Comparison of Benefit of Transcatheter Aortic Valve Implantation in Patients With Low Gradient Versus High Gradient Aortic Stenosis and Left Ventricular Dysfunction

Mostafa R Amer, MD[a], Wassim Mosleh, MD[a], Sarfaraz Memon, MD[b], Saurabh Joshi, MD[b], Bethany Sullivan[a], Musa Sharkawi, MD[b], Jeffrey F Mather, MS[b], Francis J Kiernan, MD[b], Sean McMahon, MD[b], W. Lane Duvall, MD[b], and Raymond G McKay, MD[b,*]

Patients with low gradient severe aortic stenosis (LG-AS) often exhibit significant limitations in functional status and quality of life. We aimed to evaluate the clinical effect of transcatheter aortic valve implantation (TAVI) on LG-AS patients compared to those with high transvalvular gradients and similar left ventricular dysfunction. Retrospective analysis of records for all patients with a left ventricular ejection fraction <50% who underwent TAVI at our institution was performed. Patients were grouped according to their transvalvular gradient. Data were collected from The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Clinical benefit endpoints included improvements in left ventricular ejection fraction and changes in the Kansas City Cardiomyopathy Questionnaire. Additional outcomes analyzed included 1-year all-cause mortality, stroke rates, rates of rehospitalization, need for a permanent pacemaker, and hospital length of stay. Two hundred three patients met our inclusion criteria. one hundred one LG-AS patients (mean transvalvular gradient <40 mm Hg) were compared to 102 patients with high transvalvular gradients (mean transvalvular gradient >40 mm Hg). LG-AS patients yielded similar improvements in left ventricular ejection fraction (43.5% ± 63.7 vs 37.7% ± 58.7; p = 0.525) and Kansas City Cardiomyopathy Questionnaire scores (423.51% ± 1257.02 vs 266.56% ± 822.81; p = 0.352). There were no differences between the groups with respect to 1-year mortality (16.8% vs 12.7%; p = 0.412), stroke rates, hospital length of stay, need for permanent pacemaker implantation or hospital readmissions. In conclusion, we found that TAVI is associated with comparable improvement in clinical and echocardiographic outcomes in LG-AS patients as compared to those with high gradient severe aortic stenosis. **(Am J Cardiol 2020;125:1543−1549)**

The role of transcatheter aortic valve implantation (TAVI) as a treatment for severe symptomatic aortic stenosis (AS) has been well established over recent years. With the increase in operator experience and the emergence of novel devices, the potential benefit of TAVI in certain infrequently observed AS phenotypes has been an ongoing discussion. In symptomatic patients with severe AS, 5% to 10% may exhibit low gradient AS (LG-AS).[1−3] Representing conceivably one of the highest risk subsets, patients with LG-AS continue to be a challenging population, owing to the poor outcomes observed with medical management and a high perioperative mortality rate with surgical aortic valve replacement (SAVR).[4−9] Moreover, due to a particularly high rate of comorbidities, LG-AS patients usually have significant impairment in functional status and quality of life. As such, TAVI may represent an attractive therapeutic option for this high-risk patient group, given its less-invasive nature. While the clinical benefit of TAVI in severe AS has been clearly recognized,[10,11] there is a paucity of data regarding its role in patients with LG-AS. We thus hypothesized that TAVI would be associated with comparable clinical benefit in patients with LG-AS as compared to those with high gradient severe AS and similar LV dysfunction (HG-AS).

Methods

This is a single-center retrospective, observational study. The study was approved by our local institutional review board and considered exempt with a waiver of the requirement to obtain informed consent. All patients who underwent TAVI at Hartford Hospital between February 2012 and September 2018 were considered. Patients with left ventricular ejection fraction (LVEF) >50%, low surgical risk patients, and patients with incomplete records were excluded. Patients with LVEF <50% were grouped according to their transvalvular gradient as determined by resting echocardiography. The HG-AS group was defined by a mean transvalvular gradient >40 mm Hg and an AV area

[a]Division of Cardiology, University of Connecticut, Farmington, Connecticut; and [b]Heart and Vascular Institute, Hartford Hospital, Hartford, Connecticut. Manuscript received December 31, 2019; revised manuscript received and accepted February 10, 2020.

*Corresponding author: Tel: 860-972-2975; Fax: 860.545.3558.

E-mail address: raymond.mckay@hhchealth.org (R.G. McKay).

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≤1.0 cm^2. The LG-AS group was defined by a mean transvalvular gradient of <40 mm Hg and an AV area ≤1.0 cm^2. Clinical, demographic, and procedural variables were collected from the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapy Registry as reported by our site.

