Prognostic Implications of Change in Left Ventricular Ejection Fraction After Transcatheter Aortic Valve Implantation

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Reduced left ventricular (LV) systolic function is associated with worse prognosis in patients with severe aortic stenosis (AS) treated with transcatheter aortic valve implantation (TAVI). We aimed to examine the changes in left ventricular ejection fraction (LVEF) after TAVI among patients with varying baseline LVEF. Moreover, variables associated with lack of LVEF improvement were identified and the association with long-term outcomes was investigated. A total of 560 patients (age 80 ± 7 years, 53% men) with severe AS who underwent transfemoral TAVI between 2007 and 2019 were selected. LVEF was assessed from transthoracic echocardiography at baseline (before TAVI) and at 6 and 12 months after TAVI. Patients were stratified according to baseline LVEF: (1) LVEF ≥50%, (2) LVEF 40% to 49%, and (3) LVEF <40%. The clinical end point was ≥5% LVEF improvement. The primary outcome was all-cause mortality. Patients with baseline LVEF<40% showed greater increase in LVEF than those with baseline LVEF 40% to 49% and LVEF ≥50% (from 33% ± 6% to 43% ± 10%, p <0.001; from 45% ± 3% to 52% ± 8%, p <0.001; and from 58% ± 5% to 59% ± 7%, p = 0.012, respectively, p for interaction <0.001). Coronary artery disease (odds ratio [OR] 1.80 [95% confidence interval (CI) 1.06 to 3.06], p = 0.031), myocardial infarction (OR 2.07 [95% CI 1.19 to 3.61], p = 0.010), and permanent pacemaker (OR: 1.93 [95% CI 1.25 to 3.00], p = 0.003) were independently associated with the lack of ≥5% LVEF improvement. During a median follow-up of 3.8 (interquartile range 2.6 to 5.2) years, 176 patients died (31%). Patients with ≥5% LVEF improvement had similar outcomes compared with those with <5% LVEF improvement (log-rank p = 0.89). In conclusion, patients with severe AS and baseline LVEF <40% had the greatest improvement in LVEF at 1-year follow-up after TAVI. Coronary artery disease, myocardial infarction, and permanent pacemaker were associated with lack of LVEF improvement. However, LVEF improvement at 12 months was not associated with long-term outcomes. **(Am J Cardiol 2022;177:90−99)**

Severe aortic stenosis (AS) may have a significant impact on left ventricular (LV) function. Increased afterload caused by AS may lead to LV remodeling, resulting in LV hypertrophy and impaired LV function.[1,2] Approximately 1/3 of patients with severe AS present with LV systolic dysfunction.[3,4] Moreover, LV systolic dysfunction has been linked with worse prognosis in patients with severe AS who were treated medically or underwent surgical aortic valve replacement.[5−7] Transcatheter aortic valve implantation (TAVI) has become an alternative to surgical aortic valve replacement in patients with severe symptomatic AS.[8] Similarly, reduced baseline LV ejection fraction (LVEF) is associated with an increased risk of all-cause and cardiovascular mortality after TAVI.[9−11] LVEF is an important parameter for the assessment of LV systolic function and is relevant in the management of patients with asymptomatic severe AS according to current guidelines.[12,13] Previous studies showed that LV systolic function improved after TAVI in patients with reduced LVEF.[14−17] However, data on the change of LVEF after TAVI in patients with varying LVEF at baseline are scarce. Additionally, the impact of LVEF improvement on outcomes after TAVI is not clear. Accordingly, the aims of this study were to investigate the potential improvement of LVEF after TAVI in patients with preserved baseline

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LVEF (LVEF ≥50%), midrange LVEF (LVEF 40% to 49%), and reduced LVEF (LVEF <40%). Moreover, the variables associated with lack of LVEF improvement were identified. Finally, the association between LVEF improvement with long-term outcomes after TAVI was evaluated.

Methods

Patients with severe AS who were treated with TAVI at the Leiden University Medical Center (Leiden, The Netherlands) between 2007 and 2019 were included in this retrospective analysis. Patients who underwent transapical TAVI or a valve-in-valve procedure and those whose echocardiographic data at baseline and/or follow-up were lacking were excluded. All patients underwent standard routine follow-up transthoracic echocardiography. Patients were stratified according to baseline (pre-TAVI) LVEF as appointed in the 2016 European Society of Cardiology heart failure guidelines[18]: patients with preserved LVEF (LVEF ≥50%), midrange LVEF (LVEF 40% to 49%), and reduced LVEF (LVEF <40%). Demographic and clinical characteristics at the time of TAVI were collected from the electronic patient records (EPD-vision, Leiden University Medical Center). Clinical characteristics included co-morbidities, cardiac risk factors, previous coronary revascularization, and medication use. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula and renal impairment was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2. This retrospective analysis complies with the Declaration of Helsinki and was approved by the institutional review board, which waived the need for written informed consent owing to the retrospective study design.

TAVI eligibility and feasibility and decision making on the access route and valve type were decided by the local heart team. Multidetector-row computed tomography measurements of the aortic annulus were used to select the transcatheter heart valve size, as previously described.[19] The TAVI procedure was performed according to standard practice.[20] Balloon- and self-expandable valves that were used included Edwards SAPIEN, SAPIEN XT, and SAPIEN 3 (Edwards Lifesciences, Irvine, California) and Medtronic (Minneapolis, Minnesota) CoreValve Evolut R and Evolut Pro (Medtronic).

