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ORIGINAL RESEARCH

Clinical Outcomes in High-Gradient, Classical Low-Flow, Low-Gradient, and Paradoxical Low-Flow, Low-Gradient Aortic Stenosis After Transcatheter Aortic Valve Implantation: A Report From the SwissTAVI Registry

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BACKGROUND: In view of the rising global burden of severe symptomatic aortic stenosis, its early recognition and treatment is key. Although patients with classical low-flow, low-gradient (C-LFLG) aortic stenosis have higher rates of death after transcatheter aortic valve implantation (TAVI) when compared with patients with high-gradient (HG) aortic stenosis, there is conflicting evidence on the death rate in patients with severe paradoxical low-flow, low-gradient (P-LFLG) aortic stenosis. Therefore, we aimed to compare outcomes in real-world patients with severe HG, C-LFLG, and P-LFLG aortic stenosis undergoing TAVI.

METHODS AND RESULTS: Clinical outcomes up to 5 years were addressed in the 3 groups of patients enrolled in the prospective, national, multicenter SwissTAVI registry. A total of 8914 patients undergoing TAVI at 15 heart valve centers in Switzerland were analyzed for the purpose of this study. We observed a significant difference in time to death at 1 year after TAVI, with the lowest observed in HG (8.8%) aortic stenosis, followed by P-LFLG (11.5%; hazard ratio [HR], 1.35 [95% CI, 1.16–1.56]; $P<0.001$) and C-LFLG (19.8%; HR, 1.93 [95% CI, 1.64–2.26]; $P<0.001$) aortic stenosis. Cardiovascular death showed similar differences between the groups. At 5 years, the all-cause death rate was 44.4% in HG, 52.1% in P-LFLG (HR, 1.35 [95% CI, 1.23–1.48]; $P<0.001$), and 62.8% in C-LFLG aortic stenosis (HR, 1.7 [95% CI, 1.54–1.88]; $P<0.001$).

CONCLUSIONS: Up to 5 years after TAVI, patients with P-LFLG have higher death rates than patients with HG aortic stenosis but lower death rates than patients with C-LFLG aortic stenosis.

Key Words: low-flow, low-gradient ■ outcomes in aortic stenosis ■ SwissTAVI ■ transcatheter aortic valve implantation ■ valvular heart disease

Considering the rising global burden in degenerative aortic valvular disease that results not only in higher death rate as compared with an age-standardized population but also in higher rates of disability adjusted life years, the importance of early recognition and treatment of the disease is evident.[1,2]

Patients with low-flow, low-gradient (LFLG) aortic stenosis represent a special patient group. They are

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, we analyzed the largest patient population according to their respective flow and gradient status and compared outcomes in a real-world transcatheter aortic valve implantation setting.
- In the context of conflicting evidence, our analysis covered 8914 patients undergoing transcatheter aortic valve implantation showing significant differences in time to death for patients with high-gradient, paradoxical low-flow, low-gradient and classical low-flow, low-gradient aortic stenosis.

What Are the Clinical Implications?

- Our findings may help to increase the awareness around the particular group of patients with severe paradoxical low-flow, low-gradient aortic stenosis.
- Patients with severe paradoxical low-flow, low-gradient aortic stenosis are at higher risk for death compared with patients with high-gradient aortic stenosis; early recognition and timely treatment might be useful in averting the dismal prognosis in this particular group of patients.

Nonstandard Abbreviations and Acronyms

AVA	aortic valve area
C-LFLG	classical low-flow, low-gradient
GARY	German Aortic Valve Registry
HG	high-gradient
LFLG	low-flow, low-gradient
P-LFLG	paradoxical low-flow, low-gradient
TAVI	transcatheter aortic valve implantation
TOPAS-TAVI	True or Pseudo-Severe Aortic Stenosis–TAVI

less likely to be referred for aortic valve replacement and have higher rates of death if left untreated, but yet have a survival benefit over conservative management if aortic valve replacement (surgical or interventional) is performed.[3–5] Other findings suggest that the death rate of patients with severe paradoxical low-flow, low-gradient (P-LFLG) aortic stenosis is similar to that of patients with only moderate aortic stenosis.[6] Independent of the contractile reserve, patients with classical low-flow, low-gradient (C-LFLG) aortic stenosis have a higher death rate than patients with high-gradient (HG) aortic stenosis after transcatheter aortic valve implantation (TAVI).[7–9] However, there is conflicting evidence on outcomes after TAVI in patients with severe P-LFLG aortic stenosis.[8,9] While Fisher et al described similar survival rates in patients with P-LFLG and HG aortic stenosis, Saito et al found a higher death rate in the patient group with P-LFLG after TAVI, with both trials analyzing <250 patients in their P-LFLG groups.[8,9] Whether these conflicting results are an expression of a heterogeneous patient population needs to be clarified.[10]

Since 2011, data of consecutive patients undergoing TAVI in Switzerland are prospectively collected in the national SwissTAVI registry (NCT01368250).[11–13] With this nationwide cohort study, we aim to compare longer-term outcomes as well as the periprocedural event rates in real-world patients undergoing TAVI for severe HG, C-LFLG, or P-LFLG aortic stenosis.

METHODS

Design

The SwissTAVI registry is a prospective, national, multicenter registry with standardized data monitoring and end point adjudication as recommended by the Valve Academic Research Consortium.[14,15] SwissTAVI is mandated by the Swiss Federal Office of Public Health for the ongoing assessment of patients undergoing TAVI in Switzerland. Baseline characteristics and periprocedural and interventional data were assessed in a standardized case report form, available to all the centers performing TAVI in Switzerland and uniformly reported to the Clinical Trials Unit at University Bern. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

Patients with symptomatic severe native aortic stenosis (aortic valve area [AVA] ≤1.0 cm^2) and complete hemodynamic profile were enrolled in this study. Clinical information and echocardiographic measurements were reported in standardized forms at baseline; discharge; and during follow-up at 30-day, 1-year and 5-year follow-up, using standardized report forms. In accordance with the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the management of valvular heart disease, HG, C-LFLG, and P-LFLG aortic stenosis were defined as follows: HG aortic stenosis as mean gradient ≥40 mm Hg; C-LFLG aortic stenosis as mean gradient <40 mm Hg, left ventricular ejection fraction (LVEF) <50% and aortic valve area ≤1.0 cm^2; and

P-LFLG aortic stenosis as mean gradient <40 mm Hg, LVEF ≥50% and AVA ≤1.0 cm^2.[2] Patients with missing or insufficient data on baseline echocardiographic findings, as well as patients undergoing TAVI for an indication other than severe, native aortic stenosis were excluded from this analysis. SwissTAVI was approved by the local ethics committee at each site, and all patients provided written informed consent for study participation and prospective follow-up assessment.

End Points

The primary end point was all-cause death 1 year after TAVI. Secondary end points included all-cause death at 30 days and 5 years; cardiovascular death at 30 days, 1 year, and 5 years after TAVI; and major adverse events as well as cardiovascular outcomes at 30 days and 1 year after TAVI.

Statistical Analysis

Baseline and procedural characteristics are presented as frequencies (percentage of patients), and continuous data are presented as means±SDs, with pairwise comparisons across the 3 groups using unpaired *t* tests, chi-square tests, or Fisher's exact tests. Adjudicated clinical outcomes at 30 days and at 1 year were expressed as counts of the first event occurring per patient in the indicated period (disregarding multiple events of the same type); pairwise comparisons of the 3 groups from Cox regressions (pairwise hazard ratios [HRs] with 95% CIs and Wald *P* values are reported). Cumulative incidence rates were computed using the Kaplan–Meier method. Adjusted Cox regressions, again pairwise across the 3 groups, were performed after controlling for age, sex, and Society of Thoracic Surgery Predicted Risk of Mortality (adjusted HR with CI and adjusted Wald *P* values reported). The adjusted Cox regressions were repeated in the subgroup of patients with reliable data on atrial fibrillation and in patients with transfemoral access. Data are presented as frequencies (% of patients with the measurement performed) and as means±SDs; with pairwise comparisons within the 3 groups using unpaired *t* tests, chi-square tests, or Fisher's exact tests. Statistical analyses were performed using Stata 17.0 (StataCorp LP, College Station, TX). Statistical significance was considered at $P<0.05$.

RESULTS

From February 2011 to June 2020, 10 284 patients were enrolled in SwissTAVI. Seven hundred forty-three patients were excluded from this analysis, either because they had TAVI for an indication other than severe native aortic stenosis (n=484) or because of missing and incomplete data of the baseline echocardiography (n=259), leaving 9541 patients for analysis. Six hundred twenty-seven patients did not meet any of the predefined categories and had to be excluded from this analysis (n=460 AVA >1.0 cm^2; n=105 AVA not documented; n=62 AVA ≤1.0 cm^2 but gradient or LVEF not documented) resulting in 8914 patients available for analysis. According to the type of aortic stenosis, there were 5094 (57.1%) patients with HG, 1356 (15.2%) patients with C-LFLG, and 2464 (27.6%) patients with P-LFLG aortic stenosis (Figure 1).

