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ORIGINAL RESEARCH

Prevalence and Outcomes of Low-Gradient Severe Aortic Stenosis—From the National Echo Database of Australia

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BACKGROUND: The prevalence and outcomes of the different subtypes of severe low-gradient aortic stenosis (AS) in routine clinical cardiology practice have not been well characterized.

METHODS AND RESULTS: Data were derived from the National Echocardiography Database of Australia. Of 192 060 adults (aged 62.8±17.8 [mean±SD] years) with native aortic valve profiling between 2000 and 2019, 12 013 (6.3%) had severe AS. Of these, 5601 patients (47%) had high-gradient and 6412 patients (53%) had low-gradient severe AS. The stroke volume index was documented in 2741 (42.7%) patients with low gradient; 1750 patients (64%) with low flow, low gradient (LFLG); and 991 patients with normal flow, low gradient. Of the patients with LFLG, 1570 (89.7%) had left ventricular ejection fraction recorded; 959 (61%) had paradoxical LFLG (preserved left ventricular ejection fraction), and 611 (39%) had classical LFLG (reduced left ventricular ejection fraction). All-cause and cardiovascular-related mortality were assessed in the 8162 patients with classifiable severe AS subtype during a mean±SD follow-up of 88±45 months. Actual 1-year and 5-year all-cause mortality rates varied across these groups and were 15.8% and 49.2% among patients with high-gradient severe AS, 11.6% and 53.6% in patients with normal-flow, low-gradient severe AS, 16.9% and 58.8% in patients with paradoxical LFLG severe AS, and 30.5% and 72.9% in patients with classical LFLG severe AS. Compared with patients with high-gradient severe AS, the 5-year age-adjusted and sex-adjusted mortality risk hazard ratios were 0.94 (95% CI, 0.85–1.03) in patients with normal-flow, low-gradient severe AS; 1.01 (95% CI, 0.92–1.12) in patients with paradoxical LFLG severe AS; and 1.65 (95% CI, 1.48–1.84) in patients with classical LFLG severe AS.

CONCLUSIONS: Approximately half of those patients with echocardiographic features of severe AS in routine clinical practice have low-gradient hemodynamics, which is associated with long-term mortality comparable with or worse than high-gradient severe AS. The poorest survival was associated with classical LFLG severe AS.

Key Words: aortic stenosis ■ low flow, low gradient ■ low gradient ■ normal flow, low gradient

See Editorial by Chin

Aortic stenosis (AS) is the most prevalent valvular heart disease in high-income countries associated with their progressively aging populations.[1] With no currently available medical treatment, aortic valve replacement (AVR) remains the mainstay of treatment for severe AS, which has become possible in a greater proportion of patients since the introduction of transcatheter aortic valve replacement (TAVR).

A subset of patients with echocardiographic evidence of severe AS (aortic valve area [AVA] <1 cm^2) do not meet the conventional hemodynamic criteria for intervention (ie, aortic valve [AV] mean gradient ≥40 mm Hg and/or peak velocity ≥4 m/s) and are therefore commonly termed "low-gradient" severe AS.[2] When this occurs because of a state of reduced left ventricular (LV) stroke volume (≤35 mL/m^2), patients

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CLINICAL PERSPECTIVE

What Is New?

- Severe low-gradient aortic stenosis is as common in routine clinical cardiology practice as severe high-gradient aortic stenosis, with most patients with low-gradient aortic stenosis having low-flow, low-gradient hemodynamics.
- The 5-year survival rates of patients with low-gradient severe aortic stenosis are similar or worse than that of patients with high-gradient severe aortic stenosis, with the worst survival rates seen in classical low-flow, low-gradient hemodynamics.

What Are the Clinical Implications?

- Clinicians should recognize these prevalent severe aortic stenosis subtypes with low-gradient hemodynamics and promptly refer patients for intervention as recommended by the latest American Heart Association guidelines.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AV	aortic valve
AVA	aortic valve area
AVR	aortic valve replacement
LFLG	low-flow, low-gradient
NEDA	National Echo Database of Australia
NFLG	normal-flow, low-gradient
SVI	stroke volume index
TAVR	transcatheter aortic valve replacement

are classified as "low-flow, low-gradient" (LFLG) severe AS, whereas those with normal LV stroke volume (>35 mL/m^2) are termed "normal-flow, low-gradient" (NFLG) severe AS. Patients with LFLG severe AS are often further subclassified according to their LV function into those with reduced LV ejection fraction (LVEF; classical LFLG) and those with preserved LVEF (paradoxical LFLG).

It is commonly believed that LFLG severe AS represents a small minority of the overall severe AS patient population.[3] However, this assumption is mainly informed by previous studies assessing only patients referred for AVR. Recently published data suggest that low-gradient severe AS may in fact be as common as high-gradient severe AS in routine clinical practice.[4] This raises the concern that many patients with LFLG severe AS are not referred and/or considered for AVR despite its apparent benefits in this specific patient population.[3] Similarly, the prognosis, indications for, and benefit from intervention in patients with NFLG also remain unclear, with conflicting data previously published in this regard.[3,5,6]

Our aim was to address key deficits around our knowledge of low-gradient severe AS by delineating both the prevalence and associated outcomes of these specific low-gradient severe AS subtypes as encountered in routine cardiology clinical practice. For this purpose, we examined data from NEDA (National Echo Database of Australia)[7]—a large clinical registry that has already generated important insights into the evolving understanding of AS in recent years.[4,8]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Data

The purpose and overall design of the large, multicenter clinical registry NEDA have been previously described.[7] In brief, NEDA is an ongoing observational registry containing detailed echocardiographic and basic demographic data of adults from >25 participating centers around Australia (https://www.neda.net.au/). NEDA is registered with the publicly accessible Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approval has been obtained from all relevant human research ethics committees.

At the time of study census, NEDA contained >1 million echo reports from >600 000 individual patients. The study period included patients with echocardiograms performed between January 2000 and June 2019. Survival status and date of death (when relevant) for all patients in the database was obtained during a median (interquartile range) study follow-up of 6.2 (3.8–9.8) years with case censoring in May 2019. Specifically, enhanced probability matching linkage was conducted on an individual basis with the well-validated Australian National Death Index.[9] Causes of death, as derived from medical death certificates, were categorized according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) coding.[10] Events with *ICD-10* chapter codes in the range of I00 to I99 were considered as cardiovascular-related mortality; these include valvular heart disease, ischemic heart disease, heart failure, cerebrovascular disease, and peripheral vascular disease.

Study Cohort

From the entire NEDA database at the time of study census (May 2019), only patients aged ≥18 years with

echocardiographic investigations performed since the year 2000 and containing the parameters necessary for the appropriate diagnosis of severe AS were included in this analysis. Hence, only echocardiographic investigations with available AVA, AV peak velocity, and AV mean gradient data were included. In addition, for patients with multiple available serial echocardiographic studies, only the first chronological investigation was included. Of these, 7483 had a previous AVR recorded and were excluded from further analysis (see Figure 1). This resulted in an analysis cohort of 192 060 patients that was then further assessed to specifically identify patients with severe native valve AS.