Transthoracic 2-dimensional echocardiographic examinations were performed before TAVI (to evaluate AS severity, LV systolic function, and LV dimensions) and during routine follow-up: immediately after TAVI (prosthetic valve hemodynamics) and at 6- and 12-month follow-up (prosthetic valve hemodynamics, LV function, and LV dimensions). All echocardiographic examinations were acquired by experienced echocardiographers using commercially available ultrasound systems (Vivid-7, E9 or E95, General Electric Vingmed, Horten, Norway), equipped with 3.5 MHz or M5S transducers. The echocardiographic examinations were performed with patients at rest and data were obtained from the parasternal, apical, and subcostal views. All echocardiographic examinations were reported according to current recommendations.[21,22] Echocardiographic analysis was performed offline, using commercially available software (EchoPac version 113.0.3 and 203; GE Medical Systems, Horten, Norway). Peak and mean transvalvular gradients were calculated from continuous-wave Doppler recordings of the apical 3- or 5-chamber views according to the Bernoulli equation. Aortic valve area (AVA) was calculated using the continuity equation and indexed to body surface area (indexed AVA [AVAi]). Severe AS was defined as an AVA <1.0 cm^2 or AVAi <0.6 cm^2/m^2 and a mean transvalvular pressure gradient ≥40 mm Hg or peak aortic jet velocity ≥4 m/s at rest or during dobutamine stress echocardiography.[12,13] LV volumes (end-diastolic and end-systolic) were measured using planimetry in the apical 2- and 4-chambers views and were indexed to body surface area. LVEF was calculated using Simpson biplane method. LV dimensions (end-diastolic diameter, intraventricular septum thickness, and posterior wall thickness) were obtained in the parasternal long-axis views at end-diastole.[22] LV mass was calculated using the Devereux formula and indexed to body surface area.[22] The presence of postprocedural aortic regurgitation and paravalvular leakage was detected and severity was graded according to current recommendations: mild (grade 1), moderate (grade 2), moderate to severe (grade 3), and severe (grade 4).[23] Significant paravalvular leakage was defined by a grade ≥2.

Changes in LVEF and LV volumes over time are presented as absolute numbers and LV volumes also as percentual reduction compared with baseline. Additional echocardiographic end points included the increase in LVEF ≥5% and ≥10% (as percent point) at follow-up. An increase of LVEF ≥5% was the primary end point, as used previously.[24] Variables linked with the lack of ≥5% LVEF improvement were identified. Additionally, patients were followed up for the occurrence of all-cause mortality after TAVI and survival time was restricted to 5 years. Data on mortality were collected from the departmental electronic patient files, which were linked with the Social Security Death Index and were acquired for all patients.

Continuous variables following a normal distribution are presented as mean ± SD and were compared using the 1-way analysis of variance test. Non-normally distributed continuous variables are presented as median with 25% to 75% interquartile range and were compared using the Kruskal-Wallis test. Bonferroni post hoc analysis was performed to assess between-group differences in case of a significant difference in the overall 3 group comparison. Distribution of continuous variables was evaluated using histograms and *Q-Q* plots. Categoric variables are presented as absolute numbers and percentages and were compared using the chi-square test or Fisher exact test. General linear models with repeated measures analysis were used to evaluate changes in echocardiographic variables over time and to test differences between the groups of baseline LVEF. The Greenhouse-Geisser correction was used if the sphericity assumption was violated and Bonferroni post hoc analysis was performed in case of a significant difference in the overall 3 group comparison. Additional analyses were performed to correct for potential confounders (age, gender, hypertension, diabetes mellitus, coronary artery disease,

previous myocardial infarction, concomitant moderate or severe mitral- or aortic regurgitation, moderate or severe paravalvular leakage, permanent pacemaker [before and after TAVI], atrial fibrillation, pre-TAVI AV mean gradient, and pre-TAVI LVEF) on the change of the LV parameters over time and were included as covariates in the general linear models.[25] Univariable and multivariable binary logistic regression models were used to evaluate the variables that were associated with lack of ≥5% LVEF improvement. All variables with a $p < 0.10$ in the univariable analysis were included in the multivariable model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and reported. Kaplan-Meier curves were generated to estimate the cumulative survival rates of all-cause mortality and the log-rank test was used to compare patients with ≥5% LVEF improvement at follow-up. Multivariable Cox proportional hazards regression analysis was used to evaluate the association of improvement in LVEF (as continuous and dichotomous variables) at follow-up with all-cause mortality. Potential confounders including age, gender, cardiac risk factors, coronary artery disease, previous myocardial infarction, previous stroke/transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, previous coronary revascularization, chronic kidney disease, pre-TAVI AV mean gradient, and pre-TAVI LVEF were incorporated in the multivariable Cox proportional hazard model. Hazard ratios (HRs) and 95% CI were calculated and reported. A 2-sided $p < 0.05$ was considered significant. Data analyses were performed with SPSS version 25.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

Results

A total of 560 patients (age 80 ± 7 years, 53% men) with severe AS were included in the analysis (Figure 1). The distribution of the different groups of LV systolic function before TAVI and at 6- and 12-month follow-up are shown in Figure 2. Before TAVI, 350 patients (62%) had preserved LVEF (LVEF ≥50%), 122 patients (22%) had midrange LVEF (LVEF 40% to 49%), and reduced LVEF (LVEF <40%) was present in 88 patients (16%). Baseline (pre-TAVI) demographic and clinical characteristics of the overall population and according to baseline LVEF are presented in Table 1. Patients with reduced baseline LVEF had a more frequent history of myocardial infarction, NYHA class 3 to 4, concomitant moderate or severe mitral or aortic regurgitation, and permanent pacemaker compared with patients with preserved and midrange baseline LVEF, whereas hypertension was less common. Accordingly, patients with reduced baseline LVEF were more frequently using diuretics, mineralocorticoid receptor antagonists, and oral anticoagulation and less calcium antagonists. Additionally, patients with reduced baseline LVEF had a higher logistic EuroSCORE and worse kidney function than patients with midrange and preserved baseline LVEF. However, the frequency of reduced kidney function was comparable between the groups (50% vs 52% vs 45%, respectively, $p = 0.42$).