Baseline clinical characteristics are summarized in Table 1. Mean age of the patients was 82.1±6.3 years, and 50.2% were women. Patients in the C-LFLG group had higher rates of coronary artery disease (68.3%) compared with patients with P-LFLG (57.5%; $P<0.001$) and patients with HG (52.2%; $P<0.001$). Similarly, patients with C-LFLG had a higher prevalence of previous myocardial infarction (24.9%) compared with patients with P-LFLG (10%; $P<0.001$) and patients with HG (9.6%; $P<0.001$). The burden of atrial fibrillation was highest in the C-LFLG group (44.5%) in comparison with patients with P-LFLG (38.1%, $P=0.001$) and patients with HG (26.2%; $P<0.001$). Chronic obstructive pulmonary disease, previous cardiac surgery, and previous defibrillator implantation was more frequent in the C-LFLG population than in the other groups. Patients with C-LFLG had a higher Society of Thoracic Surgery Predicted Risk of Mortality (6.1±4.8) than patients with HG (4.4±3.5; $P<0.001$) and patients with P-LFLG (4.5±3.4), while the Society of Thoracic Surgery Predicted Risk of Mortality was similar between patients with HG and patients with P-LFLG ($P=0.229$). Mean aortic valve area was 0.7 cm^2 (±0.2) at baseline and ≥1.8 cm^2 at discharge. The LVEF in the C-LFLG group improved from 34.7%±8.8% at baseline to LVEF 47.3±11.6% at 1-year follow up (Tables S1 through S3).

Procedural data are summarized in Table 2. Except for a lower number of direct aortic access in the P-LFLG group (0.4%), there was no difference in the choice of access site. Femoral access was used in 88.7% of all cases and 65.5% of interventions were performed under local anesthesia/conscious sedation. Balloon valvuloplasty was more frequently used in patients with HG aortic stenosis (67.9%) compared with patients with C-LFLG and P-LFLG aortic stenosis (51.8% and 51.7%; $P<0.001$). The details on type of valve used in each of the 3 patient groups are provided in Table S4.

At 30 days, all-cause death was 4.0% (n=54), 2.9% (n=72), and 2.4% (n=121) in patients with C-LGLG, P-LFLG, and HG aortic stenosis, respectively. There was no significant difference in time to all-cause death among the 3 groups (C-LFLG versus HG: adjusted hazard ratio [HR_{adj}], 1.36 [95% CI, 0.98–1.89]; $P=0.068$; P-LFLG versus HG: HR_{adj}, 1.23 [95% CI, 0.92–1.65];

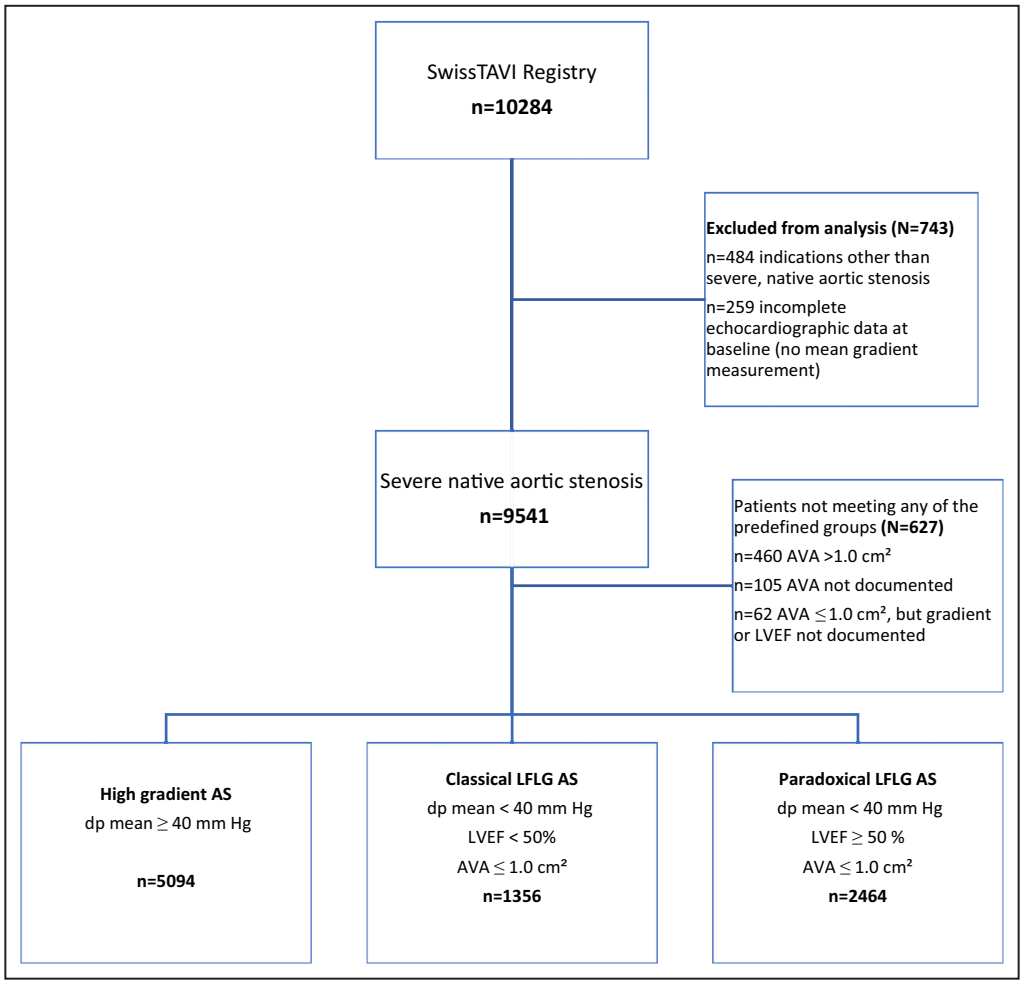


Figure 1. Flowchart of patient selection.
AS indicates aortic stenosis; AVA, aortic valve area; dp mean, mean aortic pressure gradient; LFLG, low-flow, low-gradient; LVEF, left ventricular ejection fraction; and TAVI, transcatheter aortic valve implantation.

P=0.165; P-LFLG versus C-LFLG: HR_{adj}, 0.73 [95% CI, 0.51–1.04]; *P*=0.83), after adjustment for Society of Thoracic Surgery Predicted Risk of Mortality score, age, and sex (Figure 2).

One year after TAVI, there was a significant difference in all-cause death among the 3 groups, with the lowest observed in HG (8.8%, n=438), followed by P-LFLG (11.5%, n=276, HR_{adj}, 1.35 [95% CI, 1.16–1.56]; *P*<0.001) and C-LFLG (19.8%, n=261, HR_{adj}, 1.93 [95% CI, 1.64–2.26]; *P*<0.001) aortic stenosis. Patients with P-LFLG aortic stenosis had a significantly better outcome at 1 year compared with C-LFLG (HR_{adj} for death, 0.70 [95% CI, 0.59–0.83]; *P*<0.001; Figure 2).

Five years after TAVI, these significant differences remained among the 3 groups. With an all-cause death rate of 62.8% (n=589), 52.1% (n=741), and 44.4% (n=1331) in patients with C-LFLG, P-LFLG, and HG aortic stenosis, respectively, and the following HRs: C-LFLG versus HG: HR_{adj}, 1.7 (95% CI, 1.54–1.88; *P*<0.001); P-LFLG versus HG: HR_{adj}, 1.35 (95% CI, 1.23–1.48; *P*<0.001); P-LFLG versus C-LFLG: HR_{adj}, 0.79 (95% CI, 0.71–0.88; *P*<0.001) (Figure 2).

Secondary end points are summarized in Table 3. Similar trends as for overall death rate were observed for cardiovascular death at 30 days, 1 year, and 5 years (Figure 3). Vascular access site and access-related complications were present in 803 (15.8%) patients with HG aortic stenosis and did not differ among groups at 30 days. Bleeding occurred overall in 1534 (17.2%) patients, again with no significant difference among groups at 30 days. There was no difference in rates of myocardial infarction among groups, neither at 30 days nor at 1 year after TAVI. Patients with P-LFLG aortic stenosis had a higher rate of cerebrovascular events at 1 year as compared with HG aortic stenosis (HR_{adj}, 1.28 [95% CI, 1.04–1.58]; *P*=0.021). Unadjusted analysis for primary and secondary end points are summarized in Table S5.

Subgroup analysis with auxiliary adjustment for atrial fibrillation (n=6609) showed similar outcomes to the