Severe AS was classified using criteria based on current expert recommendations[2,3]:

1. High-gradient severe AS defined as AV mean gradient ≥40 mm Hg and/or peak velocity ≥4 m/s (regardless of AVA).
2. Low-gradient severe AS defined as AVA ≤1 cm^2 with AV mean gradient <40 mm Hg and an AV peak velocity <4 m/s.
3. Classical LFLG severe AS defined as AVA ≤1 cm^2 with AV mean gradient <40 mm Hg, AV peak velocity <4 m/s, stroke volume index (SVI) ≤35 mL/m^2, and LVEF <50%.
4. Paradoxical LFLG severe AS defined as AVA ≤1 cm^2 with AV mean gradient <40 mm Hg, AV peak velocity <4 m/s, SVI ≤35 mL/m^2, and LVEF ≥50%.
5. NFLG severe AS defined as AVA ≤1 cm^2 with AV mean gradient <40 mm Hg, AV peak velocity <4 m/s, and SVI >35 mL/m^2.

AVA for all included echocardiograms was calculated from the continuity equation using either the velocity time integral and/or peak velocity ratio,[11] with the minimum value used for the aforementioned diagnostic criteria. Reported LVEF was obtained by the following hierarchal methods: physician reported, volumetric apical biplane (Simpsons), volumetric apical 4-chamber, volumetric apical 2-chamber, and the Teichholz formula. LV mass was calculated using the American Society of Echocardiography 2-dimensional linear formula.[12]

Study Outcomes

The prevalence of the different severe AS subtypes was assessed based on the aforementioned diagnostic criteria. SVI data were missing in many patients with low-gradient severe AS, whereas LVEF data were missing in a minority of patients with LFLG severe AS (see Figure 1). Therefore, the prevalence of low-gradient severe AS subtypes (NFLG and paradoxical and classical LFLG) was estimated assuming equal distribution in those with and without available SVI and/or LVEF data.

All-cause and cardiovascular-related mortality were assessed in 8162 patients with classifiable severe AS subtypes. The follow-up period for each patient was from time of the diagnostic echocardiogram to time of study census (May 2019, as noted previously). Mean±SD follow-up was 95±45 months for patients with high-gradient severe AS, 83±45 months for patients with NFLG severe AS, 76±43 months for patients with classical LFLG severe AS, and 66±39 months for patients with paradoxical LFLG severe AS. Overall, 1 year of follow-up data were available in 98% (8001) of patients, and 5 years of follow-up data were available in 79% (6421) of patients.

AVR Status

Patients were only recorded to have undergone AVR during follow-up, either surgically or with a TAVR procedure, if any of their subsequent available echocardiograms in the database reported evidence of a replaced or implanted aortic valve. As previously reported,[8] AVR was identified using text recognition software of the free text and conclusions of each analyzed echo report. NEDA data have not yet been linked to national surgical or interventional databases in Australia, and thus patients might have had an AVR during follow-up but were only known to have had this where a follow-up echo in NEDA recorded this in the report.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical variables are presented as count (percentage). Differences in presented variables between each severe low-gradient AS group and the severe high-gradient AS group were assessed by ANOVA with post hoc Bonferroni correction. The 1-year and 5-year mortality curves (both all cause and cardiovascular related) for each severe AS subgroup were plotted using the Kaplan-Meier method, with patients censored at last known survival status (ie, study census, May 2019). In addition, age-adjusted and sex-adjusted risk (hazards ratios [HRs] and 95% CI) for all-cause and cardiovascular-related mortality according to severe AS subgroup were assessed using Cox proportional hazards regression models (entry model with assumption of proportional hazards confirmed by visual inspection). The cardiovascular-related mortality analyses included 7639 patients with available cause of death data. All statistical calculations were performed using SPSS software (version 20; IBM, Armonk, NY), and significance was inferred at a 2-sided *P* value of <0.05 for all analyses.

A total of 3 sensitivity analyses (see the Supplemental Material) were performed to rule out any significant variations in outcomes that may have resulted from changing our cohort selection or diagnostic criteria

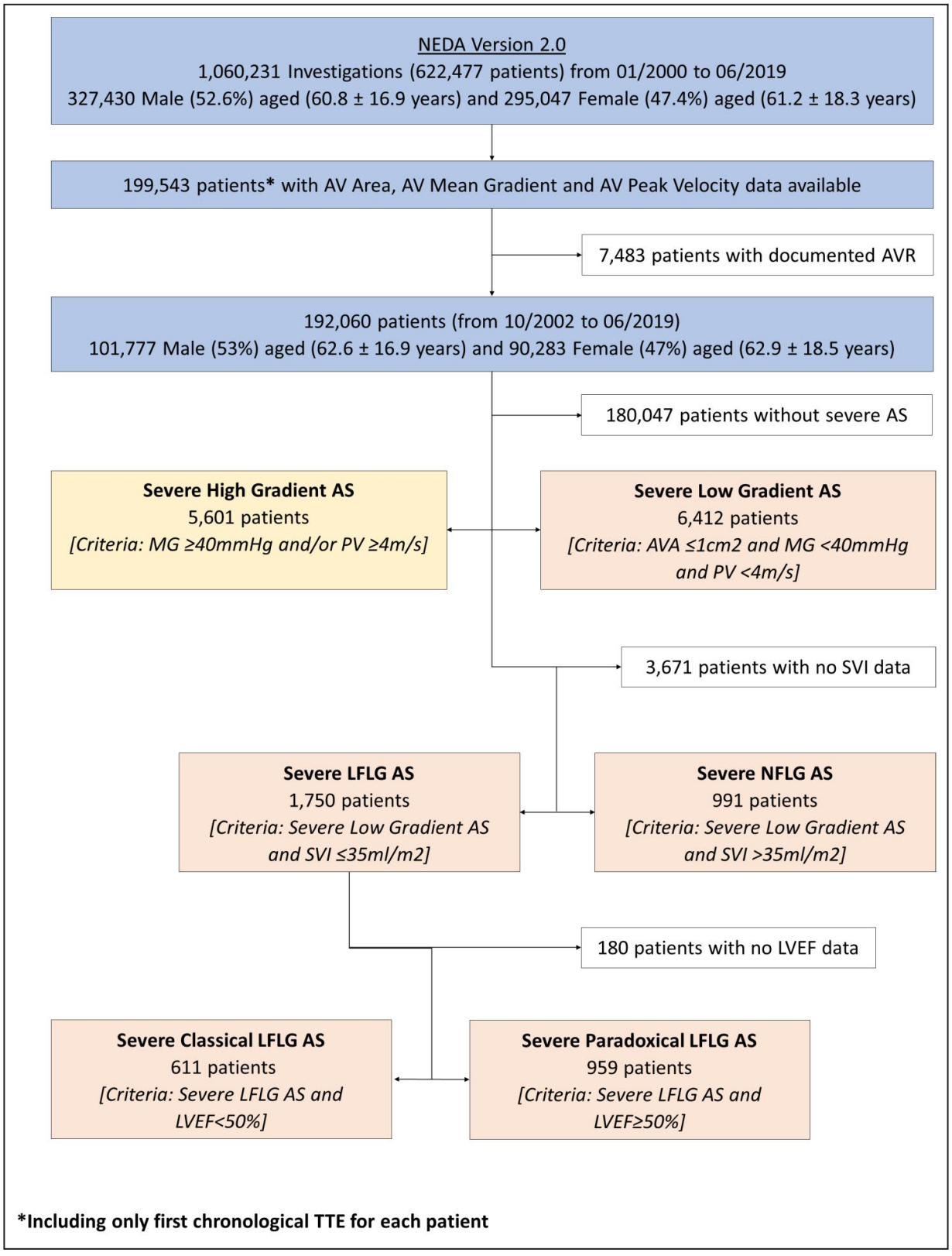

Figure 1. Study flowchart.
The main analyzed study cohort included 8162 patients with severe AS: 5601 high gradient, 991 NFLG, 611 classical LFLG, and 959 paradoxical LFLG. AS indicates aortic stenosis; AV, aortic valve; AVA, aortic valve area; AVR, aortic valve replacement; LFLG, low flow, low gradient; LVEF, left ventricular ejection fraction; MG, Mean Gradient; NEDA, National Echo Database of Australia; NFLG, normal-flow, low-gradient; PV, Peak Velocity; SVI, stroke volume index; and TTE, transthoracic echocardiogram.

