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Impact of Baseline Left Ventricular Ejection Fraction on Midterm Outcomes in Women Undergoing Transcatheter Aortic Valve Implantation: Insight from the WIN-TAVI Registry

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Limited evidence exists concerning the prognostic impact of baseline left ventricular ejection fraction (LVEF) on outcomes among women undergoing transcatheter aortic valve implantation (TAVI), which we aimed to investigate in the present analysis. Patients from the Women's International Transcatheter Aortic Valve Implantation (WIN-TAVI) registry were categorized according to baseline LVEF into 3 groups: reduced (LVEF ≤40%), mildly reduced (LVEF between 41% and 49%), and preserved (LVEF ≥50%) LVEF. The primary (Valve Academic Research Consortium 2 [VARC-2]) efficacy point was defined as a composite of mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure, or valve-related dysfunction at 1 year. The primary (VARC-2) safety end point included all-cause mortality, stroke, major vascular complication, life-threatening bleeding, stage 2 to 3 acute kidney injury, coronary artery obstruction requiring intervention, or valve-related dysfunction requiring repeated procedures. A Cox regression model was performed using the preserved LVEF group as the reference. Among the 944 patients included, 764 (80.9%) exhibited preserved, 80 (8.5%) had mildly reduced, and 100 (10.6%) had reduced LVEF. The 1-year incidence of VARC-2 efficacy end point was numerically higher in patients with reduced LVEF, albeit not resulting in a

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significant risk difference. Notably, reduced LVEF was associated with a higher risk of the 1-year VARC-2 safety end point, still significant after adjustment (28.0% vs 19.6%, Hazard Ratio 1.78, 95% Confidence Interval 1.12- 2.82, p = 0.014). These differences were primarily driven by trends toward increased rates of all-cause mortality, cardiovascular mortality, and major vascular complications. Clinical outcomes were similar between patients with mildly reduced and preserved LVEF. In conclusion, when performed in women with reduced LVEF, TAVI was associated with a worse (VARC-2) safety profile at 1-year follow-up. In contrast, patients with mildly reduced LVEF appeared to align more closely with outcomes observed in the preserved LVEF group than with the reduced LVEF group.

Left ventricular (LV) systolic dysfunction often co-exists with degenerative aortic stenosis (AS), representing a significant co-morbidity.[1] It is a well-recognized consequence of pressure overload and increased wall stress that primarily leads to hypertrophy and hypercontractility as compensatory mechanisms, helping to address the afterload mismatch and maintain adequate cardiac output. As AS progresses, myocyte apoptosis and subclinical interstitial reactive fibrosis impair diastolic function. If left untreated, this ultimately results in LV decompensation with systolic dysfunction, dilated cardiomyopathy, and symptoms of heart failure.[2–4] LV ejection fraction (EF) is a load-dependent surrogate marker of LV systolic function, and its reduction may affect clinical outcomes. For this reason, the American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease recommend surgical aortic valve replacement even in asymptomatic patients when LVEF is <50%.[5] Furthermore, a clear association has been observed between the extent of cardiac damage and all-cause or cardiovascular mortality 1 year after surgical treatment.[6] In contrast, few and controversial data exist on the prognostic impact of baseline LVEF in patients undergoing transcatheter aortic valve implantation (TAVI), with evidence being even more sparse when considering gender-specific differences in outcomes. The present study aims to address these gaps by evaluating data from the Women's International Transcatheter Aortic Valve Implantation (WIN TAVI) registry, which enrolled exclusively female patients undergoing TAVI. By clarifying the prognostic impact of preprocedural LVEF on TAVI outcomes in women, this analysis aims to inform risk stratification and treatment decision-making processes, ultimately improving care for this patient population.

Methods

From January 2013 to December 2015, intermediate- to high-risk women undergoing TAVI were recruited into the WIN-TAVI prospective, international, multicenter observational registry at 19 high-volume medical centers across Europe and North America. Local heart teams at each center determined the suitability of TAVI, adhering to standard clinical practice. All patients provided informed consent for the anonymous processing of their data. The inclusion and exclusion criteria have been previously described.[7,8] In brief, women with (1) echocardiographic evidence of severe AS (also including low-flow, low-gradient cases) and (2) symptoms of angina, congestive heart failure, syncope, or New York Heart Association class II or higher were deemed suitable for enrollment. Patients with proximal coronary artery obstruction >70%, hemodynamic instability requiring pharmacologic or mechanical support, and active endocarditis or sepsis within 6 months before the procedure were excluded. Procedural flexibility in valve choice, access site, pre or postdilation, and pharmacotherapy after TAVI reflecting diverse practices across centers was allowed. After TAVI, follow-up was conducted at 30 days, 6 months, and 12 months through telephone or clinic visits to document clinical status and any end point adverse events.

In the present analysis, only patients with available baseline echocardiographic data, including LVEF assessment, were involved. LVEF was measured using the biplane Simpson volumetric method, combining apical 4-chamber and 2-chamber views. Patients were then stratified into 3 groups based on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure and 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure[9]: (1) reduced (LVEF ≤40%), (2) mildly-reduced (LVEF between 41% and 49%), and (3) preserved (LVEF ≥50%) EF. The complete study flowchart, and the distribution of patients according to baseline LVEF, are shown in Supplementary Figures 1 and 2.