TAVI eligibility, access site selection, anesthesia type, and type of prosthesis delivered were made by our multidisciplinary heart team. Determination of AS severity was made by integrating clinical factors with findings from transthoracic echocardiogram, dobutamine stress echocardiogram, AV calcium scores, transesophageal echocardiogram, and invasive hemodynamics. A positive AV calcium score was defined as >1200 Agatston units in women or >2000 Agatston units in men, whereas a positive dobutamine stress echocardiogram was defined as AVA ≤1 cm^2 (with AV area indexed to body surface area ≤0.6 cm^2/m^2) with transvalvular mean gradient ≥40 mm Hg (or Vmax ≥4 m/s).[12] All patients underwent preprocedure catheterization, echocardiography, and computed tomography with angiography to assess TAVI suitability. Baseline risk assessment based upon society of thoracic surgeons (STS) score and functional assessment including frailty, severe systemic disease, porcelain aorta, and inimical mediastinum was determined for all patients. All cases were performed in a hybrid operating room under conscious sedation or general anesthesia. Standard techniques for valve implantation were utilized as previously described.[13–16]

Clinical benefit endpoints evaluated LVEF recovery as well as changes in functional status and quality of life utilizing the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30-days. Other key outcome measures included all-cause mortality at 1-year, rate of rehospitalization, stroke rate, need for a permanent pacemaker, and hospital length of stay. All variables were defined in accordance with the Valve Academic Research Consortium definitions.[17]

Continuous variables are expressed as mean ± standard deviation or median (interquartile range) and were tested for normality with the Shapiro-Wilk test. Categorical data were expressed as numbers and percentages. Data were compared between groups using a Student's *t* test or the Mann-Whitney U test for continuous data. A paired *t* test was used for within-group comparisons. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Event rates were generated using the Kaplan-Meier method and log-rank tests were used for group comparisons. All effects were considered significant at $p < 0.05$. The statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, Illinois).

Results

A total of 818 patients underwent TAVI at our institution between February 2012 and September 2018, of which 615 met the exclusion criteria, leaving 203 patients for further analysis. Of the included patients, 101 met the criteria for LG-AS. The remaining 102 patients presented with HG-AS.

Baseline clinical data and procedural outcomes are outlined in Tables 1 and 2, respectively. There were no significant differences between the groups with respect to age, chronic comorbidities, STS risk score, or NYHA class. Patients in the LG-AS group had a significantly higher body mass index compared to HG-AS patients ($p = 0.036$). Regarding baseline echocardiographic data, patients in the LG-AS group had a larger AV area ($p < 0.001$). AV peak velocity was lower in the LG-AS group ($p < 0.001$) as were AV peak gradient based on cardiac catheterization ($p < 0.001$) and AV mean gradient based on echocardiogram ($p < 0.001$). Baseline LVEF was lower in the LG-AS group ($p = 0.025$). Intraoperatively, a transfemoral approach was predominantly used for valve delivery and implantation in both groups and a balloon-expandable, Edwards Sapien 3 valve was used in the majority of procedures. New generation valves (Edwards Sapien 3, Medtronic Evolut R/Pro) were more commonly used in the LG-AS group compared to the HG-AS group. Device implantation was successful in all patients. There were no differences between the groups with regard to the type of anesthesia delivered or the amount of contrast used. However, fluoroscopy time was shorter in the LG-AS group ($p = 0.024$).

Clinical outcomes are summarized in Table 3. The LG-AS and HG-AS groups had no significant difference in changes in LVEF ($p = 0.525$) and KCCQ scores ($p = 0.352$) after TAVI. The within-group interval differences in LVEF and KCCQ from baseline to 1-month was statistically significant in both the LG-AS and HG-AS groups (Figure 1). There were no differences between the groups with regard to all-cause mortality at 1-year (LG-AS, 16.8% vs HG-AS, 12.7%; $p = 0.412$). Stroke rates were not significantly different between the groups. One patient in the LG-AS group had a stroke at 30-days whereas 1 stroke and 1 transient ischemic attack occurred in the HG-AS group. Similarly, there were no differences in overall hospital length of stay, need for permanent pacemaker implantation or rates of hospital readmissions between the groups.