(as described previously): (1) an analysis including all patients in the NEDA database with any (rather than all) of the diagnostic AV parameters available (ie, AVA, AV peak velocity, or AV mean gradient), (2) analysis including only patients with AVA calculated using continuity equation with velocity time integral measurement (ie, not including patients with AVA calculated from peak velocity measurement), and (3) analysis using only patients with confirmed indexed AVA ≤0.6 cm^2/m^2. Furthermore, we repeated the aforementioned Cox proportional hazards regression analyses (see the Supplemental Material) while including LV mass and body surface area as additional covariates, which were available in most (58%) but not the entire cohort. Finally, as AVR is known to alter the natural history of severe AS, regardless of subtype, we also repeated the main analyses including only patients without known AVR during follow-up (see the Supplemental Material).

RESULTS

Prevalence of Severe AS Subtypes

From a total of 192 060 patients with native aortic valves, 12 013 patients (6.3%) were identified as having severe AS (Figure 1). Of these, 5601 (46.6%) had high-gradient severe AS, whereas 6412 (53.4%) had low-gradient severe AS. Considering the 2561 low-gradient patients with available SVI and/or LVEF data (Figure 1), the prevalence of the different subgroups were 19.2% NFLG, 20.8% paradoxical LFLG, and 13.3% classical LFLG severe AS.

SVI data in patients with low-gradient severe AS was more often available in those with diagnostic transthoracic echocardiograms from 2010 onward (58% versus 43% overall); 3584 (53%) had high-gradient severe AS, and 3182 (47%) had low-gradient severe AS (data not presented in figures/tables). The prevalence of the different low-gradient subgroups diagnosed since 2010 were 14.6% NFLG, 20.1% paradoxical LFLG, and 12.3% classical LFLG severe AS. From the first sensitivity analysis (Figures S1 and S2), the prevalence of the severe AS subgroups were 56% high-gradient, 16.6% NFLG, 16.8% paradoxical LFLG, and 10.6% classical LFLG severe AS. Similarly, results from the second sensitivity analysis (Figures S3 and S4) were 49% high-gradient, 17% NFLG, 20.5% paradoxical LFLG, and 11.5% classical LFLG severe AS.

Patient Characteristics According to Severe AS Subtype

Basic demographic, anthropometric, and echocardiographic data of patients with different subtypes of severe AS are summarized in Table 1. There was a predominance of women among the patients with paradoxical LFLG (63%) and NFLG (58%) severe AS and a predominance of men among the patients with classical LFLG (64%) and high-gradient (57%) severe AS. Patients with classical LFLG presented with more cardiac abnormalities at the time of diagnosis, evidenced by larger LV and left atrium (LA) cavity sizes, higher LV mass index, higher estimated right ventricular systolic pressure, and greater severity of mitral and tricuspid valvular regurgitation. Patients with paradoxical LFLG had significantly higher body mass indexes and lower diastolic and systolic LV cavity sizes with lower indexed LV masses and smaller LV outflow tract diameters. Patients with NFLG severe AS had the largest indexed AVA and were significantly older with lower body mass indexes compared with patients with high-gradient severe AS.

For the substantial undifferentiated group of patients with low-gradient severe AS characteristics and no available SVI data (Table S1), the mean age was highest at 77.9 years, 55% were women, mean indexed AVA was 0.44 cm^2/m^2, average AV mean gradient was 21.2 mm Hg, and 27% had reduced systolic function with LVEF <50% (compared with 16% in patients with NFLG).

Mortality According to Severe AS Subtype

Recorded all-cause 1-year and 5-year mortality rates according to severe AS subgroup were 15.8% and 49.2% in high-gradient severe AS, 11.6% and 53.6% in NFLG severe AS, 16.9% and 58.8% in paradoxical LFLG severe AS, and 30.5% and 72.9% in classical LFLG severe AS, respectively.

Kaplan-Meier mortality curves at 1 and 5 years according to severe AS subgroup are presented in Figures 2 and 3. Unadjusted and adjusted (age and sex) HRs from Cox regression analyses at 1 and 5 years are summarized in Table 2. Patients with classical LFLG severe AS had significantly worse medium and long-term adjusted mortality compared with all other groups (eg, HR, 1.65 [95% CI, 1.48–1.84] at 5 years compared with high-gradient severe AS). Those with paradoxical LFLG severe AS had similar adjusted mortality at 1 and 5 years (HR, 0.91 [95% CI, 0.82–1.01] and HR, 1.01 [95% CI, 0.92–1.12], respectively) compared with patients with high-gradient severe AS. In patients with NFLG severe AS, adjusted mortality at 1 year was significantly lower (HR, 0.88; 95% CI, 0.80–0.96) and at 5 years was statistically similar (HR, 0.94; 95% CI, 0.85–1.03) compared with those with high-gradient severe AS. The recorded cause of death for patients with high-gradient severe AS and classical LFLG severe AS was predominantly cardiovascular related (Figure 4). In contrast, patients with NFLG severe AS had similar proportions of deaths from cardiovascular versus other causes of mortality, whereas the cause of death in paradoxical LFLG severe AS was more commonly not cardiovascular related (40% and

Table 1. Baseline Demographic, Anthropometric, and Echocardiographic Characteristics

