

Outcomes of Transcatheter Aortic Valve Replacement in Patients With Severely Reduced Left Ventricular Systolic Function in the Low Systolic Function and Transcatheter Aortic Valve Implantation (LOSTAVI) International Registry



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Transcatheter aortic valve replacement (TAVR) is an established therapy for severe, symptomatic aortic valve stenosis even in patients with impaired left ventricular systolic function. However, there is uncertainty on the clinical effectiveness of the currently available TAVR devices in patients with reduced left ventricular ejection fraction (LVEF). The LOSTAVI (Low Systolic function and Transcatheter Aortic Valve Implantation) registry is a retrospective observational study using baseline, procedural, discharge, and long-term follow-up details. A total of 3 groups of interest were distinguished: extremely reduced LVEF (<25%), severely reduced LVEF (25% to 30%), and reduced LVEF (31% to 35%). Unadjusted and adjusted analyses were carried out for in-hospital and follow-up outcomes. A total of 923 patients were included from 12 centers, with 146 patients (16%) with LVEF <25%, 425 (46%) with LVEF 25% to 30%, and 352 (38%) with LVEF 31% to 35%. Several baseline and procedural features were different across groups, including age, risk, functional class, and prevalence of bicuspid disease (all $p < 0.05$). In-hospital mortality was similar in the 3 groups (7 [4.8%], 18 [4.2%], and 7 [2.0%], respectively, $p = 0.661$), but major adverse events were more common in those with extremely reduced and severely reduced LVEF (19 [13%], 53 [13%], and 25 [7.1%], respectively, $p = 0.024$). The 12-month follow-up confirmed the significant detrimental impact of reduced LVEF on both death (21 [14%], 49 [12%], and 25 [7.1%], respectively, $p = 0.024$) and major adverse events (37 [25%], 89 [21%], and 53 [15%], respectively, $p = 0.016$). The adjusted analysis confirmed the significant prognostic role of LVEF on both outcomes, whereas TAVR device type was not associated with death or major adverse events (all $p > 0.05$). In conclusion, TAVR yields favorable early and 1-year results in patients with reduced LVEF, including those with

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¹See Appendix for collaborators.

See page 357 for Declaration of Competing Interest.

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extremely depressed systolic dysfunction. However, reduced LVEF still represents a major adverse prognostic factor for both short- and mid-term outcomes. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2023;201:349–358)

Transcatheter aortic valve replacement (TAVR) has expanded its clinical role from patients at prohibitive risk to those at a low risk.^{1,2} A major driver of risk for surgical aortic valve replacement and therefore a key indication for TAVR is reduced left ventricular systolic function, typically defined as left ventricular ejection fraction (LVEF) $\leq 35\%$.³ Indeed, TAVR in patients with significantly reduced LVEF may pose several challenges.^{4–7} Several studies suggest that patients with low LVEF who underwent TAVR have a higher rate of

periprocedural complications and that TAVR may be more technically demanding, especially for less experienced operators and TAVR teams.^{6,8,9} The reasons include hemodynamic instability, coronary artery disease, or mitral/pulmonary/tricuspid valve disease.¹⁰ Finally, reduced systolic function often coexists with other prognostically relevant co-morbidities.¹¹ Despite the importance of this topic, limited contemporary data are available on TAVR in patients with reduced systolic function suitable to inform patient selection,

Table 1
Baseline non-imagery features according to left ventricular ejection fraction (LVEF)