A sensitivity analysis was performed excluding 18 patients with normal-flow low gradient aortic stenosis (stroke volume index ≥35 ml/m^2) (NFLG-AS). Sensitivity analysis demonstrated similar results in clinical outcomes. LVEF improvement in LG-AS and HG-AS (46.7% ± 68.2 vs 37.7% ± 58.7; $p = 0.362$), KCCQ scores (309.81% ± 800.72) vs 199.65% ± 572.26; $p = 0.342$) respectively, remained nonsignificant. The within-group interval differences in LVEF ($p < 0.001$), and KCCQ ($p < 0.001$), from baseline to 1-month were statistically significant in both the LG-AS and HG-AS groups. There were no differences between the groups with regard to all-cause mortality at 1-year (LG-AS, 19.3% vs HG-AS, 12.7%; $p = 0.224$).

Discussion

The main findings of our single-center, retrospective study of patients with reduced LVEF are as follows: first, TAVI was associated with a significant improvement in LVEF, functional status and quality of life in the LG-AS patient population. This therapeutic benefit was comparable to that derived by patients with HG-AS and a reduced LVEF. Second, we observed a relatively low 1-year mortality rate post-TAVI in LG-AS patients. Mortality rates were not significantly different when compared to patients with

Table 1
Baseline clinical and echocardiographic data

Variable	HG-AS (n = 102)	LG-AS (n = 101)	p Value
Age (years)	81.99 ± 7.85	80.03 ± 8.11	0.082
Women	32 (31%)	26 (26%)	0.375
Body Mass Index (kg/m^2)	26.06 ± 5.42	27.82 ± 6.38	0.036
White	100 (98%)	95 (94%)	0.145
Hypertension	91 (89%)	93 (92%)	0.484
Diabetes mellitus	34 (33%)	41 (41%)	0.284
Smoker (current or within 1 year)	10 (10%)	10 (10%)	0.981
Previous Myocardial Infarction	39 (38%)	45 (45%)	0.361
Previous Percutaneous Coronary Intervention	27 (26%)	34 (34%)	0.264
Previous Coronary Bypass	24 (24%)	32 (32%)	0.194
Atrial Fibrillation/Flutter			0.886
Paroxysmal	55 (54%)	51 (50%)	
Persistent	20 (20%)	21 (21%)	
Peripheral Arterial Disease	28 (27%)	33 (33%)	0.417
Previous Stroke	12 (12%)	12 (12%)	0.979
Previous Transient Ischemic Attack	2 (2%)	6 (6%)	0.145
End Stage Renal Disease	3 (3%)	4 (4%)	0.691
Society of Thoracic Surgeons Score (%)	12.93 ± 8.88	15.24 ± 9.95	0.087
High Risk	38 (38%)	46 (46%)	
Inoperable/Extreme Risk	50 (50%)	44 (44%)	
Kansas City Cardiomyopathy Questionnaire	45.65 ± 24.26	41.83 ± 25.15	0.300
Previous Aortic Balloon Valvuloplasty	8 (8%)	9 (9%)	0.784
Creatinine (mg/dl)	1.48 ± 1.63	1.51 ± 1.13	0.893
Hemoglobin (g/dl)	11.54 ± 1.64	11.59 ± 2.91	0.878
International Normalized Ratio	1.11 ± 0.16	1.17 ± 0.32	0.090
Albumin (g/dl)	3.60 ± 0.49	3.64 ± 0.47	0.541
Forced Expiratory Volume 1 (% predicted)	65.86 ± 20.79	63.54 ± 21.62	0.452
Diffusing Capacity for Carbon Monoxide (% predicted)	76.25 ± 18.84	65.44 ± 19.43	0.790
Left Ventricular Ejection Fraction (%) #	34.7 ± 9.4	31.5 ± 10.8	0.025
Aortic Valve Mean Gradient (mm Hg)	49.81 ± 9.81	26.70 ± 6.79	<0.001
Aortic Valve Annulus Size (mm)	25.44 ± 2.46	25.54 ± 3.20	0.812
Mitral Regurgitation	#N/A	#N/A	0.455
None	0	2 (3%)	
Trace/trivial	5 (9%)	4 (6%)	
Mild	25 (45%)	26 (41%)	
Moderate	23 (42%)	26 (41%)	
Severe	2 (4%)	6 (9%)	
Aortic Regurgitation	#N/A	#N/A	0.410
None	17 (17%)	20 (20%)	
Trace/trivial	15 (15%)	14 (14%)	
Mild	45 (45%)	51 (51%)	
Moderate	22 (22%)	15 (15%)	
Severe	2 (2%)	0	
Aortic Valve Peak Velocity (m/s)	4.46 ± 0.42	3.33 ± 0.41	0.000
Left Ventricular Internal Systolic Dimension (cm)	4.10 ± 0.69	4.37 ± 0.83	0.012
Left Ventricular Internal Diastolic Dimension (cm)	5.06 ± 0.66	5.24 ± 0.71	0.076
Septal Wall Thickness (cm)	1.18 ± 0.21	1.14 ± 0.28	0.225
Posterior Wall Thickness (cm)	1.14 ± 0.20	1.08 ± 0.21	0.029
Number of Narrowed Coronary Arteries	#N/A916	#N/A	0.388
None	26 (25%)	25 (26%)	
1	16 (16%)	16 (16%)	
2	21 (21%)	29 (30%)	
3	39 (38%)	28 (29%)	
Left Main ≥ 50%	11 (11%)	8 (8%)	0.484
Proximal Left Anterior Descending ≥70%	26 (25%)	26 (26%)	0.967
Right Ventricular systolic Pressure (mm Hg)	47.53 ± 14.3	51.64 ± 15.4	0.065
Aortic Valve Peak Gradient (mm Hg)	81.59 ± 17.1	44.86 ± 11.5	0.000
Heart Failure Prior 2 Weeks	76 (75%)	74 (73%)	0.840
New York Heart Association Class (Within 2 weeks)	#N/A	#N/A	0.941
I	6 (6%)	6 (6%)	
II	15 (15%)	18 (18%)	
III	41 (40%)	40 (40%)	
IV	40 (39%)	37 (37%)	