The primary (Valve Academic Research Consortium 2 [VARC-2]) efficacy end point was defined as a composite of mortality, stroke, myocardial infarction (MI), hospitalization due to valve-related symptoms or heart failure, and valve-related dysfunction at 1-year follow-up. The primary (VARC-2) safety point was a composite of all-cause mortality, stroke, major vascular complication, life-threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction requiring intervention, or valve-related dysfunction requiring repeated procedure. As secondary outcomes, we considered individual components of the primary end points, cardiovascular mortality, the composite of VARC-2 severe or major bleeding (corresponding to Bleeding Academic Research Consortium type 3 or 5), major vascular complications according to VARC-2 definition, new pacemaker implantation, new-onset atrial fibrillation, and TAV-in-TAV (re-do TAVI within a previously implanted prosthesis) after 1 year.[10]

The Icahn School of Medicine at Mount Sinai in New York was responsible for monitoring electronic data entry, data management, and statistical analysis, serving as the clinical and data coordinating center. An independent clinical events committee adjudicated all events, evaluating source documents provided by the sites. Ethical approval was obtained from local committees at all participating sites, and the study adhered to the principles outlined in the World Medical Association Declaration of Helsinki, International Organization for Standardization Guidelines, and Good Clinical Practice Guidelines.[11]

Categoric data are presented as percentages and frequencies and compared using the chi-square or Fischer's exact test. Continuous variables are presented as mean ± SD, and comparisons were made using the Student's *t* test or Wilcoxon signed-rank test. Time-to-event analyses were performed using the Kaplan-Meier method. Associations between baseline LVEF and clinical outcomes were analyzed using a Cox regression model, with the preserved LVEF group as the reference. Adjustment for prespecified and clinically relevant baseline characteristics was performed. These included age, body mass index, anemia, chronic obstructive pulmonary disease, Society of Thoracic Surgeons score, EuroSCORE, previous stroke, surgical aortic valve replacement, MI, percutaneous coronary intervention, or coronary artery bypass graft surgery. Data analysis was performed using Stata

version 18.0 (Stata Corp., College Station, Texas). A p value <0.05 was considered statistically significant.

Results

Out of the 1,019 intermediate to high-risk women enrolled in the WIN-TAVI registry, 944 with available baseline LVEF were included in the present analysis. Among them, 764 (80.9%) exhibited preserved, 80 (8.5%) had mildly reduced, and 100 (10.6%) had reduced LVEF. Baseline clinical characteristics are listed in Supplementary Table 1, Table 1. The mean age was 82.8 ± 5.8 in patients with preserved LVEF, whereas 80.8 ± 8.5 in those with mildly reduced and 81.6 ± 7.6 in those with reduced LVEF. Patients with mildly reduced and reduced LVEF were more likely to have co-morbidities such as diabetes mellitus, hypertension, and chronic kidney disease, and a history of MI and arrhythmic events. They also exhibited a higher New York Heart Association functional class at admission, with 54.7% (n = 415), 63.6% (n = 49), and 70% (n = 70) of patients in the preserved, mildly reduced, and reduced LVEF groups, respectively, being in class III, whereas 3.7% (n = 29), 16.9% (n = 13), and 12% (n = 12) in class IV.

Reasons for TAVI versus surgical aortic valve replacement were similar among the groups, except for the higher prevalence of pulmonary hypertension, renal failure, and high surgical risk in patients with impaired LVEF. Laboratory values and cardiac computed tomography