Table 1. Baseline Characteristics

	All groups	High gradient	Classical LFLG	Paradoxical LFLG	*P* value		
	N=8914	N=5094	N=1356	N=2464	Classical LFLG vs HG	Paradoxical LFLG vs HG	Paradoxical vs classical LFLG
Age, y	82.10±6.26	82.09±6.13	81.94±6.90	82.21±6.14	0.411	0.461	0.215
Female sex, n (%)	4471 (50.2)	2625 (51.5)	454 (33.5)	1392 (56.5)	<0.001	<0.001	<0.001
Body mass index, kg/cm^2	26.76±5.09	26.87±5.17	26.29±4.80	26.79±5.05	<0.001	0.534	0.003
Diabetes, n (%)	2281 (25.6)	1262 (24.8)	429 (31.6)	590 (23.9)	<0.001	0.441	<0.001
Arterial hypertension, n (%)	7075 (79.5)	3976 (78.2)	1089 (80.4)	2010 (81.7)	0.079	<0.001	0.340
Dyslipidemia, n (%)	4826 (54.2)	2643 (52.0)	802 (59.2)	1381 (56.1)	<0.001	0.001	0.065
COPD, n (%)	987 (11.1)	491 (9.7)	206 (15.2)	290 (11.8)	<0.001	0.005	0.003
History of cerebrovascular accident, n (%)	1042 (11.7)	542 (10.6)	187 (13.8)	313 (12.7)	0.001	0.008	0.341
Atrial fibrillation, n (%)	2141 (32.4)	964 (26.2)	439 (44.5)	738 (38.1)	<0.001	<0.001	0.001
Previous pacemaker implantation, n (%)	783 (8.8)	337 (6.6)	207 (15.3)	239 (9.7)	<0.001	<0.001	<0.001
Previous defibrillator implantation, n (%)	65 (0.7)	19 (0.4)	34 (2.5)	12 (0.5)	<0.001	0.450	<0.001
Coronary artery disease, n (%)	4998 (56.1)	2656 (52.2)	925 (68.3)	1417 (57.5)	<0.001	<0.001	<0.001
History of PCI, n (%)	2439 (27.4)	1198 (23.5)	502 (37.0)	739 (30.0)	<0.001	<0.001	<0.001
History of myocardial infarction, n (%)	1072 (12.0)	488 (9.6)	337 (24.9)	247 (10.0)	<0.001	0.535	<0.001
Peripheral artery disease, n (%)	1378 (15.5)	715 (14.0)	291 (21.5)	372 (15.1)	<0.001	0.221	<0.001
History of cardiac surgery, n (%)	855 (9.6)	344 (6.8)	228 (16.8)	283 (11.5)	<0.001	<0.001	<0.001
Dyspnea, NYHA class, n (%)					<0.001	0.001	<0.001
NYHA I	894 (10.3)	573 (11.5)	90 (6.8)	231 (9.7)	<0.001	0.017	0.003
NYHA II	2737 (31.5)	1676 (33.7)	311 (23.5)	750 (31.4)	<0.001	0.044	<0.001
NYHA III	4306 (49.6)	2358 (47.4)	702 (52.9)	1246 (52.1)	<0.001	<0.001	0.631
NYHA IV	751 (8.6)	363 (7.3)	223 (16.8)	165 (6.9)	<0.001	0.563	<0.001
CCS angina class, n (%)					0.189	0.276	0.093
No angina	7023 (80.0)	3994 (79.6)	1105 (82.5)	1924 (79.5)	0.017	0.902	0.025
CCS1	359 (4.1)	215 (4.3)	46 (3.4)	98 (4.0)	0.187	0.666	0.376
CCS2	923 (10.5)	521 (10.4)	120 (9.0)	282 (11.6)	0.138	0.102	0.011
CCS3	386 (4.4)	236 (4.7)	54 (4.0)	96 (4.0)	0.338	0.168	0.931
CCS4	87 (1.0)	52 (1.0)	14 (1.0)	21 (0.9)	1.000	0.532	0.598
STS-PROM, %	4.68±3.76	4.38±3.51	6.14±4.77	4.48±3.41	<0.001	0.229	<0.001

CCS indicates Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; HG, high-gradient; LFLG, low-flow, low-gradient; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

primary analysis, with lowest death in patients with HG (8.3%), followed by P-LFLG (11.7%; HR_{adj}, 1.34 [95% CI, 1.12–1.60]; *P*=0.001) and C-LFLG (19.5%; HR_{adj}, 1.75 [95% CI, 1.44–2.13]; *P*<0.001) aortic stenosis (Table S6). In the subgroup of patients who underwent TAVI via transfemoral access (n=6156; with 3451 HG, 903 C-LGLG, 1802 P-LFLG), again similar outcomes were observed. With the lowest death rate in patients with HG (8.1%), followed by P-LFLG (11.2%; HR_{adj}, 1.31 [95% CI, 1.09–1.58]; *P*=0.004) and C-LFLG (18.6%; HR_{adj}, 1.71 [95% CI, 1.39–2.10]; *P*<0.001) aortic stenosis. (Table S7 in the appendix). Outcomes according to preprocedural Society of Thoracic Surgery risk and postprocedural paravalvular leak or prosthesis–patient mismatch is provided in Figure S1 without significant difference among the subgroups.

DISCUSSION

Our study shows that in a large population of real-world patients undergoing TAVI, both overall and cardiovascular death up to 5 years is highest in patients with C-LFLG aortic stenosis, while patients with HG aortic stenosis have the lowest risk. Of note, patients

Table 2. Procedural Information

	All groups, n (%)	High-gradient, n (%)	Classical LFLG, n (%)	Paradoxical LFLG, n (%)	*P* value		
	N=8914	N=5094	N=1356	N=2464	Classical LFLG vs HG	Paradoxical LFLG vs HG	Paradoxical vs classical LFLG
Type of anesthesia					0.316	0.296	0.883
Local	5835 (65.5)	3363 (66.0)	875 (64.6)	1597 (64.8)	0.318	0.301	0.887
General	3077 (34.5)	1730 (34.0)	480 (35.4)	867 (35.2)	0.318	0.301	0.887
Main access site					0.074	0.015	0.002
Right femoral	6614 (74.2)	3794 (74.5)	979 (72.2)	1841 (74.7)	0.094	0.844	0.091
Left femoral	1296 (14.5)	756 (14.8)	204 (15.0)	336 (13.6)	0.864	0.173	0.244
Transapical	496 (5.6)	266 (5.2)	96 (7.1)	134 (5.4)	0.010	0.701	0.046
Right subclavian	17 (0.2)	8 (0.2)	1 (0.1)	8 (0.3)	0.695	0.180	0.172
Left subclavian	74 (0.8)	39 (0.8)	14 (1.0)	21 (0.9)	0.314	0.680	0.597
Direct aortic	87 (1.0)	55 (1.1)	21 (1.5)	11 (0.4)	0.158	0.005	0.001
External iliac artery	275 (3.1)	149 (2.9)	35 (2.6)	91 (3.7)	0.582	0.080	0.072
Carotid access	42 (0.5)	23 (0.5)	4 (0.3)	15 (0.6)	0.635	0.387	0.234
Transcaval	10 (0.1)	4 (0.1)	1 (0.1)	5 (0.2)	1.000	0.162	0.432
Left axillary	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)		0.326	1.000
Other	2 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	0.210	0.326	1.000
Balloon valvuloplasty	5431 (60.9)	3456 (67.9)	702 (51.8)	1273 (51.7)	<0.001	<0.001	0.973
Device type					0.080	0.102	0.143
Balloon-expandable	4394 (49.4)	2501 (49.2)	701 (51.8)	1192 (48.4)	0.099	0.539	0.050
Self-expanding	4191 (47.1)	2383 (46.9)	614 (45.3)	1194 (48.5)	0.327	0.184	0.062
Mechanically expanding	313 (3.5)	199 (3.9)	39 (2.9)	75 (3.0)	0.075	0.066	0.843
Valve size, mm	26.7±2.5	26.6±2.5	27.6±2.5	26.3±2.5	<0.001	<0.001	<0.001

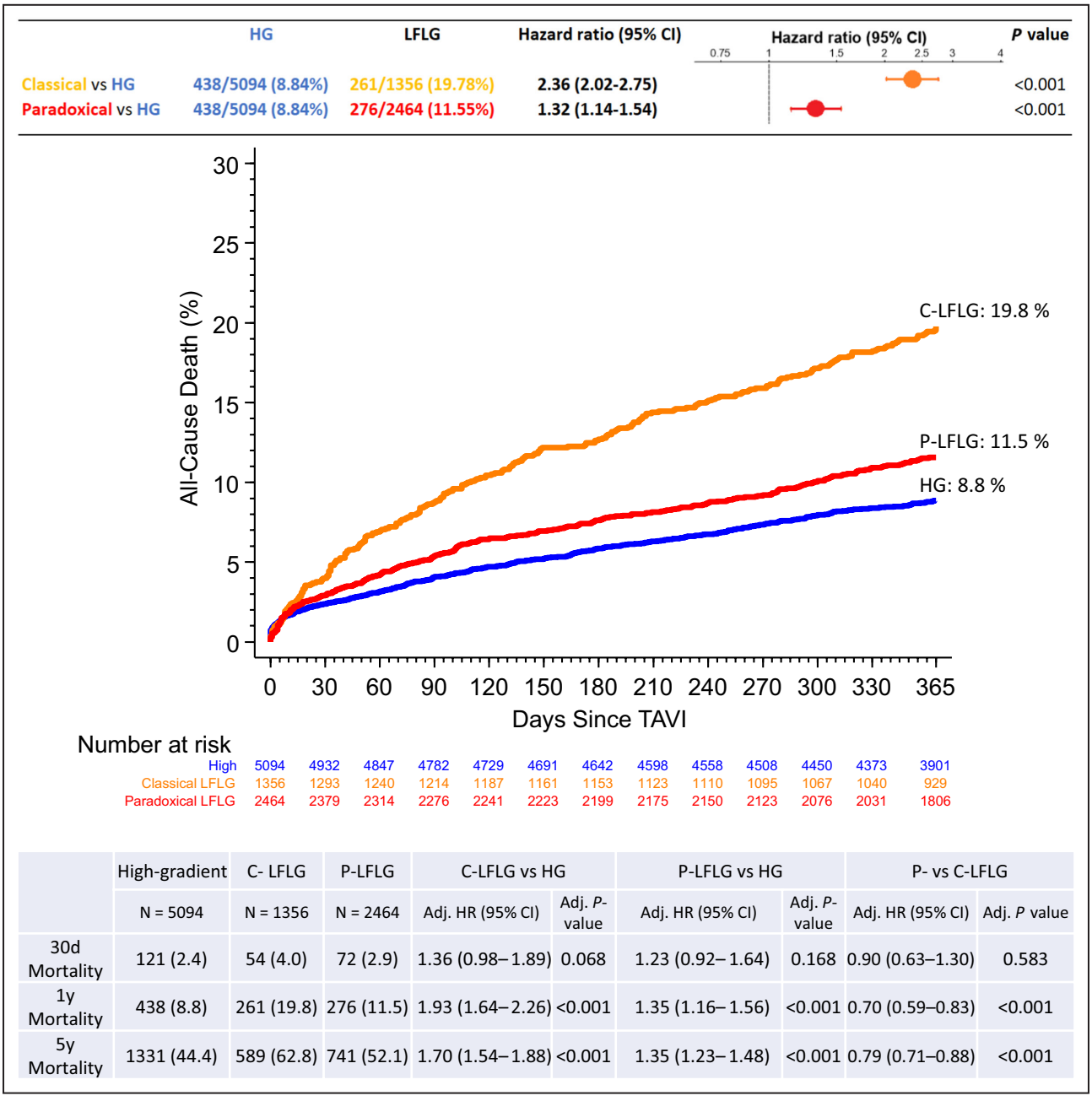
HG indicates high-gradient; and LFLG, low-flow, low-gradient.

with P-LFLG have higher death rates than patients with HG aortic stenosis but lower death rates than patients with C-LFLG aortic stenosis.

