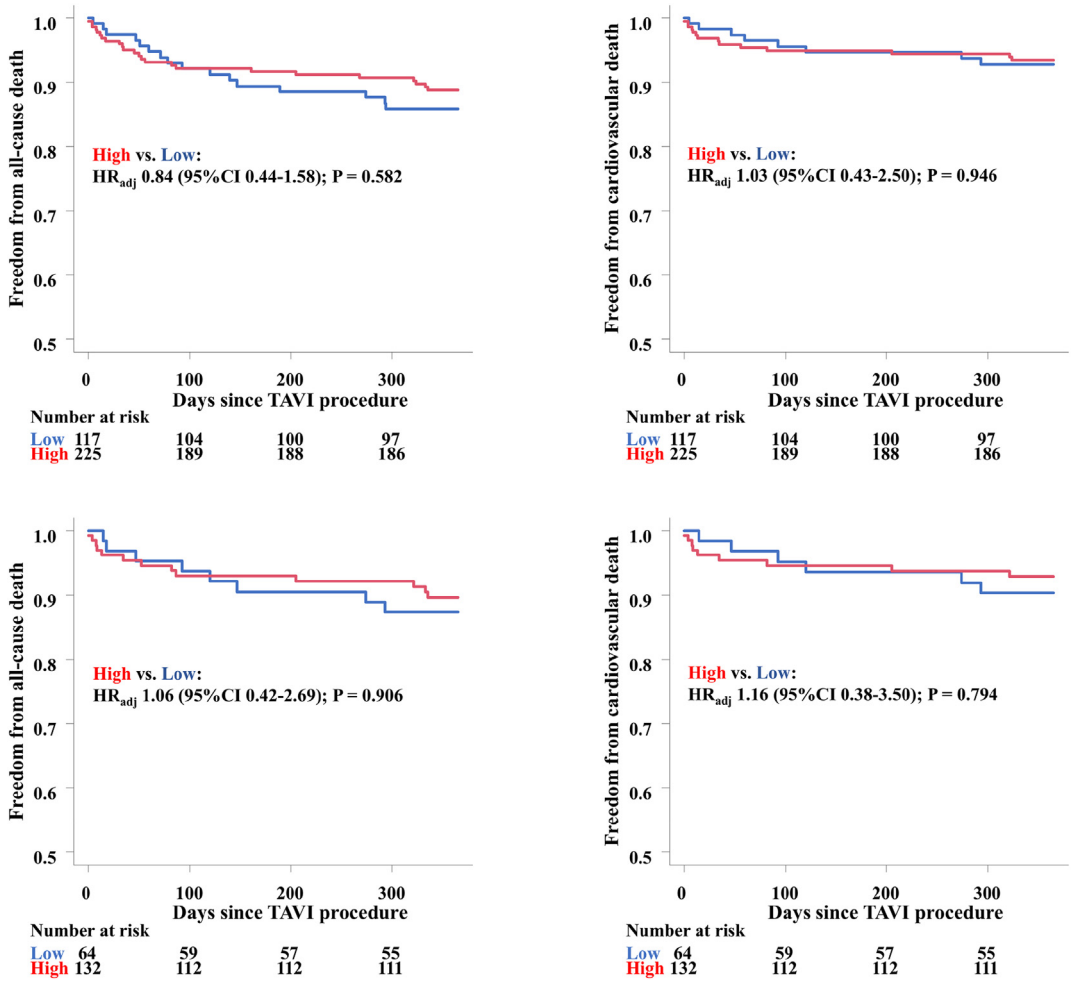

Fig. 5. Kaplan-Meier curves for clinical outcomes stratified flow-states.
Kaplan-Meier curves for all-cause death (left) and cardiovascular death (right) comparing high vs. low LVEF1 in HFLG (upper) and LFLG AS patients (lower). Hazard ratios and *p*-values were calculated with the use of Cox proportional hazards models. AS = aortic stenosis; CI = confidence interval; HFLG = high-flow low-gradient; HR_{adj} = adjusted hazard ratio; LFLG = low-flow low-gradient; LVEF1 = first-phase ejection fraction; TAVI = transcatheter aortic valve implantation.

