Outcomes of Patients with Severe Aortic Stenosis and Left Ventricular Obstruction Undergoing Transcatheter Aortic Valve Implantation

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Scarce data exist on clinical features and prognosis of patients with severe aortic stenosis (AS), concomitant with left ventricular obstruction (LVO). We aimed to evaluate the prevalence, characteristics, and outcomes in patients with severe AS and LVO undergoing transcatheter aortic valve implantation (TAVI). Consecutive patients with severe AS undergoing TAVI between January 2013 to December 2017 at our institution were included. Significant LVO was defined as resting peak left ventricular (LV) systolic gradient ≥30 mm Hg on pre-TAVI echocardiography. We analyzed the primary composite outcome of all-cause mortality and rehospitalization for heart failure (HHF) at 1-year in patients with LVO and those without LVO in the overall and propensity-matched populations. Among 1,729 patients who underwent TAVI, significant LVO was observed in 31 (1.8%) patients. This group was more likely to be female, had smaller aortic annulus and LV cavity, and received a smaller size of the transcatheter heart valve. The most common phenotype of LV hypertrophy causing LVO was concentric LV hypertrophy (58%), and mid-LV obstruction was more common than LV outflow tract obstruction (77% vs 23%, respectively). After adjustment for baseline differences, the primary outcome was not significantly different between patients with LVO and those without LVO (15% vs 16%, respectively; hazard ratio: 0.83; 95% confidence interval: 0.19 to 3.72; p = 0.809). In conclusion, in patients undergoing TAVI, concomitant LVO was relatively uncommon and occurred more often at mid-LV. The presence of pre-TAVI LVO was not associated with worse outcomes defined as increase all-cause mortality or HHF at 1-year. **(Am J Cardiol 2020;133:105−115)**

Severe aortic stenosis (AS) commonly leads to progressive left ventricular (LV) hypertrophy in response to chronic pressure overload. LV volumes are also noted to decline with increasing age.[1] Due to combined effects of concentric LV hypertrophy and lower LV volumes, intraventricular pressure gradients may develop, leading to various degrees of LV obstruction (LVO). The prevalence of a hemodynamically significant LVO in patients with severe AS is low and was reported at 4.4% in one study.[2] However, the prevalence and clinical significance of LVO in the era of transcatheter aortic valve implantation (TAVI) are unknown. For many years, the conventional approach for severe AS accompanied by LVO resulting from interventricular septum (IVS) hypertrophy was surgical aortic valve replacement (SAVR) combined with a septal myectomy.[3] In the setting of TAVI, the presence of concomitant LVO can have periprocedural adverse hemodynamic implications as the immediate reduction in LV afterload after transcatheter heart valve (THV) deployment may exacerbate LV outflow tract (LVOT) obstruction.[4,5] Therefore, this study aimed to investigate the prevalence and characteristics of LVO in patients with severe AS undergoing TAVI, as well as its impact on clinical outcomes.

Methods

We retrospectively reviewed medical records of consecutive patients with severe AS who underwent TAVI at Cedars-Sinai medical center between January 2013 to December 2017 and included in our TAVI database. We excluded patients if (1) they had preexisting left-sided mechanical or bioprosthetic heart valve, (2) no available pre-TAVI transthoracic echocardiography (TTE) within 6 months prior to the procedure, or (3) if the pre-TAVI TTE image quality was poor. The remaining cohort constituted the study population and was divided into severe AS with LVO and severe AS without LVO. All patients provided

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written informed consent for the procedure. All data for this study were collected from an established interventional cardiology laboratory database approved by the Cedars-Sinai Medical Center Institutional Review Board.

Pre-TAVI TTE was performed by well-trained sonographers. Measurements were obtained according to the American Society of Echocardiography guidelines,[6,7] and systematically reviewed by an experienced cardiologist. In addition, post-TAVI TTE was performed at the approximate intervals of day 1, 30-day, and 1-year post-procedure. Severe AS was diagnosed according to current guidelines,[8,9] in the setting of concomitant LVO, aortic valve area (AVA) was corroborated using planimetry by either transesophageal echocardiography or multidetector computed tomography (MDCT) showing an AVA $\leq$1.0 cm^2. The peak systolic intraventricular flow velocity was assessed through a simultaneous analysis of the color-Doppler and the pulsed-wave Doppler spectra in the apical 5-chamber view. Significant LVO was defined as a resting peak systolic gradient at any part of the LV cavity $\geq$30 mm Hg (using continuous-wave Doppler) with a late systolic peaking (dagger-shaped) appearance on spectral Doppler flow imaging.[7,10] To categorize the location of intraventricular accelerated flow, the LVOT was defined as the section of the LV between the aortic valve and the tip of the anterior mitral leaflet while the mid-LV was defined as the section below the tip of the anterior mitral leaflet and above the insertion point of the papillary muscle.[11] Concentric LV hypertrophy was defined as follows: (1) Symmetrical LV hypertrophy. (2) LV mass index >115 g/m^2 for men, or >95 g/m^2 for women[12]. (3) Relative wall thickness >0.42.[13] Asymmetrical septal hypertrophy (ASH) was considered when a disproportionate thickening of the IVS occurred and was defined as septal thickness >1.3 times the width of the posterior wall. A sigmoid septum variant was defined when the IVS had a typical "S" like contour.

