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Transcatheter Aortic Valve Implantation in Patients With Low-Flow, Low-Gradient Aortic Stenosis

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Objectives The purpose of this study was to evaluate the efficacy and outcome of transcatheter aortic valve implantation (TAVI) in patients with low-flow, low-gradient aortic stenosis (LG-AS).

Background Patients with LG-AS have a poor prognosis with medical treatment and a high risk for surgical aortic valve replacement.

Methods Between January 2009 and June 2010, a total of 1,302 patients underwent TAVI for severe AS and were prospectively included in the multicenter German TAVI registry.

Results LG-AS was present in 149 patients (11.4%; mean age: 80.2 ± 6.3 years). In this subgroup, the EuroSCORE was significantly higher (26.8 ± 16.6 vs. 20.0 ± 13.3; $p < 0.0001$) compared with patients with high-gradient AS (HG-AS). The procedural success rate (LG-AS: 95.3% vs. HG-AS: 97.5%; $p = 0.13$) and the rate of TAVI-associated complications were comparable in both groups (new pacemaker: 27.0% vs. 28.1%; $p = 0.76$; cerebrovascular events: 3.4% vs. 3.1%, $p = 0.83$). However, post-operative low-output syndrome occurred more frequently in the LG-AS-group (LG-AS: 14.9% vs. HG-AS: 5.7%, $p < 0.0001$), and mortality at 30 days and 1 year was significantly higher in this subgroup (LG-AS: 12.8% and 36.9% vs. HG-AS: 7.4% and 18.1%; $p < 0.001$ and $p < 0.0001$, respectively). Post-operative New York Heart Association functional class improved, and self-assessed quality of life increased significantly, demonstrating a substantial benefit in the LG-AS group at 30 days and 1 year after TAVI.

Conclusions In high-risk patients with LG-AS, TAVI is associated with a significantly higher mortality at 30 days and at 1 year. However, long-term survivors benefit from TAVI with functional improvement and a significantly increased quality of life. Therefore, in view of the poor prognosis with medical treatment, TAVI should be considered an option in high-risk patients with LG-AS. (J Am Coll Cardiol Intv 2012;5:552–9) © 2012 by the American College of Cardiology Foundation

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Transcatheter aortic valve implantation (TAVI) has been introduced as a less invasive treatment for severe aortic stenosis (AS) (1). Since its introduction, the technology has been rapidly adopted. With increasing operator experience and the development of novel devices, results have improved significantly. Recently, randomized controlled trials have demonstrated favorable outcome after TAVI in nonsurgical and high-risk surgical patients compared with standard treatment (2,3). However, despite these advances, current experience regarding safety and efficacy of TAVI in subsets of patients with additional risk factors is still limited.

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Patients with severe aortic stenosis (AS), but a moderate transvalvular gradient (valve area <1 cm^2, mean gradient <40 mm Hg) and reduced left ventricular (LV) function (ejection fraction $<40\%$), constitute such a high-risk subset (low-flow, low-gradient AS [LG-AS]) for surgical aortic valve replacement (AVR) (4). When treated medically, this subgroup has a dismal prognosis, with poor long-term survival (5–7). Although TAVI could offer a viable treatment option for these patients, the feasibility and outcome of the procedure have not been studied in this subgroup of patients with aortic valve disease. Patients with LG-AS present with a particularly unfavorable combination of risk factors, and it is questionable whether they benefit from the procedure. Therefore, the purpose of this study was to evaluate the feasibility and outcome of TAVI in this subgroup based on data from a prospective multicenter German Transcatheter Aortic Valve Interventions Registry (8,9).

Methods

Study design and collection of data. The German Transcatheter Aortic Valve Interventions Registry is a prospective multicenter registry designed to monitor the current use of TAVI and the procedural characteristics, the efficacy, and the outcome of patients undergoing TAVI (8,9). The registry was initiated by the scientific interest of the participating institutions and receives no funding from industrial companies but is financed by the Institut für Herzinfarktforschung (IHF) in Ludwigshafen. A total of 27 tertiary cardiovascular centers contributed data to the registry. Data were collected at each site using standardized case report forms to record demographic and clinical characteristics as well as procedural and follow-up data. Follow-up was obtained at 30 days and at 1 year based on the medical records and on physician and patient interviews. The investigators had full access to the data and control of the analysis.