Table 1
Baseline characteristics

	LVEF < 40% N=100 (10.6%)	40% < LVEF < 50% N=80 (8.5%)	LVEF > 50% N=764 (80.9%)	P-value
Age, years	81.6±7.6	80.8±8.5	82.8±5.8	0.011
Height (m)	1.6±0.1	1.6±0.1	1.6±0.1	0.425
Weight (kg)	65.2±17.3	66.6±14.2	65.9±14.7	0.817
BMI (kg/m^2)	25.5±6.1	26.4±6.2	26.1±5.3	0.522
Diabetes	33 (33.7%)	26 (32.5%)	184 (24.2%)	0.048
Hypertension	82 (84.5%)	56 (70.9%)	622 (82.4%)	0.032
Hypercholesterolemia	43 (43.4%)	33 (41.3%)	353 (46.4%)	0.611
Previous stroke	7 (7.1%)	6 (7.5%)	55 (7.2%)	0.994
Previous TIA	3 (3.3%)	4 (5.6%)	42 (6.2%)	0.646
Anemia	47 (54.7%)	34 (53.1%)	350 (51.7%)	0.863
Peripheral artery disease	7 (7.2%)	6 (7.5%)	66 (8.8%)	0.824
CKD (<60ml/min.1.73m^2)	52 (65.0%)	49 (81.7%)	394 (60.2%)	0.004
Cardiac history				
Pre-existent pacemaker	11 (11.0%)	11 (13.8%)	58 (7.6%)	0.109
Previous ICD	1 (1.1%)	3 (3.8%)	7 (1.0%)	0.070
Previous CABG	4 (4.0%)	9 (11.3%)	49 (6.4%)	0.140
Previous PCI	27 (27.0%)	16 (20.3%)	175 (23.0%)	0.543
Previous MI	19 (19.0%)	12 (15.0%)	60 (7.9%)	<.001
Congestive heart failure	94 (94.0%)	72 (91.1%)	634 (83.1%)	0.004
History of arrhythmia	24 (24.2%)	20 (25.3%)	99 (13.0%)	<.001
Atrial fibrillation/flutter	21 (21.2%)	24 (31.6%)	144 (19.2%)	0.037
STS Score	9.1±7.4	10.1±7.3	7.8±6.8	0.022
EuroScore I	26.3±15.4	22.6±12.4	16.2±10.2	<.001
Echo Characteristics				
LVEF (%)	33.1±6.1	45.5±1.8	59.7±6.5	<.001
Peak aortic valve gradient (mmHg)	68.2±23.7	72.6±25.7	79.8±22.3	<.001
Mean aortic valve gradient (mmHg)	43.2±15.8	44.7±16.5	50.4±15.2	<.001
Effective orifice aortic valve area (cm2)	0.6±0.2	0.7±0.3	0.7±0.2	0.291
LV intracavitary gradient (mmHg)	4.1±3.6	4.1±1.8	8.3±11.6	0.547
Pulmonary artery pressure (mmHg)	48.3±15.6	47.6±13.0	42.6±13.3	<.001
Total aortic regurgitation grade				0.031
Mild	38 (39.2%)	35 (46.7%)	369 (50.2%)	
Moderate	28 (28.9%)	12 (16.0%)	111 (15.1%)	
None	28 (28.9%)	26 (34.7%)	243 (33.1%)	
Severe	3 (3.1%)	2 (2.7%)	12 (1.6%)	
Mitral regurgitation grade				<.001
None	6 (6.1%)	8 (10.5%)	114 (15.4%)	
Mild	39 (39.8%)	36 (47.4%)	402 (54.2%)	
Moderate	44 (44.9%)	27 (35.5%)	204 (27.5%)	
Severe	9 (9.2%)	5 (6.6%)	22 (3.0%)	
Tricuspid regurgitation grade				0.037
Mild	52 (54.7%)	36 (49.3%)	409 (57.7%)	
Moderate	24 (25.3%)	16 (21.9%)	103 (14.5%)	
None	15 (15.8%)	19 (26.0%)	180 (25.4%)	
Severe	4 (4.2%)	2 (2.7%)	17 (2.4%)	
Medications				
Acetylsalicylic acid	56 (57.1%)	39 (48.8%)	459 (61.4%)	0.075
Anti-platelet therapy	35 (35.7%)	15 (18.8%)	192 (25.8%)	0.031
Oral anticoagulants	22 (22.4%)	27 (33.8%)	158 (21.3%)	0.040
Low molecular weight heparin	13 (13.3%)	7 (8.8%)	46 (6.2%)	0.034

Values are n (%) or mean±SD

BMI = body mass index; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; ICD = Implantable Cardioverter-Defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

Table 2
Procedural characteristics and periprocedural complications

	LVEF < 40% N=100 (10.6%)	40% < LVEF < 50% N=80 (8.5%)	LVEF > 50% N=764 (80.9%)	P-value
Procedural characteristics				
Access site location				0.949
Trans-subclavian	4 (4.0%)	2 (2.5%)	19 (2.5%)	
Transapical	2 (2.0%)	2 (2.5%)	21 (2.7%)	
Transfemoral	91 (91.0%)	72 (90.0%)	690 (90.3%)	
Sheath size ≤ 18 French	89 (89.0%)	71 (88.8%)	704 (92.1%)	0.368
Valve type implanted				0.387
Edwards Sapien 3	19 (20.4%)	17 (21.5%)	178 (24.2%)	
Edwards Sapien XT	14 (15.1%)	17 (21.5%)	144 (19.5%)	
Medtronic Evolut R	13 (14.0%)	3 (3.8%)	55 (7.5%)	
Medtronic CoreValve	38 (40.9%)	37 (46.8%)	281 (38.1%)	
Direct Flow	5 (5.4%)	2 (2.5%)	24 (3.3%)	
Portico	0 (0.0%)	0 (0.0%)	7 (0.9%)	N/A
Lotus	3 (3.2%)	3 (3.8%)	44 (6.0%)	
Boston Scientific Acurate Neo	1 (1.1%)	0 (0.0%)	4 (0.5%)	N/A
Persistent aortic regurgitation	51 (51.0%)	23 (29.5%)	333 (44.5%)	0.013
Aortic regurgitation severity				0.361
Mild	42 (42.4%)	23 (30.7%)	273 (37.1%)	
Moderate	12 (12.1%)	6 (8.0%)	95 (12.9%)	
None	42 (42.4%)	44 (58.7%)	353 (48.0%)	
Severe	3 (3.0%)	2 (2.7%)	14 (1.9%)	
Peri-procedural complications				
Complete AV-block	4 (4.0%)	6 (7.6%)	68 (9.1%)	0.223
Actionable bleeding	2 (2.0%)	2 (2.5%)	37 (4.9%)	0.389
Vascular complication	19 (19.0%)	11 (13.9%)	121 (16.1%)	0.645
Use of inotropes	5 (5.1%)	5 (6.6%)	21 (2.9%)	0.124
Blood product transfusion	5 (5.2%)	8 (10.4%)	52 (7.1%)	0.416
ICU length of stay (days)	3.0±5.2	2.6±2.6	2.5±3.1	0.487
Hospitalization length of stay (days)	13.2±10.3	11.7±5.9	11.7±7.7	0.300
Medications at discharge				
Acetylsalicylic acid	62 (74.7%)	52 (73.2%)	543 (78.7%)	0.441
Anti-platelet therapy	49 (59.0%)	44 (61.1%)	430 (62.1%)	0.854
Oral anticoagulants	21 (25.3%)	25 (34.7%)	186 (26.9%)	0.332
Low molecular weight heparin	12 (14.6%)	8 (11.4%)	59 (8.6%)	0.174