The primary outcome was a composite of 1-year all-cause mortality and rehospitalization for heart failure (HHF). The secondary outcomes were each component of the primary outcome, 30-day all-cause mortality, new permanent pacemaker (PPM) implantation, need for the second THV, and progression of LV peak gradient (LVPG) after procedure. We defined TAVI endpoints and adverse events using the Valve Academic Research Consortium-2 criteria.[14]

Table 1
Baseline characteristics

Variable	Total population (N=1729)	Overall population			Matched population		
		LVO (N=31)	No LVO (N=1698)	p value	LVO (N=26)	No LVO (N=26)	p value
Age (years)	81.5±8.7	83.6±6.2	81.4±8.7	0.171	82.9±6.0	82.6±6.8	0.888
Women	712 (41%)	23 (74%)	689 (41%)	<0.001	19 (73%)	19 (73%)	1.000
Body surface area (m^2)	1.84±0.25	1.77±0.27	1.84±0.25	0.119	1.79±0.28	1.76±0.19	0.607
Body mass index (kg/m^2)	27.1±5.7	27.3±6.9	27.1±5.7	0.898	18.1±7.0	27.2±5.1	0.634
Diabetes mellitus	570 (33%)	9 (29%)	561 (33%)	0.638	8 (31%)	6 (23%)	0.774
Hypertension	1579 (91%)	29 (94%)	1550 (91%)	0.657	25 (96%)	25 (96%)	1.000
Chronic kidney disease ≥stage 3	1363 (79%)	22 (71%)	1341 (79%)	0.279	20 (77%)	19 (73%)	1.000
Atrial fibrillation	375 (22%)	4 (13%)	371 (22%)	0.278	4 (15%)	4 (15%)	1.000
Coronary artery disease	819 (47%)	7 (23%)	812 (48%)	0.005	6 (23%)	8 (31%)	0.754
Previous MI	199 (12%)	1 (3%)	198 (12%)	0.249	1 (4%)	3 (12%)	0.625
Previous PCI	385 (22%)	3 (10%)	382 (22%)	0.124	3 (12%)	2 (8%)	1.000
Previous CABG	336 (19%)	1 (3%)	335 (20%)	0.019	1 (4%)	3 (12%)	0.500
Peripheral artery disease	388 (22%)	5 (16%)	383 (23%)	0.395	5 (19%)	5 (19%)	1.000
Previous stroke or TIA	287 (17%)	5 (16%)	282 (17%)	0.943	4 (15%)	5 (19%)	1.000
COPD	359 (21%)	9 (29%)	350 (21%)	0.252	7 (27%)	10 (38%)	0.549
STS score	6.3±4.6	5.8±3.7	6.3±4.7	0.562	6.0±3.8	7.0±4.9	0.374
NYHA functional class III/IV	1622 (94%)	28 (90%)	1633 (96%)	0.120	23 (88%)	25 (96%)	0.500
Hemoglobin (g/dl)	12.2±1.8	12.5±1.8	12.2±1.8	0.406	12.4±1.9	11.6±1.7	0.242
BNP (pg/ml)	237.0 (109.0-540.0)	191.0 (113.0-428.5)	237.0 (107.0-551.2)	0.514	180.0 (110.0-447.0)	166.0 (69.0-439.0)	0.904
Medications							
Beta blocker	862 (50%)	11 (36%)	854 (50%)	0.102	11 (42%)	13 (50%)	0.791
Calcium blocker	110 (6%)	2 (6%)	110 (6%)	1.000	2 (8%)	5 (19%)	0.453
Diuretics	804 (46%)	13 (42%)	791 (46%)	0.607	11 (42%)	9 (35%)	0.754
ACEI or ARB	740 (43%)	11 (36%)	729 (43%)	0.406	8 (31%)	13 (50%)	0.267
Sacubitril/valsartan	24 (1%)	0 (0%)	24 (1%)	0.505	0 (0%)	0 (0%)	-
Aldosterone antagonist	110 (6%)	0 (0%)	110 (6%)	0.258	0 (0%)	0 (0%)	-
Antiplatelet	1122 (65%)	19 (61%)	1103 (65%)	0.672	17 (65%)	17 (65%)	1.000
Anticoagulant	368 (21%)	2 (6%)	366 (22%)	0.045	2 (8%)	6 (23%)	0.289
Statin	1149 (66%)	13 (42%)	1136 (67%)	0.004	13 (50%)	20 (77%)	0.118

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVO = left ventricular obstruction; MI = myocardial infarction; NYHA = New York heart association; PCI = percutaneous coronary intervention; STS = society of thoracic surgeon; TIA = transient ischemic attack.

Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range).

Table 2
Baseline echocardiographic and multidetector computed tomography characteristics

Variable	Total population (N=1729)	Overall population			Matched population		
		LVO (N=31)	No LVO (N=1698)	p value	LVO (N=26)	No LVO (N=26)	p value
		Echocardiographic findings					
LVEF (%)	56.8±15.2	70.3±7.5	56.5±15.2	<0.001	69.0±6.9	70.3±7.4	0.423
Peak LV gradient (mm Hg)	4.3±5.6	38.5±11.0	3.7±2.8	<0.001	36.8±8.5	5.2±4.0	<0.001
Peak aortic valve gradient (mm Hg)	70.9±22.8	95.0±29.1	70.5±22.5	<0.001	90.5±26.4	95.0±30.2	0.520
Mean aortic valve gradient (mm Hg)	43.4±14.0	52.1±15.3	43.2±13.9	0.001	50.5±15.9	56.5±17.2	0.156
AVA by continuity equation (cm^2)	0.66±0.18	0.73±0.24	0.66±0.18	0.148	0.74±0.25	0.66±0.16	0.131
IVSD (cm)	1.32±0.26	1.58±0.35	1.31±0.25	<0.001	1.63±0.36	1.38±0.28	0.009
LVEDD (cm)	4.5±0.8	3.6±0.7	4.5±0.8	<0.001	3.6±0.8	4.2±0.6	0.001
LVESD (cm)	3.1±0.9	2.1±0.5	3.1±0.9	<0.001	2.1±0.5	2.6±0.5	0.003
LV mass index (g/m^2)	113.1±35.5	108.8±42.0	113.2±35.4	0.503	119.9±41.7	109.5±23.6	0.277
LVEDV (ml)	94.1±39.9	62.3±35.8	94.8±39.7	<0.001	63.9±37.9	77.0±25.7	0.064
LVESV (ml)	42.5±33.8	17.9±13.7	43.0±33.9	<0.001	19.6±15.8	24.7±14.0	0.106
LA volume index (ml/m^2)	41.8±23.4	44.0±23.8	41.8±23.4	0.661	55.2±35.6	44.6±21.6	0.592
Moderate or severe mitral regurgitation	442 (26%)	2 (6%)	440 (26%)	0.011	2 (8%)	4 (15%)	0.687
Moderate or severe mitral stenosis	170 (10%)	12 (39%)	158 (9%)	<0.001	9 (35%)	9 (35%)	1.000
Moderate or severe aortic regurgitation	255 (15%)	4 (13%)	251 (15%)	0.770	3 (12%)	5 (19%)	0.727
Moderate or severe tricuspid regurgitation	338 (20%)	5 (16%)	333 (20%)	0.628	5 (19%)	5 (19%)	1.000
PA systolic pressure (mm Hg)	37.9±14.9	38.0±12.6	37.9±14.9	0.982	40.4±13.7	36.7±14.8	0.502
		Multidetector computed tomography findings					
Bicuspid aortic valve	125 (7%)	3 (10%)	122 (7%)	0.487	1 (4%)	1 (4%)	1.000
Aortic annular area (mm^2)	469.6±95.3	400.2±75.1	470.9±95.2	<0.001	397.1±80.9	429.0±71.8	0.059
Aortic annular perimeter (mm)	77.7±7.8	71.9±6.8	77.8±7.8	<0.001	71.6±7.3	74.5±6.1	0.041
Mean sinus of Valsalva diameter (mm)	32.4±3.7	30.1±3.9	32.4±3.7	0.002	30.1±4.2	31.2±2.9	0.119
LVOT area (mm^2)	461.8±114.2	350.2±70.8	464.3±113.9	<0.001	373.1±73.6	396.6±71.6	0.260
Total leaflet calcium (ml)	159.6 (72.0-311.9)	204.7 (144.6-433.0)	158.6 (71.2-310.6)	0.059	204.4 (141.2-343.7)	148.8 (105.5-277.0)	0.372
MAC	388 (22%)	12 (39%)	376 (22%)	0.028	10 (38%)	15 (58%)	0.302
LVOT calcium	530 (31%)	14 (45%)	516 (30%)	0.077	12 (46%)	10 (38%)	0.774