Feature	LVEF <25%	LVEF 25-30%	LVEF 31-35%	P
Patients (N)	146	425	352	-
Age (years)	77.2±8.6	79.6±7.0	80.5±7.1	<0.001
Male gender	97 (66%)	274 (65%)	218 (61.9%)	0.641
Height (cm)	169.0±9.0	167.0±8.9	166.3±8.6	0.001
Weight (kg)	74.7±16.5	72.7±14.8	72.2±4.4	0.126
BMI	26.1±4.8	25.9±4.6	26.0±4.6	0.854
BSA	1.86±0.23	1.83±0.21	1.82±0.21	0.129
Diagnosis				0.630
Aortic stenosis	138 (94%)	384 (90%)	314 (89%)	
Aortic regurgitation	0	2 (0.5%)	2 (0.6%)	
Mixed aortic valve disease	5 (3.4%)	28 (6.6%)	28 (8.0%)	
Failing bioprosthesis	4 (2.7%)	11 (2.6%)	8 (2.3%)	
Surgical risk				0.002
Inoperable	8 (5.4%)	12 (2.8%)	12 (3.4%)	
High	33 (23%)	152 (36%)	108 (31%)	
Intermediate	95 (65%)	218 (51%)	176 (50%)	
Low	11 (7.5%)	43 (10%)	56 (16%)	
New York Heart Association class				0.007
I	1 (0.7%)	2 (0.5%)	2 (0.6%)	
II	21 (14%)	92 (22%)	99 (28%)	
III	97 (66%)	286 (67%)	211 (60%)	
IV	28 (19%)	45 (11%)	40 (11%)	
Surgical scores				
Logistic EuroSCORE	24.0±16.9	20.8±15.2	19.9±15.3	0.266
EuroSCORE II	10.6±9.8	8.6±7.7	6.7±6.0	<0.001
STS	6.2±4.9	5.8±5.3	6.1±5.0	0.737
Prior implantation of cardiac resynchronization therapy device	10 (6.8%)	9 (2.1%)	9 (2.6%)	0.027
Prior implantation of implantable-cardioverter defibrillator	23 (16%)	38 (8.9%)	24 (6.8%)	0.011
Pacemaker dependency	9 (6.1%)	28 (6.6%)	32 (9.1%)	0.359
Diabetes mellitus	47 (32%)	143 (34%)	112 (32%)	0.865
Dyslipidemia	56 (38%)	188 (44%)	162 (46%)	0.260
Hypertension	95 (65%)	327 (77%)	268 (76%)	0.011
Smoking history	30 (28%)	87 (26%)	77 (30%)	0.639
Atrial fibrillation	53 (36%)	122 (29%)	92 (26%)	0.087
Peripheral artery disease	25 (17%)	67 (16%)	67 (19%)	0.482
Prior stroke	34 (23%)	90 (21%)	59 (17%)	0.159
Coronary artery disease	74 (50%)	197 (46%)	150 (43%)	0.259
Prior myocardial infarction	30 (20%)	93 (22%)	82 (23%)	0.783
Prior percutaneous coronary intervention	56 (38%)	148 (35%)	115 (33%)	0.500
Prior cardiac surgery	24 (16%)	59 (14%)	63 (18%)	0.301
Prior coronary artery bypass grafting	17 (12%)	48 (11%)	44 (13%)	0.888
Hemoglobin (g/dL)	12.4±1.8	12.4±1.7	12.4±1.7	0.938
Hematocrit (%)	37.3±5.3	38.5±5.0	38.7±4.8	0.250
Serum creatinine (mg/dL)	1.61±1.29	1.59±1.29	1.53±1.27	0.799
Estimated glomerular filtration rate (mL/min/1.73 m ²)	52.3±23.9	52.1±21.3	52.2±22.1	0.996

decision-making, and follow-up, with most earlier studies of relatively small size or focus only on early-generation TAVR devices.^{5,6,12} We aimed to conduct a registry focusing on patients with reduced LVEF who underwent TAVR.

Methods

The LOSTAVI (Low Systolic function and Transcatheter Aortic Valve Implantation) registry was designed to collect retrospectively anonymized patient, procedural, and outcome details on patients with LVEF $\leq 35\%$ who underwent TAVR, in keeping with previous similar works from our collaborative research group on structural heart disease.^{13–15} Notably, we invited high-volume international TAVR centers to participate. The only exclusion criterion was ineligibility for at least 12-month follow-up. Individual centers were responsible for obtaining written informed consent and institutional review board approval for data collection and analysis, whereas the data provided by Pineta Grande Hospital, Castel Volturno, Italy were extracted from the RISPEVA (Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea) registry (<https://clinicaltrials.gov/ct2/show/NCT02713932>), which was already approved by the competent ethics committee for Pineta Grande Hospital and has been reported previously elsewhere.¹⁶

Patient selection and procedural strategy, including device choice, ancillary medical therapy, and follow-up measures, were at the operator's discretion. Several clinically relevant end points were appraised, applying the

Valve Academic Research Consortium 2 definitions whenever appropriate, focusing on the following outcomes: device success, procedural success, death, myocardial infarction, stroke, access site complication, bleeding, pacemaker implantation, and major adverse event, which was operatively defined as the composite of death, myocardial infarction, stroke, unplanned cardiac surgery, major or life-threatening bleeding, or major vascular complication.¹⁷

Descriptive analysis was based on reporting mean \pm SD for continuous variables and count (%) for categorical variables. A bivariate analysis was performed stratifying patients according to LVEF into 3 groups (extremely reduced LVEF $<25\%$, severely reduced LVEF 25% to 30%, and reduced LVEF 31% to 35%) and was based on the analysis of variance for continuous variables and Fisher's exact test for categorical variables.

Survival analysis was based on the Kaplan–Meier method and log-rank test. In addition, a logistic regression analysis was performed, computing odds ratios, with corresponding 95% confidence intervals, for the unadjusted and adjusted models. Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustment. Computations were performed with Stata 13 (StataCorp, College Station, Texas).