Baseline (pre-TAVI) echocardiographic data are presented in Table 2. LV volumes and LV mass index were larger in patients with reduced LVEF than those with midrange and preserved LVEF before TAVI. In contrast, AV

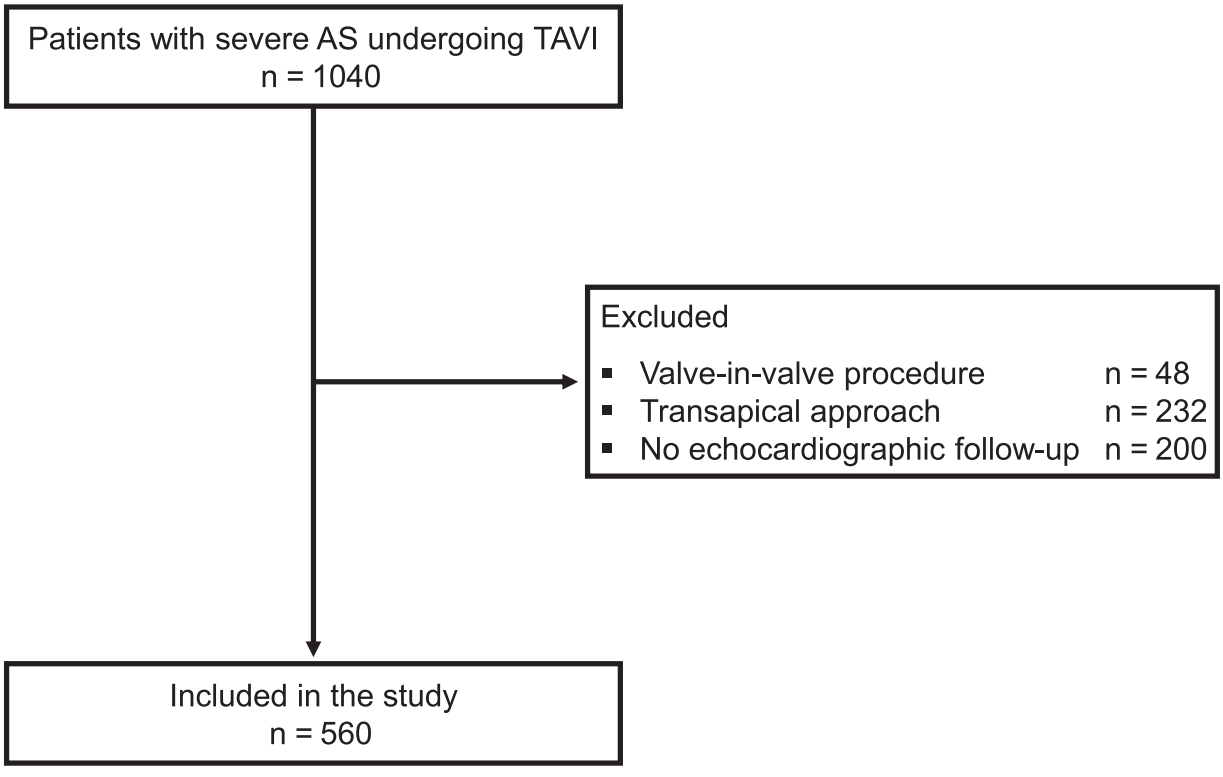

Figure 1. Flowchart of the study population.

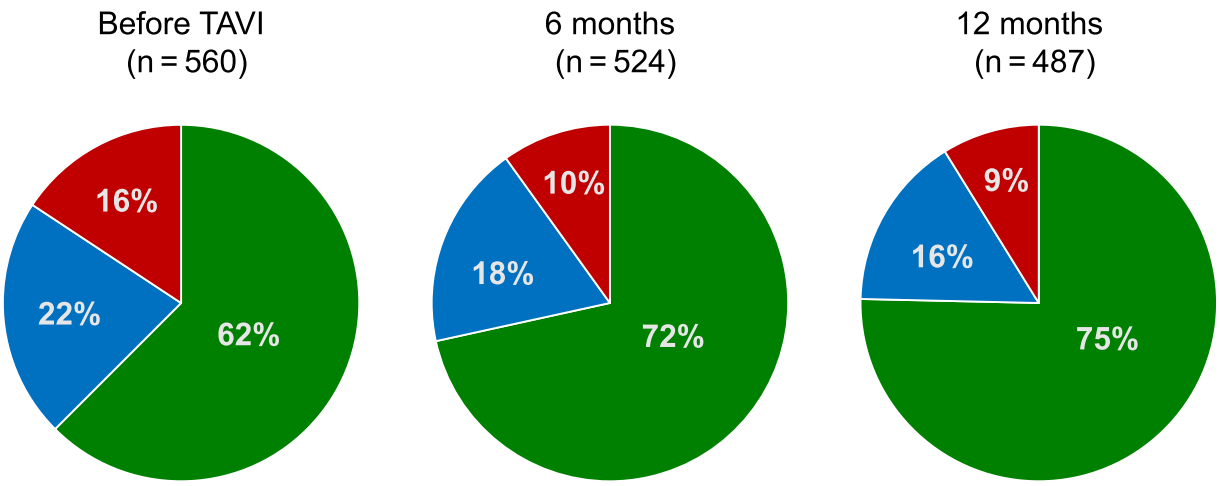

Figure 2. Distribution of LVEF before TAVI and at follow-up. Pie chart displaying the distribution of patients with preserved LVEF ≥50% (green), midrange LVEF 40% to 49% (blue), and reduced LVEF <40% (red) at baseline and 6 and 12 months after transcatheter aortic valve implantation.