Values are expressed as number (percentage), mean ± standard deviation.

Abbreviation: AVA = aortic valve area; IVSD = interventricular septal diameter; LA = left atrium; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVO = left ventricular obstruction; LVOT = left ventricular outflow tract; MAC = mitral annular calcification; PA = pulmonary artery.

Continuous variables were tested for distribution normality with the Shapiro−Wilk test and expressed as mean ± standard deviation or median and interquartile range (IQR). They were compared using the two-sided Student's t-test or Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as number (percentage) and compared using the Pearson Chi-square or Fisher exact test, as appropriate. The effect of concomitant LVO on the primary outcome was assessed using Cox proportional hazard model, adjusted for clinically relevant variables with p-value <0.10 by univariable analysis. In addition, given the difference in baseline characteristics, propensity score adjustment was performed. The propensity score was generated using a logistic regression model and constructed based on the following baseline characteristics: age, sex, body mass index, diabetes mellitus, chronic kidney disease ≥stage 3, peripheral artery disease, chronic obstructive pulmonary disease, coronary artery disease, prior percutaneous coronary intervention, coronary artery bypass grafting, acute myocardial infarction, stroke or transient ischemic attack, society of thoracic surgeon score, atrial fibrillation, LV ejection fraction (LVEF), peak aortic valve gradient, concomitant at-least moderate mitral regurgitation (MR) or mitral stenosis (MS), nontransfemoral approach, and early generation THV. Pairs of patients were derived using nearest-neighbor 1:1 matching with a caliper width of 0.20 of the standard deviation of the logit of the propensity score. The Kaplan-Meier method was used to analyze the main outcomes, which were compared using the log-rank test. In the LVO group, the median of LVPG at each interval post-TAVI was compared to the baseline using the Wilcoxon signed-rank test. All analyses were considered statistically significant at a two-tailed p-value <0.05. The SPSS statistical package, version 24.0, was used to perform all statistical evaluations (SSPS Inc. Chicago, IL).

Results

We identified 1756 consecutive patients with severe AS who underwent TAVI during the study period. We excluded patients with prior left-sided mechanical or bioprosthetic heart valve replacement (N = 20), and 7 patients who did not have pre-TAVI TTE within 6 months before TAVI. The remaining 1729 patients constituted our study population. Baseline clinical, echocardiographic, MDCT, and periprocedural characteristics of the overall and matched populations are provided in Tables 1, 2, and 3, respectively. In the overall population, LVO was detected in 31 (1.8%) patients. This group was more likely to be female, had a lower prevalence of coronary artery disease and previous coronary artery bypass grafting, and was less likely to take statin or anticoagulants. Compared to patients without LVO, patients with LVO had significantly higher baseline LVEF by echocardiography (70.3 ± 7.5 vs 56.5±15.2 %; p < 0.001) as well as higher mean aortic valve gradients (52.1 ± 15.3 vs 43.2 ± 13.9 mm Hg; p = 0.001), thicker IVS, greater prevalence of moderate to severe MS but had smaller LV both by linear LV dimension and LV volume. By MDCT, patients in the LVO group had smaller aortic annulus, sinus of Valsalva, and LVOT areas. Notably, patients with concomitant