Inclusion criteria and treatment. The registry design and inclusion criteria have been reported previously (8,10). In brief, all patients with severe AS undergoing TAVI were eligible for inclusion. The diagnosis of severe AS and the indication for TAVI were based upon the established criteria: aortic valve area ≤ 1 cm^2 (with or without aortic valve regurgitation), a transvalvular gradient >40 mm Hg, and either age ≥ 80 years and a logistic EuroSCORE $\geq 20\%$ or a logistic EuroSCORE $\leq 20\%$ if 1 of the following was present: porcelain aorta, cirrhosis of the liver of pulmonary insufficiency (forced expiratory volume at 1 s ≤ 1 l). Severe low-gradient aortic stenosis was defined according to current guideline criteria if the aortic valve area was <1 cm^2 in the presence of a mean transvalvular gradient <40 mm Hg and a reduced LV ejection fraction $<40\%$ (4). Preinterventional patient screening included transthoracic and transesophageal echocardiography as well as dobutamine stress echocardiography (DSE) for exclusion of pseudostenosis and determination of severity if LG-AS was suspected. The baseline operative risk was estimated by the logistic EuroSCORE, and the choice of treatment was made at the discretion of the treating physician, surgeon, and/or the heart team.

Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
DSE = dobutamine stress echocardiography
EQ-5D-VAS = EuroQol-5D visual analogue scale
HG-AS = high-gradient aortic stenosis
LG-AS = low-flow, low-gradient aortic stenosis
LV = left ventricular
NYHA = New York Heart Association
TAVI = transcatheter aortic valve implantation

Device. At the time of patient enrollment, 2 devices for TAVI procedures were commercially available in Germany: the balloon-expandable Edwards SAPIEN (23 mm and 26 mm; recently, the Edwards SAPIEN XT composed of a cobalt-chromium stent; Edwards Lifesciences, Irvine, California) and the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota), a porcine pericardial tissue valve in a self-expanding nitinol stent frame. The 29-mm Edwards SAPIEN XT was not available during the time covered by the registry. The implantation procedures of both devices have been reported previously (11,12). For implantation of the balloon-expandable device, the Ascendra delivery catheter was used for transapical access, and the Retroflex, or recently the Novaflex, delivery catheter for transfemoral access.

Endpoints. Major clinical endpoints were analyzed according to the criteria proposed by the Valve Academic Research Consortium (VARC) (13). The primary endpoint of the study was all-cause mortality at 30 days and 1 year. Mortality at both time points was further subdivided into cardiovascular and noncardiovascular mortality. According to VARC definitions, all unknown deaths were considered as cardiovascular in origin.

The secondary endpoint evaluated procedural characteristics (procedural success, device type and access route, device function) as well as the rate of adverse events

(myocardial infarction, stroke, acute kidney injury, bleeding and vascular complications, permanent pacemaker requirement, and post-operative low cardiac output syndrome [a state of decreased cardiac output due to severely depressed LV function leading to secondary multiple organ failure]). After device implantation, the degree of aortic regurgitation was classified angiographicly into 4 grades based upon the method of Sellers et al. (14). Clinical benefit endpoints evaluated New York Heart Association (NYHA) functional class and quality of life using the EuroQol-5D visual analogue scale (EQ-5D-VAS). Clinical benefit was assessed within the first 30 days (NYHA functional class, EQ-5D-VAS) and at 1 year (EQ-5D-VAS) after TAVI.

Statistics. Continuous data are presented as mean ± SD, and categorical variables are depicted as percentages and numbers. Categorical variables were compared by means of the chi-square test, and continuous variables using the 2-tailed Wilcoxon rank sum test. Two-sided p values <0.05 were considered statistically significant. Mortality at 30 days was calculated by the Kaplan-Meier survival analysis method. The vital status of patients already discharged or transferred to a rehabilitation program was verified by follow-up calls performed by the IHF. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test.

Univariate Cox proportional hazards regression analysis was performed among established predictors of 30-day mortality. In addition, ejection fraction was dichotomized to above and below 30%. All covariates with a p value of <0.1 were included in the multivariate Cox regression model. Backward stepwise elimination was subsequently performed to identify independent predictors for 30-day mortality. A covariate was removed from the model if the p value exceeded 0.10. All p values <0.05 were considered statistically significant. In multivariate models, adjustments were made for the potential confounders of age, sex, diabetes, chronic obstructive pulmonary disease, 3-vessel coronary artery disease, pulmonary hypertension, peripheral vascular disease, previous cardiac procedures, previous cardiac decompensations <12 months, previous myocardial infarctions, EuroSCORE >20%, LV ejection fraction ≤30%, and LG-AS. All statistical analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient population. Between January 2009 and June 2010, a total of 1,302 TAVI procedures were performed in 27 participating hospitals. The mean number of patients included per hospital was 49 (range: 1 to 268). In the overall group, 149 patients were diagnosed with LG-AS according to current guideline criteria (4). The remaining 1,153 patients presented with severe AS and a high transvalvular gradient >40 mm Hg.