The concept of LVEF1 is based on the biophysics of myocyte contraction. The contraction of cardiomyocytes ensures during the first phase of systole and reaches its peak around the time of peak aortic jet velocity. When early systolic dysfunction occurs, global LVEF is maintained at the expense of a slower sustained contraction [7,24]. The measurement of LVEF1 allows for the quantification of these pathophysiologic compensatory mechanisms and may help identify the early stage of LV remodeling due to AS.

In the present study, the mean LVEF1 was 29.4%, which is similar to that documented in previous studies conducted in patients with severe AS [8,10,11]. Previous studies suggested an inverse relationship between the severity of AS and LVEF1 [9,10]. Furthermore, previous evidence demonstrated an association between LVEF1 and markers of LV myocardial damage as assessed by cardiac magnetic resonance and advanced echocardiography [9–11]. In line with these findings, patients with low LVEF1 had lower LVEF and higher LV mass index in the present analysis. These findings may reflect the pathophysiological continuum of AS and their effect on LV myocardium [8–11].

Recent studies suggested that LVEF1 predicts adverse outcomes in patients with AS. In an analysis by Gu and colleagues, an LVEF1 $< 25\%$ predicted the composite outcome of symptoms requiring AVR, cardiac-related hospitalizations, or death at 2 years in asymptomatic patients with moderate or severe AS. Moreover, the predictive performance of LVEF1 was superior to LVEF, global longitudinal strain, and transaortic flow rate [8]. Similarly, Bing et al. reported that low LVEF1 was associated with a 6-fold increased risk of symptoms requiring AVR or death in patients with mild or greater AS [9]. In addition, Carter-Storch et al. reported that low LVEF1 predicted the risk of AVR, death, or development of heart failure in patients with asymptomatic severe AS [11]. In contrast to these studies that investigated the importance of LVEF1 in patients with AS pre-AVR, we assessed the impact of LVEF1 on clinical outcomes after TAVI. Our findings indicate that reduced LVEF1 in patients with preserved LVEF does not compromise prognosis after TAVI. It may therefore represent a sensitive marker of potentially reversible LV remodeling and may be a useful tool to guide timing of intervention in patients with AS.

4.1. Study limitations

Several limitations of the present study need to be mentioned. First, only 40% of patients with preserved ejection fraction had adequate echocardiographic images for the assessment of LVEF1, introducing a potential selection bias. In addition, due to the modest sample size, the study may have been underpowered to show an association between LVEF1 and adverse outcome. Second, we could not evaluate the impact of LVEF1 on more specific heart failure related outcomes, such as heart failure hospitalization and the Kansas City Cardiomyopathy Questionnaire. Third, the studied population in the present analysis was limited to elderly patients (mean age > 80 years) undergoing TAVI; the results are hence not generalizable to other populations such as younger patients. Finally, as this was a retrospective analysis based on a prospective registry, the possibility of residual confounding cannot be excluded despite rigorous statistical techniques.

5. Conclusion

Reduced LVEF1 was not associated with adverse clinical outcomes in patients with severe aortic stenosis and preserved LVEF undergoing TAVI.

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None.

CRediT authorship contribution statement

Daijiro Tomii: Writing – original draft, Investigation, Data curation, Formal analysis, Visualization, Methodology. **Taishi Okuno:** Investigation, Data curation, Writing – review & editing. **Caglayan Demirel:** Investigation, Writing – review & editing. **Fabien Praz:** Writing – review & editing. **Jonas Lanz:** Writing – review & editing. **Stefan Stortecky:** Writing – review & editing. **Stephan Windecker:** Supervision, Writing – review & editing. **Thomas Pilgrim:** Conceptualization, Supervision, Methodology, Writing – review & editing.