Variable	High gradient (n=5601)	NFLG (n=991)	Classical LFLG (n=611)	Paradoxical LFLG (n=959)
Age, y	75.0±13.0	77.2±12.0*	76.2±12.2	74.3±14.4
Female sex	2392 (42.7)	578 (58.3)*	222 (36.3)*	602 (62.8)*
BMI, kg/m^2	27.8±6.1	26.2±5.2*	26.9±5.7*	28.6±6.9*
BSA, m^2	1.89±0.26	1.75±0.22*	1.87±0.25	1.85±0.27*
AVR performed†	2300 (41.1)	273 (27.5)*	119 (19.5)*	126 (13.2)*
Echocardiographic data				
LVOT diameter, cm	2.15±0.25	2.10±0.22*	2.08±0.28*	1.84±0.28*
AVA—VTI, cm^2	0.80±0.28	0.94±0.17*	0.83±0.28	0.87±0.26*
AVA—peak velocity, cm^2	0.80±0.28	0.92±0.12*	0.85±0.21*	0.87±0.19*
Indexed AVA—VTI, cm^2/m^2	0.43±0.15	0.54±0.12*	0.45±0.16*	0.48±0.15*
Peak AV velocity, m/s	4.6±0.5	3.4±0.4*	2.8±0.7*	2.7±0.7*
Mean AV gradient, mm Hg	49.8±12.4	27.6±7.1*	19.2±9.7*	18.0±9.6*
Stroke volume index	45.6±14.8	42.8±6.1*	24.1±7.0*	25.9±6.1*
LVEF, %	60.8±13.3	59.3±12.2*	33.3±10.5*	63.1±7.9*
LV mass index, g/m^2	118±33	103±30*	122±35*	91±27*
LVDD, cm	4.6±0.7	4.4±0.7*	5.2±0.9*	4.3±0.6*
LVSD, cm	3.0±0.8	3.0±0.8	4.2±1.0*	2.8±0.6*
LA volume index, mL/m^2	45.5±18.3	46.0±18.8	53.2±18.1*	40.6±20.1*
Mitral regurgitation (greater than or equal to moderate)	763 (13.6)	178 (18.0)*	200 (32.7)*	111 (11.6)
Tricuspid regurgitation (greater than or equal to moderate)	447 (8.0)	110 (11.1)*	161 (26.4)*	174 (18.1)*
Estimated RVSP, mm Hg	44.3±13.6	41.0±13.1*	46.0±12.8*	41.8±14.6*

Data are provided as mean±SD or number (percentage). AV indicates aortic valve; AVA, aortic valve area; AVR, aortic valve replacement; BMI, body mass index; BSA, body surface area; LA, left atrium; LFLG, low flow, low gradient; LV, left ventricle; LVDD, left ventricle diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVSD, left ventricle systolic diameter; NFLG, normal flow, low gradient; RVSP, right ventricle systolic pressure; and VTI, velocity time integral.

*P<0.05 compared with high-gradient severe AS group.

†P<0.001 compared with high-gradient severe AS group.

‡AVR performed before study census follow-up.

46% for cardiovascular-related death at 1 and 5 years, respectively).

The additional multivariate regression analysis, with further mortality risk adjustment for LV mass and body surface area (both available for 58% of cohort), showed similar results apart from the relative outcomes in patients with paradoxical LFLG severe AS (Figures S5 and S6); compared with patients with high-gradient severe AS, adjusted all-cause 5-year mortality was significantly higher in patients with paradoxical LFLG severe AS (HR, 1.14; 95% CI, 1.00–1.29). Regarding the 3 additional sensitivity analyses performed (Table S2, Figures S7 through S12), there was no significant change in either unadjusted or adjusted mortality for the different severe AS subtypes. As expected, removing patients with known AVR during follow-up from the analysis resulted in higher long-term mortality for all severe AS subgroups (Figure S13); the relative mortality increase correlated directly with the relative rate of AVR performed in each subgroup, most pronounced in the high-gradient severe AS subgroup.

AVR in Severe AS Subtypes

Overall, the highest rate of AVR was in patients with high-gradient severe AS (41%) followed by patients with NFLG severe AS (27.5%) and classical LFLG severe AS (19.5%) and lowest in patients with paradoxical LFLG severe AS (13%). Per mean follow-up years, the rate of AVR was 5.2% for patients with high-gradient severe AS, 4.0% for patients with NFLG severe AS, 3.1% for patients with classical LFLG severe AS, and 2.4% for patients with paradoxical LFLG severe AS (P<0.001).

DISCUSSION

This large, real-world cohort study, including >12 000 patients with severe AS and detailed AV and LV echocardiographic assessments, delineates the prevalence and outcomes for the different subtypes of severe AS seen in routine cardiology practice. Our results show that (1) approximately half of patients with severe AS have low-gradient hemodynamics; (2) the relative prevalence of

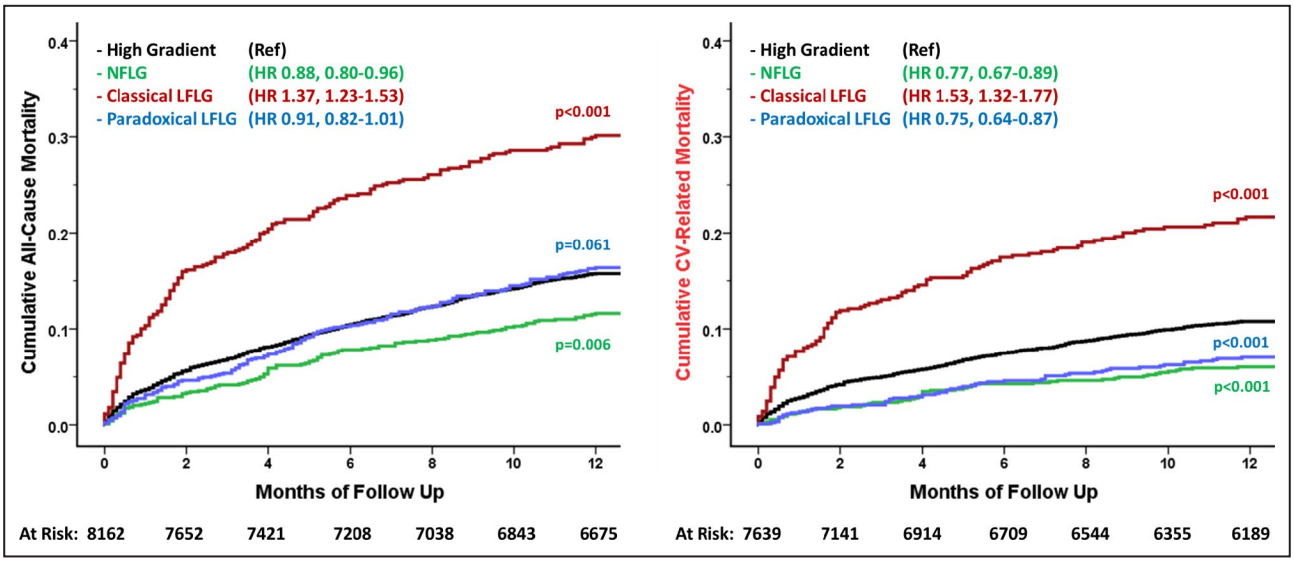

Figure 2. One-year all-cause and CV-related mortality.
Kaplan-Meier curves for all-cause mortality (Left Hand Side) and CV-related mortality (Right Hand Side), including the results of Cox regression analyses showing adjusted (age and sex) HR (95% CI) and P values compared with the high-gradient severe aortic stenosis subgroup. CV indicates cardiovascular; HR, hazard ratio; LFLG, low flow, low gradient; NFLG, normal flow, low gradient; and Ref, reference.

LFLG severe AS in routine clinical practice is higher than previously estimated, likely representing 30% to 35% of patients; and (3) within the study timeframe (2000–2019), patients with low-gradient severe AS had at least as serious and often worse long-term outcomes than those for patients with high-gradient severe AS, with the worst outcomes seen in patients with LFLG severe AS with reduced LVEF (classical LFLG).