Values are n (%) or mean±SD.
AV = atrio-ventricular; ICU = intensive care unit.

characteristics were largely similar across the groups. On echocardiogram, patients with reduced and mildly reduced LVEF showed lower mean aortic valve gradients and a higher prevalence of concomitant moderate aortic, mitral, or tricuspid regurgitation compared with their counterparts. No significant procedural differences between the groups were observed, as listed in Table 2. Approximately 90% of TAVI were performed through transfemoral access, with most patients receiving Edwards Sapien 3 or Edwards Sapien XT and Medtronic Evolut R or Medtronic CoreValve prostheses. Of note, a higher incidence of postprocedural mild aortic regurgitation was observed in the reduced LVEF group (51%, n = 51) compared with the preserved one (44.5%, n = 333). The rate of periprocedural complications was similar among the groups, with vascular complications accounting for 19% (n = 19), 13.9% (n = 11), and 16.1% (n = 121) in patients with reduced, mildly reduced, and preserved LVEF, respectively. Antiplatelet therapy or oral anticoagulation at discharge did not significantly differ across the cohorts.

The 30-day VARC-2 efficacy end point occurred in 6% (n = 6), 6.2% (n = 5), and 5% (n = 38) of patients with reduced, mildly reduced, and preserved LVEF, respectively, with no significant risk difference between the groups. The 30-day VARC-2 safety end point was detected in 16% (n = 16), 12.5% (n = 10), and 12.7% (n = 97) of patients with reduced, mildly reduced, and preserved LVEF, respectively, resulting in similar unadjusted risks for this outcome. After adjustment for covariates, the risk of the VARC-2 efficacy end point remained similar across the groups, whereas a greater risk of VARC-2 safety was observed in patients with reduced compared with those with preserved LVEF (hazard ratio [HR] 1.88, 95% confidence interval [CI] 1.04 - 3.42, p = 0.038). Regarding secondary end points, no notable differences were reported except for a higher adjusted hazard of major vascular complications (adjusted HR 2.25, 95% CI 1.10 - 4.62) in patients with reduced LVEF (unadjusted and adjusted HRs for secondary outcomes at 30 days are reported in Supplementary Table 2).

At 1 year, the incidence of VARC-2 efficacy end point was numerically higher in patients with reduced LVEF compared with those with preserved LVEF (19.1% vs 15.4%, HR 1.27, 95% CI 0.78 - 2.07). With regard to the VARC-2 safety end point, there was a stepwise increase of event rates with declining LVEF, with outcomes occurring in 19.6% (n = 150), 21.2% (n = 17), and 28% (n = 28) of patients with preserved, mildly reduced, and reduced LVEF, respectively (log-rank p = 0.150) (Figure 1). After multivariable regression analysis, the adjusted risk of the VARC-2 efficacy end point remained similar among the cohorts (Figure 2, Table 3). Conversely, reduced compared with preserved LVEF was associated with a higher risk of the 1-year VARC-2 safety end point (adjusted HR 1.78, 95% CI 1.12 - 2.82, p = 0.014). This result was primarily driven by all-cause mortality, cardiovascular mortality, and major vascular complications (Figure 3). No significant differences across the groups were detected concerning all other secondary end points at 1 year (Supplementary Table 3, Table 3).

Discussion

This study is the first to evaluate the prognostic impact of baseline LVEF in an all-women population undergoing TAVI. The main findings can be summarized as follows (Graphical Abstract):

(1) approximately 20% of female patients who underwent TAVI presented with LVEF <50%;
(2) the 1-year incidence of VARC-2 efficacy end point was numerically higher in patients with reduced LVEF, albeit not resulting in a significant risk difference;
(3) reduced LVEF was associated with an increased risk for composite VARC-2 safety end point, mainly driven by the rates of all-cause mortality, cardiovascular mortality, and major vascular complications;
(4) patients with mildly reduced LVEF appeared to align more closely with outcomes observed in the preserved LVEF group than with the reduced LVEF group.

In the present investigation, we describe the first gender-specific analysis of baseline LVEF impact on short and midterm clinical outcomes in patients undergoing TAVI. We observed a slightly lower prevalence of patients with LVEF <50% compared with the previous PARTNER (Placement of Aortic Transcatheter Valves) trials, which reported approximately 30% in the PARTNER IA and IB studies and 28% in a PARTNER 2 patient pooled analysis.[12-14] Our percentage aligns with existing literature, which indicates that a baseline reduction in LVEF is more prevalent in men than in women, with the latter