Table 3
Periprocedural characteristics

Variable	Total population (N=1729)	Overall population			Matched population		
		LVO (N=31)	No LVO (N=1698)	p value	LVO (N=26)	No LVO (N=26)	p value
Transcatheter heart valve type							
Balloon-expandable valve	1469 (85%)	22 (71%)	1447 (85%)	0.028	18 (69%)	21 (81%)	0.581
-Sapien	94 (5%)	0 (0%)	94 (6%)	0.178	0 (0%)	2 (8%)	-
-Sapien XT	362 (21%)	5 (16%)	357 (21%)	0.507	4 (15%)	5 (19%)	1.000
-Sapien 3	1013 (59%)	17 (55%)	996 (59%)	0.669	14 (54%)	14 (54%)	1.000
Self-expandable valve	260 (15%)	9 (29%)	251 (15%)	0.028	8 (31%)	5 (19%)	0.581
-CoreValve	104 (6%)	2 (6%)	102 (6%)	0.710	2 (8%)	1 (4%)	1.000
-Evolut R	136 (8%)	4 (13%)	132 (8%)	0.300	3 (12%)	3 (12%)	1.000
-Evolut pro	20 (1%)	3 (10%)	17 (1%)	0.005	3 (12%)	1 (4%)	0.625
Transcatheter heart valve size*							
-Small	513 (30%)	18 (58%)	495 (29%)	<0.001	15 (58%)	15 (58%)	1.000
-Medium	753 (44%)	10 (32%)	743 (44%)	0.201	8 (31%)	8 (31%)	1.000
-Large	463 (27%)	3 (10%)	460 (27%)	0.038	3 (12%)	3 (12%)	1.000
Procedural techniques							
Transfemoral approach	1606 (93%)	29 (94%)	1577 (93%)	0.885	24 (92%)	24 (92%)	1.000
Predilatation	448 (26%)	9 (29%)	439 (26%)	0.689	8 (31%)	11 (42%)	0.607
Postdilatation	166 (10%)	5 (16%)	161 (10%)	0.213	5 (19%)	4 (15%)	1.000
Planned or bailout alcohol septal ablation	1 (0.1%)	0 (0%)	1 (0.1%)	1.000	0 (0%)	1 (4%)	-
Contrast volume (ml)	79.4±42.3	81.8±44.1	79.3±42.3	0.747	83.4±47.0	87.0±36.6	0.767
Fluoroscopic time (minutes)	14.6±9.1	14.0±6.5	14.6±9.1	0.745	14.5±6.9	16.2±9.5	0.515

LVO = left ventricular obstruction.

Values are expressed as number (percentage), mean ± standard deviation.

* Small = 20, 23 mm for Sapien/Sapien XT/Sapien 3 and ≤26 mm for CoreValve/Evolut R/Evolut Pro; medium = 26 mm for Sapien/Sapien XT/Sapien 3 and 29 mm for CoreValve/Evolut R/Evolut Pro; large = 29 mm for Sapien/Sapien XT/Sapien 3, 31 mm for CoreValve, and 34 mm for Evolut R/Evolut Pro.

LVO were more likely to be implanted with a smaller THV and treated using a self-expandable valve compared with those who had severe AS alone. A bailout alcohol septal ablation was performed during the TAVI procedure in one patient without pre-procedural LVO because of hemodynamic instability exacerbated by acute LVOT obstruction after THV deployment. In the LVO group, Mid-LV was the most common anatomical location for LVO (77%), while the accelerated flow was observed at the LVOT in the rest of patients (23%). Systolic anterior motion of the anterior mitral valve leaflet was detected in 10 (32%) patients. In addition, the most common LV hypertrophy phenotype was concentric LV hypertrophy and sigmoid shaped IVS (58% and 52%, respectively), while ASH was found in 26% (Supplementary Table S1). After propensity score matching, 26 patients with LVO and 26 patients without LVO constituted the matched population (N = 52). As shown in Tables 1 and 3, baseline clinical and periprocedural characteristics were well balanced between the matched groups. Baseline echocardiographic and MDCT characteristics were also similar between both matched groups except for a higher peak LV gradient (36.8 ± 8.5 vs 5.2 ± 4.0 mm Hg;

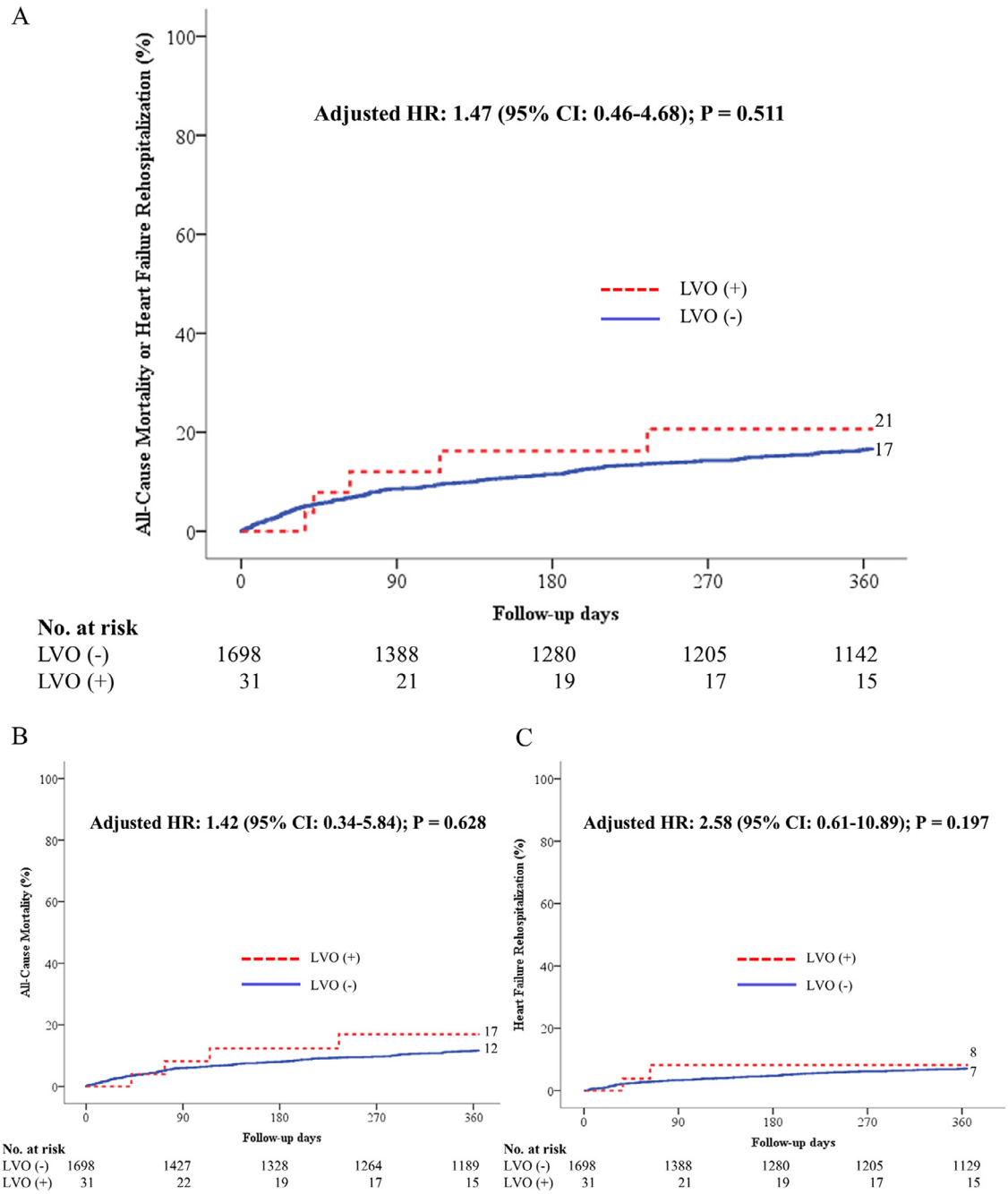

Figure 1. Kaplan-Meier estimates of the primary outcome in the overall population at 1-year follow-up. (*A*) The composite outcome of all-cause mortality and HHF. (*B*) All-cause mortality. (*C*) HHF. CI = confidence interval; HHF = rehospitalization for heart failure; LVO = left ventricular obstruction.