From the results of our main analysis and supplementary sensitivity analyses of 12 013 patients with severe AS diagnosed in routine clinical practice between 2000 and 2019, the relative prevalence can be estimated as 45% to 55% for high-gradient severe AS, 15% to 20% for NFLG severe AS, 17% to 21% paradoxical LFLG severe AS, and 10% to 13% for classical LFLG severe AS. These estimates assume an equal distribution of LFLG and NFLG between patients with low-gradient severe AS in the cohort with and those without available SVI flow data. The relative prevalence of classical LFLG severe AS in our cohort was

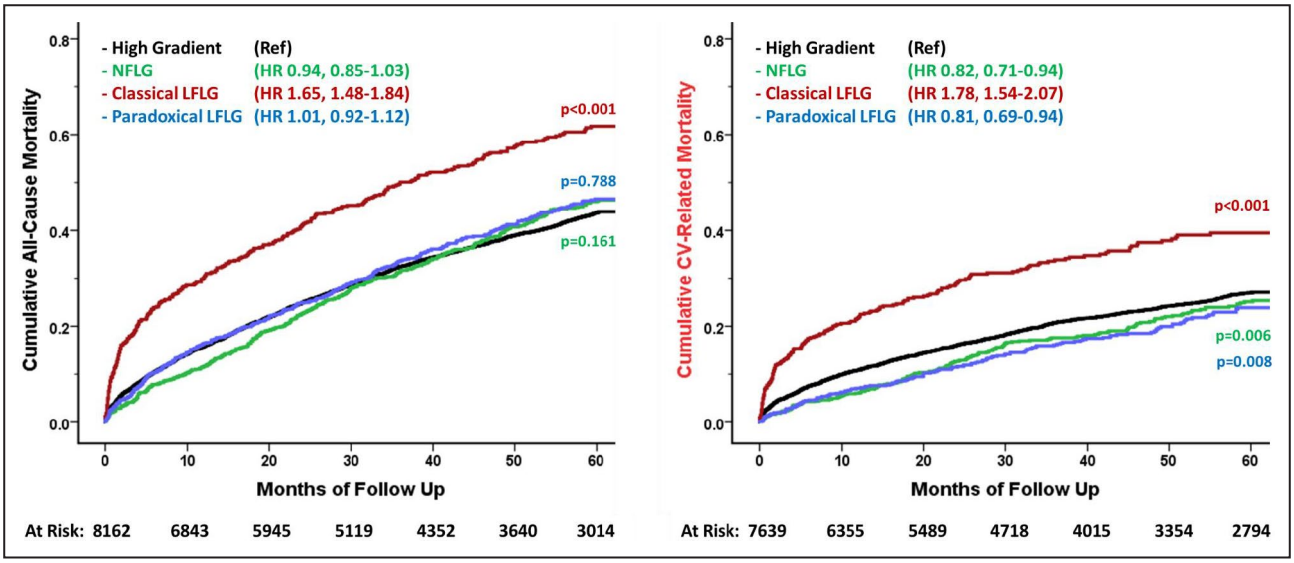

Figure 3. Five-year all-cause and CV-related mortality.
Kaplan-Meier curves for all-cause mortality (LHS) and CV-related mortality (RHS), including the results of Cox regression analyses showing adjusted (age and sex) HR (95% CI) and P values compared with the high-gradient severe aortic stenosis subgroup. CV indicates cardiovascular; HR, hazard ratio; LFLG, low flow, low gradient; NFLG, normal flow, low gradient; and Ref, reference.

Table 2. Relative Mortality Risk According to Severe Aortic Stenosis Subgroup

	High gradient	NFLG, HR (95% CI)	Classical LFLG, HR (95% CI)	Paradoxical LFLG, HR (95% CI)
1-year all-cause mortality				
Unadjusted	Reference	0.95 (0.86–1.04)	1.40 (1.25–1.55)	0.89 (0.80–0.98)
Adjusted, age and sex	Reference	0.88 (0.80–0.96)	1.37 (1.23–1.53)	0.91 (0.82–1.01)
1-year cardiovascular-related mortality				
Unadjusted	Reference	0.85 (0.74–0.98)	1.55 (1.34–1.80)	0.74 (0.63–0.86)
Adjusted, age and sex	Reference	0.77 (0.67–0.89)	1.53 (1.32–1.77)	0.75 (0.64–0.87)
5-year all-cause mortality				
Unadjusted	Reference	1.03 (0.94–1.13)	1.64 (1.47–1.83)	1.00 (0.90–1.11)
Adjusted, age and sex	Reference	0.94 (0.85–1.03)	1.65 (1.48–1.84)	1.01 (0.92–1.12)
5-year cardiovascular-related mortality				
Unadjusted	Reference	0.92 (0.80–1.06)	1.76 (1.52–2.04)	0.80 (0.68–0.94)
Adjusted, age and sex	Reference	0.82 (0.71–0.94)	1.78 (1.54–2.01)	0.81 (0.69–0.94)

Calculated unadjusted and adjusted (for patient age and sex) HR (95% CI) from Cox proportional hazards regression analyses are provided for both all-cause and CV-related mortality at 1 and 5 years for each severe low-gradient aortic stenosis subgroup in reference to patients with high-gradient severe aortic stenosis. HR indicates hazard ratio.

similar to previously reported small cohorts focusing on patients with high-risk TAVR,[13,14] whereas that of paradoxical LFLG severe AS was higher than the variable prevalence (3%–14%) reported in previous studies including patients with echocardiographic severe AS (AVA<1 cm^2) and preserved ejection fraction.[15,16] It is conceivable that SVI measurement during the index diagnostic echocardiogram was biased toward those patients suspected to have low-flow hemodynamics, which may lead to overestimation of the relative prevalence of LFLG severe AS in our cohort. However, several of the echo characteristic of the subgroup of patients with low-gradient severe AS without recorded SVI measurements, such as indexed AVA and AV mean gradient, were more consistent with those observed in confirmed LFLG than confirmed NFLG subgroups.

To our knowledge, with >5500 adults, this is by some margin the largest reported cohort of patients with high-gradient severe AS in routine cardiology clinical practice containing detailed echocardiographic and validated long-term mortality data. Demographic and echo characteristics (such as mitral regurgitation and LVEF) for patients with high-gradient AS in our cohort fall between those reported in recent large cohorts of patients with low[17] and intermediate to high-risk[18] severe AS undergoing AVR. However, both all-cause and cardiovascular-related 1-year mortality in our patients with high-gradient severe AS (16% and 11%, respectively) were higher than those reported for the intermediate to high-risk pre-AVR cohort (12.6% and 7.6%, respectively).[18] Long-term mortality was higher (49% versus 40% at 5 years) than that recently described in a smaller cohort of both symptomatic and asymptomatic 2097 patients with high-gradient severe AS as part of a multicenter registry of patients with severe AS in the pre-TAVR era.[19] These observations may be (at least partly) explained by the premise that a proportion of patients with high-gradient severe AS in routine clinical practice are not adequately referred to large tertiary centers for treatment.

The diagnosis and management of severe AS often becomes more challenging for that subset of patients who do not meet the current echocardiographic criteria for valve intervention despite evidence of important valve stenosis. Nevertheless, this heterogenous low-gradient group appears to have a poor prognosis and requires prompt assessment and intervention. Our results indicate that low-gradient severe AS is common, representing at the very least 45% of the patient population with severe AS in routine clinical practice. The common method of classifying this group is based on the flow across the AV (according to the calculated SVI) into patients with low flow (ie, SVI≤35 mL/m^2; LFLG AS) and those with normal flow (ie, SVI>35 mL/m^2; NFLG AS). Those with LFLG severe AS are often further subdivided into 2 groups, distinguished by the associated LV systolic function. In 1 group, termed classical LFLG, there is reduced LVEF as well as severe AS.