Values are number (%), mean ± SD, unless otherwise indicated.

Table 2
Procedural outcomes

Variable	HG-AS (n = 102)	LG-AS (n = 101)	p-Value
Procedure duration (minutes, median and interquartile range)	92 (73.5 − 116.5)	93 (69.0 − 117.5)	0.715
Anesthesia Type			0.595
General Anesthesia	49 (48%)	47 (47%)	
Conscious Sedation	53 (52%)	53 (52%)	
Device Type			<0.001
Edwards Sapien	7 (7%)	5 (5%)	
Edwards Sapien XT	7 (7%)	3 (3%)	
Edwards Sapien 3	56 (55%)	63 (62%)	
Medtronic Corevalve	17 (17%)	1 (1%)	
Medtronic Evolut R	9 (9%)	26 (26%)	
Medtronic Evolut Pro	6 (6%)	3 (3%)	
Vascular Access			0.694
Femoral	88 (86%)	83 (82%)	
Subclavian	7 (7%)	11 (11%)	
Direct Aortic	2 (2%)	1 (1%)	
Transapical	3 (3%)	2 (2%)	
Transcarotid	2 (2%)	4 (4%)	
Bleed/Vascular Compromise*	13 (13%)	11 (11%)	0.682
Conversion to Surgical Aortic Valve Replacement	0	0	-
Annular Rupture	0	0	-
Contrast volume (ml)	100.55 ± 55.08	100.63 ± 50.96	0.991
Fluoroscopy time (minutes)	26.48 ± 10.08	23.61 ± 7.74	0.024
Fluoroscopy Dose Area Product (mGy.cm2)	51,924 ± 112,714	51,689 ± 60,307	0.986
Fluoroscopy Dose Kerma (mGy)	1,923 ± 1,772	1,403 ± 1,298	0.020

Values are number (%) or mean ± SD, unless otherwise indicated.
* Bleed/Vascular: The composite outcome of bleed/vascular adverse events as defined by the STS/ACC TVT Registry's Adverse Event Definitions v2.0.