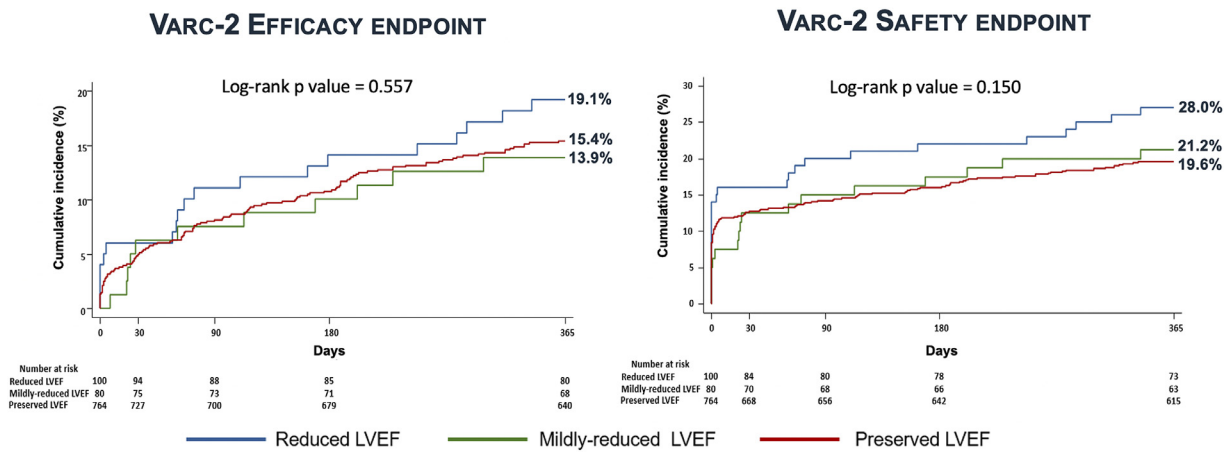

Figure 1. Cumulative incidence of VARC-2 efficacy end point and VARC-2 safety end point at 1-year follow-up according to baseline LVEF.

often presenting distinct characteristics, including a smaller aortic valve area, lower stroke volume, and a higher incidence of diastolic dysfunction.[15,16] Furthermore, consistent with previous evidence, a significant proportion of women with reduced LVEF exhibited an increased burden of co-morbidities, including hypertension, diabetes, and a history of coronary artery disease or arrhythmias, thus suggesting a more pronounced baseline risk profile.[17,18]

Despite a numerically higher rate of events in patients with reduced LVEF, the risk of the VARC-2 efficacy end point remained similar across the groups. Conversely, reduced LVEF was associated with an increased risk for the composite VARC-2 safety end point, primarily determined by higher rates of all-cause mortality, cardiovascular mortality, and major vascular complications. These findings must be interpreted with caution, considering the lower event rates detected in terms of efficacy end points and the limited follow-up duration. Nonetheless, they offer new insights into a topic with previously conflicting evidence in the literature. Indeed, although impaired LV systolic dysfunction is known to be associated with worse outcomes in patients with AS, whether treated conservatively or surgically, data on patients who underwent TAVI are controversial.[19,20] Initially the PARTNER I trials (IA and IB), which investigated TAVI in a high-risk or inoperable population, showed similar outcomes irrespective of LVEF function at 30 days and 1-year follow-up.[13] Similarly, a recent real-world analysis including 11,292 patients wundergoing TAVI failed to demonstrate an association between LV dysfunction and mortality or recurrent heart failure at 1 year. Subsequent observational studies and systematic reviews were in contrast with previous evidence, aligning more closely with our observations. Sannino et al,[21] in a meta-analysis of 26 studies involving 6,898 patients with AS deemed inoperable or at high surgical risk, demonstrated that a baseline LVEF reduction (<50%) significantly increases both short- and long-term mortality despite a significant improvement in systolic function after the procedure. Similarly, a pooled analysis of the PARTNER 2 trial observed a heightened risk of cardiovascular mortality at 2 years in patients with AS and intermediate surgical risk presenting reduced LVEF.[14] These results were further corroborated by Eleid et al,[22] using 2 separate EF cut-off points (<30% and <50%) for LVEF, and by the recent LOSTAVI registry, which