Table 1
Baseline (pre-TAVI) demographical and clinical characteristics of the overall population and according to baseline left ventricular ejection fraction

Variable	Overall population (n=560)	Left ventricular ejection fraction ≥50% (n=350)	Left ventricular ejection fraction 40-49% (n=122)	Left ventricular ejection fraction <40% (n=88)	p-Value
Age (years)	80 ± 7	80 ± 7	80 ± 6	79 ± 9	0.46
Male sex	296 (53%)	178 (51%)	68 (56%)	50 (57%)	0.47
Body mass index (kg/m^2)	26.7 ± 4.6	26.7 ± 4.8	27.0 ± 4.2	26.4 ± 4.4	0.67
Logistic EuroSCORE	12.3 [8.6-20.1]	10.7 [7.9-17.1]	13.4 [9.5-21.6]*	21.9 [13.8-31.9]*,†	<0.001
eGFR (ml/min)	61 ± 20	63 ± 19	58 ± 21*	57 ± 21*,†	0.007
Hypertension	407 (73%)	266 (76%)	88 (72%)	53 (60%)	0.009
Hypercholesterolemia	338 (61%)	206 (59%)	80 (66%)	52 (59%)	0.43
Diabetes mellitus	159 (28%)	97 (28%)	35 (29%)	27 (31%)	0.86
Smoker	76 (14%)	47 (14%)	14 (12%)	15 (18%)	0.58
CAD	351 (63%)	208 (60%)	80 (66%)	63 (72%)	0.089
Previous myocardial infarction	112 (20%)	55 (16%)	30 (25%)	27 (31%)	0.003
Previous revascularization	293 (52%)	172 (49%)	67 (55%)	54 (61%)	0.099
PCI	173 (31%)	108 (31%)	36 (30%)	29 (33%)	0.22
CABG	120 (21%)	64 (18%)	31 (25%)	25 (28%)	
NYHA class					
I-II	231 (41%)	156 (45%)	50 (41%)	25 (28%)	0.020
III-IV	327 (59%)	192 (55%)	72 (59%)	63 (72%)	
Previous stroke/TIA	103 (19%)	62 (18%)	23 (19%)	18 (21%)	0.86
Peripheral vascular disease	100 (18%)	56 (16%)	24 (20%)	20 (23%)	0.28
Atrial fibrillation	147 (26%)	76 (22%)	42 (34%)	29 (33%)	0.007
Chronic obstructive pulmonary disease	101 (18%)	63 (18%)	17 (14%)	21 (24%)	0.19
Concomitant mitral/aortic regurgitation ≥grade 2	148 (26%)	64 (18%)	45 (37%)	39 (44%)	<0.001
Permanent pacemaker	83 (15%)	37 (11%)	23 (19%)	23 (26%)	<0.001
Medication					
Beta-blocker	326 (58%)	207 (60%)	72 (59%)	47 (53%)	0.58
ACE-I / ARB II	290 (52%)	178 (51%)	61 (50%)	51 (58%)	0.46
Calcium antagonist	136 (24%)	81 (23%)	41 (34%)	14 (16%)	0.010
Diuretics	295 (53%)	159 (46%)	75 (62%)	61 (69%)	<0.001
MR antagonist	57 (10%)	27 (8%)	14 (12%)	16 (18%)	0.014
Statins	349 (63%)	222 (64%)	79 (65%)	48 (55%)	0.24
Antiplatelet	325 (58%)	204 (58%)	71 (58%)	50 (57%)	0.97
Anticoagulation	211 (38%)	111 (32%)	51 (43%)	49 (56%)	<0.001

Data are presented as mean ± SD, median [25-75% interquartile range] and n (%).

ACE-I = angiotensin-converting enzyme; ARB II = angiotensin-II receptor blocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; MR = mineralocorticoid receptor; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

*p<0.05 vs group 'Left Ventricular Ejection Fraction ≥50%' with Bonferroni's post-hoc analysis.

†p<0.05 vs group 'Left Ventricular Ejection Fraction 40-49%' with Bonferroni's post-hoc analysis.

Table 2
Baseline (pre-TAVI) echocardiographic data of the overall population and according to baseline left ventricular ejection fraction

Variable	Overall population (n=560)	Left ventricular ejection fraction ≥50% (n=350)	Left ventricular ejection fraction 40-49% (n=122)	Left ventricular ejection fraction <40% (n=88)	p-Value
LVEF (%)	51 ± 11	58 ± 5	45 ± 3*	33 ± 6*,†	<0.001
AV peak gradient (mmHg)	66 ± 25	70 ± 25	63 ± 26*	55 ± 25*,†	<0.001
AV mean gradient (mmHg)	42 ± 17	45 ± 16	41 ± 18	35 ± 15*,†	<0.001
AVA (cm^2)	0.80 ± 0.28	0.82 ± 0.28	0.78 ± 0.27	0.75 ± 0.30	0.13
AVAi (cm^2/m^2)	0.43 ± 0.15	0.44 ± 0.15	0.42 ± 0.15	0.41 ± 0.16	0.19
LVEDVi (ml/m^2)	44 [36-54]	40 [34-48]	47 [36-54]*	60 [50-74]*,†	<0.001
LVESVi (ml/m^2)	20 [15-29]	17 [14-20]	25 [20-30]*	41 [33-50]*,†	<0.001
SVi (ml/m^2)	39 ± 12	41 ± 12	37 ± 12*	32 ± 10*,†	<0.001
LV mass index (g/m^2)	119 ± 32	112 ± 27	126 ± 36*	138 ± 34*,†	<0.001
LVEDD (mm)	47.7 ± 7.4	45.7 ± 6.5	49.0 ± 7.2*	53.9 ± 7.1*,†	<0.001
IVST (mm)	13.1 ± 1.8	13.2 ± 1.7	13.2 ± 2.1	12.5 ± 1.7*,†	0.004
PWT (mm)	12.2 ± 2.1	12.3 ± 2.1	12.5 ± 2.1	11.9 ± 2.0	0.12
RWT	0.52 ± 0.13	0.54 ± 0.13	0.51 ± 0.12	0.44 ± 0.10*,†	<0.001

Data are presented as mean ± SD, median [25-75% interquartile range] and n (%).