Patient demographics and baseline characteristics are listed in Table 1. Compared with patients with high-gradient AS (HG-AS), those in the LG-AS group were significantly younger (80.9 ± 6.3 years vs. 81.9 ± 6.2 years; $p < 0.001$) and presented with a higher number of comorbidities. This is reflected by a significantly higher logistic EuroSCORE in the LG-AS group compared with patients with HG-AS (26.8 ± 16.6 vs. 20.0 ± 13.2; $p < 0.0001$). Patients in both groups were severely symptomatic at the time of the procedure. There was a significantly higher number of patients with NYHA functional class IV in the LG-AS group (LG-AS: 28.2% vs. HG-AS: 16.0%, $p < 0.001$).

Interventional characteristics. Preoperative hemodynamics and characteristics of the TAVI procedure are presented in Tables 2 and 3. Prior to device implantation, the aortic valve area was severely reduced in both groups (LG-AS: 0.69 ± 0.18 cm^2 vs. HG-AS: 0.67 ± 0.37 cm^2; $p < 0.01$). Ejection

Table 1. Baseline Characteristics

	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
Age, yrs	80.2 ± 12.2	81.9 ± 6.2	<0.01
Male	85 (57)	459 (39.8)	<0.001
Body mass index, kg/m^2	27.0 ± 9.7	26.9 ± 10.1	0.4
Logistic EuroSCORE, %	26.8 ± 16.6	20.0 ± 13.7	<0.0001
Previous medical history			
Chronic obstructive pulmonary disease	39 (26.2)	289 (25.1)	0.77
Peripheral vascular disease	36 (30.9)	237 (20.6)	<0.01
Pulmonary hypertension	120 (81.1)	738 (64.7)	<0.0001
Systolic pulmonary pressure, mm Hg	47.3 ± 15.2	44.8 ± 33.9	<0.01
CAD	119 (89.9)	670 (58.3)	<0.0001
1-vessel CAD	27 (18.1)	254 (22.1)	0.27
2-vessel CAD	26 (17.4)	153 (13.3)	0.17
3-vessel CAD	66 (44.3)	263 (22.9)	<0.0001
Previous PCI	75 (50.3)	385 (33.5)	<0.0001
Previous myocardial infarction	38 (25.7)	168 (14.6)	<0.001
Previous cardiac surgery	41 (27.5)	243 (21.1)	0.07
CABG	38 (25.5)	198 (17.18)	0.08
Valve	1 (0.67)	46 (3.99)	<0.01
Diabetes mellitus	62 (41.6)	391 (34)	0.07
Mitral regurgitation ≥II°	71 (48.0)	373 (32.6)	<0.01
Chronic renal failure*	96 (64.6)	699 (60.6)	0.37
Stroke or TIA, intracranial hemorrhage	15 (10.1)	88 (7.6)	0.3
Permanent pacemaker/ defibrillator	31 (20.8)	158 (13.8)	<0.05

Values are mean ± SD or n (%). *Chronic renal failure: glomerular filtration rate <60 ml/min/1.73 m^2.

AS = aortic stenosis; CABG= coronary artery bypass grafting; CAD = coronary artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2. Pre-Operative Hemodynamics

Hemodynamics	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
Ejection fraction	37.8 ± 14.4	54.5 ± 13.7	<0.0001
Aortic valve area, cm^2	0.69 ± 0.18	0.67 ± 0.37	<0.01
Mean pressure gradient (echo), mm Hg	31.3 ± 13.3	49.9 ± 16.52	<0.0001
Peak-to-peak gradient (invasive), mm Hg	37.2 ± 20.4 (n = 121)	65.7 ± 32.35 (n = 829)	<0.0001
Minor calcification*	12 (8.1)	54 (4.7)	0.08
Moderate calcification*	52 (34.9)	337 (29.5)	0.18
Severe calcification*	85 (57.0)	752 (65.8)	<0.05

Values are mean ± SD or n (%). *Grading according to Rosenhek et al. (24).
AS = aortic stenosis.

fraction and mean transvalvular gradient were significantly lower in the LG-AS group compared with the HG-AS group (37.8 ± 14.5% and 31.3 ± 13.3 mm Hg vs. 54.5 ± 13.7% and 49. 9± 16.5 mm Hg; both $p < 0.0001$). In both groups, the majority of interventions were performed as elective procedures. The rate of urgent TAVI procedures was significantly higher (LG-AS: 24.8% vs. HG-AS: 14.5; $p < 0.01$) in patients with LG-AS. Regarding the preferred device or access route, no differences in LG-AS patients were observed compared with HG-AS patients. The Medtronic CoreValve was used in the majority of procedures (LG-AS: 85.9% vs. HG-AS: 79.9%; $p = 0.08$), whereas the Edwards SAPIEN device was used less frequently (LG-AS: 14.1% vs. HG-AS: 19.8%; $p = 0.1$). Thus, the majority of procedures were performed transfemorally in both groups (LG-AS: 87.0% vs. HG-AS 86.4%; $p = 0.6$). A transapical access was preferred in 8.1% (LG-AS) and 9.6% (HG-AS), respectively. Other access routes (transaxillary, transaortic) were used in the remaining 4.0% of patients in both groups.