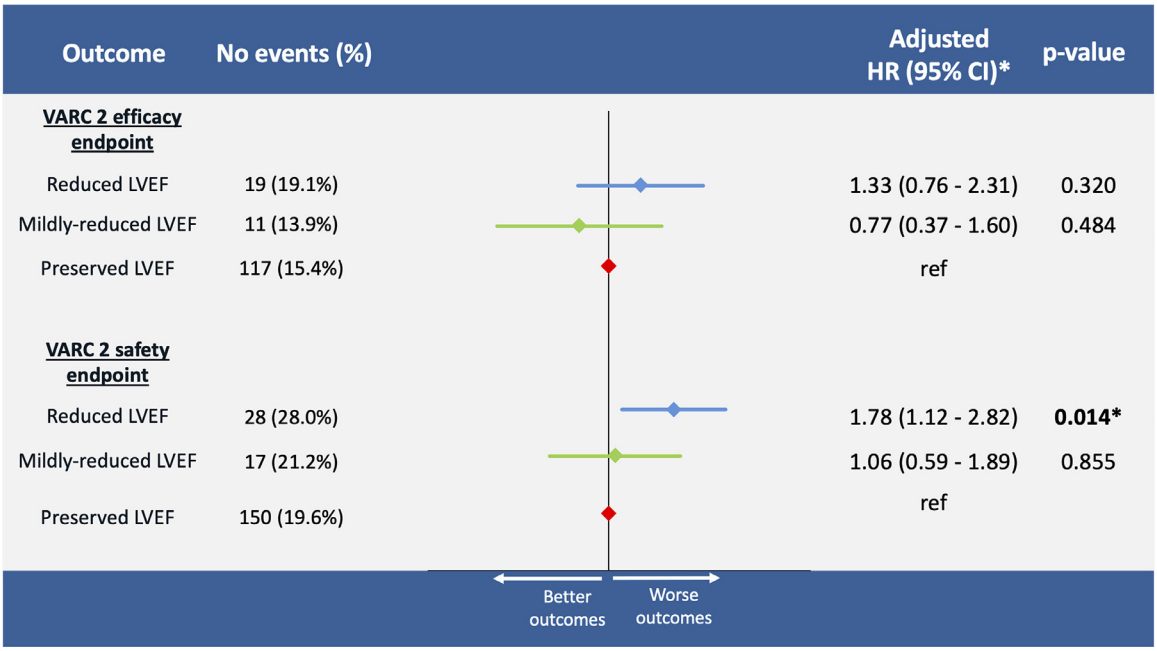

Figure 2. Adjusted HRs for primary (VARC-2) efficacy and safety end points at 1 year.

Table 3
Unadjusted and adjusted hazard ratios for clinical outcomes at 1 year

	No. of patients	No. of event (%)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Trend p-value
VARC-2 efficacy endpoint							
Reduced LVEF	100	19 (19.1%)	1.27 (0.78 - 2.07)	0.330	1.33 (0.76 - 2.31)	0.320	0.092
Mildly reduced LVEF	80	11 (13.9%)	0.89 (0.48 - 1.66)	0.724	0.77 (0.37 - 1.60)	0.484	
Preserved LVEF	764	117 (15.4%)	Ref.		Ref.		
VARC-2 safety endpoint							
Reduced LVEF	100	28 (28.0%)	1.48 (0.99 - 2.21)	0.058	1.78 (1.12 - 2.82)	0.014	0.063
Mildly reduced LVEF	80	17 (21.2%)	1.08 (0.65 - 1.78)	0.764	1.06 (0.59 - 1.89)	0.855	
Preserved LVEF	764	150 (19.6%)	Ref.		Ref.		
All-cause mortality							
Reduced LVEF	100	15 (15.1%)	1.40 (0.81 - 2.43)	0.230	1.39 (0.73 - 2.61)	0.315	0.076
Mildly reduced LVEF	80	9 (11.3%)	1.04 (0.52 - 2.07)	0.908	0.86 (0.37 - 2.01)	0.727	
Preserved LVEF	764	83 (10.9%)	Ref.		Ref.		
Cardiovascular mortality							
Reduced LVEF	100	13 (13.2%)	1.38 (0.76 - 2.49)	0.285	1.42 (0.71 - 2.82)	0.320	0.071
Mildly reduced LVEF	80	7 (9.0%)	0.92 (0.42 - 2.00)	0.834	0.69 (0.25 - 1.93)	0.483	
Preserved LVEF	764	73 (9.6%)	Ref.		Ref.		
Myocardial infarction							
Reduced LVEF	100	2 (2.2%)	1.94 (0.41 - 9.14)	0.402	2.35 (0.41 - 13.4)	0.336	0.634
Mildly reduced LVEF	80	1 (1.4%)	1.21 (0.15 - 9.65)	0.859	1.04 (0.11 - 9.64)	0.975	
Preserved LVEF	764	8 (1.1%)	Ref.		Ref.		
Stroke							
Reduced LVEF	100	2 (2.0%)	0.86 (0.20 - 3.72)	0.842	1.22 (0.24 - 6.34)	0.809	0.225
Mildly reduced LVEF	80	2 (2.7%)	1.06 (0.25 - 4.57)	0.938	1.51 (0.33 - 6.88)	0.595	
Preserved LVEF	764	18 (2.4%)	Ref.		Ref.		
Hospitalization for heart failure or valve-related symptoms							
Reduced LVEF	100	3 (3.2%)	0.96 (0.29 - 3.19)	0.948	1.06 (0.29 - 3.91)	0.936	0.957
Mildly reduced LVEF	80	2 (2.5%)	0.80 (0.19 - 3.40)	0.766	0.96 (0.22 - 4.19)	0.955	
Preserved LVEF	764	24 (3.4%)	Ref.		Ref.		
Major vascular complications							
Reduced LVEF	100	11 (11.0%)	1.46 (0.77 - 2.79)	0.248	2.21 (1.08 - 4.52)	0.030	0.102
Mildly reduced LVEF	80	7 (8.9%)	1.15 (0.53 - 2.52)	0.724	1.50 (0.63 - 3.56)	0.361	
Preserved LVEF	764	58 (7.6%)	Ref.		Ref.		
Life-threatening bleeding							
Reduced LVEF	100	4 (4.0%)	0.93 (0.33 - 2.61)	0.884	1.28 (0.40 - 4.03)	0.678	0.368
Mildly reduced LVEF	80	1 (1.2%)	0.29 (0.04 - 2.10)	0.220	0.40 (0.05 - 3.02)	0.377	
Preserved LVEF	764	33 (4.3%)	Ref.		Ref.		
VARC-2 major bleeding							
Reduced LVEF	100	9 (9.1%)	1.10 (0.55 - 2.21)	0.789	1.72 (0.80 - 3.66)	0.162	0.191
Mildly reduced LVEF	80	8 (10.0%)	1.21 (0.58 - 2.53)	0.610	1.52 (0.68 - 3.40)	0.307	
Preserved LVEF	764	63 (8.3%)	Ref.		Ref.		
BARC 3 or 5 bleeding							
Reduced LVEF	100	13 (13.0%)	1.04 (0.58 - 1.86)	0.895	1.64 (0.87 - 3.08)	0.127	0.143
Mildly reduced LVEF	80	9 (11.2%)	0.89 (0.45 - 1.76)	0.733	1.13 (0.54 - 2.36)	0.752	
Preserved LVEF	764	96 (12.6%)	Ref.		Ref.		
Acute kidney injury (stage 2 or 3)							
Reduced LVEF	100	1 (1.0%)	0.70 (0.09 - 5.38)	0.728	0.64 (0.07 - 5.53)	0.681	0.973
Mildly reduced LVEF	80	1 (1.2%)	0.86 (0.11 - 6.66)	0.885	0.85 (0.10 - 6.85)	0.876	
Preserved LVEF	764	11 (1.5%)	Ref.		Ref.		