Results

A total of 923 patients were included from 12 centers, with 146 patients (16%) with LVEF $<25\%$, 425 (46%) with LVEF 25% to 30%, and 352 (38%) with LVEF 31% to 35% (Table 1; Supplementary Tables). Several baseline

Table 2
Baseline imaging features according to left ventricular ejection fraction (LVEF)

Feature	LVEF $<25\%$	LVEF 25-30%	LVEF 31-35%	P
Patients (N)	146	425	352	-
Bicuspid aortic valve	16 (10.9%)	19 (4.5%)	19 (5.4%)	0.024
Aortic valve area (cm ²)	0.66 \pm 0.23	0.68 \pm 0.22	0.69 \pm 0.22	0.567
End-diastolic diameter (mm)	61.0 \pm 11.8	56.4 \pm 7.3	54.9 \pm 6.8	<0.001
End-systolic diameter (mm)	47.0 \pm 2.4	42.2 \pm 8.2	40.5 \pm 7.0	0.002
Septal thickness (mm)	12.0 \pm 2.7	12.5 \pm 2.2	12.9 \pm 2.1	0.049
Posterior wall thickness (mm)	11.2 \pm 2.3	11.3 \pm 2.3	11.2 \pm 2.2	0.966
Left ventricular ejection fraction (%)	19.2 \pm 3.2	28.2 \pm 2.2	34.4 \pm 1.1	<0.001
Peak aortic valve gradient (mm Hg)	53.3 \pm 22.1	59.0 \pm 19.9	64.0 \pm 22.1	<0.001
Mean aortic valve gradient (mm Hg)	30.1 \pm 13.8	34.5 \pm 14.4	38.5 \pm 15.5	<0.001
Peak aortic velocity (m/s)	3.62 \pm 0.88	3.62 \pm 0.62	3.79 \pm 0.61	0.254
Aortic valve calcification				0.110
None	2 (4.6%)	10 (5.8%)	7 (4.9%)	
Minimal or mild	3 (6.8%)	27 (16%)	25 (17%)	
Moderate	18 (41%)	42 (24%)	27 (19%)	
Severe	21 (48%)	94 (54%)	85 (59%)	
Aortic regurgitation				0.602
None	38 (30%)	97 (25%)	68 (23%)	
Minimal	40 (32%)	122 (32%)	94 (32%)	
Mild	34 (27%)	94 (24%)	75 (25%)	
Moderate	13 (10%)	60 (16%)	46 (16%)	
Severe	2 (1.6%)	14 (3.6%)	14 (4.7%)	
Mitral regurgitation				0.324
None	14 (9.9%)	36 (8.8%)	17 (5.1%)	
Minimal or mild	52 (37%)	151 (37%)	126 (38%)	
Moderate	42 (30%)	122 (30%)	121 (36%)	
Moderate to severe	20 (14%)	56 (14%)	44 (13%)	
Severe	14 (9.9%)	43 (11%)	25 (7.5%)	
Systolic pulmonary artery pressure (mm Hg)	49.8 \pm 15.8	46.4 \pm 15.3	45.7 \pm 13.9	0.074

differences were evident in reference to LVEF, including age, height, surgical risk, New York Heart Association, EuroSCORE II, previous implant of cardiac resynchronization therapy, previous implant of implantable cardioverter-defibrillator, and hypertension (all $p < 0.05$). Other significant differences were evident focusing on imaging features, such as left ventricular end-diastolic and end-systolic diameters, septal thickness, peak and mean aortic valve gradient, and prevalence of bicuspid aortic valve disease (all $p < 0.05$; [Table 2](#)).

The procedural details are outlined in [Table 3](#). Specifically, significant differences for these features according to LVEF group were evident for use of local anesthesia, pacing during implant, use of sheaths and embolic protection devices, and means of hemostasis (all $p < 0.05$). The procedural time was longer in patients with lower LVEF ($p < 0.001$), and in-hospital major adverse events were more

common in those with lower LVEF (19 [13%], 53 [13%], and 25 [7.1%], respectively; $p = 0.024$; [Table 4](#)), whereas all remaining in-hospital events occurred with similar frequency in the 3 groups ([Figures 1 and 2](#)).

The 12-month follow-up, available in 95% of the eligible patients, disclosed a higher rate of death (21 [14%], 49 [12%], and 25 [7.1%], respectively, $p = 0.024$), cardiovascular death (12 [8.2%], 32 [7.5%], and 12 [3.4%], respectively, $p = 0.022$), and major adverse events (37 [25%], 89 [21%], and 53 [15%], respectively, $p = 0.016$) in patients with lower LVEF ([Figures 3 and 4](#), [Table 5](#)), despite having largely similar medical regimens ([Supplementary Table 2](#)). Notably, LVEF improved in most patients comparing both the baseline and discharge assessments, even if more evidently in the lower baseline LVEF group ($17 \pm 11\%$, $10 \pm 11\%$, and $8 \pm 10\%$, $p < 0.001$ and $8 \pm 12\%$, $3 \pm 10\%$, and $3 \pm 9\%$, respectively, $p = 0.011$).