Rates of death and predictors of early mortality after TAVI. Thirty-day mortality after TAVI was significantly higher in patients with LG-AS compared with HG-AS (12.8% vs. 7.4%, $p < 0.001$) (Fig. 1A). At the 1-year follow-up, the rate of death from any cause was 36.9% in the LG-AS group as compared with 18.1% in the HG-AS group ($p < 0.0001$) (Fig. 1B). The rate of death from cardiovascular causes at 1 year was also significantly higher in the LG-AS group than in the HG-AS group (LG-AS: 34.2% vs. HG-AS 16.6%; $p < 0.0001$) (Table 4).

Cox proportional hazards models were used to assess the value of LG-AS and covariates for the prediction of early mortality after TAVI (Table 5). All covariates potentially associated with death after TAVI were included in a multivariate Cox model. Hazard ratios and their 95% confidence intervals are reported from the proportional hazards models. After adjustment for confounding variables, predictive factors for mortality after TAVI were the presence of a LG-AS, a logistic EuroSCORE >20, previous myocardial infarction, and decompensated heart failure within the preceding 12 months.

Post-operative clinical course. The 30-day post-operative clinical course is detailed in Table 6. In patients with LG-AS, duration of post-operative treatment in the intensive care unit was comparable to patients with HG-AS (3.0 ± 3.0 vs. 3.0 ± 2.9; $p = 0.36$). Characteristic TAVI-associated complications occurred with similar frequencies in both groups during hospital treatment: implantation of a new permanent pacemaker due to atrioventricular conductance disturbances was required in LG-AS and HG-AS patients in 27.0% and 28.1% ($p = 0.76$), respectively. Cerebrovascular complications were reported in 3.4% (LG-AS) and 3.1% (HG-AS; $p = 0.83$). Vascular compli-

Table 3. Secondary Endpoint: Procedural Characteristics

	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
Decision for TAVI made by "Heart Team"	112 (75.2)	824 (71.5)	0.34
Priority of procedure			
Elective	108 (72.5)	970 (84.1)	<0.001
Urgent	37 (24.8)	167 (14.5)	<0.01
Emergency	4 (2.7)	11 (1.0)	0.06
Duration of procedure, min	90.5 ± 51.5	89.3 ± 49.9	0.85
Access route for valve implantation			
Transfemoral	131 (87.9)	996 (86.4)	0.6
Apical	12 (8.1)	111 (9.6)	0.54
Transaortic	1 (0.7)	9 (0.8)	0.89
Transaxillary	5 (3.4)	37 (3.2)	0.92
Device			
Medtronic CoreValve	128 (85.9)	921 (79.9)	0.08
26 mm	53 (41.4)	441 (47.9)	0.17
29 mm	75 (58.6)	480 (52.1)	0.17
Edwards SAPIEN	21 (14.1)	228 (19.8)	0.08
23 mm	6 (28.6)	110 (48.2)	0.08
26 mm	15 (71.4)	118 (51.8)	0.08
Immediate result			
Successful device implantation	142 (95.3%)	1,123 (97.5)	0.13
Conversion to surgery	3 (2.0)	14 (1.2)	0.42
Procedure aborted	4 (2.7)	15 (1.3)	0.19
Device function			
Post-operative gradient, mm Hg	5.6 ± 5.3	6.1 ± 6.9	0.84
Residual AR	105 (70.9)	773 (68.0)	0.48
No AR	43 (29.1)	363 (32.0)	0.48
AR I°	79 (53.4)	617 (54.3)	0.83
AR II°	26 (17.6)	138 (12.1)	0.06
AR III°	0 (0)	16 (1.4)	0.15
AR IV°	0 (0)	2 (0.1)	0.61
Additional procedures			
Adjunctive PCI	10 (6.2)	49 (4.3)	0.18

Values are n (%) or mean ± SD.
AR = aortic regurgitation; TAVI = transcatheter aortic valve implantation; other abbreviations as in Table 1.