AV = aortic valve; AVA = aortic valve area; AVAi = indexed aortic valve area; IVST = intraventricular septum thickness; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; PWT = posterior wall thickness; RWT = relative wall thickness; SVi = stroke volume index.

*p<0.05 vs group 'Left Ventricular Ejection Fraction ≥50%' with Bonferroni's post-hoc analysis.

†p<0.05 vs group 'Left Ventricular Ejection Fraction 40-49%' with Bonferroni's post-hoc analysis.

peak and mean gradient and stroke volume index were lower in patients with reduced baseline LVEF. AVAi was comparable between patients with reduced, midrange, and preserved baseline LVEF.

All patients underwent TAVI using the transfemoral approach. The majority of patients received balloon-expandable valves: Edwards SAPIEN 3,341 (61%), SAPIEN XT 46 (8%), SAPIEN 36 (6%), and SAPIEN Ultra 3 (0.5%). Self-expandable valves were used in 133 patients (24%). Prothesis size ranged from 23 to 31 mm, with 26 mm being most frequent in 221 patients (40%).

LVEF improved significantly during follow-up (from 51 ± 11% to 54 ± 10% at 6 months and to 55 ±10% at 12 months, p <0.001). The changes in LVEF according to baseline LVEF are displayed in Figure 3. The largest increase in LVEF after TAVI was noted in patients with reduced baseline LVEF versus those with midrange LVEF (from 33 ± 6% to 42 ± 10% at 6 months and to 43 ± 10% at 12 months, p <0.001; and from 45 ± 3% to 51 ± 8% at

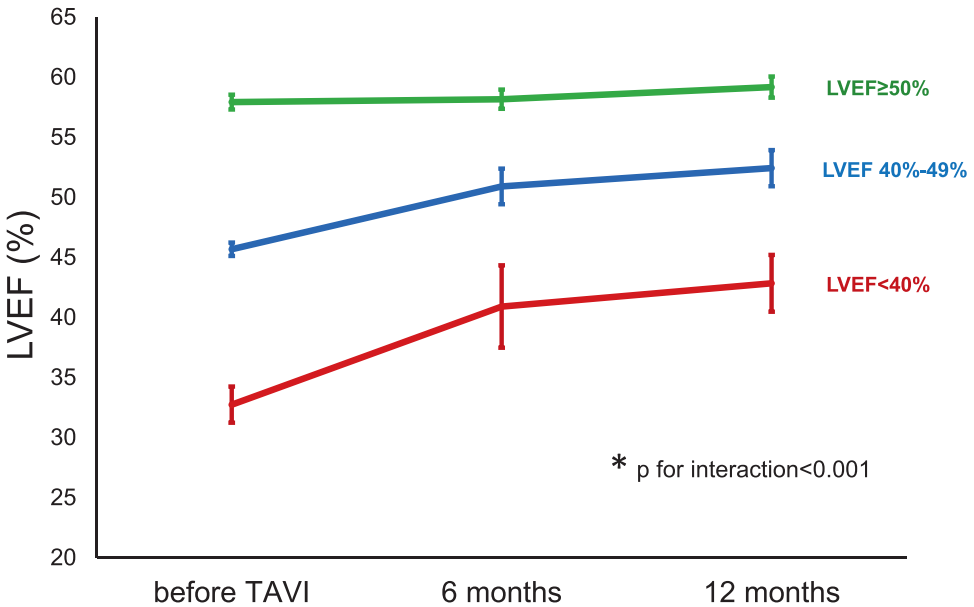

Figure 3. Evolution of LVEF after transcatheter aortic valve implantation. Changes in LVEF of patients with preserved baseline LVEF ≥50% (green line), midrange LVEF 40% to 49% (blue line), and patients with reduced LVEF <40% (red line) from baseline to 6 months and 12 months follow-up after transcatheter aortic valve implantation. *Shows p-value for interaction between the varying groups of baseline LVEF over time. Error bars indicate 95% confidence intervals.

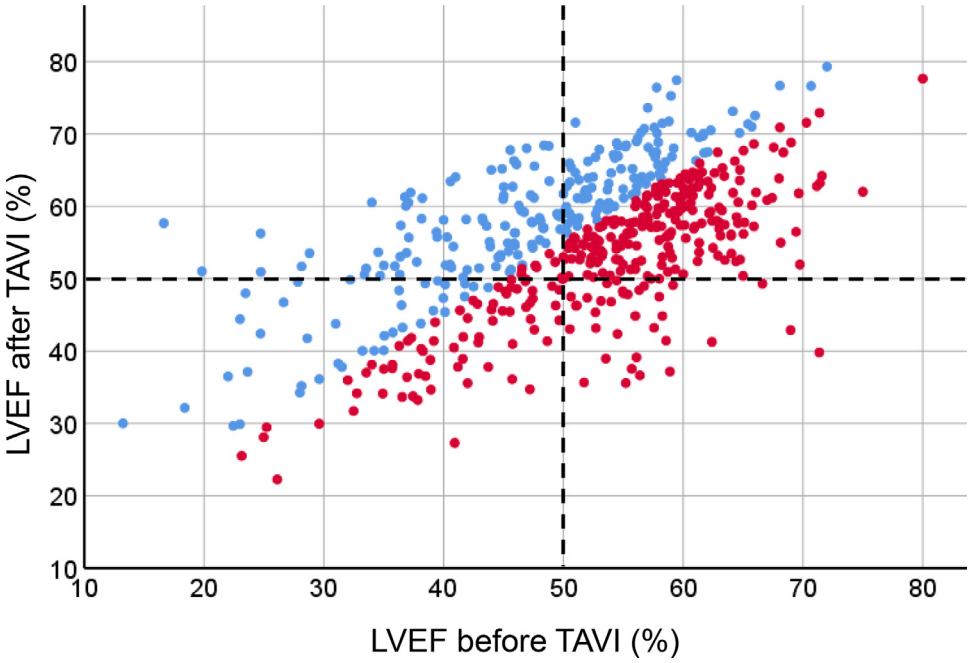

Figure 4. Scatterplot of LVEF before transcatheter aortic valve implantation and at follow-up. Blue dots represent patients with ≥5% LVEF improvement; red dots represent patients with <5% LVEF improvement.