Table 3
Procedural features according to left ventricular ejection fraction (LVEF)

Feature	LVEF <25%	LVEF 25-30%	LVEF 31-35%	P
Patients (N)	146	425	352	-
Local anesthesia	115 (78%)	318 (75%)	241 (69%)	0.042
Percutaneous approach	134 (91%)	393 (93%)	316 (90%)	0.418
Access				0.907
Apical	4 (2.7%)	8 (1.9%)	9 (2.6%)	
Axillary	7 (4.8%)	20 (4.7%)	14 (4.0%)	
Femoral	136 (93%)	397 (93%)	329 (94%)	
Sheath use	72 (49%)	235 (55%)	160 (46%)	0.022
Sheath size (French)	15.0±1.7	15.4±2.0	15.7±2.2	0.088
Predilation	85 (58%)	232 (55%)	169 (48%)	0.073
Predilation balloon size (mm)	22.6±1.5	21.8±1.9	21.9±1.9	0.107
Pacing during implant	93 (63%)	250 (59%)	183 (52%)	0.039
Embolic protection device	66 (45%)	133 (31%)	76 (22%)	<0.001
Hemostasis				0.031
Proglide(s)	47 (35%)	171 (44%)	152 (48%)	
Proglide(s) and Angioseal	3 (2.2%)	9 (2.3%)	8 (2.5%)	
Prostar	16 (12%)	71 (18%)	54 (17%)	
Prostar and Angioseal	8 (6.0%)	18 (4.6%)	7 (2.2%)	
Surgical	60 (45%)	124 (32%)	95 (30%)	
Self-expandable device	93 (64%)	304 (72%)	256 (73%)	0.120
Device				0.201
Acurate	7 (4.8%)	34 (8.0%)	22 (6.3%)	
CoreValve	19 (13%)	55 (13%)	60 (17%)	
Evolut/R/Pro/Pro Plus	45 (31%)	123 (29%)	98 (28%)	
Portico/Navitor	19 (13%)	75 (18%)	69 (20%)	
Sapien XT/S3/S3 Ultra	53 (36%)	121 (29%)	96 (27%)	
Other	3 (2.0%)	17 (4.0%)	7 (2.0%)	
Device size (mm)	28.1±3.0	27.9±2.8	27.8±3.0	0.531
Paravalvular leak				0.633
None	78 (53%)	257 (61%)	218 (62%)	
Minimal	58 (40%)	137 (32%)	111 (32%)	
Mild	9 (6.2%)	28 (6.6%)	22 (6.3%)	
Moderate or severe	1 (0.7%)	3 (0.7%)	1 (0.3%)	
Postdilation	37 (25%)	119 (28%)	84 (24%)	0.417
Valve migration	1 (0.7%)	2 (0.5%)	1 (0.3%)	0.815
Bailout valve-in-valve	1 (0.7%)	2 (0.5%)	1 (0.3%)	0.815
Fluoroscopy time (minutes)	24±27	22±16	21±23	0.604
Procedural time (minutes)	106±58	94±52	86±39	<0.001
Contrast volume (mL)	152±80	152±86	140±76	0.199
Device success	140 (96%)	397 (93%)	335 (95%)	0.446
Procedural success	144 (99%)	407 (96%)	341 (97%)	0.264

Table 4
Discharge outcomes according to left ventricular ejection fraction (LVEF)

Feature	LVEF <25%	LVEF 25-30%	LVEF 31-35%	P
Patients (N)	146	425	352	-
Major adverse event*	19 (13%)	53 (13%)	25 (7.1%)	0.024
Death	7 (4.8%)	18 (4.2%)	7 (2.0%)	0.127
Myocardial infarction	0	3 (0.7%)	1 (0.3%)	0.661
Unplanned cardiac surgery	0	1 (0.2%)	0	1
Percutaneous coronary intervention	0	5 (1.2%)	0	0.089
Transient ischeemic attack	0	4 (0.9%)	4 (1.1%)	0.571
Stroke	0	3 (0.7%)	1 (0.3%)	0.661
Vascular complication				0.839
None	133 (91%)	389 (92%)	325 (92%)	
Minor	7 (4.8%)	23 (5.4%)	19 (5.4%)	
Major	6 (4.1%)	13 (3.1%)	8 (2.3%)	
Bleeding				0.363
None	128 (88%)	368 (87%)	312 (89%)	
Minor	6 (4.1%)	26 (6.1%)	25 (7.1%)	
Major	7 (4.8%)	22 (5.2%)	11 (3.1%)	
Life-threatening	5 (3.4%)	9 (2.1%)	4 (1.1%)	
Bailout valve-in-valve	1 (0.7%)	2 (0.5%)	1 (0.3%)	0.815
Pacemaker implantation	16 (11%)	52 (12%)	35 (9.9%)	0.595
Renal replacement therapy	1 (0.7%)	0	3 (0.9%)	0.123
Hospital stay (days)	7±5	6±5	7±5	0.589
Discharge echocardiogram				
Left ventricular ejection fraction (%)	29±10	36±9	39±8	<0.001
Change in left ventricular ejection fraction (%)	10±9	7±9	5±8	<0.001
Peak aortic valve gradient (mm Hg)	13±6	15±9	14±7	0.509
Mean aortic valve gradient (mm Hg)	8±4	8±5	8±4	0.517
Aortic regurgitation				0.426
None	108 (75%)	282 (70%)	230 (69%)	
Minimal or mild	34 (24%)	111 (27%)	96 (29%)	
Moderate	1 (0.7%)	11 (2.7%)	9 (2.7%)	
Severe	1 (0.7%)	2 (0.5%)	0	
Paravalvular leak				0.613
None	68 (54%)	159 (46%)	129 (47%)	
Minimal	50 (39%)	158 (45%)	130 (47%)	
Mild	8 (6.3%)	28 (8.1%)	16 (5.8%)	
Moderate	1 (0.8%)	3 (0.9%)	1 (0.4%)	
Severe	0	0	0	
Mitral regurgitation				0.052
None	17 (14%)	43 (12%)	15 (5.0%)	
Minimal or mild	17 (14%)	40 (11%)	47 (16%)	
Moderate	52 (42%)	173 (49%)	152 (50%)	
Moderate to severe	29 (23%)	72 (20%)	65 (22%)	
Severe	4 (3.2%)	14 (3.9%)	6 (2.0%)	
Systolic pulmonary artery pressure (mm Hg)	38±9	38±11	37±12	0.508