$p < 0.001$) and IVS diameter (1.63 ± 0.36 vs 1.38 ± 0.28 cm; $p = 0.009$) in the LVO group, as well as a smaller LV end-diastolic diameter (LVEDD; 3.6 ± 0.8 vs 4.2 ± 0.6 cm; $p = 0.001$), LV end-systolic diameter (LVESD; 2.1 ± 0.5 vs 2.6 ± 0.5 cm; $p = 0.003$), and aortic annular perimeter (71.6 ± 7.3 vs 74.5 ± 6.1 mm; $p = 0.041$) in the LVO group (Table 2).

In the overall population, during the median follow-up period of 633 days (IQR: 236 to 991 days), 409 patients died (5 in the LVO group and 404 in the severe AS alone group). One hundred and ninety-one patients were readmitted to the hospital with heart failure (3 in the LVO group and 188 in the severe AS alone group). After adjusting for potential confounding factors (Supplementary Table S2), the primary composite outcome of all-cause mortality and HHF at 1-year was not significantly different between patients with LVO and those without LVO (21% vs 17%, respectively; adjusted hazard ratio: 1.47; 95% confidence interval: 0.46 to 4.68; $p = 0.511$; Figure 1A). For each component of the primary outcome, all-cause mortality and

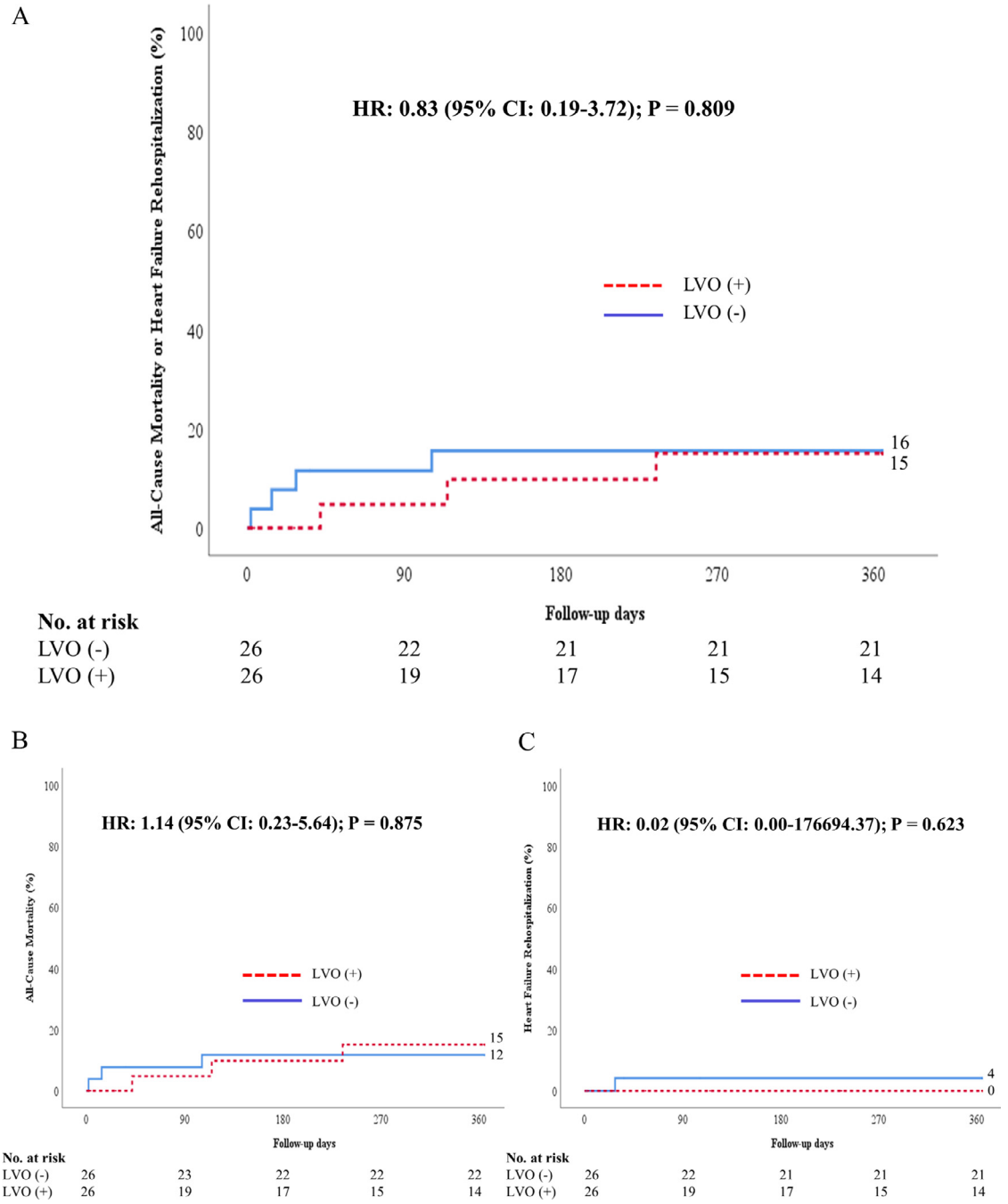

Figure 2. Kaplan-Meier estimates of the primary outcome in the matched population at 1-year follow-up. (*A*) The composite outcome of all-cause mortality and HHF. (*B*) All-cause mortality. (*C*) HHF. CI = confidence interval; HHF = rehospitalization for heart failure; LVO = left ventricular obstruction.