Previously published literature in the field showed discrepant findings. One of the largest meta-analyses (n=7459) in the field compared overall death rates in patients with severe HG, moderate-gradient, and P-LFLG aortic stenosis, and overall death rate differed among groups of different flow states (LFLG or normal-flow–low-gradient).[3] Compared with severe HG aortic stenosis, only patients with LFLG but not with normal-flow–low-gradient presented a higher overall death rate, with HRs of 1.67 (95% CI, 1.16–2.39) and 1.12 (95% CI, 0.89–1.42), respectively.[3] Considering the significant heterogeneity (I^2=80% in HG versus LFLG comparison), exclusion of patients with reduced LVEF,[3] inclusion of patients who did not undergo aortic valve replacement,[16] and an underrepresentation of patients undergoing TAVI (n=1069 with inhomogeneous flow-state groups from 3 TAVI studies),[13,17,18] our results allow us to clarify and discriminate outcomes in a real-world population of patients with severe HG, C-LFLG, and P-LFLG aortic stenosis undergoing TAVI.

In our study, patient groups with severe P-LFLG and C-LFLG had higher rates of all-cause death compared with patients in the HG group, whereas patients with severe P-LFLG aortic stenosis had lower rates of all-cause death as compared with patients with severe C-LFLG aortic stenosis. This result is in contrast to the findings of a meta-analysis, where outcomes were similar between patients with C-LFLG and P-LFLG aortic stenosis.[19] This may partly be due to the observed amount of heterogeneity (I^2=62%) within the studies included in the analysis. Although there was no statistically significant difference in death rates between C-LFLG and P-LFLG, a trend of better outcome in favor of patients with P-LFLG aortic stenosis was described (odds ratio, 0.74 [95% CI, 0.52–1.00] for 30 days all-cause death; and OR, 0.81 [95% CI, 0.51–1.28] for mid-term [≥12 months] all-cause death).[19]

Results from the GARY (German Aortic Valve Registry) showed similar rates of all-cause death in patients with P-LFLG compared with patients with HG aortic stenosis (22.3% versus 19.8%; *P*=0.192) at 1 year follow-up.[20] In comparison with our study, selection criteria were different, leading to an exclusion of



	High-gradient	C- LFLG	P-LFLG	C-LFLG vs HG		P-LFLG vs HG		P- vs C-LFLG	
	N = 5094	N = 1356	N = 2464	Adj. HR (95% CI)	Adj. *P*-value	Adj. HR (95% CI)	Adj. *P*-value	Adj. HR (95% CI)	Adj. *P* value
30d Mortality	121 (2.4)	54 (4.0)	72 (2.9)	1.36 (0.98–1.89)	0.068	1.23 (0.92–1.64)	0.168	0.90 (0.63–1.30)	0.583
1y Mortality	438 (8.8)	261 (19.8)	276 (11.5)	1.93 (1.64–2.26)	<0.001	1.35 (1.16–1.56)	<0.001	0.70 (0.59–0.83)	<0.001
5y Mortality	1331 (44.4)	589 (62.8)	741 (52.1)	1.70 (1.54–1.88)	<0.001	1.35 (1.23–1.48)	<0.001	0.79 (0.71–0.88)	<0.001

Figure 2. All-cause deaths.
Patients with high-gradient aortic stenosis as reference (top), all-cause death in patients with high gradient (blue), classical low-flow, low-gradient (orange), and paradoxical low-flow, low-gradient (red), aortic stenosis (middle), and all-cause death at 30 d, 1 y, and 5 y adjusted for age, sex, and STS-PROM (bottom). adj indicates adjusted; C-LFLG, classical low-flow, low-gradient; HG, high-gradient, HR, hazard ratio; LFLG, low-flow, low-gradient; P-LFLG, paradoxical low-flow, low-gradient; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

214 patients with an LVEF of 41% to 49% in an overall population of N=2863.[20]

Contributing factors to the particular entity of severe P-LFLG aortic stenosis are, among others, a small left ventricular cavity size, concentric remodeling–altered filling pressures, and a restrictive physiology.[21] When compared with HG aortic stenosis, patients with severe P-LFLG aortic stenosis suffer from chronic exposure to higher afterload levels. Apart from concentric remodeling, this leads to an impairment of intrinsic myocardial function, shown by significantly lower midwall fractional shortening and stroke work index.[22] This pathophysiological rationale may at least in part explain the worse outcome in patients with P-LFLG in comparison with patients with HG aortic stenosis. Nonetheless, it is important to note that patients with P-LFLG have a

Table 3. Secondary Outcomes at 30 Days and 1 Year

	High gradient	C-LFLG	P-LFLG	C-LFLG vs HG		P-LFLG vs HG		P- vs C-LFLG	
	N=5094	N=1356	N=2464	Adjusted HR (95% CI)	Adjusted *P* value	Adjusted HR (95% CI)	Adjusted *P* value	Adjusted HR (95% CI)	Adjusted *P* value
At 30 d									
Death rate	121 (2.4)	54 (4.0)	72 (2.9)	1.36 (0.98–1.89)	0.068	1.23 (0.92–1.64)	0.168	0.90 (0.63–1.30)	0.583
Cardiovascular death	110 (2.2)	48 (3.6)	60 (2.4)	1.33 (0.94–1.88)	0.109	1.13 (0.82–1.54)	0.462	0.85 (0.58–1.25)	0.402
Myocardial infarction	32 (0.6)	6 (0.4)	9 (0.4)	0.70 (0.29–1.71)	0.434	0.58 (0.28–1.21)	0.146	0.82 (0.29–2.36)	0.720
Periprocedural myocardial infarction	25 (0.5)	4 (0.3)	7 (0.3)	0.62 (0.21–1.82)	0.383	0.57 (0.25–1.32)	0.193	0.93 (0.26–3.23)	0.903
Spontaneous myocardial infarction	7 (0.1)	2 (0.2)	2 (0.1)	0.96 (0.19–4.84)	0.963	0.59 (0.12–2.86)	0.517	0.62 (0.08–4.57)	0.637
Cerebrovascular accident	172 (3.4)	40 (3.0)	86 (3.5)	0.85 (0.60–1.21)	0.361	1.02 (0.79–1.32)	0.891	1.20 (0.82–1.76)	0.353
Disabling stroke	104 (2.1)	18 (1.3)	44 (1.8)	0.61 (0.36–1.01)	0.053	0.86 (0.61–1.23)	0.413	1.43 (0.82–2.49)	0.213
Nondisabling stroke	57 (1.1)	15 (1.1)	32 (1.3)	1.01 (0.56–1.80)	0.984	1.14 (0.74–1.76)	0.552	1.13 (0.60–2.13)	0.695
Bleeding	890 (17.5)	226 (16.7)	418 (17.0)	0.96 (0.82–1.11)	0.577	0.95 (0.85–1.07)	0.421	0.99 (0.84–1.17)	0.952
Life-threatening bleeding	268 (5.3)	70 (5.2)	111 (4.5)	0.96 (0.73–1.26)	0.760	0.84 (0.67–1.04)	0.114	0.87 (0.64–1.19)	0.383
Major bleeding	387 (7.6)	93 (6.9)	191 (7.8)	0.92 (0.73–1.16)	0.493	1.00 (0.84–1.19)	0.989	1.08 (0.84–1.40)	0.537
Minor bleeding	253 (5.0)	67 (5.0)	122 (5.0)	1.02 (0.77–1.35)	0.879	1.00 (0.80–1.24)	0.969	0.97 (0.72–1.32)	0.869
Acute kidney injury	146 (2.9)	72 (5.4)	87 (3.6)	1.49 (1.11–1.99)	0.007	1.23 (0.94–1.60)	0.134	0.82 (0.60–1.13)	0.236
Stage 1	70 (1.4)	26 (1.9)	44 (1.8)	1.18 (0.74–1.87)	0.479	1.30 (0.89–1.90)	0.170	1.10 (0.67–1.81)	0.699
Stage 2	32 (0.6)	15 (1.1)	19 (0.8)	1.55 (0.82–2.92)	0.174	1.20 (0.68–2.11)	0.533	0.77 (0.39–1.55)	0.468
Stage 3	44 (0.9)	31 (2.3)	24 (1.0)	1.88 (1.17–3.01)	0.009	1.10 (0.67–1.81)	0.709	0.59 (0.34–1.00)	0.052
Vascular access site/access-related complications	803 (15.8)	193 (14.3)	387 (15.7)	0.93 (0.79–1.10)	0.406	0.98 (0.86–1.10)	0.685	1.04 (0.87–1.25)	0.632
Major vascular complications	501 (9.8)	125 (9.2)	235 (9.5)	0.98 (0.80–1.20)	0.876	0.94 (0.81–1.10)	0.466	0.96 (0.77–1.20)	0.714
Minor vascular complications	305 (6.0)	68 (5.0)	149 (6.1)	0.85 (0.65–1.11)	0.231	1.00 (0.82–1.21)	0.978	1.18 (0.88–1.58)	0.280
Pacemaker implantation	836 (16.6)	238 (17.7)	377 (15.4)	0.97 (0.84–1.12)	0.689	0.93 (0.83–1.06)	0.273	0.96 (0.82–1.14)	0.655