* Composite of death, myocardial infarction, stroke, unplanned cardiac surgery, major or life-threatening bleeding, or major vascular complication.

The exploratory analysis comparing balloon- versus self-expandable devices showed lower rates of vascular complications with self-expandable valves ($p = 0.027$) and lower valve gradients ($p = 0.001$) but higher prevalence of residual aortic regurgitation ($p = 0.029$) and paravalvular leak ($p < 0.001$; [Supplementary Table 3](#)). The 12-month follow-up according to device type showed a lower rate of stroke ($p = 0.020$) and rehospitalization ($p = 0.007$) in patients receiving balloon-expandable devices, with follow-up imaging confirming the previous findings on aortic valve gradients ($p < 0.05$), regurgitation ($p < 0.001$), paravalvular leak ($p < 0.001$), and systolic pulmonary artery pressure ($p = 0.002$; [Supplementary Table 4](#)). However, almost all these differences were no longer significant at the adjusted analysis, suggesting that the confounding features played a

key role in the comparative profile of balloon- versus self-expandable devices in this data set.

Conversely, the multivariable adjusted analyses confirmed the independent prognostic impact of lower LVEF on the risk of death (odds ratio 0.34 [0.12 to 1.00], $p = 0.049$ comparing LVEF 31% to 35% vs <25% and odds ratio 0.44 (0.20 to 1.00), $p = 0.051$ comparing LVEF 31% to 35% vs 25% to 30%; [Supplementary Table 5](#)), and major adverse events (odds ratio 0.33 [0.14 to 0.75], $p = 0.009$ comparing LVEF 31% to 35% vs <25% and odds ratio 0.54 [0.29 to 0.98], $p = 0.042$ comparing LVEF 31% to 35% vs 25% to 30%). Conversely, the TAVR device type was not significantly associated with death (odds ratio 0.96 [0.46 to 2.02], $p = 0.921$) or major adverse events (odds ratio 0.58 [0.31 to 1.09], $p = 0.093$) when considering potential confounding features.

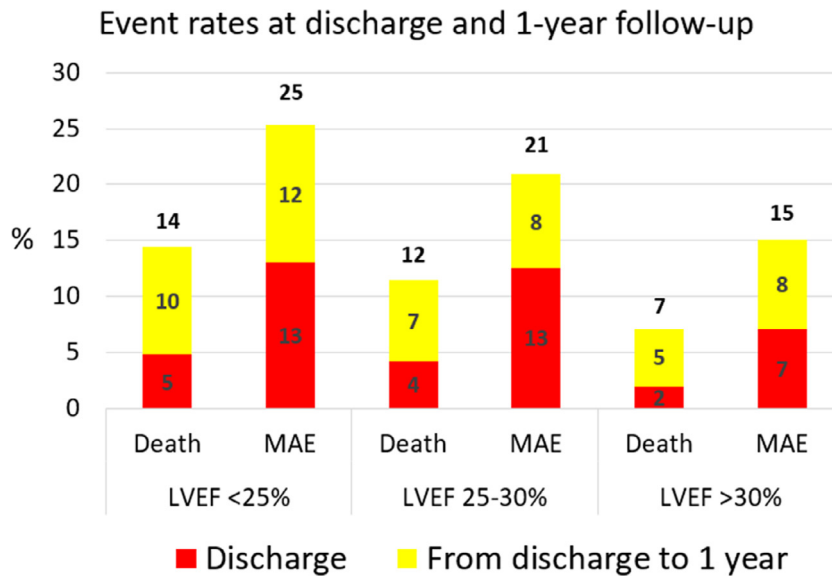


Figure 1. Event rates at discharge and 1-year follow-up according to LVEF ($p < 0.05$ for MAE at discharge and 1 year, and for death at 1 year). MAE = major adverse events.