HHF at 1-year were not significantly different in the LVO group compared to the severe AS alone group (17% vs 12%; p = 0.628, and 8% vs 7%; p = 0.197, respectively; Figure 1B and 1C). As shown in Figure 2A, 2B, and 2C, in the matched population, the primary composite outcome of all-cause mortality and HHF at 1-year, as well as each component of the primary outcome, was comparable with those in the overall population. Data regarding the primary outcome and its components in overall and matched populations are summarized in Table 4.

In the secondary outcomes, there was no significant difference between patients with LVO and those without LVO in terms of 30-day all-cause mortality, new permanent pacemaker, and need for the second THV. However, the median LVPG at 1-day, 30-day, and 1-year postprocedure was significantly higher in the LVO group in both overall and matched populations (Supplementary Table S3). In order to evaluate the progression of post-TAVI LVPG in the LVO group, we analyzed TTE data from 16 (51.6%) patients for whom TTE results were available at all time intervals of 1-day, 30-day, and 1-year post-procedure. The median LVPG at baseline was 33.0 mm Hg (IQR: 31.2 to 47.2 mm Hg). At 30-day follow-up, the median LVPG was significantly reduced from baseline to 18.7 mm Hg (IQR: 7.9 to 29.1 mm Hg; p = 0.011). At 1-year follow-up, the median LVPG slightly increased from that at 30-day to 21.0 mm Hg (IQR: 9.5 to 38.9 mm Hg) but was not significantly different from baseline (p = 0.098). The median and individual LVPG at each time point are illustrated in Figure 3.

Table 4
Primary outcome at 1-year

Outcomes	Overall population						Matched population			
	LVO (N=31)	No LVO (N=1698)	HR (95% CI)	p value	Adjusted* HR (95% CI)	P-value	LVO (N=26)	No LVO (N=26)	HR (95% CI)	p value
All-cause mortality or HHF	5 (21%)	253 (17%)	1.27 (0.52-3.08)	0.595	1.47 (0.46-4.68)	0.511	3 (15%)	4 (16%)	0.83 (0.19-3.72)	0.809
All-cause mortality	4 (17%)	177 (12%)	1.47 (0.54-3.95)	0.450	1.42 (0.34-5.84)	0.628	3 (15%)	3 (12%)	1.14 (0.23-5.64)	0.875
HHF	2 (8%)	102 (7%)	1.26 (0.31-5.11)	0.745	2.58 (0.61-10.89)	0.197	0 (0%)	1 (4%)	0.02 (0.00-176694.37)	0.623

CI = confidence interval; HHF = rehospitalization for heart failure; HR = hazard ratio; LVO = left ventricular obstruction.
Values are expressed as number (percentage).
* Adjusted for body mass index, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, chronic kidney disease ≥stage 3, atrial fibrillation, STS score, LVEF, mean aortic valve pressure gradient, concomitant with moderate or severe mitral regurgitation, leaflet calcium, nontransfemoral access, early generation valve, paravalvular leakage ≥mild degree postprocedure, and preprocedural statin usage.

Discussion

We conducted a retrospective observational study to evaluate the prevalence, clinical characteristics, and outcomes in patients with severe AS and concomitant LVO undergoing TAVI. To the best of our knowledge, this is the largest study looking at LVO in this population. The main findings of the present study were as follow: (1) The prevalence of LVO in patients with severe AS who underwent TAVI was low (1.8%). (2) The most common phenotypes of LV hypertrophy causing LVO were concentric LV hypertrophy and sigmoid shaped IVS (58% and 52%, respectively), which were more common than ASH (26%). (3) The mid-LV portion was the most common location for the development of intracavitary pressure gradients (77%). (4) Pre-TAVI LVO did not significantly increase all-cause mortality or HHF at 1-year (Figure 4).

The prevalence of LVO in our cohort was 1.8%, which is lower than previously reported.[2] This can be explained by temporal trends favoring SAVR with septal myectomy over TAVI in the early years of data collection. In addition, in the previous study, the smaller body surface area and LVEDD may have contributed to the higher prevalence of LVO observed in their study cohort. Compared to patients without LVO, the LVO group had higher rates of female as well as smaller LV cavity, higher LVEF, and higher rates of MS. These characteristics may predispose LVO as they are associated with small LV volume and increased contractility. Compared with the typical hypertrophy and obstruction patterns associated with hypertrophic obstructive