(*Continued*)

Table 3. Continued

	High gradient	C-LFLG	P-LFLG	C-LFLG vs HG		P-LFLG vs HG		P- vs C-LFLG	
	N=5094	N=1356	N=2464	Adjusted HR (95% CI)	Adjusted *P* value	Adjusted HR (95% CI)	Adjusted *P* value	Adjusted HR (95% CI)	Adjusted *P* value
At 1 y									
Mortality	438 (8.8)	261 (19.8)	276 (11.5)	1.93 (1.64–2.26)	<0.001	1.35 (1.16–1.56)	<0.001	0.70 (0.59–0.83)	<0.001
Cardiovascular death	285 (5.8)	188 (14.6)	180 (7.6)	2.11 (1.74–2.55)	<0.001	1.34 (1.12–1.62)	0.002	0.64 (0.52–0.79)	<0.001
Myocardial infarction	57 (1.2)	11 (0.9)	24 (1.1)	0.69 (0.36–1.34)	0.275	0.88 (0.55–1.42)	0.613	1.28 (0.62–2.64)	0.512
Spontaneous myocardial infarction	32 (0.7)	7 (0.6)	17 (0.8)	0.75 (0.33–1.74)	0.507	1.14 (0.63–2.05)	0.669	1.51 (0.61–3.71)	0.371
Cerebrovascular accident	226 (4.6)	62 (4.9)	140 (6.0)	1.02 (0.76–1.35)	0.917	1.28 (1.04–1.58)	0.021	1.26 (0.93–1.72)	0.135
Disabling stroke	135 (2.7)	29 (2.3)	66 (2.8)	0.78 (0.52–1.18)	0.237	1.01 (0.75–1.35)	0.962	1.29 (0.83–2.02)	0.263
Nondisabling stroke	73 (1.5)	22 (1.7)	56 (2.4)	1.14 (0.70–1.86)	0.597	1.59 (1.12–2.25)	0.009	1.39 (0.84–2.31)	0.200
Bleeding	975 (19.3)	264 (20.0)	487 (20.1)	1.02 (0.89–1.17)	0.800	1.02 (0.91–1.14)	0.719	1.00 (0.86–1.17)	0.980
Life-threatening bleeding	313 (6.2)	92 (7.1)	149 (6.2)	1.09 (0.86–1.38)	0.482	0.97 (0.80–1.18)	0.766	0.89 (0.68–1.16)	0.397
Major bleeding	429 (8.5)	105 (7.9)	212 (8.7)	0.94 (0.76–1.17)	0.603	1.00 (0.85–1.18)	0.968	1.06 (0.84–1.35)	0.616
Minor bleeding	281 (5.6)	80 (6.1)	145 (6.0)	1.07 (0.82–1.38)	0.627	1.07 (0.88–1.31)	0.480	1.01 (0.76–1.34)	0.951
Pacemaker implantation	890 (17.8)	264 (20.0)	422 (17.4)	1.03 (0.89–1.18)	0.727	0.98 (0.88–1.10)	0.783	0.96 (0.82–1.12)	0.606

Adjusted for age, sex, and STS-PROM number of first event (%). Administrative censoring was performed at 30 days and 1 year of follow-up. adj. adjusted; HG indicates high gradient; C-LFLG, classical low-flow, low-gradient; P-LFLG, paradoxical low-flow, low-gradient; and STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

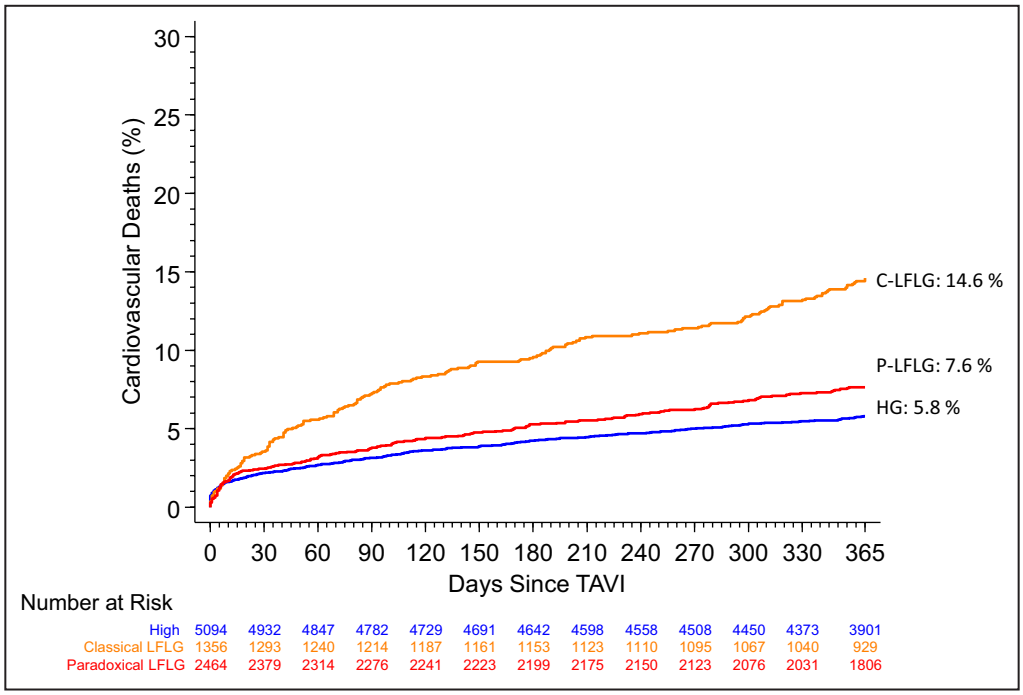


Figure 3. Cardiovascular death in patients undergoing TAVI with high-gradient (HG) (blue), classical low-flow, low-gradient (C-LFLG) (orange) and paradoxical low-flow, low-gradient (P-LFLG) (red) aortic stenosis.
Adjusted hazard ratio (HR), 2.11 (95% CI, 1.74–2.55; *P*<0.001); C-LFLG vs HG (HR, 1.34 [95% CI, 1.12–1.62]; *P*=0.002); P-LFLG vs HG (HR, 0.64 [95% CI, 0.52–0.79]; *P*<0.001) P-LFLG vs C-LFLG. C-LFLG indicates classical low-flow, low-gradient; HG, high-gradient; LFLG, low-flow, low-gradient; and P-LFLG, paradoxical low-flow, low-gradient.

survival benefit if treated by aortic valve replacement in comparison with medical treatment alone.[22] The difference in death rates we found between patients with P-LFLG and patients with C-LFLG may be an expression of a later stage of disease and resulting from progressive left ventricular dysfunction.[18,23]

Our results are in line with the findings of 3 other analyses, FRANCE 2, 1 large German tertiary single-center registry, and a Canadian trial, with low-gradient and low-flow states being independent predictors of death in patients with severe aortic stenosis.[17,23,24] In an analysis of the TOPAS-TAVI (True or Pseudo-Severe Aortic Stenosis–TAVI) registry, looking for predictors of death in patients LFLG aortic stenosis undergoing TAVI, the absence of contractile reserve in dobutamine stress echocardiography at baseline, was not associated with any negative effect on clinical outcome, which underlines the fact that further research is needed to define prognostic markers in this particular group of patients.[7]

The results from a smaller trial showed no difference in death rates (*P*=0.49) among patients with HG and P-LFLG aortic stenosis.[25] These findings stand in contrast to our findings and those of the other larger trials mentioned above and may be interpreted with caution because although propensity score matching was performed, overall sample size was small (n=290).[25]

A recent study by Stassen et al[26] demonstrated that even in patients with moderate aortic stenosis, discordant pressure and flow-gradients are associated with a higher death rate. Similar to our results, the death rate was highest in patients with classical LFLG, followed by P-LFLG, and finally normal-flow–low-gradient and concordant-gradient moderate aortic stenosis. As referral for evaluation tends to be late in patients with severe C-LFLG and P-LFLG aortic stenosis compared with HG aortic stenosis, awareness of higher death rates in both of these groups is to be promoted to optimize the outpatient evaluation process.[3]

Limitations

Due to the registry design of our study, several limitations have to be accounted for. First, some patients did not meet any of the 3 predefined groups according to the European Society of Cardiology Guidelines, and the exact variables that led to exclusion from analysis have not been assessed. Nevertheless, our cohort consists of a contemporary and real-world patient population representing all comers in an everyday clinical scenario. Second, data on indexed stroke volume have not been assessed in a consistent manner in SwissTAVI, but all patients met the current guideline criteria for group

attribution (HG, C-LFLG, and P-LFLG).[2] Furthermore, detailed information on calcification of the native aortic valve or the left ventricular outflow tract as well as dedicated frailty indices are not available in SwissTAVI and thus cannot be included in an outcome analysis. Third, this study was not designed to assess for possible differences in patients treated with self-expanding and balloon-expandable valves. Fourth, the Valve Academic Research Consortium 3 end point definitions were released after the inclusion period; thus, this analysis is based on the previous consensus definitions.