The exploratory analysis for the change in LVEF from baseline to follow-up and from discharge to follow-up suggested that both were significantly and favorably associated with a lower risk of death at the unadjusted analyses ($p = 0.035$ and $p = 0.007$, respectively) but not at the adjusted analyses ($p = 0.167$ and $p = 0.225$, respectively).

Discussion

This study summarizes the contemporary TAVR practice in patients with reduced LVEF, including a variety of indications, techniques, and devices, in a large patient sample. The main findings are that, notwithstanding the increased risk of these patients, TAVR yields favorable early and

midterm outcomes in patients with reduced LVEF, including those with severe systolic dysfunction. However, reduced LVEF still represents a major adverse prognostic factor at both the short-term and 1-year follow-up. Therefore, TAVR should be meticulously planned and carefully performed in such patients while aiming at maximizing medical therapy with the currently available medications even when TAVR has been effective and uneventful.

Transcatheter aortic valve implantation has improved substantially over the years, and from a niche therapy for patients with prohibitive or very high surgical risk, it is now offered to a large range of patients with significant aortic valve disease, even those at an intermediate or relatively low operative risk.¹⁸⁻²⁰ Reduced left ventricular systolic function, epitomized by low LVEF, is a firmly established

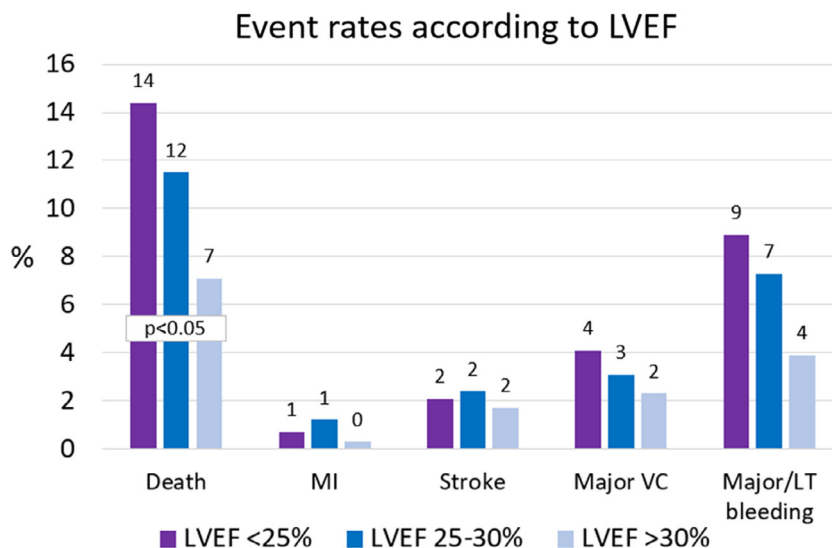


Figure 2. Event rates for components of major adverse events a 1-year follow-up according to LVEF. LT = life-threatening; VC = vascular complication.

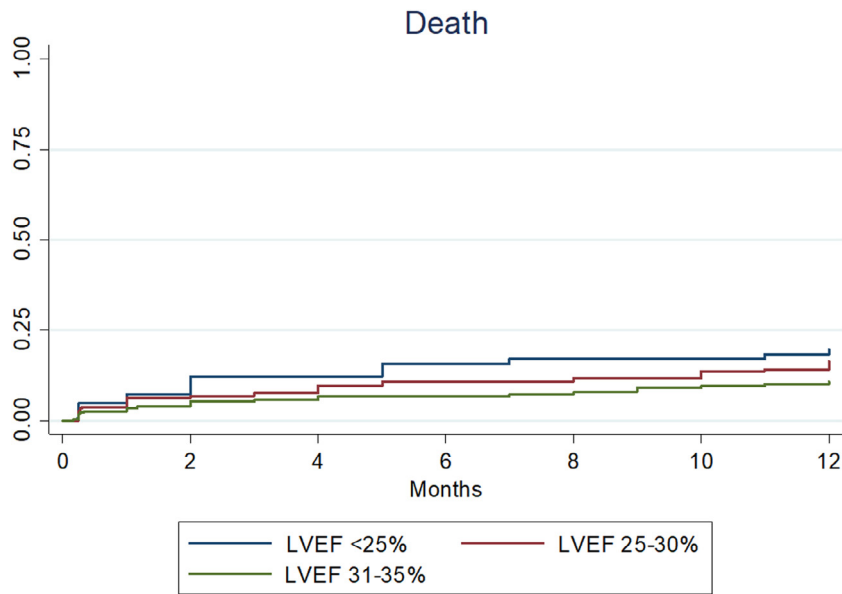


Figure 3. Failure curves for death according to LVEF ($p = 0.047$ at log-rank test).

prognostic feature in cardiovascular medicine in general and also in TAVR.^{21,22} Thus, LVEF is a major component of all risk scores used to guide the decision-making between TAVR and surgical aortic valve replacement.^{2,23,24} However, the outlook of TAVR in patients with reduced LVEF continues to be debated, given the developments in techniques and devices, which may progressively improve outcomes, and the focus on patients with low-flow, low-gradient aortic valve disease, which may prove clinically elusive in routine clinical practice.