adjHR = adjusted hazard ratio; BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; VARC = Valve Academic Research Consortium.

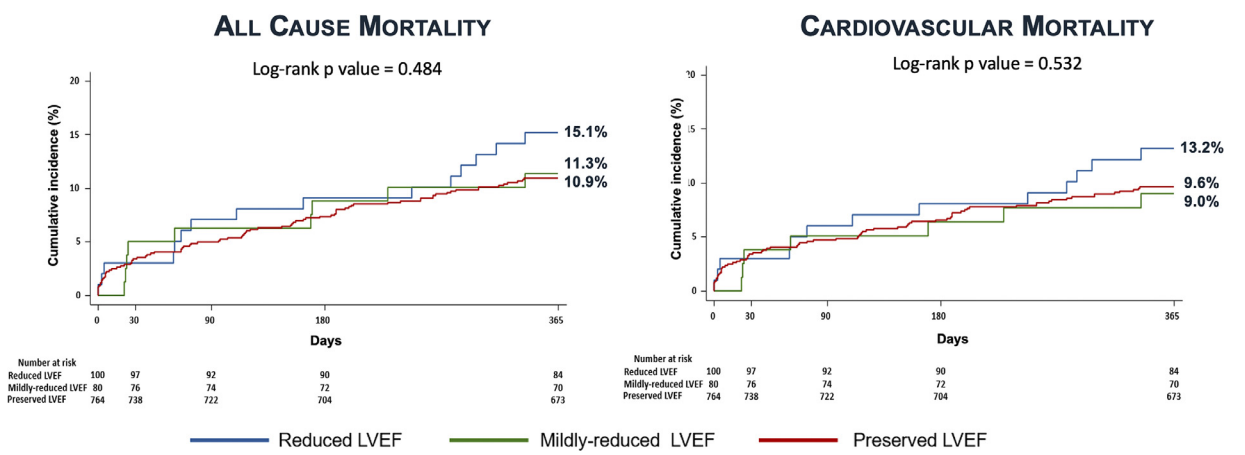

Figure 3. Cumulative incidence of all-cause mortality and cardiovascular mortality at 1-year follow-up according to baseline LVEF.

included and stratified patients with severely depressed LVEF (LVEF <35%).[23] What our study adds to the existing evidence is that, in an all-women patient population, baseline LVEF reduction has a negative prognostic impact on the safety outcomes of TAVI patients at 1-year follow-up. This finding remains robust even after adjusting for potential confounders in the multivariable model, thereby minimizing bias from the higher burden of co-morbidities observed in the reduced LVEF group. In contrast, the impact on the efficacy end point, as indicated by the numerically higher rates of events in the reduced LVEF group, may require a longer follow-up period to become significantly evident.

Another important finding from our analysis is the similar outcomes observed when comparing patients with mildly reduced and preserved LVEF. A possible explanation is that LVEF reduction is initially a consequence of increased afterload due to aortic valve disease; thereby, removing the cause may translate into outcomes similar to those observed in patients with normal EF.[24] Conversely, when wall stress advances to the point of causing real damage to myocardial fibers, as likely occurs in patients with reduced LVEF, TAVI outcomes tend to become worse. This observation further raises the debate on the optimal timing for intervention in patients with AS. Taniguchi et al,[25] in the CURRENT AS registry examining 3,815 patients undergoing surgical aortic valve replacement or conservative treatment, have already proposed reconsidering the cutoff for surgical intervention by moving the LVEF threshold from 50% to 60%. Their pathophysiologic rationale derived from hypertrophic remodeling in response to aortic disease, often accompanied by significant shortening of myocardial fibers, thus suggesting that an EF <60% should be regarded as already reduced.[26] Similarly, our results highlight the importance of incorporating LVEF assessment into the risk stratification of patients with AS and avoiding delays in treatment once LVEF has irreversibly decreased, advocating for earlier intervention—before LVEF falls <40%—to achieve better outcomes.

Further research is imperative to validate our observations in larger and more contemporary cohorts receiving new-generation devices, which are associated with lower rates of paravalvular leaks or vascular complications. This will provide deeper insights into the importance of integrating LVEF into standardized risk stratification algorithms and help define the optimal timing for intervention in patients with AS who underwent TAVI.