Declaration of competing interest

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References

[1] Genereux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38:3351–8.
[2] Okuno T, Heg D, Lanz J, et al. Refined staging classification of cardiac damage associated with aortic stenosis and outcomes after transcatheter aortic valve implantation. Eur Heart J Qual Care Clin Outcomes. 2021;7(6):532–41.
[3] Okuno T, Heg D, Lanz J, et al. Staging cardiac damage associated with aortic stenosis in patients undergoing transcatheter aortic valve implantation. Int J Cardiol Heart Vasc. 2021.;33:100768.
[4] Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. J Am Coll Cardiol. 2021;77:e25-197.
[5] Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2021. https://doi.org/10.1093/eurheartj/ehab395. [online ahead of print].
[6] Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and impact of myocardial fibrosis in aortic stenosis. JACC Cardiovasc Imaging. 2019;12:283–96.
[7] Gu H, Li Y, Fok H, et al. Reduced first-phase ejection fraction and sustained myocardial wall stress in hypertensive patients with diastolic dysfunction: a manifestation of impaired shortening deactivation that links systolic to diastolic dysfunction and preserves systolic ejection fraction. Hypertension. 2017;69:633–40.
[8] Gu H, Saeed S, Boguslavskyi A, Carr-White G, Chambers JB, Chowienczyk P. First-phase ejection fraction is a powerful predictor of adverse events in asymptomatic patients with aortic stenosis and preserved total ejection fraction. JACC Cardiovasc Imaging. 2019;12:52–63.
[9] Bing R, Gu H, Chin C, et al. Determinants and prognostic value of echocardiographic first-phase ejection fraction in aortic stenosis. Heart. 2020;106:1236–43.
[10] Einarsen E, Hjertaas JJ, Gu H, et al. Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis. Eur Heart J Cardiovasc Imaging. 2021;22(6):650–7.
[11] Carter-Storch R, Mortensen NSB, Christensen NL, et al. First-phase ejection fraction: association with remodelling and outcome in aortic valve stenosis. Open Heart. 2021.;8(1):e001543.

[12] Stortecky S, Franzone A, Heg D, et al. Temporal trends in adoption and outcomes of transcatheter aortic valve implantation: a SwissTAVI Registry analysis. Eur Heart J Qual Care Clin Outcomes. 2019;5:242–51.
[13] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39.e14.
[14] Baumgartner HC, Hung JC-C, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J CardiovascImaging. 2017;18:254–75.
[15] Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the valve academic research consortium. J Am Coll Cardiol. 2011;57:253–69.
[16] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60:1438–54.
[17] Généreux P, Piazza N, Alu MC, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. J Am Coll Cardiol. 2021;77:2717–46.
[18] Elmariah S, Palacios IF, McAndrew T, et al. Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort A). Circ Cardiovasc Interv. 2013;6:604–14.
[19] Lindman BR, Dweck MR, Lancellotti P, et al. Management of asymptomatic severe aortic stenosis: evolving concepts in timing of valve replacement. JACC Cardiovasc Imaging. 2020;13:481–93.
[20] Furer A, Chen S, Redfors B, et al. Effect of baseline left ventricular ejection fraction on 2-year outcomes after transcatheter aortic valve replacement: analysis of the PARTNER 2 trials. Circ Heart Fail. 2019.;12:e005809.
[21] Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiol. 2018;3:1060–8.
[22] Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of subclinical left ventricular dysfunction in aortic stenosis. JACC Cardiovasc Imaging. 2019;12:163–71.
[23] Papanastasiou CA, Kokkinidis DG, Kampaktsis PN, et al. The prognostic role of late gadolinium enhancement in aortic stenosis: a systematic review and meta-analysis. JACC Cardiovasc Imaging. 2020;13:385–92.
[24] Linari M, Brunello E, Reconditi M, et al. Force generation by skeletal muscle is controlled by mechanosensing in myosin filaments. Nature. 2015;528:276–9.