We hereby report on a comprehensive international registry focusing on patients with reduced LVEF and providing detailed comparisons based on 3 meaningful LVEF groups:

LVEF <25%, LVEF 25% to 30%, and LVEF 31% to 35%. We found that, despite having substantially adverse clinical features, patients with significant systolic dysfunction had favorable rates of device and procedural success and in-hospital outcomes, including death (<5%) and major adverse events ($\leq 13\%$). The midterm outcomes were also quite favorable, despite an evident event attrition, with death occurring in up to 14% of patients and major adverse events in up to 25% of patients (in both cases in the LVEF <25% group). Despite this, prosthetic valve function appeared quite favorable, with remarkably low residual aortic valve gradients and no case of severe aortic regurgitation or paravalvular leak. Notably, remarkable improvements in LVEF

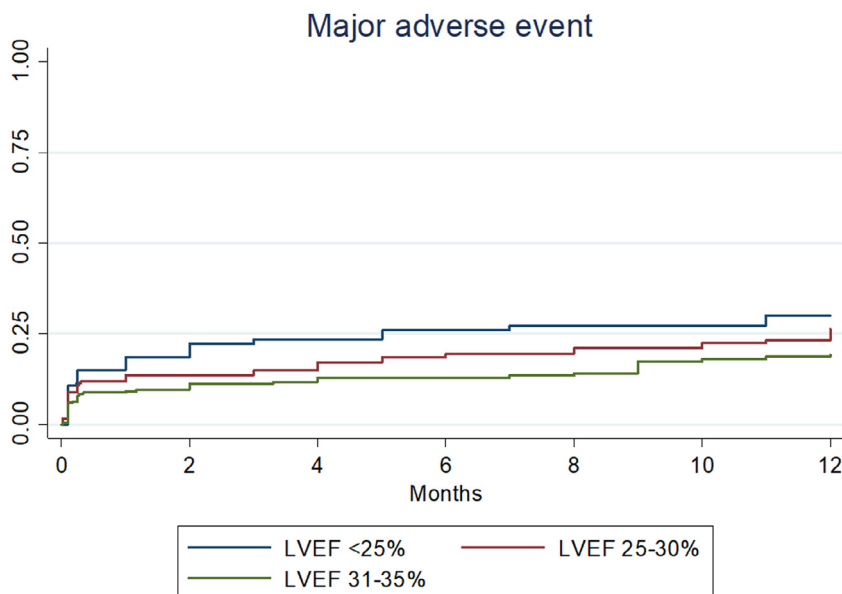


Figure 4. Failure curves for major adverse event according to LVEF ($p = 0.028$ at log-rank test).*

Table 5
Twelve-month outcomes according to left ventricular ejection fraction (LVEF)

Feature	LVEF <25%	LVEF 25-30%	LVEF 31-35%	P
Patients (N)	147	425	352	-
Major adverse event*	37 (25%)	89 (21%)	53 (15%)	0.016
Death	21 (14%)	49 (12%)	25 (7.1%)	0.024
Cardiovascular death	12 (8.2%)	32 (7.5%)	12 (3.4%)	0.022
Myocardial infarction	1 (0.7%)	5 (1.2%)	1 (0.3%)	0.336
Stroke	3 (2.1%)	10 (2.4%)	6 (1.7%)	0.819
Vascular complication				0.700
None	133 (91%)	383 (90%)	324 (92%)	
Minor	7 (4.8%)	29 (6.8%)	20 (5.7%)	
Major	6 (4.1%)	13 (3.1%)	8 (2.3%)	
Bleeding				0.230
None	127 (87%)	369 (87%)	312 (89%)	
Minor	6 (4.1%)	25 (5.9%)	26 (7.4%)	
Major	8 (5.5%)	22 (5.2%)	10 (2.8%)	
Life-threatening	5 (3.4%)	9 (2.1%)	4 (1.1%)	
Aortic valve reintervention	0	0	1 (0.3%)	0.540
Pacemaker implantation	10 (6.9%)	28 (6.6%)	13 (3.7%)	0.140
Rehospitalization	19 (13.0%)	34 (8.0%)	26 (7.4%)	0.117
New York Heart Association class				0.271
I	22 (42%)	73 (39%)	68 (41%)	
II	20 (39%)	73 (39%)	77 (46%)	
III	8 (15%)	35 (19%)	21 (13%)	
IV	2 (3.9%)	6 (3.2%)	1 (0.6%)	
Echocardiogram				
Left ventricular ejection fraction (%)	35±11	38±11	43±10	<0.001
Change in left ventricular ejection fraction (%) in comparison to baseline	17±11	10±11	8±10	<0.001
Change in left ventricular ejection fraction (%) in comparison to discharge	8±12	3±10	3±9	0.011
Peak aortic valve gradient (mm Hg)	16±9	15±8	15±7	0.889
Mean aortic valve gradient (mm Hg)	9±5	9±5	8±4	0.780
Aortic regurgitation				0.066
None	47 (76%)	132 (72%)	112 (65%)	
Minimal or mild	15 (23%)	51 (28%)	56 (33%)	
Moderate	1 (1.6%)	0	4 (2.3%)	
Severe	0	0	0	
Paravalvular leak				0.5333
None	31 (52%)	99 (55%)	77 (49%)	
Minimal	25 (42%)	55 (31%)	61 (39%)	
Mild	4 (6.7%)	20 (11%)	15 (9.6%)	
Moderate	0	5 (2.8%)	4 (2.6%)	
Severe	0	0	0	
Mitral regurgitation				0.084
None	5 (8.5%)	23 (13%)	10 (6.2%)	
Minimal or mild	41 (70%)	114 (65%)	112 (70%)	
Moderate	8 (14%)	28 (16%)	32 (20%)	
Moderate to severe	3 (5.1%)	3 (1.7%)	7 (4.4%)	
Severe	2 (3.4%)	7 (4.0%)	0	
Systolic pulmonary artery pressure (mm Hg)	37±13	36±11	37±11	0.874