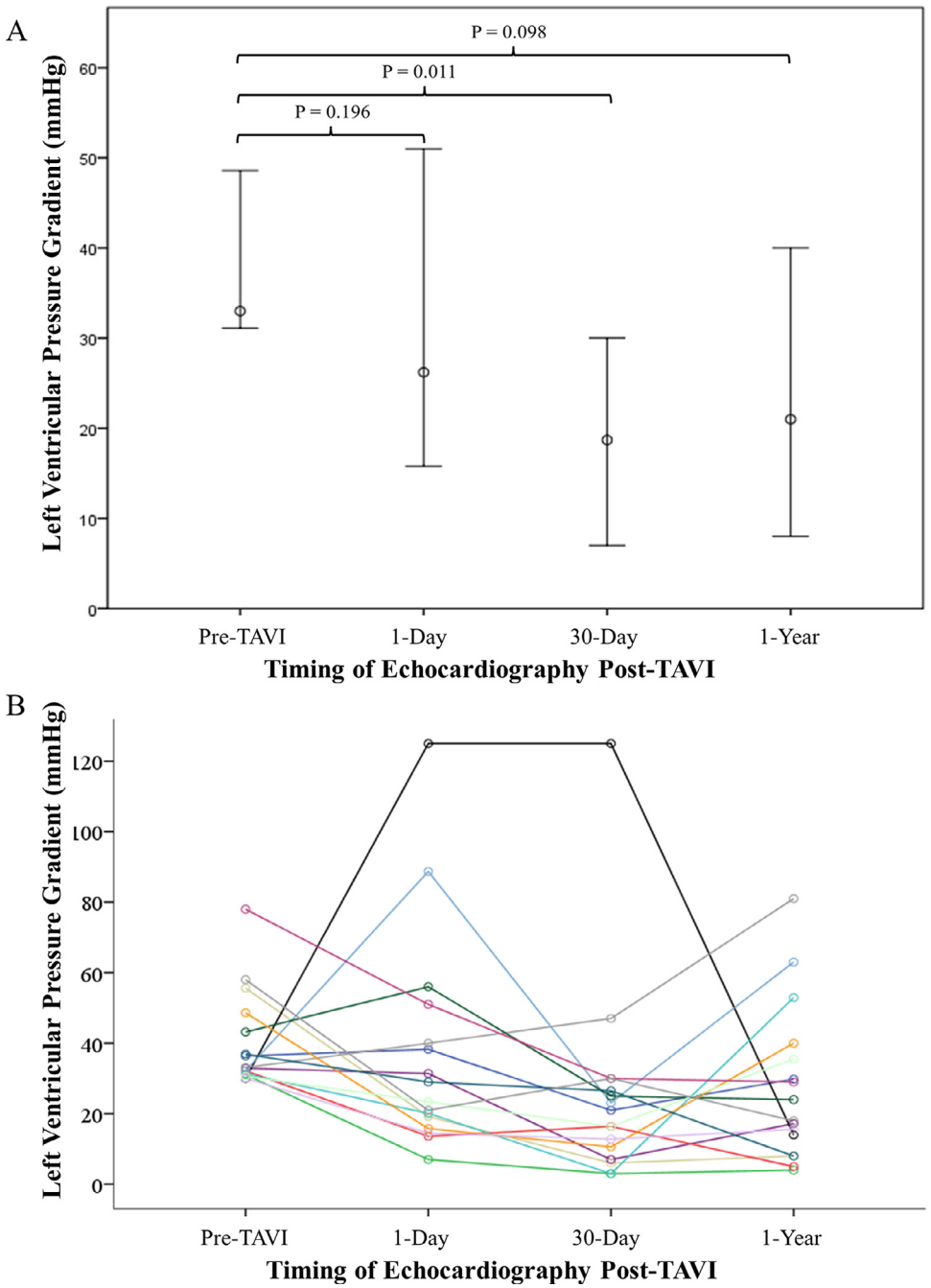

Figure 3. Changes in left ventricular pressure gradient from baseline to 1-year follow-up in patients with left ventricular obstruction. (*A*) Median and 95% confidence interval of left ventricular pressure gradient at baseline (pre-TAVI), 1-day, 30-day, and 1-year follow-up. (*B*) Individual left ventricular pressure gradient at baseline (pre-TAVI), 1-day, 30-day, and 1-year follow-up. TAVI = transcatheter aortic valve implantation.

cardiomyopathy, the LVO occurred in our AS cohort most commonly originated from the mid-LV portion rather than the LVOT. The phenotypes of LV hypertrophy causing obstruction were more likely to be concentric LV hypertrophy and sigmoid shaped IVS than ASH. Furthermore, Systolic anterior motion was detected in only 32% of these patients. This is likely explained by multifactorial underlying etiologies that trigger LV hypertrophy.

Long-standing and progressive AS leads to LV hypertrophy in response to chronic pressure overload. Underlying infiltrative or hypertrophic cardiomyopathies, especially transthyretin cardiac amyloidosis which was found in 16% of patients undergoing TAVI[15] and the genetic hypertrophic cardiomyopathies (found in 1:500 of the general population),[16] can also occur simultaneously with severe AS and result in concentric LV hypertrophy. In addition, aging and uncontrolled systemic hypertension, which are common in this population, possibly aggravate this process and lead to a significant increase in LV wall thickness as well as papillary muscle hypertrophy.[17,18] This may explain why the