Table 3
Clinical and echocardiographic outcomes

Variable	HG-AS (n = 102)	LG-AS (n = 101)	p Value
30 Day Outcomes			
Stroke/Transient Ischemic Attack	2 (1%)	1 (1%)	0.567
Need for Pacemaker	11 (11%)	9 (9%)	0.671
Left Ventricular Ejection Fraction Improvement, (% change)	37.7 ± 58.7	43.5 ± 63.7	0.525
Kansas City Cardiomyopathy Questionnaire Improvement, (% change)	266.56% ± 822.81	423.51% ± 1257.02	0.352
Length of Stay (days, median and interquartile range)	6.5 (4.0 − 12.3)	8.0 (3.5 − 14.0)	0.739
Intensive Care Unit (hours, median and interquartile range)	25.0 (0 − 49.0)	23.7 (0 − 49.1)	0.535
Discharge Home	66 (65.3%)	64 (62.7%)	0.699
One-Year Outcomes			
Mortality	12.7%	16.8%	0.412
Hospital Readmission	23.5%	23.8%	0.970
Echocardiographic Outcomes			
Left Ventricular Ejection Fraction (%)#N/A			
Pre-procedure	34.7 ± 9.4	31.5 ± 10.8	0.025
30-day	44.5 ± 12.9	41.2 ± 13.5	0.097
Aortic Valve Mean Gradient (mm Hg)			
Pre-Procedure	49.81 ± 9.81	26.70 ± 6.79	<0.001
Post-Procedure	7.72 ± 10.52	6.15 ± 14.30	0.569
30-day	9.53 ± 3.72	8.67 ± 3.91	0.135
Post-Procedure Aortic Regurgitation			0.021
None	30 (30%)	38 (38%)	
Trace/Trivial	24 (24%)	36 (36%)	
Mild	39 (39%)	23 (23%)	
Moderate	8 (8%)	3 (8%)	
Severe	0	0	
30-day Aortic Regurgitation			0.073
None	31 (36%)	43 (47%)	
Trace/Trivial	14 (16%)	21 (23%)	
Mild	33 (38%)	23 (25%)	
Moderate	9 (10%)	4 (4%)	
Severe	0	0	

Values are number (%) or mean ± SD, unless otherwise indicated.