CONCLUSIONS

Up to 5 years after TAVI, patients with severe P-LFLG aortic stenosis have higher rates of death than patients with HG aortic stenosis, but lower rates than C-LFLG patients. Differences in all-cause and cardiovascular death underline the importance of patient differentiation in patients with HG, C-LFLG, and P-LFLG aortic stenosis to make individual treatment decisions in the appropriate prognostic setting.

PERSPECTIVES

Our findings confirm the current state of research, that patients with C-LFLG aortic stenosis have worse outcomes than those with HG aortic stenosis. Our findings help to better understand the particular group of patients with P-LFLG aortic stenosis, with so far conflicting evidence considering outcomes. Based on our findings, we can now differentiate 3 different outcome groups, and we should raise awareness of the specific particular group with P-LFLG aortic stenosis to promote early evaluation, diagnosis, and treatment allocation. For future research, this analysis underlines the importance and impact of large national registries to collect real-world data of the treatment of structural heart disease, and we will continue to include an all-comer population in the SwissTAVI registry.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7
Figure S1

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SUPPLEMENTAL MATERIAL

TABLE S1 – Echocardiographic assessment at baseline.

	All groups	High gradient	Classical LFLG	Paradoxical LFLG	p-value		
					Classical LFLG vs HG	Paradoxical LFLG vs HG	Paradoxical vs Classical LFLG
	N = 8914	N = 5094	N = 1356	N = 2464			
Aortic Valve Area (cm²)	0.69 ± 0.19	0.65 ± 0.20	0.72 ± 0.17	0.74 ± 0.16	<0.001	<0.001	<0.001
Mean Gradient (mmHg)	43.43 ± 17.26	54.50 ± 13.91	26.88 ± 7.83	29.64 ± 7.07	<0.001	<0.001	<0.001
LVEF (%)	56.07 ± 13.52	58.86 ± 11.24	34.69 ± 8.76	62.24 ± 7.03	<0.001	<0.001	<0.001
LV dimension SD (mm)	32.00 ± 10.57	30.71 ± 10.10	41.79 ± 10.80	28.86 ± 7.69	<0.001	<0.001	<0.001
LV dimension DD (mm)	46.66 ± 9.05	45.95 ± 8.38	52.79 ± 10.18	44.52 ± 8.13	<0.001	<0.001	<0.001
LV mass (g)	211.14 ± 103.29	213.08 ± 120.45	237.78 ± 74.83	191.29 ± 67.29	0.001	<0.001	<0.001
LV mass index (g/m²)	119.59 ± 42.10	121.03 ± 43.79	131.31 ± 40.17	110.63 ± 37.63	<0.001	<0.001	<0.001
Aortic Regurgitation Grade					0.155	<0.001	<0.001
none	2247 (27.5%)	1210 (25.9%)	304 (24.5%)	733 (32.4%)	0.306	<0.001	<0.001
mild	5173 (63.3%)	3014 (64.6%)	798 (64.2%)	1361 (60.1%)	0.815	<0.001	0.017
moderate	648 (7.9%)	379 (8.1%)	116 (9.3%)	153 (6.8%)	0.185	0.048	0.007
severe	107 (1.3%)	64 (1.4%)	25 (2.0%)	18 (0.8%)	0.115	0.043	0.003
Mitral regurgitation grade					<0.001	<0.001	<0.001
None	1269 (15.2%)	832 (17.5%)	91 (7.1%)	346 (14.8%)	<0.001	0.005	<0.001
mild	5447 (65.2%)	3176 (66.9%)	705 (55.0%)	1566 (67.2%)	<0.001	0.809	<0.001
moderate	1376 (16.5%)	657 (13.8%)	397 (31.0%)	322 (13.8%)	<0.001	1.000	<0.001
severe	267 (3.2%)	83 (1.7%)	88 (6.9%)	96 (4.1%)	<0.001	<0.001	<0.001
Tricuspid Regurgitation Grade					<0.001	<0.001	<0.001
none	2352 (29.4%)	1494 (33.0%)	226 (18.3%)	632 (28.1%)	<0.001	<0.001	<0.001
mild	4717 (58.9%)	2634 (58.2%)	739 (59.7%)	1344 (59.8%)	0.329	0.218	1.000
moderate	764 (9.5%)	348 (7.7%)	213 (17.2%)	203 (9.0%)	<0.001	0.059	<0.001
severe	180 (2.2%)	51 (1.1%)	59 (4.8%)	70 (3.1%)	<0.001	<0.001	0.015

DD=diastolic diameter, HG=high gradient, LFLG=low-flow-low-gradient, LV=left ventricular, LVEF=left ventricular ejection fraction, SD=systolic diameter

Table S2 – Echocardiographic assessment at discharge.

	All groups	High gradient	Classical LFLG	Paradoxical LFLG	p-value		
					Classical LFLG vs HG	Paradoxical LFLG vs HG	Paradoxical vs Classical LFLG
	N = 8914	N = 5094	N = 1356	N = 2464			
Aortic valve area (cm2)	1.86 ± 0.53	1.87 ± 0.54	1.81 ± 0.52	1.86 ± 0.53	0.005	0.408	0.049
LVEF (%)	57.35 ± 11.86	59.98 ± 9.68	40.77 ± 11.41	61.36 ± 7.53	<0.001	<0.001	<0.001
Mean gradient (mmHg)	9.12 ± 4.39	9.75 ± 4.57	7.94 ± 3.76	8.48 ± 4.12	<0.001	<0.001	<0.001
Prosthesis-patient mismatch	1016 (25.1%)	560 (24.5%)	185 (31.3%)	271 (23.3%)	0.001	0.474	<0.001
Aortic Regurgitation Grade					0.102	0.006	0.017
none	3175 (38.1%)	1778 (37.5%)	461 (36.0%)	936 (40.7%)	0.329	0.008	0.005
mild	4835 (58.1%)	2766 (58.3%)	781 (60.9%)	1288 (56.1%)	0.096	0.076	0.005
moderate	305 (3.7%)	192 (4.0%)	40 (3.1%)	73 (3.2%)	0.141	0.082	1.000
severe	8 (0.1%)	8 (0.2%)	0 (0.0%)	0 (0.0%)	0.216	0.060	.
Mitral Regurgitation Grade					<0.001	<0.001	<0.001
none	1302 (16.5%)	849 (19.0%)	97 (8.0%)	356 (16.2%)	<0.001	0.007	<0.001
mild	5372 (68.1%)	3081 (68.9%)	776 (63.7%)	1515 (69.1%)	0.001	0.822	0.001
moderate	1028 (13.0%)	489 (10.9%)	282 (23.2%)	257 (11.7%)	<0.001	0.342	<0.001
severe	181 (2.3%)	55 (1.2%)	63 (5.2%)	63 (2.9%)	<0.001	<0.001	0.001
Tricuspid Regurgitation Grade					<0.001	<0.001	<0.001
none	1778 (23.6%)	1123 (26.2%)	183 (15.7%)	472 (22.5%)	<0.001	0.002	<0.001
mild	4821 (63.9%)	2757 (64.3%)	745 (64.1%)	1319 (62.9%)	0.945	0.292	0.495
moderate	772 (10.2%)	355 (8.3%)	186 (16.0%)	231 (11.0%)	<0.001	<0.001	<0.001
severe	178 (2.4%)	55 (1.3%)	48 (4.1%)	75 (3.6%)	<0.001	<0.001	0.443
Depicted are count (%) and means (+- SD) with p-values from Fisher's tests (2x2), chi-square tests (if more than 2x2 categorical variables) and t-tests							
PPM - indexed aortic valve area (aortic valve area cm^2 divided by body surface area m^2) ≤0.85 for body mass index BMI <30 or unknown BMI; ≤0.70 for BMI ≥30 after TAVI.							

DD=diastolic diameter, HG=high gradient, LFLG=low-flow-low-gradient, LV=left ventricular, LVEF=left ventricular ejection fraction, SD=systolic diameter

Table S3 – Echocardiographic assessment at 1-year follow-up.