6 months and to 52 ± 8% at 12 months, p <0.001, respectively), and a modest improvement in LVEF was noted in patients with preserved baseline LVEF (from 58 ± 5% to 58 ± 7% at 6 months and to 59 ± 7% at 12 months, p = 0.012; p for interaction <0.001). LV volumes decreased significantly after TAVI. The largest decrease in LV end-diastolic volume index was noted in patients with reduced LVEF compared with patients with preserved baseline LVEF (from 60 [50 to 74] ml/m^2 to 51 [43 to 70] ml/m^2 at 6 months and to 55 [38 to 67] ml/m^2 at 12 months, p <0.001; and from 40 [34 to 48] ml/m^2 to 39 [32 to 47] ml/m^2 at 6 months and to 38 [30 to 45] ml/m^2 at 12 months, p <0.001, respectively), whereas LV end-diastolic volume index was not significantly decreased among patients with midrange baseline LVEF (from 47 [36 to 54] ml/m^2 to 44 [38 to 55] ml/m^2 at 6 months and to 43 [34 to 50] ml/m^2 at 12 months, p = 0.055; p for interaction = 0.001). Similarly, patients with decreased LVEF had the largest reduction in LV end-systolic volume index after TAVI compared with those with midrange LVEF and preserved LVEF (reduced LVEF: from 41 [33 to 50] ml/m^2 to 32 [23 to 41] ml/m^2 at 6 months and to 30 [21 to 41] ml/m^2 at 12 months, p <0.001; midrange LVEF: from 25 [20 to 30] ml/m^2 to 22 [17 to 27] ml at 6 months and to 20 [16 to 25] ml/m^2 at 12 months, p <0.001; and preserved LVEF: from 17 [14 to 20] ml/m^2 to 16 [13 to 20] ml/m^2 at 6 months and to 15 [11 to 19] ml/m^2 at 12 months, p< 0.001; p for interaction <0.001). LV mass index regressed significantly after TAVI (from 119 ± 32 g/m^2 to 105 ± 26 g/m^2 at 6 months and to 99 ± 26 g/m^2 at 12 months, p <0.001) and was comparable between the varying groups of baseline LVEF over time (p for interaction = 0.48). Prosthetic AV mean gradient was similar during follow-up (from 9 ± 4 mm Hg immediately after TAVI to 10 ± 5 mm Hg at 6 months and to 10 ± 5 mm Hg at 12 months) without significant changes between groups over time (p for interaction = 0.48). Additional analysis was performed to correct for confounders of the change in LVEF after TAVI and showed similar results (Supplementary Table 1). The absolute change in LVEF and LV volumes and mass at 6- and 12-month follow-up are shown in Supplementary Table 2.

An improvement in LVEF ≥5% at follow-up was noted in 233 patients (42%) and was most frequently observed among patients with reduced LVEF (67%), followed by patients with midrange LVEF (58%) and those with preserved baseline LVEF (29%, p <0.001). Similarly, ≥10% LVEF improvement was observed in 121 patients (22%) and most common in patients with reduced baseline LVEF (48% vs 32% vs 11%, respectively, p <0.001). A scatterplot of LVEF at baseline versus follow-up according to ≥5% LVEF improvement is displayed in Figure 4.

Patients with ≥5% LVEF improvement at follow-up had less hypertension than those with <5% LVEF improvement (68% vs 77%, p = 0.021) and less coronary artery disease (55% vs 68%, p = 0.001), less myocardial infarction (15% vs 24%, p = 0.007), less previous percutaneous coronary interventions (25% vs 35%, p = 0.016), and less permanent pacemaker implantation (25% vs 35%, p = 0.021). In contrast, atrial fibrillation (32% vs 22%, p = 0.012) and concomitant moderate or severe mitral or aortic regurgitation (31% vs 23%, p = 0.026) were more frequent in patients with ≥5% LVEF improvement. Similar results were noted in the comparison of patients with ≥10% LVEF improvement. Additionally, the baseline clinical and echocardiographic characteristics of patients with LVEF <50% at baseline and follow-up versus patients with preserved LVEF at baseline and follow-up among patients with <5% LVEF improvement are summarized in Supplementary Table 3.

The baseline clinical and echocardiographic variables associated without ≥5% LVEF improvement are displayed

Table 3
Uni- and multivariable logistic regression of clinical and echocardiographic parameters associated without ≥5% LVEF improvement after transcatheter aortic valve implantation