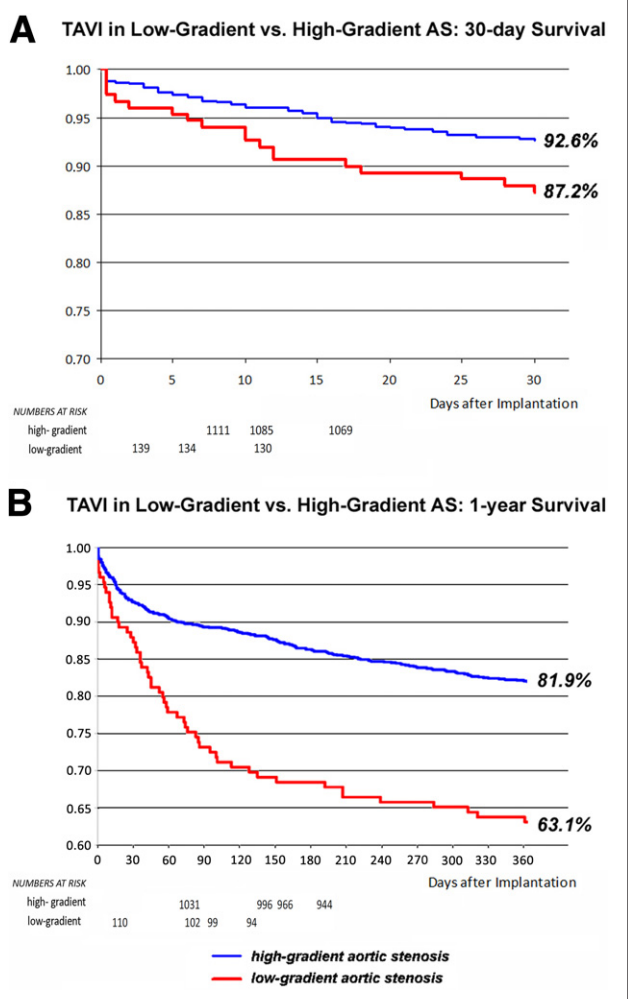

Figure 1. Survival at 30 Days and 1 Year After TAVI in LG-AS Versus HG-AS

Kaplan-Meier survival curves for patients with severe aortic stenosis (AS) after transcatheter aortic valve implantation (TAVI) stratified by transvalvular gradient. In patients with low-flow, low-gradient aortic stenosis (LG-AS), survival at 30 days **(A)** and at 1 year **(B)** is significantly lower compared with patients with high-gradient aortic stenosis (HG-AS) (log-rank test: $p = 0.0194$ and $p < 0.0001$, respectively).

cations associated with transfemoral access occurred more frequently in LG-AS patients, although these were not significant (LG-AS: 28.4% vs. HG-AS: 23.5%; $p = 0.12$). However, complications potentially associated with reduced left ventricular function (e.g., low cardiac output syndrome) were more common in the LG-AS group: Post-operative low-output syndrome was reported in 14.9% of LG-AS patients versus 5.7% of HG-AS patients ($p < 0.0001$). Thus, in the LG-AS group, a significantly higher proportion required mechanical circulatory support (LG-AS: 5.4% vs. HG-AS: 1.7%; $p < 0.001$) and cardiopulmonary resuscitation was more often necessary (LG-AS: 12.8% vs. HG-AS: 5.3%; $p < 0.001$).

Clinical benefit endpoints at 30 days and 1 year. Details on pre- and post-operative functional status are listed in Table 7. At baseline, the majority of patients with LG-AS and HG-AS were in NYHA functional class III or IV. In the LG-AS group, there was a significantly higher proportion of patients in NYHA functional class IV compared with the HG-AS group (LG-AS: 28.2% and HG-AS: 16.0%, $p < 0.001$). Within 30 days after TAVI, the NYHA functional class improved in both groups, with the majority of patients reaching NYHA functional class I and II (NYHA I: LG-AS 46.7% vs. HG-AS 55.1, $p = 0.16$; NYHA II: LG-AS 22.7 vs. HG-AS 28.2, $p = 0.31$). However, a significantly higher proportion of LG-AS patients remained in NYHA functional class IV at 30 days after TAVI (LG-AS: 12.0% vs. HG-AS 4.5%; $p < 0.01$).

Quality of life as measured with the EQ-5D-VAS improved significantly in both groups at 30 days (Table 5). Quality of life was reassessed after 1 year, demonstrating a larger benefit in long-term survivors in the LG-AS group compared with the HG-AS group. Thus, in both groups TAVI achieves comparable early and long-term postoperative functional results according to EQ-5D-VAS.