	All groups	High gradient	Classical LFLG	Paradoxical LFLG	p-value		
					Classical LFLG vs HG	Paradoxical LFLG vs HG	Paradoxical vs Classical LFLG
	N = 8914	N = 5094	N = 1356	N = 2464			
Aortic valve area (cm2)	1.81 ± 1.74	1.86 ± 2.28	1.76 ± 0.50	1.73 ± 0.47	0.524	0.208	0.504
Mean gradient (mmHg)	9.84 ± 4.94	10.39 ± 5.21	8.70 ± 4.21	9.18 ± 4.49	<0.001	<0.001	0.031
LVEF (%)	59.01 ± 10.05	60.87 ± 8.74	47.27 ± 11.56	60.68 ± 7.85	<0.001	0.507	<0.001
LV dimension SD (mm)	30.80 ± 8.75	29.93 ± 8.46	36.36 ± 9.71	30.08 ± 7.90	<0.001	0.739	<0.001
LV dimension DD (mm)	46.82 ± 11.48	46.03 ± 7.69	52.12 ± 24.21	45.91 ± 7.11	<0.001	0.690	<0.001
LV mass (g)	193.27 ± 69.90	193.60 ± 70.51	226.71 ± 77.39	178.26 ± 59.89	<0.001	0.004	<0.001
LV mass index (g/m2)	113.64 ± 37.04	112.12 ± 36.06	127.65 ± 40.58	110.37 ± 35.94	<0.001	0.307	<0.001
Aortic Regurgitation Grade					0.133	0.058	0.615
none	2067 (44.1%)	1191 (42.7%)	274 (45.1%)	602 (46.9%)	0.278	0.012	0.490
mild	2361 (50.4%)	1434 (51.4%)	308 (50.7%)	619 (48.2%)	0.788	0.064	0.324
moderate	251 (5.4%)	165 (5.9%)	24 (4.0%)	62 (4.8%)	0.063	0.186	0.478
severe	3 (0.1%)	1 (0.0%)	1 (0.2%)	1 (0.1%)	0.325	0.531	0.539
Mitral Regurgitation Grade					<0.001	<0.001	0.134
none	962 (21.7%)	656 (25.0%)	86 (14.8%)	220 (17.9%)	<0.001	<0.001	0.107
mild	2931 (66.2%)	1702 (65.0%)	400 (69.0%)	829 (67.6%)	0.066	0.117	0.589
moderate	485 (11.0%)	241 (9.2%)	88 (15.2%)	156 (12.7%)	<0.001	0.001	0.161
severe	49 (1.1%)	21 (0.8%)	6 (1.0%)	22 (1.8%)	0.614	0.008	0.307
Tricuspid Regurgitation Grade					<0.001	<0.001	0.612
none	1458 (35.4%)	921 (38.0%)	166 (30.9%)	371 (32.0%)	0.002	<0.001	0.695
mild	2258 (54.8%)	1327 (54.8%)	306 (57.0%)	625 (53.9%)	0.363	0.641	0.249
moderate	337 (8.2%)	155 (6.4%)	52 (9.7%)	130 (11.2%)	0.009	<0.001	0.355
severe	65 (1.6%)	19 (0.8%)	13 (2.4%)	33 (2.8%)	0.004	<0.001	0.748
Depicted are count (%) and means (+- SD) with p-values from Fisher's tests (2x2), chisquare tests (if more than 2x2 categorical variables) and t-tests							

DD=diastolic diameter, HG=high gradient, LFLG=low-flow-low-gradient, LV=left ventricular, LVEF=left ventricular ejection fraction, SD=systolic diameter

Table S4 - TAVI Prosthesis and Valve sizes used.

	All groups	High gradient	Classical LFLG	Paradoxical LFLG	p Value	p Value	p Value
					C-LFLG vs HG	P-LFLG vs HG	P-LFLG vs C-LFLG
Device	n = 8898	n = 5083	n = 1354	n = 2461	0.001	<0.001	<0.001
Medtronic CoreValve	800 (9.0%)	499 (9.8%)	150 (11.1%)	151 (6.1%)	0.171	<0.001	<0.001
Edwards Sapien XT	521 (5.9%)	326 (6.4%)	79 (5.8%)	116 (4.7%)	0.488	0.003	0.144
Acurate/-Neo	813 (9.1%)	438 (8.6%)	97 (7.2%)	278 (11.3%)	0.086	<0.001	<0.001
JenaValve	52 (0.6%)	37 (0.7%)	6 (0.4%)	9 (0.4%)	0.347	0.060	0.789
SJM Portico	626 (7.0%)	352 (6.9%)	103 (7.6%)	171 (6.9%)	0.403	0.961	0.471
Medtronic Engager	2 (0.0%)	1 (0.0%)	1 (0.1%)	0 (0.0%)	0.376	1.000	0.355
Direct Flow Medical	32 (0.4%)	17 (0.3%)	6 (0.4%)	9 (0.4%)	0.607	0.836	0.789
Edwards Sapien 3	3281 (36.9%)	1866 (36.7%)	532 (39.3%)	883 (35.9%)	0.082	0.491	0.039
BSC Lotus	280 (3.1%)	176 (3.5%)	37 (2.7%)	67 (2.7%)	0.200	0.095	1.000
Medtronic Evolut R	1170 (13.1%)	633 (12.5%)	186 (13.7%)	351 (14.3%)	0.215	0.031	0.697
BSC Lotus Edge	33 (0.4%)	23 (0.5%)	2 (0.1%)	8 (0.3%)	0.140	0.565	0.510
Allegra NVT	66 (0.7%)	43 (0.8%)	2 (0.1%)	21 (0.9%)	0.003	1.000	0.007
Medtronic Evolut PRO	630 (7.1%)	363 (7.1%)	63 (4.7%)	204 (8.3%)	0.001	0.077	<0.001
Edwards Centera	21 (0.2%)	14 (0.3%)	1 (0.1%)	6 (0.2%)	0.219	1.000	0.433
Edwards Sapien 3 ULTRA	571 (6.4%)	295 (5.8%)	89 (6.6%)	187 (7.6%)	0.301	0.004	0.267
Valve size (mm)	n = 8896, 26.7 ± 2.5	n = 5081, 26.6 ± 2.5	n = 1354, 27.6 ± 2.5	n = 2461, 26.3 ± 2.5	<0.001	<0.001	<0.001

C=classical, HG=high gradient, LFLG=low-flow-low-gradient, p=paradoxical

Table S5 – Unadjusted primary and secondary outcomes at 30 days and 1 year.

	High gradient	Classical LFLG	Paradoxical LFLG	Classical LFLG vs HG		Paradoxical LFLG vs HG		Paradoxical vs Classical LFLG	
	N = 5094	N = 1356	N = 2464	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
At 30 days									
Mortality	121 (2.4)	54 (4.0)	72 (2.9)	1.68 (1.22-2.32)	0.002	1.23 (0.92-1.65)	0.165	0.73 (0.51-1.04)	0.083
Cardiovascular Mortality	110 (2.2)	48 (3.6)	60 (2.4)	1.64 (1.17-2.31)	0.004	1.13 (0.82-1.54)	0.456	0.69 (0.47-1.00)	0.052
Myocardial Infarction	32 (0.6)	6 (0.4)	9 (0.4)	0.70 (0.29-1.69)	0.431	0.58 (0.28-1.22)	0.150	0.82 (0.29-2.32)	0.714
Periprocedural Myocardial Infarction	25 (0.5)	4 (0.3)	7 (0.3)	0.60 (0.21-1.73)	0.344	0.58 (0.25-1.34)	0.201	0.96 (0.28-3.29)	0.951
Spontaneous Myocardial Infarction	7 (0.1)	2 (0.2)	2 (0.1)	1.08 (0.22-5.18)	0.927	0.59 (0.12-2.84)	0.512	0.55 (0.08-3.90)	0.549
Cerebrovascular Accident	172 (3.4)	40 (3.0)	86 (3.5)	0.87 (0.62-1.23)	0.434	1.03 (0.80-1.34)	0.810	1.18 (0.81-1.72)	0.377
Disabling Stroke	104 (2.1)	18 (1.3)	44 (1.8)	0.65 (0.39-1.07)	0.089	0.87 (0.61-1.24)	0.448	1.35 (0.78-2.33)	0.287
NonDisabling Stroke	57 (1.1)	15 (1.1)	32 (1.3)	0.99 (0.56-1.75)	0.969	1.16 (0.75-1.79)	0.503	1.17 (0.64-2.17)	0.611
Bleeding	890 (17.5)	226 (16.7)	418 (17.0)	0.95 (0.82-1.10)	0.511	0.97 (0.86-1.09)	0.593	1.02 (0.87-1.20)	0.834
Life Threatening Bleeding	268 (5.3)	70 (5.2)	111 (4.5)	0.98 (0.75-1.28)	0.890	0.85 (0.68-1.07)	0.163	0.87 (0.65-1.17)	0.362
Major Bleeding	387 (7.6)	93 (6.9)	191 (7.8)	0.90 (0.72-1.13)	0.367	1.02 (0.86-1.21)	0.829	1.13 (0.88-1.45)	0.330
Minor Bleeding	253 (5.0)	67 (5.0)	122 (5.0)	0.99 (0.76-1.30)	0.970	1.00 (0.80-1.24)	0.971	1.00 (0.74-1.35)	0.994
Acute Kidney Injury	146 (2.9)	72 (5.4)	87 (3.6)	1.86 (1.40-2.47)	<0.001	1.23 (0.94-1.61)	0.124	0.66 (0.48-0.90)	0.010
Stage 1	70 (1.4)	26 (1.9)	44 (1.8)	1.39 (0.89-2.19)	0.147	1.30 (0.89-1.89)	0.175	0.93 (0.57-1.51)	0.771
Stage 2	32 (0.6)	15 (1.1)	19 (0.8)	1.76 (0.95-3.25)	0.070	1.22 (0.69-2.16)	0.487	0.69 (0.35-1.37)	0.291
Stage 3	44 (0.9)	31 (2.3)	24 (1.0)	2.65 (1.68-4.20)	<0.001	1.13 (0.68-1.85)	0.640	0.42 (0.25-0.72)	0.002
Vascular Access Site and Access Related Complications	803 (15.8)	193 (14.3)	387 (15.7)	0.90 (0.77-1.05)	0.190	1.00 (0.88-1.12)	0.950	1.11 (0.93-1.32)	0.251
Major Vascular Complications	501 (9.8)	125 (9.2)	235 (9.5)	0.94 (0.77-1.14)	0.511	0.97 (0.83-1.13)	0.689	1.03 (0.83-1.29)	0.759
Minor Vascular Complications	305 (6.0)	68 (5.0)	149 (6.1)	0.84 (0.64-1.09)	0.181	1.01 (0.83-1.23)	0.923	1.21 (0.91-1.61)	0.196
Pacemaker implantation	836 (16.6)	238 (17.7)	377 (15.4)	1.07 (0.92-1.23)	0.374	0.92 (0.82-1.04)	0.203	0.87 (0.74-1.02)	0.081
At 1 year									
Mortality	438 (8.8)	261 (19.8)	276 (11.5)	2.36 (2.02-2.75)	<0.001	1.32 (1.14-1.54)	<0.001	0.56 (0.47-0.66)	<0.001
Cardiovascular Mortality	285 (5.8)	188 (14.6)	180 (7.6)	2.59 (2.16-3.12)	<0.001	1.32 (1.10-1.60)	0.003	0.51 (0.42-0.63)	<0.001
Myocardial Infarction	57 (1.2)	11 (0.9)	24 (1.1)	0.75 (0.39-1.44)	0.388	0.88 (0.55-1.42)	0.599	1.17 (0.57-2.39)	0.668
Spontaneous Myocardial Infarction	32 (0.7)	7 (0.6)	17 (0.8)	0.88 (0.39-1.98)	0.750	1.12 (0.62-2.02)	0.707	1.28 (0.53-3.08)	0.584
Cerebrovascular Accident	226 (4.6)	62 (4.9)	140 (6.0)	1.05 (0.79-1.39)	0.728	1.29 (1.05-1.60)	0.017	1.23 (0.91-1.66)	0.176
Disabling Stroke	135 (2.7)	29 (2.3)	66 (2.8)	0.82 (0.55-1.22)	0.330	1.02 (0.76-1.36)	0.918	1.24 (0.80-1.92)	0.335
NonDisabling Stroke	73 (1.5)	22 (1.7)	56 (2.4)	1.16 (0.72-1.87)	0.545	1.60 (1.13-2.27)	0.008	1.38 (0.84-2.26)	0.200
Bleeding	975 (19.3)	264 (20.0)	487 (20.1)	1.02 (0.89-1.17)	0.741	1.03 (0.93-1.15)	0.558	1.01 (0.87-1.17)	0.900
Life Threatening Bleeding	313 (6.2)	92 (7.1)	149 (6.2)	1.12 (0.89-1.41)	0.340	0.99 (0.81-1.20)	0.888	0.88 (0.68-1.14)	0.338
Major Bleeding	429 (8.5)	105 (7.9)	212 (8.7)	0.92 (0.75-1.14)	0.461	1.02 (0.87-1.21)	0.790	1.11 (0.88-1.40)	0.390
Minor Bleeding	281 (5.6)	80 (6.1)	145 (6.0)	1.08 (0.84-1.38)	0.545	1.07 (0.87-1.31)	0.513	0.99 (0.75-1.30)	0.944
Pacemaker implantation	890 (17.8)	264 (20.0)	422 (17.4)	1.12 (0.98-1.28)	0.107	0.97 (0.87-1.09)	0.650	0.87 (0.75-1.01)	0.075