	Univariable			Multivariable		
Variable	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	0.995	0.971-1.019	0.66			
Male sex	1.272	0.908-1.782	0.16			
Body mass index	1.021	0.983-1.060	0.28			
Logistic EuroSCORE	0.983	0.966-1.000	0.056	0.989	0.967-1.011	0.33
eGFR<60ml/min	1.210	0.864-1.696	0.27			
Hypertension	1.555	1.068-2.265	0.021	1.281	0.825-1.990	0.27
Hypercholesterolemia	1.198	0.850-1.689	0.30			
Diabetes mellitus	0.970	0.668-1.407	0.87			
CAD	1.776	1.254-2.515	0.001	1.796	1.055-3.057	0.031
Previous myocardial infarction	1.833	1.176-2.858	0.007	2.072	1.189-3.611	0.010
PCI	1.578	1.087-2.291	0.016	0.976	0.571-1.670	0.93
CABG	1.301	0.858-1.973	0.22			
Previous stroke/TIA	1.012	0.655-1.564	0.96			
Peripheral vascular disease	0.804	0.520-1.242	0.33			
Atrial fibrillation	0.618	0.423-0.902	0.013	0.761	0.486-1.190	0.23
Chronic obstructive pulmonary disease	0.827	0.536-1.276	0.39			
Concomitant mitral/aortic regurgitation ≥grade 2	0.938	0.550-1.601	0.82			
Baseline LVEF<50%	0.257	0.179-0.368	<0.001	0.224	0.145-0.346	<0.001
Paravalvular leakage ≥moderate (grade 2)	1.443	0.637-3.272	0.38			
Permanent pacemaker	1.548	1.066-2.249	0.022	1.931	1.245-2.995	0.003

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

in Table 3. Baseline LVEF <50% was independently associated with ≥5% LVEF improvement at follow-up (OR for lack of ≥5% LVEF improvement 0.22 [95% CI 0.15 to 0.35], p <0.001), whereas coronary artery disease (OR 1.80 [95% CI 1.06 to 3.06], p = 0.031), myocardial infarction (OR 2.07 [95% CI 1.19 to 3.61], p = 0.010), and need for permanent pacemaker (OR 1.93 [95% CI 1.25 to 3.00], p = 0.003) were independently associated with lack of ≥5% LVEF improvement after TAVI.

During a median follow-up of 3.8 (interquartile range 2.6 to 5.2) years, 176 patients died (31%). Kaplan-Meier analysis demonstrated similar outcomes for patients with versus without ≥5% LVEF improvement after TAVI (log-rank chi-square: 0.19, p = 0.89; Figure 5). Moreover, long-term survival was comparable for patients with and without ≥5% LVEF improvement after TAVI among patients with preserved baseline LVEF (log-rank chi-square: 0.002, p = 0.97), baseline LVEF <50% (n = 210; log-rank chi-square: 0.27, p = 0.60), and among patients with reduced baseline LVEF (log-rank chi-square: 0.18, p = 0.68; Figure 5). Additionally, baseline LVEF (as a continuous variable, HR 0.995 [95% CI 0.980 to 1.009], p = 0.47), a 1% improvement in LVEF after TAVI (HR 0.996 [95% CI 0.979 to 1.013], p = 0.64), ≥5% LVEF improvement (HR 0.927 [95% CI 0.670 to 1.283], p = 0.65), and ≥10% LVEF improvement (HR 1.129 [95% CI 0.776 to 1.643], p = 0.53) were not associated with all-cause mortality after TAVI in multivariable Cox regression analysis.

Discussion

In patients with severe AS, LVEF improved significantly at 1-year follow-up after TAVI. Patients with reduced baseline LVEF showed the greatest improvement in LVEF. Additionally, coronary artery disease, myocardial infarction, and need for a permanent pacemaker were independently associated with lack of LVEF improvement after TAVI. However, improvement in LVEF at 1-year follow-up was not associated with long-term outcomes.

LV systolic dysfunction is common among patients with severe AS; this may be secondary to severe AS or coexistent cardiomyopathy. In severe AS, the LV myocardium may remodel and develop LV hypertrophy, as a consequence of the chronic LV pressure overload associated with severe AS, to normalize wall stress and maintain cardiac output.[1,26] However, with AS progression, this compensation mechanism may fail and subsequently lead to heart failure and mortality.[27,28] Aortic valve replacement results in immediate relief of LV afterload and is associated with LV reverse remodeling and improvement in LV systolic function.[14,29] The present study evaluated the development of LVEF after TAVI among patients with varying baseline LVEF. The greatest improvement in LVEF at 1-year follow-up was noted in patients with reduced LVEF (<40%), despite a higher prevalence of ischemic heart disease, which potentially could limit LV reverse remodeling. Patients with reduced LV function may have the greatest potential for LV recovery after TAVI, as confirmed by the present results.

Ewe et al[15] evaluated the LV systolic function of 147 patients with severe AS who underwent TAVI with preserved baseline LVEF and impaired LVEF (<50%). In line with our findings, patients with impaired LVEF showed significant improvement in LVEF at follow-up. However, LVEF was comparable in patients with preserved baseline LVEF at follow-up, whereas in the present study, including