Discussion

The present report is based on data from the German Transcatheter Aortic Valve Interventions Registry, which

Table 4. Primary Endpoints: Mortality and MACCE at 30 Days and After 1 Year

	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
In-hospital mortality	24 (16.1)	83 (7.2)	<0.001
Follow-up at 30 days			
Completeness of follow-up	148 (99.3)	1,140 (98.9)	0.50
30-day all-cause mortality	19 (12.8)	84 (7.4)	<0.001
Cardiovascular cause	17 (11.4)	75 (6.8)	<0.001
Noncardiovascular cause	2 (1.3)	7 (0.6)	0.91
Follow-up at 1 year			
Completeness of follow-up	141 (94.6)	1,087 (94.3)	0.85
1-year all-cause mortality	52 (36.9)	197 (18.1)	<0.0001
Cardiovascular cause	48 (34.2)	180 (16.6)	<0.0001
Noncardiovascular cause	4 (2.7)	16 (1.5)	0.29
Combined endpoints at 30 days			
MACCE (death, MI, stroke)	10 (6.6)	26 (2.3)	<0.0001
Combined MAE (MACCE, re-OP, bleeding, dialysis)	11 (7.4)	40 (3.5)	<0.01
Combined endpoints at 1 year (after discharge)			
MACCE (death, MI, stroke)	33 (23.5)	143 (13.2)	<0.001
Combined MAE (MACCE, re-OP, bleeding, dialysis)	34 (24.3)	164 (15.1)	<0.01

Values are n (%) or mean ± SD

AS = aortic stenosis; MACCE = major adverse cardiac and cerebral event(s); MAE= major adverse event(s); MI = myocardial infarction; re-OP = reoperation.

Table 5. Predictors of Mortality After TAVI: Cox Proportional Hazards Model

	Hazard Ratio	95% CI	p Value
Age	0.987	0.960–1.013	0.32
Female	0.722	0.527–0.987	0.04
Diabetes	0.975	0.717–1.325	0.87
COPD	1.009	0.724–1.407	0.96
Pulmonary hypertension	1.029	0.734–1.442	0.87
3-vessel CAD	0.921	0.614–13.81	0.69
PVD	1.307	0.940–1.818	0.11
Previous cardiac procedures	0.615	0.388–0.976	0.039
Previous decompensation within 12 months	1.678	1.219–2.311	0.0015
Myocardial infarction	1.592	1.116–2.271	0.01
EuroSCORE >20	1.747	1.200–2.543	0.004
LV ejection fraction ≤30%	1.088	0.711–1.664	0.67
Low-gradient AS	2.201	1.466–3.303	0.0001

CI = confidence interval; COPD = chronic obstructive pulmonary disease; LV = left ventricular; PVD = peripheral vascular disease; other abbreviations as in Tables 1 and 3.

includes the biggest-ever reported series of patients treated with TAVI. Recent publications from this registry reflect the current state of adoption of the technique in Germany and have demonstrated a high success rate of TAVI associated with a moderate rate of complications (8,9).

LG-AS is an infrequent condition observed in approximately 5% of all patients with severe AS (7,15–17). However, these patients represent a controversial and challenging subpopulation with a particularly poor prognosis when undergoing conservative or surgical treatment (5–7,18). TAVI is an alternative treatment option in this difficult subgroup. However, due to the paucity of clinical data, the feasibility and outcome of TAVI have not yet been investigated in these patients. Since it is still uncertain whether patients with LG-AS benefit from less invasive treatment, we aimed at evaluating the feasibility and outcome of TAVI in this high-risk subgroup with aortic valve disease.

TAVI procedure and complication rate. The observations made in this analysis can be summarized to 3 major findings. One important primary finding is that TAVI can be performed safely in LG-AS despite the unfavorable risk profile of these patients. Although this subgroup presented with a higher rate of comorbidities, a lower ejection fraction, and hence a higher EuroSCORE (LG-AS: 26.8 ± 16.6% vs. HG-AS: 20.0 ± 13.2%; p<0.0001), TAVI was associated with a similarly high procedural success rate and a similar rate of procedure-associated complications compared with patients with HG-AS (Table 6) (8,9).

The majority of procedures in both groups were performed transfemorally (LG-AS: 89.6% vs. HG-AS: 91.3%; p = 0.6) employing the Medtronic CoreValve. Cerebrovascular events were reported in 3.1% of patients with LG-AS versus 3.4% of patients with HG-AS (p = 0.83), a finding that is in good agreement with other reports (19,20). As demonstrated by diffusion-weighted magnetic resonance imaging studies, new clinically imperceptible perfusion deficits occur frequently during TAVI due to atherothrombotic emboli. Our data suggest that despite the higher-risk profile of the LG-AS group, TAVI is not associated with higher rate of cerebrovascular events in these patients.