Consistent with this, classical LFLG in our cohort was associated with greater degrees of other valvular and extravalvular cardiac damage, including greater incidences of LV cavity dilatation and severe mitral and tricuspid valve regurgitation. Patients with classical LFLG in our cohort had significantly worse medium-term to long-term survival compared with all other patients. Particularly, cardiovascular-related mortality for these patients at 1 and 5 years was nearly twice that in patients with high-gradient severe AS (22% versus 10.5% and 40% versus 27%, respectively). This is consistent with results from smaller previous cohorts

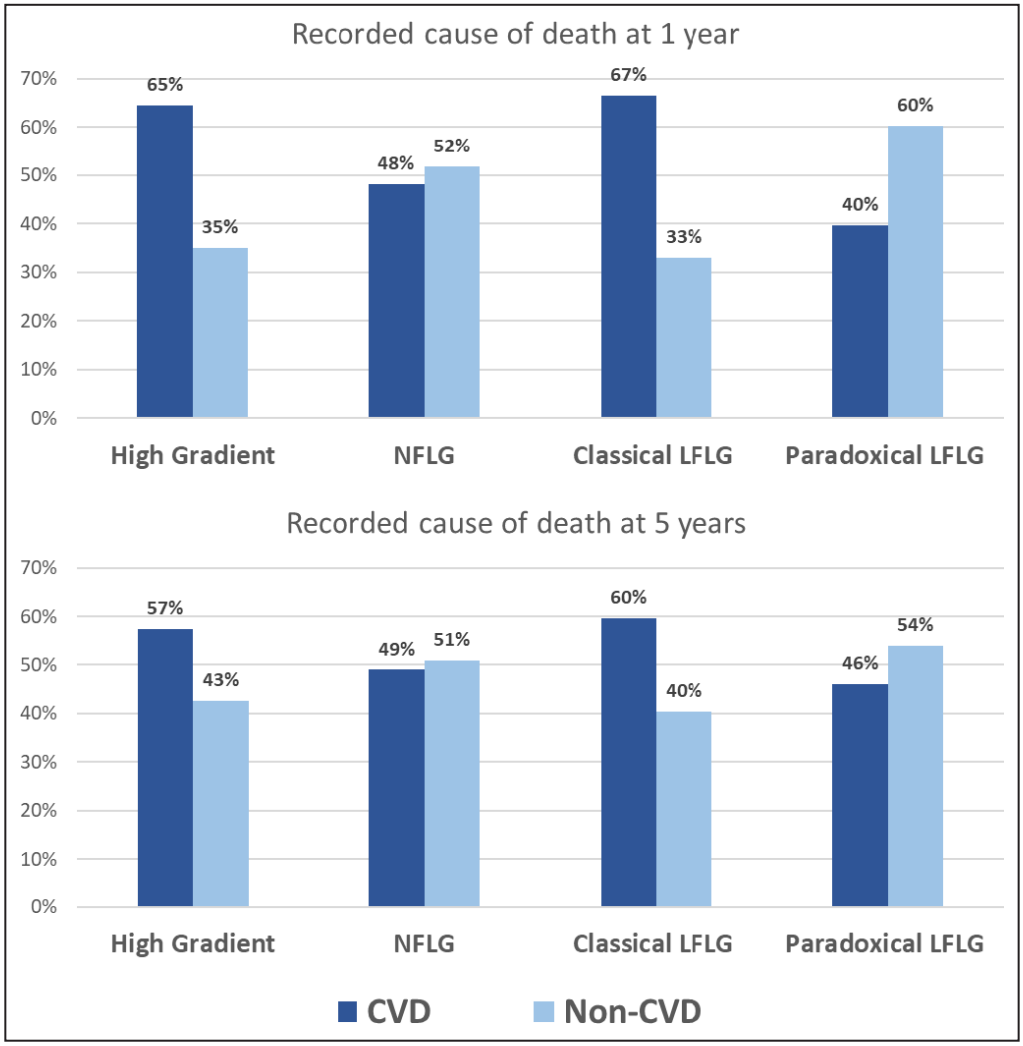

Figure 4. Cardiovascular-related vs other causes of mortality according to severe aortic stenosis subgroup.
Recorded cause of death (cardiovascular related vs not cardiovascular related) according to severe aortic stenosis subgroup for both 1-year (top) and 5-year (bottom) mortality. CVD indicates cardiovascular disease; LFLG, low flow, low gradient; and NFLG, normal flow, low gradient.

showing a poorer prognosis, both in general[19] and specifically following AVR,[14,20,21] in this classical LFLG population. Nevertheless, there is growing evidence to support a benefit for valve intervention in these patients compared with conservative management.[22–24] As comprehensive ascertainment of AVR was not possible in the NEDA database, without linkage to intervention databases nationally, we could not analyze the differential effects of AVR on outcomes in the different AS subtypes; this analysis may be possible in the future, when linkage data become available. Clinical trials are ongoing to address this important issue.[25]

The other LFLG group, paradoxical LFLG, is composed of patients with severe AS with reduced flow states attributed to restrictive LV pathophysiology and/or small ventricular volumes; these are often compared with patients with heart failure with preserved ejection fraction.[3] Paradoxical LFLG in our cohort was associated with similar medium-term (0–3 years) but worse long-term mortality than high-gradient severe AS (59% versus 49% at 5 years). We note that a higher proportion of deaths in this group with paradoxical LFLG AS were non-cardiovascular related compared with the other AS groups studied, consistent with a higher prevalence of significant comorbidities in this patient group.

The management of patients with NFLG severe AS can also be challenging. Although current guidelines[2] generally regard such patients as having only moderate AS, it has been argued that up to 50% have severe stenosis with evidence backing the case for early intervention.[3] It is likely that systemic hypertension and/or reduced aortic compliance may account for this

observed discordant valve area–gradient relationship in some patients.[3] It is important to emphasize that the accepted AVA cutoff for severe stenosis of 1 cm^2 corresponds in many patients to a mean gradient of 30 to 35 mm Hg[26] and that this AVA threshold has been independently associated with a survival benefit following AVR.[27] Outcomes for patients with NFLG severe AS at 1 year were significantly better than those of patients with high-gradient severe AS; however, at 2.5 years, both groups had similar mortality rates (~30%) with statistically similar adjusted 5-year survival rates. These data support a clinical approach to patients with NFLG AS that is more akin to that for patients with high-gradient AS and is consistent with our recent publication about the gradient "threshold" mortality effect for AS being lower than that previously considered.[4]

From the available data in our cohort, we observed a significant discrepancy in the rates of AVR (surgical or TAVR) between the different severe AS groups. Whereas close to half of the high-gradient group had documented AVR during follow-up (on a repeat echo study in the database), the rate of documented intervention in patients with LFLG AS was substantially lower (41.1% versus 15.6%). This significant difference persisted even after an adjustment for durations of follow-up and is consistent with results from previous smaller cohorts.[19] These data must be interpreted with caution, however, as the detection of AVR was based on follow-up echocardiograms rather than on a nationwide database linkage with cardiac surgeries performed in Australia during the follow-up period. Therefore, our reported AVR rates will undoubtedly underestimate the true incidence (because of early postoperative mortality or loss to follow-up, for example). Nevertheless, we believe this substantial observed discrepancy in the incidence of AVR among different severe AS subtypes in this large, inclusive, and contemporary cohort should not be ignored.