Number of first event (%). Administrative censoring was performed at 30days and 1 year follow-up;

CI = confidence interval, HG = high gradient, HR = hazard ratio, LFLG= low-flow-low-gradient

Table S6 – Mortality at 30 days, 1 year and 5 years; adjusted for age, sex, atrial fibrillation and STS PROM.

	High gradient	Classical LFLG	Paradoxical LFLG	Classical LFLG vs HG		Paradoxical LFLG vs HG		Paradoxical vs Classical LFLG	
	N=3685	N=986	N=1938	Adj. HR (95% CI)	Adj. p-value	Adj. HR (95% CI)	Adj. p-value	Adj. HR (95% CI)	Adj. p-value
30d Mortality	76 (2.1)	36 (3.7)	54 (2.8)	1.28 (0.85-1.93)	0.245	1.26 (0.88-1.79)	0.203	0.98 (0.64-1.52)	0.945
1y Mortality	295 (8.3)	185 (19.5)	219 (11.7)	1.75 (1.44-2.13)	<0.001	1.34 (1.12-1.60)	0.001	0.76 (0.62-0.94)	0.009
5y Mortality	737 (43.8)	373 (64.7)	501 (52.2)	1.61 (1.41-1.84)	<0.001	1.33 (1.18-1.49)	<0.001	0.83 (0.72-0.95)	0.007

Administrative censoring was performed sharply at 30 days, 1 year and 5 years of follow-up.

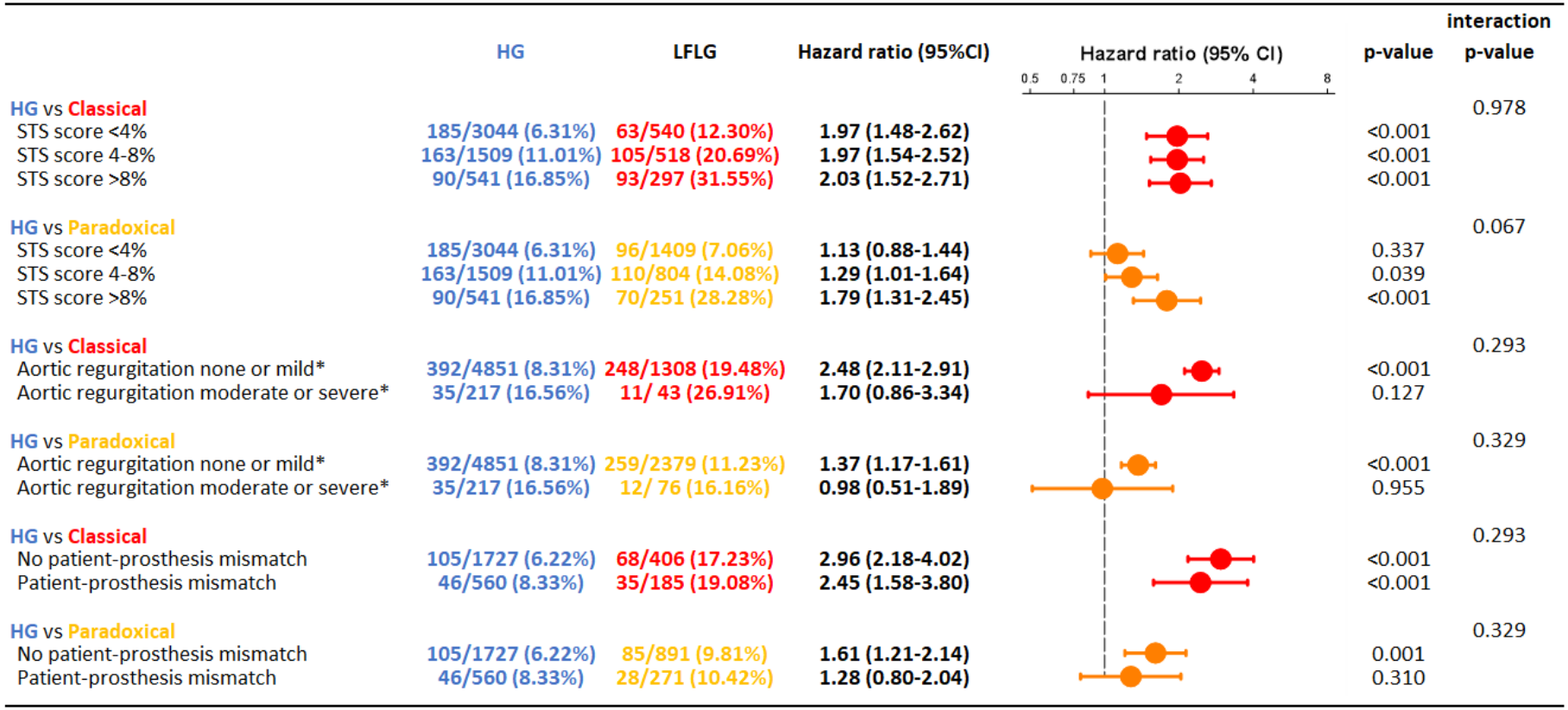
adj=adjusted, CI=confidence interval, d=days, HG=high gradient, HR=hazard ratio, LFLG=low-flow-low-gradient, y=year(s)

Table S7 – Mortality at 30 days, 1 year and 5 years; adjusted for age, sex, atrial fibrillation and STS PROM in patients with **transfemoral access**.

	High gradient	Classical LFLG	Paradoxical LFLG	Classical LFLG vs HG		Paradoxical LFLG vs HG		Paradoxical vs Classical LFLG	
	N=3451	N=903	N=1802	Adj. HR (95% CI)	Adj. p-value	Adj. HR (95% CI)	Adj. p-value	Adj. HR (95% CI)	Adj. p-value
30d Mortality	65 (1.9)	29 (3.2)	45 (2.5)	1.22 (0.77-1.92)	0.392	1.23 (0.84-1.81)	0.282	1.01 (0.63-1.63)	0.959
1y Mortality	269 (8.1)	162 (18.6)	194 (11.2)	1.71 (1.39-2.10)	<0.001	1.31 (1.09-1.58)	0.004	0.77 (0.62-0.95)	0.017
5y Mortality	671 (43.2)	334 (64.3)	448 (51.1)	1.60 (1.39-1.83)	<0.001	1.29 (1.14-1.46)	<0.001	0.81 (0.70-0.94)	0.005

adj=adjusted, CI=confidence interval, d=days, HG=high gradient, HR=hazard ratio, LFLG=low-flow-low-gradient, y=year(s)

FIGURE S1. Subgroup analysis.



Nr of deaths at 1 year / sample size (Kaplan-Meier estimate %); *discharge echo or post-procedure assessment used;

PPM - indexed aortic valve area (aortic valve area cm² divided by body surface area m²) ≤0.85 for body mass index BMI <30 or unknown BMI; ≤0.70 for BMI ≥30 after TAVI (discharge echo).

CI=confidence interval, HG=high gradient, LFLG=low-flow-low-gradient