However, in patients with LG-AS, a higher rate of post-operative low cardiac output syndromes (LGAS: 14.9% vs. HGAS: 5.7%; p ≤0.0001), a more frequent requirement for mechanical circulatory support devices including intra-aortic counterpulsation (LG-AS: 5.4% vs. HG-AS: 1.7%; p < 0.0001) and a higher rate of post-operative cardiopulmonary resuscitations (LG-AS: 12.8% vs. HG-AS: 5.3%; p < 0.001). This increased rate of low cardiac output in the LG-AS subgroup is related to the

Table 6. Secondary Endpoints at 30 Days: Early Complications Classified According to VARC (13)

	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
Duration of treatment in ICU, days	3.0 ± 3.0	3.0 ± 2.9	0.36
Post-operative complications			
Low cardiac output	22 (14.9)	65 (5.7)	<0.0001
Conservative	14 (9.5)	46 (4.0)	<0.01
Mechanical assist device (e.g., IABP)	8 (5.4)	19 (1.7)	<0.0001
Myocardial infarction	2 (1.3)	5 (0.4)	0.15
Stroke	5 (3.4)	35 (3.1)	0.83
Transient ischemic attack (<24 h)	0 (0)	16 (1.4)	0.05
Minor stroke (Rankin score <2)	1 (0.7)	5 (0.43)	0.33
Major stroke (Rankin score ≥2)	5 (3.4)	16 (1.4)	0.59
Acute kidney injury (modified RIFLE classification)			
Stage 1 (creatinine increase 150% to 200%)	22 (17.7)	118 (11.8)	0.06
Stage 2 (creatinine increase 200% to 300%)	5 (4.0)	45 (4.5)	0.81
Stage 3 (creatinine increase >300%)	2 (1.6)	35 (3.5)	0.27
Vascular complications	42 (28.4)	269 (23.5)	0.12
Major	8 (5.4)	40 (3.5)	0.25
Minor	34 (23.0)	229 (20.0)	0.40
Bleeding complications	30 (20.1)	168 (14.6)	0.08
Life-threatening or disabling (or ≥4 RBC units)	11 (36.7)	13 (7.5)	0.31
Major bleeding (or 2 or 3 RBC units)	15 (50)	109 (64.9)	0.25
Minor bleeding (1 RBC unit)	4 (13.3)	46 (27.6)	0.28
Cardiopulmonary resuscitation	19 (12.8)	61 (5.3)	<0.001
Permanent pacemaker/defibrillator (total)	56 (37.8)	417 (36.6)	0.77
Permanent pacemaker/defibrillator (new)	40 (27.0)	324 (28.1)	0.76
Pulmonary embolism	3 (2.0)	18 (1.6)	0.67

Values are mean ± SD or n (%).

AS = aortic stenosis; IABP = intra-aortic balloon pump counterpulsation; ICU = intensive care unit; RBC = packed red blood cells; RIFLE = risk, injury, failure, loss, end-stage renal disease; VARC = Valve Academic Research Consortium.

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Table 7. Clinical Benefit Endpoints: NYHA Functional Class and Quality of Life During Follow-Up

	Low-Gradient AS (n = 149)	High-Gradient AS (n = 1,153)	p Value
Functional status at baseline and 30 days			
NYHA functional class (baseline)			
I	3 (2.0)	14 (1.2)	0.43
II	5 (3.4)	117 (10.2)	<0.01
III	99 (66.4)	830 (72.6)	0.12
IV	42 (28.2)	183 (16.0)	<0.001
NYHA functional class (30 days)			
I	35 (46.7)	391 (55.1)	0.16
II	17 (22.7)	200 (28.2)	0.31
III	14 (18.7)	87 (12.3)	0.11
IV	9 (12.0)	32 (4.5)	<0.01
Quality of life benefit (EQ-5D-VAS)			
Baseline	0.57 ± 0.32	0.63 ± 0.27	0.12
30 days	0.64 ± 0.26*	0.69 ± 0.24*	0.41
1 year	0.69 ± 0.28*	0.68 ± 0.25*	0.48

Values are n (%) or mean ± SD. *Values significantly different from baseline ($p < 0.0001$).
AS = aortic stenosis; EQ-5D-VAS = EuroQol-5D visual analogue scale; NYHA = New York Heart Association.

pre-operatively impaired LV function and has also been observed after surgical AVR in LG-AS (5–7).

The rate of newly implanted permanent pacemakers in this study is higher than in many other reports. In the current registry, a permanent pacer was implanted in 27.0% of patients with LG-AS and 28.1% with HG-AS ($p = 0.76$). This number is in line with the results recently reported by Khawaja et al. (21), who reported a permanent pacemaker requirement in up to 33.3% of 270 patients undergoing TAVI. By contrast, Eltchaninoff et al. (19) and Piazza et al. (20) reported a rate of 9.3% and 11.8%, respectively. Apart from device-related issues, the higher rate of pacemaker implantations in this registry can possibly be explained by the lower threshold of the treating cardiologist regarding safety issues in order to avoid complications associated with third-degree atrioventricular block (8). Thus, this observation reflects the currently limited knowledge concerning mechanisms and factors leading to this unpredictable complication after TAVI.