* Composite of death, myocardial infarction, stroke, aortic valve reintervention, major or life-threatening bleeding, or major vascular complication.

occurred during follow-up, and such improvements were significantly associated with better prognosis. The importance of distinguishing different levels of LVEF even in the general category of patients with LVEF \leq 35 is demonstrated by adjusted analyses, which confirmed that both death and major adverse events were significantly more common in subjects with LVEF <25% and 25% to 30% than in those with LVEF 31% to 35%, even after considering several key prognostic features. Several differences in clinical and imaging outcomes were evident in comparing TAVR device types at the unadjusted analysis, but the multivariable adjusted models did not show significant

differences for death or major adverse events comparing balloon- and self-expandable devices. Although these results are relevant and impactful, the inclusion of a variety of TAVR devices may have created background heterogeneity, limiting the scope of such device-wise comparisons. Furthermore, in light of recent momentous developments of medical therapy for heart failure, even asymptomatic, such as the introduction of angiotensin receptor and neprilysin inhibitors, sodium-glucose co-transporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists, we may speculate that even better midterm outcomes can be obtained in the current clinical practice by arguably reducing the

mortality rates by at least an additional 20% to 30% in relative terms.²⁵ The importance of optimal medical management before, during, and after TAVR in patients with severe aortic stenosis and significant systolic dysfunction is also corroborated by the surprising finding of similar systolic pulmonary artery pressure. Indeed, this could be explained by the optimal hemodynamic compensation achieved before TAVR (when the baseline echocardiogram was performed) or by other features which were similar (e. g., aortic valve area) or possibly compensated such differences in systolic function (for instance, patients with LVEF <25% were significantly younger).

The limitations of this work were several and include the observational and pragmatic study design, limited collection of imaging details (for instance aortic valve area was measured in only a paucity of patients, thus impeding its analysis), without any core laboratory processing and analysis, enrollment of patients spanning several years and types of devices, including some recently discontinued, and focus on early and midterm outcomes, which limits the capability to appraise long-term device durability, for instance.²⁶ Furthermore, LVEF is a complex factor in the decision-making process of TAVR, and it is plausible that patients with less pronounced LVEF reduction presented other surgical risk factors, which were not attentively captured by our case report form. In addition, we did not collect details on mechanical support devices, which may be of substantial benefit in carefully selected patients, with individualized decision-making to aptly match the device type with patient features.^{27,28} Similarly, we did not appraise the role of vasopressors during TAVR in such a challenging setting. However, this is clearly a topic worth researching.

In conclusion, TAVR yields favorable early and 1-year results in patients with reduced LVEF, including those with extremely depressed systolic dysfunction. However, reduced LVEF still represents a major adverse prognostic factor at both short- and mid-term outcomes.

Data availability statement

The data sets used and/or analyzed during the present study available from the corresponding author on reasonable request.

Appendix

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Declaration of Competing Interest

Dr. Biondi-Zoccai has consulted for Amarin, Balmed, Cardionovum, Cranmedical, Endocore Lab, Eukon, Innovheart, Guidotti, Meditrial, MicroPort, Opsens Medical, Terumo, and Translumina. Lars Sondergaard has received consultant fees and/or institutional research grants from Abbott, Boston Scientific, Medtronic, and SMT. Dr. Schaefer has received speaker honoraria from Abbott. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2023.06.025>.

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