Despite the valuable insights provided by our study, certain limitations warrant consideration. First, the observational nature of the WIN-TAVI registry precludes causal inference and may introduce confounding biases despite adjustments. Second, the relatively small sample size of women with mildly reduced and reduced LVEF limits the statistical power to detect significant differences in outcomes, necessitating validation in larger cohorts or pooled analyses. Third, although our study utilizes the Simpson EF measurements, which are more accurate than the simple visual estimation used in the initial PARTNER trials, it still relies on a subjective method of evaluating systolic function. In any case, by employing ranges of LVEF rather than the precise value as an ordinal variable, we mitigate the impact of variability resulting from visual estimation on the generalizability of the results. Fourth, the use of the VARC-2 criteria to define the study end points instead of the updated VARC-3 criteria might be considered a limitation.[27] Nonetheless, we chose to retain the VARC-2 criteria because they were used for event adjudication during the study period.

Ultimately, our findings should not be extrapolated to heart failure in its entirety, as the diagnosis of heart failure is multidimensional. It involves not only LVEF but also a combination of laboratory, echocardiographic, and hemodynamic parameters that were not captured in our analysis. Moreover, the absence of specific echocardiographic measurements such as cardiac reserve or indexed stroke volume prevents us from drawing conclusions about the etiology of LV dysfunction, nor can we distinguish the impact of different flow-gradient patterns on outcomes. Therefore, further research with a more detailed echocardiographic evaluation and information on patients' medical management is crucial not only to clarify the interplay between heart failure, particularly heart failure with preserved EF and TAVI outcomes but also to explore the potential prognostic influence of different etiologies of LV dysfunction.

In conclusions, the prevalence of reduced LVEF in women undergoing TAVI is noteworthy and correlates with a worse VARC-2 safety profile at 1-year follow-up. Our findings support the idea of integrating LVEF assessment into risk stratification algorithms to define the optimal timing of intervention in patients with AS, using a tailored approach that accounts for gender-specific factors. Further research is needed to explore any additional underlying mechanisms of LV dysfunction in patients with AS and validate our observations in larger cohorts.

Declaration of competing interest

Dr. Bay is supported by a grant from the German Heart Foundation, grant no. S/06/23. Dr. Petronio received consultancy fees from Medtronic, Abbott, and Boston and funds from Boston and Abbott. Dr. Mehilli received institutional grants from Boston Scientific and lecture fees from AstraZeneca, Bristol-Myers Squibb, Boston Scientific, and Edwards Lifesciences. Dr. Lefèvre proctors for Edwards, Boston, and Abbott. Dr. Sardella received sponsorships from Medtronic in terms of technical training courses and congress assistance. Dr. Van Mieghem received research grant support and advisory fees from Abbott, Boston Scientific, and Medtronic, and research grant support from Edwards Lifesciences. Dr. Dumonteil received proctoring and consultancy fees from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Mikhail is the Director of Imperial Valve and Cardiovascular Course, which is supported by several device and pharmaceutical companies; he has received an educational grant from Abbott for an Interventional Fellowship. Dr. Ferrer-Gracia received sponsorships from Medtronic and Edwards companies in terms of technical training courses and congress assistance. Dr. Sharma served on the Speakers Bureau of Abbott Vascular, Boston Scientific, and Cardiovascular Systems, Inc. Dr. Morice is CEO and shareholder of CERC, a CRO based in Massy that had no role in WIN-TAVI. Dr. Dangas received consulting fees from GE Healthcare, Janssen Pharmaceuticals, Inc., and Medtronic, Inc.; <1% equity with Claret Medical and Elixir Medical; delivered industry-sponsored lectures for The Medicines Company; and is on the Scientific Advisory Board of AstraZeneca. Dr. Chieffo received speaker/consultant fees from Abiomed, Abbott Vascular, Biosensor, Cardinal Health, GADA, and Magenta Medical. Dr. Mehran received research grants to the institution from Abbott, Abiomed, Alleviant Medical, AM-Pharma, Amgen, Applied Therapeutics, Arena, AstraZeneca, BAIM, Bayer, Beth Israel Deaconess, Biosensors, Biotronik, Boston Scientific, Bris- tol-Myers Squibb, CardiaWave, CellAegis, CeloNova, CERC, Chiesi, Concept Medical, CSL Behring, Cytosorb- ents, DSI, Duke University, Element Science, Faraday, Humacyte, Idorsia, Insel Gruppe AG, Magenta, Medtronic, Novartis, OrbusNeich, PhaseBio, Philips, RenalPro, Shockwave, Vivasure, and Zoll and consulting fees from Cine-Med Research, WebMD. The authors have no competing interests to declare.

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Petronio: Visualization. **Julinda Mehilli:** Visualization. **Benjamin Bay:** Visualization. **Mauro Gitto:** Visualization. **Thierry Lefevre:** Visualization. **Patrizia Presbitero:** Visualization. **Piera Capranzano:** Visualization. **Angelo Oliva:** Visualization. **Alessandro Iadanza:** Visualization. **Gennaro Sardella:** Visualization. **Nicolas Van Mieghem:** Visualization, Validation. **Emanuele Meliga:** Visualization. **Pier Pasquale Leone:** Visualization, Validation. **Nicolas Dumonteil:** Visualization. **Chiara Fraccaro:** Visualization. **Daniela Trabattoni:** Visualization. **Ghada Mikhail:** Visualization. **Maria-Cruz Ferrer-Gracia:** Visualization. **Christoph Naber:** Visualization. **Samin K. Sharma:** Visualization. **Yusuke Watanabe:** Visualization. **Marie-Claude Morice:** Visualization. **George Dangas:** Visualization. **Alaide Chieffo:** Visualization, Supervision. **Roxana Mehran:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.11.004.

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