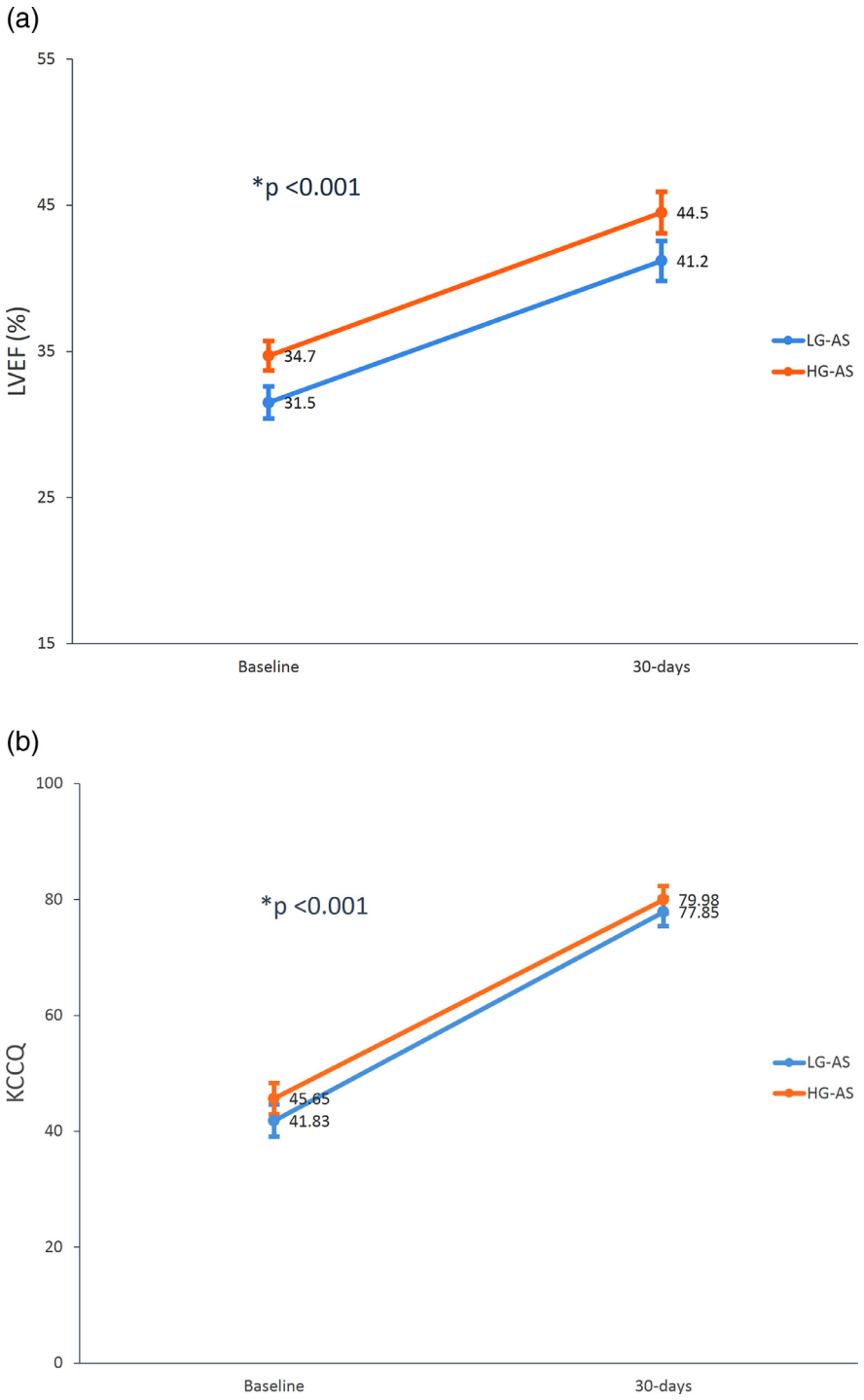

Figure 1. (a) Within-group interval differences in left ventricular ejection fraction at 30-days. *Changes within the group over time. (b) Within-group interval differences in KCCQ score at 30-days. *Changes within the group over time.

HG-AS. Furthermore, rehospitalization rates after TAVI were similar between the 2 patient populations analyzed. Third, we found through sensitivity analysis that a stroke volume index ≥35 ml/m^2 did not impact the aforementioned outcomes. Overall, our findings suggest that TAVI yields favorable outcomes in LG-AS patients, comparable to those observed in patients with HG-AS and left ventricular dysfunction.

Among the main findings of our study are the significant improvements in KCCQ scores that were derived by LG-AS patients after TAVI. This benefit was similar to that observed in the HG-AS group, possibly suggesting that a low AV gradient may not primarily prohibit the potential clinical improvement that may be achieved by performing TAVI in this patient population. Congruently, Baron et al reported substantial improvement in health status outcomes

at 30 days after TAVI in patients with low LVEF and AV mean gradients.[18] The authors found no significant differences in the magnitude of health status improvement with stratifying the groups according to AV gradient. Our findings are also consistent with those documented by Lauten et al in their study of 149 LG-AS patients from the German Transcatheter Aortic Valve Interventions Registry.[19]

In accordance with multiple prior studies, the present study shows that significant improvements in LVEF can be achieved with TAVI in LG-AS patients. Importantly, TAVI has previously been found to result in faster improvements in LVEF when compared to SAVR,[5,20] which is noteworthy in LG-AS patients with prohibitive surgical risk. However, conflicting findings have been reported in prior literature with regard to improvements in LVEF. For example, O'Sullivan et al reported smaller improvements in LVEF after TAVI in LG-AS patients compared to their HG-AS counterparts.[21] The authors postulated that the smaller rates of improvement in the LG-AS group may be attributed to the lack of contractile reserve. Complementing that study, Ben-Dor et al reported similar findings, stating that a high AV gradient is independently associated with improvements in LVEF after TAVI.[20] In contrast, 2 separate studies by Ribeiro et al and Maes et al found no association between pre-TAVI AV gradient or presence of contractile reserve and a smaller increase in LVEF over time.[22,23] The results of our study contribute to this ongoing discussion as we report a similar rate of LVEF improvement amongst patients with both high and low AV gradients and impaired left ventricular function, thus suggesting that patients with low AV gradients should not be excluded from consideration for TAVI given the potential clinical benefit.

Despite the unfavorable baseline risk profile, our study documents a fairly low, 16.8% all-cause mortality rate at 1-year in the LG-AS group. Our observed mortality rate was lower than that reported for LG-AS in prior reports[19,24–26] which may be related to improvements in procedural technique over time. For example, our patients received predominantly newer generation valve types, in contrast to some of the prior studies[19,24,26] that included mostly older generation valves. Hence, it is encouraging to observe a trend towards improved survival over time in this complex patient group. Additionally, inherent heterogeneity in baseline characteristics observed in prior studies, which may drive access site selection in some cases, can potentially impact TAVI outcomes with respect to mortality.[27] Our study included patients with comparable baseline as well as procedural characteristics which may explain the similar 1-year mortality rate that we observed between the groups. This particular finding underscores the continued need for careful patient selection and meticulous planning through a multidisciplinary approach.

The sensitivity analysis performed excluding NFLG-AS patients was important as prior literature recommended that those patients be examined as a separate entity.[28] Some of the patients in this subgroup may, in fact, have high gradient AS that was uncaptured due to technical reasons (under or overestimation of stroke volume and AV gradient because of nonparallel Doppler acquisition angles, Doppler envelope contamination, small LV cavities, or beat-beat variability during arrhythmia). Thus, including NFLG-AS patients in the LG-AS group can contaminate it and exaggerate the benefit of TAVI in LG-AS patients.