Our study has important limitations. Despite representing the full range of cases seen in real-world clinical cardiology practice across an advanced health system, NEDA has a certain selection bias considering that it draws on results only from those adults undergoing cardiac ultrasound. The network of >25 participating centers included both inpatient and outpatient services across all of the states of Australia, but other sources of selection bias cannot be confidently excluded. Australia's universal health care system, however, minimizes the chance of important referral bias based on patients' ability to pay for diagnosis or treatment. NEDA does not contain clinical data (beyond age and sex), and we acknowledge the importance of considering symptoms and comorbidities when choosing the appropriate management strategy for patients with echocardiographic evidence of severe AS. Nevertheless, overreliance on symptomatology in the natural history of severe AS may be detrimental considering that many patients do not present with overt symptoms as a result of progressively adopting a more sedentary lifestyle.[28] Indeed, current guidelines highlight the diagnostic and prognostic benefit of exercise testing and other imaging modalities in presumed asymptomatic patients with severe AS.[29] We also acknowledge that the echo studies available in NEDA are performed at rest, rather than during stress, and that stress echo may give valuable prognostic information, especially in patients with LFLG severe AS.[23]

Concomitant cardiac amyloid, mostly of the transthyretin type, may be relatively common among elderly patients with severe AS (reported in up to 16% of patients referred for TAVR). Recent evidence[30] suggested that these patients with coexisting severe AS and cardiac amyloid have a worse prognosis than patients with "lone AS" unless treated with TAVR. As NEDA does not contain data on patient medical history, we are unable to document the prevalence of cardiac amyloid in the subtypes of severe AS examined; it is therefore possible that amyloid, if overrepresented in any AS subtype, could have contributed to a relatively adverse prognosis of that subgroup.

The reported relative prevalence and outcomes of severe AS subtypes must be interpreted in the context of our chosen inclusion and diagnostic criteria. In this analysis, we followed the accepted definitions for high-gradient, NFLG, and LFLG severe AS.[2] We also performed 3 additional sensitivity analyses that showed nearly identical results; the first broadening the inclusion criteria by considering all patients in the NEDA database with any (rather than all) of the diagnostic AV parameters available, with the second and third analyses increasing the specificity of the low-gradient diagnostic criteria by only including AVA calculated using velocity time integral measurement and only including patients with confirmed indexed AVA in the severe range[2] ($\leq$0.6 cm^2/m^2), respectively. Nevertheless, despite these additional analyses substantiating the high prevalence of low-gradient severe AS, there remains a degree of uncertainty regarding the relative prevalence between the LFLG and NFLG subtypes, considering the substantial proportion of patients with low-gradient AS without recorded/measured SVI.

Regarding the mortality data presented, all-cause mortality is the more reliable outcome, as the data have been derived from the National Death Index of Australia; cardiovascular-related mortality data may be less reliable as they depend on the accuracy of the coding of death certificates. Finally, we did not have blood pressure measurements at the time of echocardiography, which could alter the interpretation of

certain echo parameters reported, and we acknowledge sources of echo-related measurement error, especially those related to LV outflow tract diameter assessment.[31]

CONCLUSIONS

In this large series of adults with severe native valve AS diagnosed on transthoracic echocardiography in routine clinical practice, approximately half of the patients had low-gradient hemodynamics. The long-term outcomes for the low-gradient severe AS sub-populations were at least as serious and often worse than for patients with high-gradient severe AS. The lowest survival rates were seen in patients with LFLG and underlying LV systolic impairment (classical LFLG severe AS).

ARTICLE INFORMATION

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Supplementary Material

Table S1–S3
Figures S1–S13

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SUPPLEMENTAL MATERIAL

Table S1 – Baseline demographic, anthropometric and echocardiographic characteristics for entire severe aortic stenosis cohort

Variable	High Gradient (n=5601)	NFLG (n=991)	Classical LFLG (n=611)	Paradoxical LFLG (n=959)	Undifferentiated Low Gradient (n=3671)
Age (years)	75.0 (±13.0)	77.2 (±12.0)†	76.2 (±12.2)	74.3 (±14.4)	77.9 (±12.1)†
Female sex	2392 (42.7%)	578 (58.3%)†	222 (36.3%)*	602 (62.8%)†	2111 (54.8%)†
Body Mass Index (kg/m^2)	27.8 (±6.1)	26.2 (±5.2)†	26.9 (±5.7)*	28.6 (±6.9)*	26.6 (±5.6)†
Body Surface Area (m^2)	1.89 (±0.26)	1.75 (±0.22)†	1.87 (±0.25)	1.85 (±0.27)†	1.79 (±0.24)†
AVR Performed ‡	2300 (41.1%)	273 (27.5%)†	119 (19.5%)†	126 (13.2%)†	539 (14.7%)†
Echocardiographic Data					
LVOT diameter (cm)	2.15 (±0.25)	2.10 (±0.22)†	2.08 (±0.28)†	1.84 (±0.28)†	1.95 (±0.25)†
AVA - VTI (cm^2)	0.80 (±0.28)	0.94 (±0.17)†	0.83 (±0.28)	0.87 (±0.26)†	0.85 (±0.20)†
Indexed AVA - VTI (cm^2/m^2)	0.43 (±0.15)	0.54 (±0.12)†	0.45 (±0.16)*	0.48 (±0.15)†	0.44 (±0.12)
Peak AV velocity (m/s)	4.6 (±0.5)	3.4 (±0.4)†	2.8 (±0.7)†	2.7 (±0.7)†	3.0 (±0.6)†
Mean AV gradient (mmHg)	49.8 (±12.4)	27.6 (±7.1)†	19.2 (±9.7)†	18.0 (±9.6)†	21.2 (±8.8)†
Stroke Volume Index	45.6 (±14.8)	42.8 (±6.1)†	24.1 (±7.0)†	25.9 (±6.1)†	N/A
LVEF (%)	60.8 (±13.3)	59.3 (±12.2)*	33.3 (±10.5)†	63.1 (±7.9)†	57.2 (±16.0)†
LV Mass index (g/m^2)	118 (±33)	103 (±30)†	122 (±35)*	91 (±27)†	107 (±32)†
LVDD (cm)	4.6 (±0.7)	4.4 (±0.7)†	5.2 (±0.9)†	4.3 (±0.6)†	4.6 (±0.8)
LVSD (cm)	3.0 (±0.8)	3.0 (±0.8)	4.2 (±1.0)†	2.8 (±0.6)†	3.1 (±0.9)†
LA volume index (mL/m^2)	45.5 (±18.3)	46.0 (±18.8)	53.2 (±18.1)†	40.6 (±20.1)†	43.5 (±21.3)†
Mitral Regurgitation (≥Moderate)	763 (13.6%)	178 (18.0%)*	200 (32.7%)†	111 (11.6%)	505 (13.8%)
Tricuspid Regurgitation (≥Moderate)	447 (8.0%)	110 (11.1%)*	161 (26.4%)†	174 (18.1%)†	624 (17.0%)†
Estimated RVSP (mmHg)	44.3 (±13.6)	41.0 (±13.1)†	46.0 (±12.8)*	41.8 (±14.6)†	44.8 (±13.4)

*p<0.05 compared to high-gradient severe AS group, †p<0.001 compared to high-gradient severe AS group, ‡ AVR performed prior to study census follow-up. *[BMI (Body Mass Index), BSA (Body Surface Area), LVOT (Left Ventricular Outflow Tract), AVR (Aortic Valve Replacement), AVA (Aortic Valve Area), VTI (Velocity Time Integral), LVEF (Left Ventricular Ejection Fraction), LV (Left Ventricle), LVDD (Left Ventricle Diastolic Diameter), LVSD (Left Ventricle Systolic Diameter), LA (Left Atrium), RVSP (Right Ventricle Systolic Pressure)].*

Table S2 – Showing eligible patients for the third sensitivity analysis (including only main cohort patients with confirmed indexed AVA $\leq 0.6 cm^2/m^2$), according to severe aortic stenosis subtype.