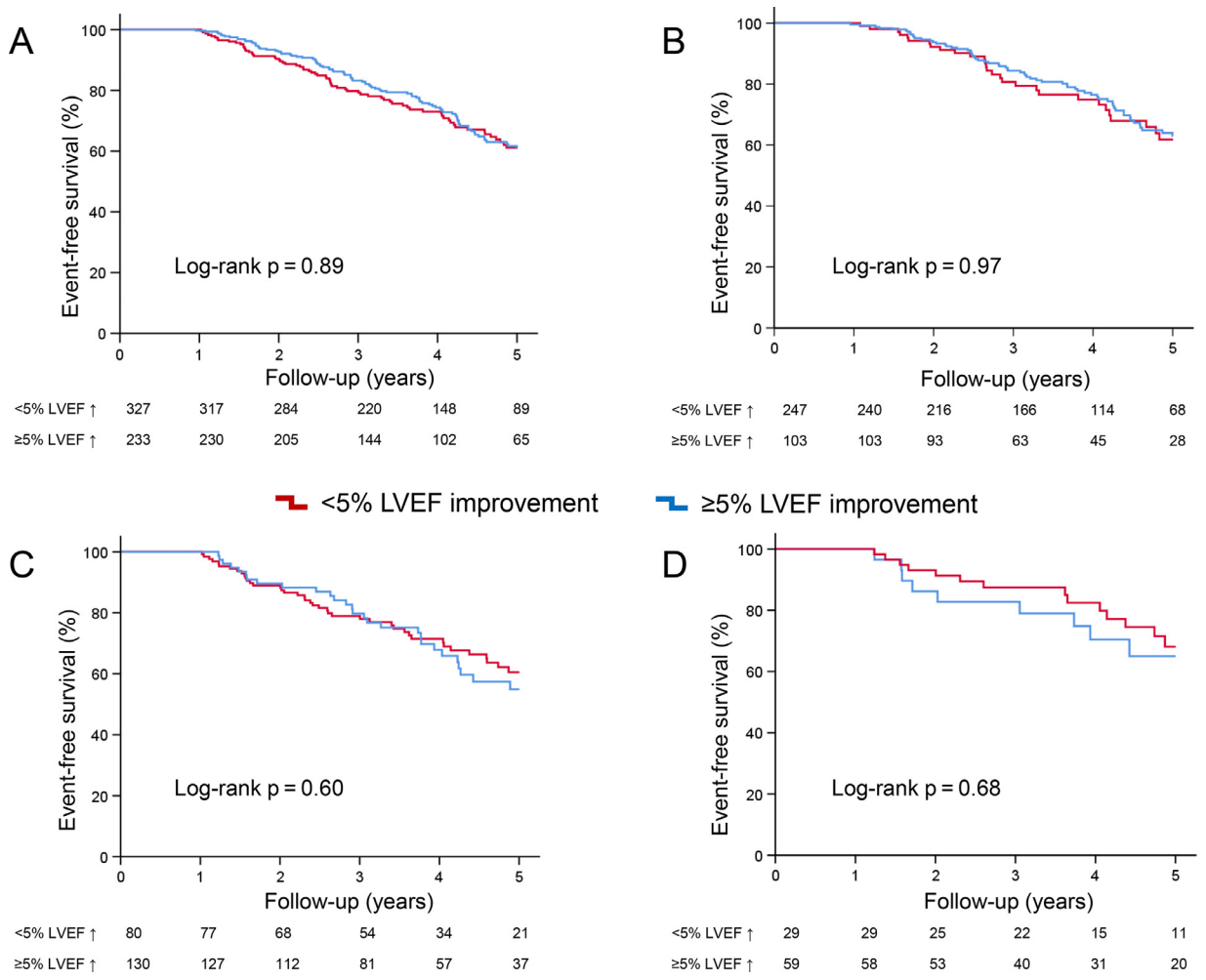

Figure 5. Kaplan-Meier curves demonstrating the event-free survival for all-cause mortality according to ≥5% improvement in LVEF of the overall population (*A*) and among patients with baseline preserved LVEF (LVEF>50%, *B*), LVEF <50% (*C*), and reduced LVEF (LVEF<40%, *D*).

more patients and longer echocardiographic follow-up, a modest but significant improvement in LVEF was noted in patients with preserved baseline LVEF at 1-year after TAVI. Similarly, a study including 505 patients with severe AS who underwent TAVI demonstrated that patients with severe LV dysfunction (<35%) had the greatest improvement in LVEF at 6-month follow-up compared with those with moderate LV dysfunction (35% to 50%).[30] Moreover, a meta-analysis including 26 articles reported significant improvement in LVEF among patients with severe AS and low baseline LVEF (<50%) at 30 days, 6 months, and at 1 year after TAVI.[11]

Next, the variables related to lack of LVEF improvement were evaluated. Permanent pacemaker implantation, more specifically right ventricular pacing, is known to affect LV function and LV recovery after TAVI.[25,31] The present analysis showed that the majority of patients with a permanent pacemaker did not improve in LVEF at follow-up. Additionally, coronary artery disease and myocardial infarction were also associated with lack of LVEF improvement, whereas baseline LVEF <50% was linked with LVEF improvement that is similar to previous studies.[30,32]

LV systolic function yields important prognostic information in patients with severe AS who underwent surgical aortic valve replacement.[6] Similarly, it has been shown that baseline LVEF is an independent predictor of outcomes after TAVI.[9–11] However, data on LVEF improvement versus long-term outcomes after TAVI are scarce. In a cohort of patients with severe AS and reduced LVEF (<45%) who underwent TAVI, Angelillis et al[33] reported that a ≥10% increase in LVEF at 1-month follow-up was associated with improved outcomes, although patients with previous coronary revascularization were excluded from the analysis. Similarly, Dauerman et al[32] evaluated early LV recovery after TAVI in patients with severe AS and reduced LVEF (<40%) with high operative risk. Patients with a ≥10% increase in LVEF at 1-month follow-up had fewer adverse events, although not statistically different possibly because of small patient numbers. In the present study, which includes more patients, an improvement of ≥5% in LVEF at 6- or 12-month follow-up after TAVI was not associated with long-term outcomes, even in the patients with reduced baseline LVEF.

Several limitations should be acknowledged. First, this is a single-center retrospective analysis, with inherent

limitations related to the study design. Second, patients without echocardiographic follow-up have been excluded from the analysis, which may have caused selection bias. However, the baseline clinical characteristics of this population versus the study population are comparable (Supplementary Table 4). Third, the group of patients with reduced LVEF was limited. Finally, the present study used LVEF as a marker of LV systolic function, where LV strain may be a more sensitive marker to assess LV dysfunction.

In conclusion, LVEF improved significantly in patients with severe AS at 1-year follow-up after TAVI. Patients with reduced baseline LVEF revealed the greatest improvement in LVEF. Coronary artery disease, myocardial infarction, and the need for a permanent pacemaker were independently associated with lack of LVEF improvement. However, LVEF improvement at 12-month follow-up was not associated with long-term outcomes.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.060.

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