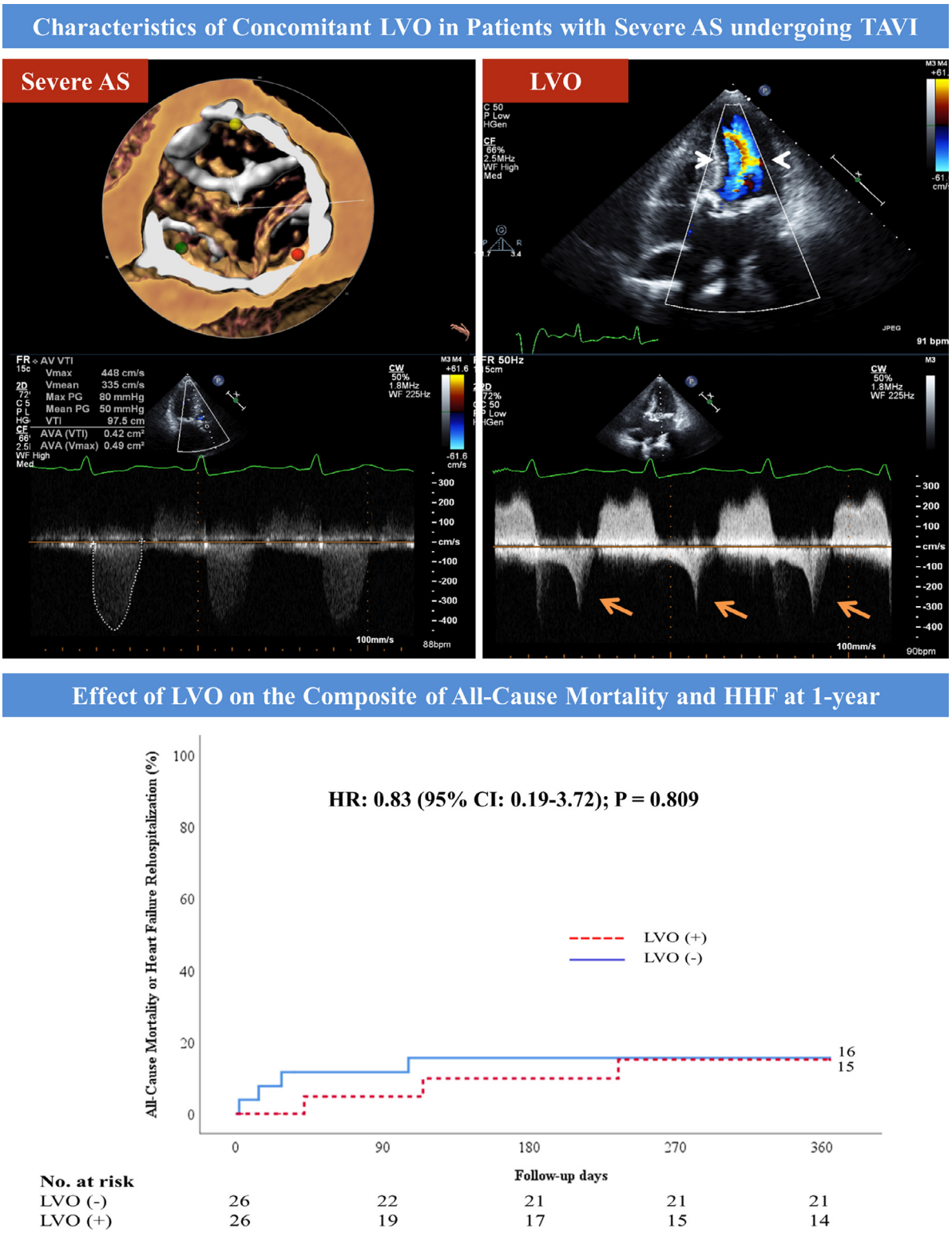

Figure 4. Left ventricular obstruction in patients with severe AS undergoing TAVI. The *top panel* illustrates the typical features of LVO, including mid-left ventricular location (arrowheads) and dagger-shaped appearance (arrows) of the left ventricular systolic gradient in the spectral Doppler flow tracing. The *bottom panel* shows the composite outcome of all-cause mortality and HHF at 1-year for the matched population according to the appearance of pre-TAVI LVO. AS = aortic stenosis; HHF = rehospitalization for heart failure; LVO = left ventricular obstruction; TAVI = transcatheter aortic valve implantation.

location of obstruction occurred more frequently at the mid-LV region. In addition, age-related anatomical changes in the sigmoid shaped IVS, leads to bulging of the basal ventricular septum into the LV cavity, which can also facilitate midventricular obstruction in these patients.[19]

The composite outcome of all-cause mortality and HHF at 1-year was not significantly different between patients with or without LVO after adjusting confounders by using multivariable analysis and propensity score matching methods. One possible explanation is that the TAVI procedure, which may acutely increase LVO from the sudden afterload reduction, overtime induces reverse remodeling, regression of hypertrophy, and subsequent relief of LVO.[20] The gradual decrease in LVPG observed during follow-up supports this hypothesis. However, the ways myocardial responses after aortic valve replacement vary in each patient and depend on the changes of LV myocardium (hypertrophy, remodeling, and fibrosis) in response to AS afterload prior to intervention.[21]

For patients with severe AS and concomitant LVO resulting from IVS hypertrophy, SAVR combined with septal myectomy is conventionally considered standard treatment. Lim et al. reported that concomitant septal myectomy was performed in 11.6% of patients with severe AS who underwent SAVR. This group was predominantly female, had lower body surface area, and smaller LV size, which was similar to the characteristics of the LVO group in our study. No difference in short and mid-term mortality was observed between SAVR with or without septal myectomy; however, a higher rate of small prosthetic valve implantation was detected in the concomitant septal myectomy group.[3] As patient-prosthesis mismatch typically occurs with a small surgical valve and is associated with worse outcomes,[22] TAVI would be a reasonable option in this setting because of the superior hemodynamic profile compared to SAVR[23] and the comparable outcomes to those without LVO.

Our study has several limitations. First, this was a retrospective observational study in a single center. Confounding factors that we did not expect may not have been accounted for in our analyses. However, we attempted to include all known potential risk factors into the multivariable model as well as performed a propensity score matching to mitigate the effect of these confounders. Second, there was a possibility that technical limitations of continuous-wave Doppler and suboptimal alignment of the Doppler curser may have underdiagnosed or underestimated the frequency and severity of LVO. Third, LVO and severe AS interfere with each other when trying to ascertain the diagnoses. However, we attempted to reduce this error by setting clear criteria. We used the dagger-shaped appearance in the spectral Doppler flow tracing to differentiate LVO flow from severe AS flow. Furthermore, we added the AVA calculated by planimetry from either transesophageal echocardiography or MDCT to confirm the severity of AS in cases with concomitant LVO in which the continuity equation method for AVA might be inaccurate. Fourth, as only 51.6% of patients with LVO had follow-up TTE at all-time intervals, the LVPG response post-TAVI should be interpreted with caution. Finally, only one patient in our study required a periprocedural alcohol septal ablation. Thus, we did not have enough data to address the effectiveness of this procedure during TAVI in this population.

In conclusion, despite high rates of LV hypertrophy among patients with severe AS undergoing TAVI, LVO is a relatively uncommon finding and is more likely to develop at the midventricular region than at the LVOT. In a propensity-matched cohort, the presence of pre-TAVI LVO was not associated with worse 1-year outcomes.

Disclosures

Dr. Makkar has received grant support from Edwards Lifesciences Corporation; is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. Dr. Chakravarty is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic; he is a consultant for Abbott Lifesciences, and he is a consultant and speaker for Boston Scientific. Other authors have no conflicts of interest to disclose.

Author Contribution

Danon Kaewkes: Conceptualization, Methodology, Formal analysis, Investigation, Writing -Original Draft. Tomoki Ochiai: Conceptualization, Methodology, Writing - Review & Editing. Nir Flint: Conceptualization, Writing - Review & Editing. Vivek Patel: Investigation, Writing - Review & Editing. Sahar Mahani: Investigation, Writing - Review & Editing. Matthias Raschpichler: Writing - Review & Editing. Sung-Han Yoon: Conceptualization, Writing - Review & Editing. Sabah Skaf: Writing - Review & Editing. Siddharth Singh: Writing - Review & Editing. Tarun Chakravarty: Writing - Review & Editing. Mamoo Nakamura: Writing - Review & Editing. Wen Cheng: Writing - Review & Editing. Raj Makkar: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.051.

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