While TAVI may represent an attractive alternative to SAVR in LG-AS patients, offering several potential advantages due to its less-invasive approach, important limitations must be considered. TAVI has been associated with higher rates of vascular complications, permanent pacemaker implantation, and paravalvular regurgitation. The effects of these factors, especially paravalvular regurgitation, may be more detrimental in patients with LG-AS and low LVEF compared to HG-AS patients. Therefore, further studies are warranted to examine its long-term consequences compared to SAVR in this specific cohort.

The findings in this report should be interpreted with caution in light of the single-center, retrospective, and observational nature of the study. While our cohorts were well-matched, we cannot discount the influence of residual bias inherent in observational studies. The use of third-generation valves more commonly in the LG-AS patients compared to the HG-AS patients may have exaggerated the observed improvement in outcomes for the LG-AS group. Therefore, our conclusions may not extend to cases where older generation valves are used in LG-AS patients. The absence of a negative control arm (i.e., medical management alone in classical LG-AS patients) effectively limits our ability to definitively attribute the observed clinical benefit exclusively to the TAVI procedure. Nonetheless, the comparison to a positive control group of HG-AS patients where TAVI has been established to be superior to medical management provides valuable conclusions on the equivalent feasibility, safety, and efficacy of TAVI in LG-AS patients. As a single-center, observational study with a relatively small sample size where the level of expertise of the TAVI team can affect results, further studies in multiple centers are recommended.

In summary, we found that TAVI is associated with improved clinical and echocardiographic outcomes in the LG-AS population. LG-AS patients had equivalent 1-year mortality, and improvements in LVEF and KCCQ scores compared to HG-AS patients.

Author Contribution

Mostafa R Amer: Conceptualization, Methodology, Investigation, Writing-Original Draft Preparation. Wassim Mosleh: Conceptualization, Methodology, Writing-Reviewing and Editing. Sarfaraz Memon: Investigation Saurabh Joshi: Methodology, Investigation. Bethany Sullivan: Investigation. Musa Sharkawi: Writing-Reviewing and Editing. Jeffrey F Mather: Data Curation, Validation. Francis J Kiernan: Writing-Reviewing and Editing. Sean McMahon: Conceptualization, Writing-Reviewing and Editing. W. Lane Duvall: Conceptualization, Writing-Reviewing and Editing. Raymond G McKay: Supervision, Conceptualization, Methodology, Writing-Reviewing and Editing.

1. Kulik A, Burwash IG, Kapila V, Mesana TG, Ruel M. Long-term outcomes after valve replacement for low-gradient aortic stenosis: impact of prosthesis-patient mismatch. *Circulation* 2006;114:553–558.
2. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and

severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000;101:1940–1946.
3. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol* 2012;60:1845–1853.
4. Clavel M-A, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J* 2016;37:2645–2657.
5. Clavel MA, Webb JG, Rodés-Cabau J, Masson JB, Dumont E, Larochellière R De, Doyle D, Bergeron S, Baumgartner H, Burwash IG, Dumesnil JG, Mundigler G, Moss R, Kempny A, Bagur R, Bergler-Klein J, Gurvitch R, Mathieu P, Pibarot P. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. *Circulation* 2010;122:1928–1936.
6. Clavel M-A, Fuchs C, Burwash IG, Mundigler G, Dumesnil JG, Baumgartner H, Bergler-Klein J, Beanlands RS, Mathieu P, Magne J, Pibarot P. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS Study. *Circulation* 2008;118:S234–S242.
7. Monin J-L, Quéré J-P, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Guéret P. Low-gradient aortic stenosis. *Circulation* 2003;108:319–324.
8. Monin J-L, Monchi M, Kirsch MEW, Petit-Eisenmann H, Baleynaud S, Chauvel C, Metz D, Adams C, Quere J-P, Gueret P, Tribouilloy C. Low-gradient aortic stenosis: impact of prosthesis-patient mismatch on survival. *Eur Heart J* 2007;28:2620–2626.
9. Tribouilloy C, Lévy F, Rusinaru D, Guéret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Quéré J-P, Monin J-L. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol* 2009;53:1865–1873.
10. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
11. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–1705.
12. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57–e185.
13. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007;116:755–763.
14. Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the Corevalve self-expanding valve prosthesis in high-risk patients with aortic valve disease. *Circulation* 2006;114:1616–1624.
15. Binder RK, Rodés-Cabau J, Wood DA, Mok M, Leipsic J, De Larochellière R, Toggweiler S, Dumont E, Freeman M, Willson AB, Webb JG. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. *JACC Cardiovasc Interv* 2013;6:293–300.
16. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, George I, Deeb GM, Chetcuti S, Kipperman R, Brown J, Qiao H, Slater J, Williams MR. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery. *JACC Cardiovasc Interv* 2017;10:268–275.
17. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM van, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A van, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–1454.
18. Baron SJ, Arnold SV, Herrmann HC, Holmes DR, Szeto WY, Allen KB, Chhatriwalla AK, Vemulapali S, O'Brien S, Dai D, Cohen DJ. Impact of ejection fraction and aortic valve gradient on outcomes of transcatheter aortic valve replacement. *J Am Coll Cardiol* 2016;67:2349–2358.
19. Lauten A, Figulla HR, Möllmann H, Holzhey D, Kötting J, Beckmann A, Veit C, Cremer J, Kuck K-H, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Böhm M, Heusch G, Meinertz T, Neumann T, Welz A, Mohr FW, Hamm CW, GARY Executive Board. TAVI for low-flow, low-gradient severe aortic stenosis with preserved or reduced ejection fraction: a subgroup analysis from the German aortic valve registry (GARY). *EuroIntervention* 2014;10:850–859.
20. Ben-Dor I, Maluenda G, Iyasu GD, Laynez-Carnicero A, Hauville C, Torguson R, Okubagzi P, Xue Z, Goldstein SA, Lindsay J, Satler LF, Pichard AD, Waksman R. Comparison of outcome of higher versus lower transvalvular gradients in patients with severe aortic stenosis and low. *Am J Cardiol* 2012;109:1031–1037.
21. O'Sullivan CJ, Stortecky S, Heg D, Pilgrim T, Hosek N, Buellesfeld L, Khattab AA, Nietlispach F, Moschovitis A, Zanchin T, Meier B, Windecker S, Wenaweser P. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013;34:3437–3450.
22. Ribeiro HB, Lerakis S, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, Windecker S, Enriquez-Sarano M, Cheema AN, Nombela-Franco L, Amat-Santos I, Muñoz-García AJ, Garcia del Blanco B, Zajarias A, Lisko JC, Hayek S, Babaliaros V, Ven F Le, Gleason TG, Chakravarty T, Szeto WY, Clavel M-A, Agustin A de, Serra V, Schindler JT, Dahou A, Puri R, Pelletier-Beaumont E, Côté M, Pibarot P, Rodés-Cabau J. Transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis. *J Am Coll Cardiol* 2018;71:1297–1308.
23. Maes F, Lerakis S, Barbosa Ribeiro H, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, Windecker S, Enriquez-Sarano M, Cheema AN, Nombela-Franco L, Amat-Santos I, Muñoz-García AJ, Garcia del Blanco B, Zajarias A, Lisko JC, Hayek S, Babaliaros V, Ven F Le, Gleason TG, Chakravarty T, Szeto W, Clavel M-A, Agustin A de, Serra V, Schindler JT, Dahou A, Salah-Annabi M, Pelletier-Beaumont E, Côté M, Puri R, Pibarot P, Rodés-Cabau J. Outcomes from transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis and left ventricular ejection fraction less than 30%. *JAMA Cardiol* 2019;4:64.
24. O'Sullivan CJ, Stortecky S, Heg D, Pilgrim T, Hosek N, Buellesfeld L, Khattab AA, Nietlispach F, Moschovitis A, Zanchin T, Meier B, Windecker S, Wenaweser P. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013;34:3437–3450.
25. Fischer-Rasokat U, Renker M, Liebetrau C, Linden A van, Arsalan M, Weferling M, Rolf A, Doss M, Möllmann H, Walther T, Hamm CW, Kim W-K. 1-year survival after TAVR of patients with low-flow, low-gradient and high-gradient aortic valve stenosis in matched study populations. *JACC Cardiovasc Interv* 2019;12:752–763.
26. Elhmidi Y, Piazza N, Krane M, Deutsch M-A, Mazzitelli D, Lange R, Bleiziffer S. Clinical presentation and outcomes after transcatheter aortic valve implantation in patients with low flow/low gradient severe aortic stenosis. *Catheter Cardiovasc Interv* 2014;84:283–290.
27. Chandrasekhar J, Hibbert B, Ruel M, Lam B-K, Labinaz M, Glover C. Transfemoral vs non-transfemoral access for transcatheter aortic valve implantation: a systematic review and meta-analysis. *Can J Cardiol* 2015;31:1427–1438.
28. Clavel M-A, Guzzetti E, Annabi M-S, Salaun E, Ong G, Pibarot P. Normal-flow low-gradient severe aortic stenosis: myth or reality? *Struct Hear* 2018;2:1–8.