Mortality and clinical benefit endpoints. A second major finding is that TAVI in LG-AS is associated with a significantly higher mortality at 30 days (LG-AS: 12.8% vs. HG-AS: 7.4%; $p < 0.001$) and at 1 year (LG-AS: 36.9% vs. HG-AS: 18.1%; $p < 0.0001$). Among all patients included in the registry, Cox regression analysis determined the presence of LG-AS as a significant predictor of early mortality, which is associated with a proportional hazard of 2.2. Other predictors of mortality were previous cardiac decompensations ≤12 months (hazard ratio: 1.7), previous myocardial infarctions (hazard ratio: 1.6), and a logistic EuroSCORE >20 (hazard ratio: 1.7). Putting these findings in perspective with other published data, the 30-day mortality observed in the present study lies within the range of 11% to 21% of early mortality reported in multiple other reports (6,7,16). In another recent paper by Gotzmann et al. (22) reviewing a small series of patients undergoing TAVI, an increased mortality was observed in the LG-AS subgroup. However, in this report, surviving patients experienced a symptomatic benefit and functional improvement. The TAVI approach in patients with reduced LV function is further supported by a recent report from Clavel et al. (23), who observed better recovery of LV function after TAVI compared with surgical AVR. These findings suggest that the TAVI approach is feasible in patients with LG-AS and leads to clinical improvement. However, this observation requires further validation by clinical data.

Third, patients with LG-AS benefit from TAVI, with a reduction in symptoms of heart failure at 30 days and a significant improvement in quality of life at 30 days and at 1 year. EQ-5D-VAS demonstrates a lower quality of life at baseline in the LG-AS group compared with the HG-AS group. During follow-up, EQ-5D-VAS improved significantly in both subgroups, reaching comparable values at 1 year. Although this improvement may partly be related to the higher mortality in the LG-AS subgroup, it suggests a larger quality-of-life benefit from TAVI in surviving patients with LG-AS. Thus, in view of the lack of treatment options and the dismal prognosis of LG-AS, the increased mortality in patients with LG-AS after TAVI may be considered acceptable (5).

Study limitations. First, this report reflects the experience in a limited number of patients. Although this is the largest series of patients undergoing TAVI for LG-AS published to date to our knowledge, further data on efficacy and outcome in this difficult subgroup are required. Second, hemodynamic assessment was performed by DSE, and patients with pseudostenosis were excluded from TAVI. However, data on contractility reserve derived from DSE are not available in this registry. These data should be taken into consideration when designing future studies as they may yield valuable information regarding risk stratification in patients with LG-AS. Third, the present report is limited to reporting follow-up at 30 days and 1 year. Further studies should focus on longer follow-up and should include data on post-operative recovery of LV function, which may also serve as an indicator for better outcome. Fourth, this version of the registry evaluated the logistic EuroSCORE, but not the Society of Thoracic Surgeons–predicted risk score of mortality, thus making comparisons with other data more difficult.

Conclusions

High-risk patients with LG-AS benefit from less invasive therapy. Since conservative treatment does not improve

survival, these patients should be considered for TAVI, which can be performed safely with a moderate complication rate. Although the mortality is significantly higher after TAVI for LG-AS, long-term survivors benefit from the procedure with significantly improved quality of life.

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Key Words: aortic stenosis ■ low-flow, low-gradient ■ transcatheter aortic valve replacement.

Appendix
List of participating centers (in order of numbers of included patients)

Klinikum Siegburg: U. Gerckens, Universität Leipzig Herzzentrum: G. Schuler, Herzzentrum Ludwigshafen: R. Zahn, Universitätsklinikum Essen: H. Eggebrecht, Cardio Vasculäres Centrum (CVC) Frankfurt Sankt Katharinen: H. Sievert, Krankenhaus der barmherzigen Brüder Trier: K.E. Hauptmann, Asklepios Klinik St Georg Hamburg: K.H. Kuck, Klinikum Links der Weser Bremen, R. Hambrecht, Segeberger Kliniken GmbH: G. Richardt, Universitätsklinikum Bonn, Med Klinik und Poliklinik II: G. Nickenig, Elisabeth-Krankenhaus Essen: C.H. Naber, Klinikum Schwabing, München: S. Sack, Universitätsklinikum Jena: H.R. Figulla, Augustinum Klinik München: M. Block, Städt Klinikum München Klinik Bogenhausen: E. Hoffmann, Robert-Bosch-Krankenhaus, Stuttgart: U. Sechtem, HELIOS Klinikum Wuppertal: H. Gülker, Universitäts Klinikum Regensburg: G. Riegger, Krankenhaus München—Neuperlach: H. Mudra, Herzzentrum Bad Krozingen: F.J. Neumann, Universitätsklinikum Freiburg: C. Bode, Klinikum Coburg: J. Brachmann.