Severe AS group	Indexed AVA $\leq 0.6 cm^2/m^2$
High Gradient (n*=2675)	2425 (90.7%)
NFLG (n*=983)	776 (78.9%)
Classical LFLG (n*=609)	561 (92.1%)
Paradoxical LFLG (n*=958)	842 (87.9%)

*n denotes patients with available BSA data for Indexed AVA calculations. *[AVA: Aortic Valve Area, NFLG: normal-low low-gradient, LFLG: low-flow low-gradient]*

Figure S1 – Flowchart for first sensitivity analysis – Including all patients in the NEDA database with any (rather than all) of the diagnostic aortic valve parameters available (that is, AVA, AV peak velocity or AV mean gradient).

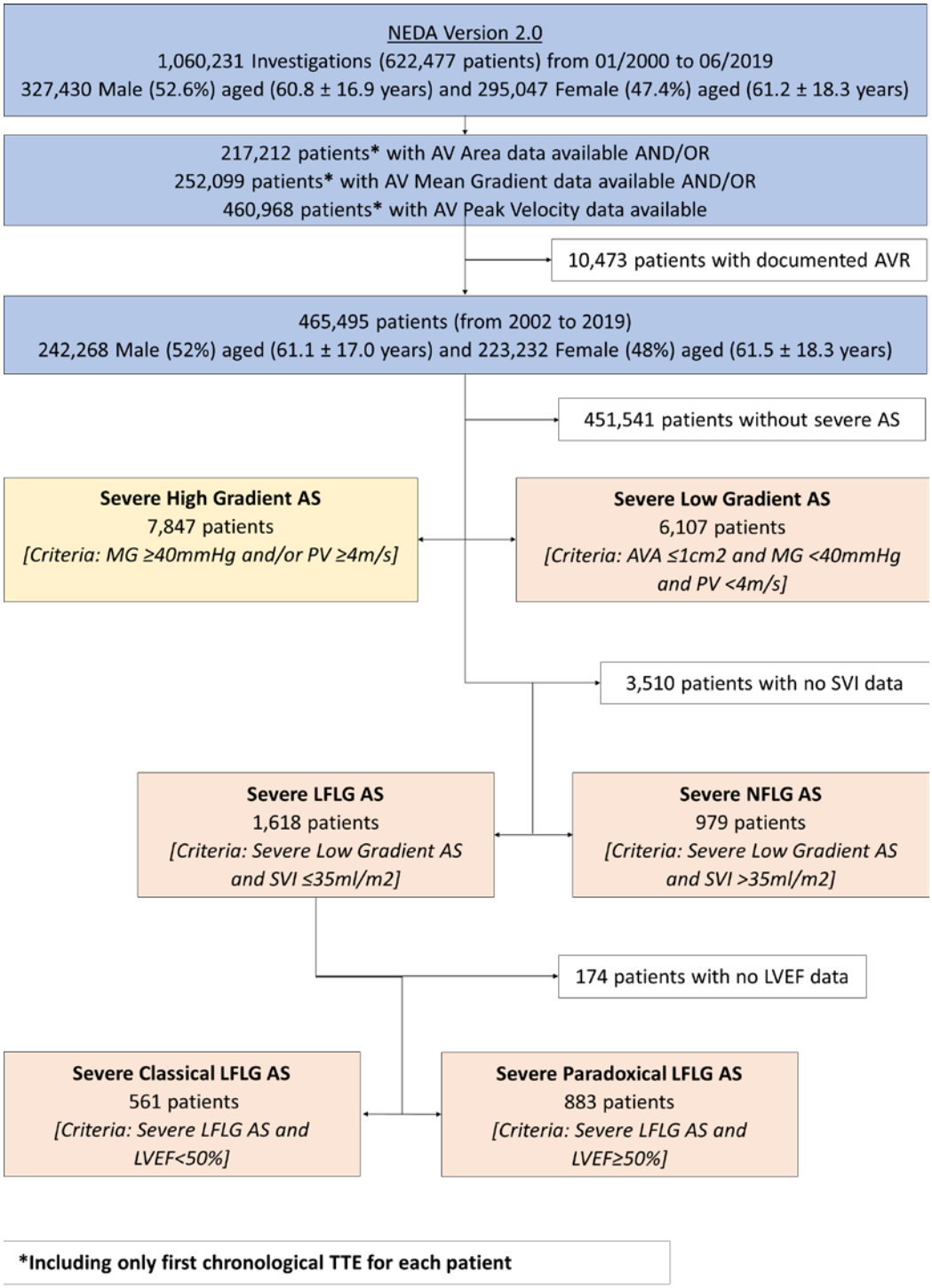

Figure S2 – Distribution of severe aortic stenosis subtypes – Results from first sensitivity analysis (see Figure S1).

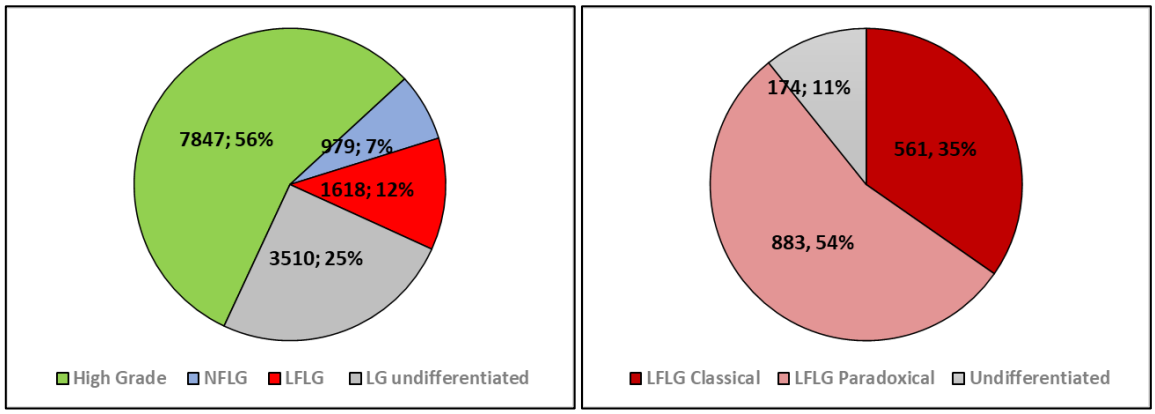

Figure S3 – Flowchart for second sensitivity analysis – Including only patients with AVA calculated using continuity equation with VTI measurement.

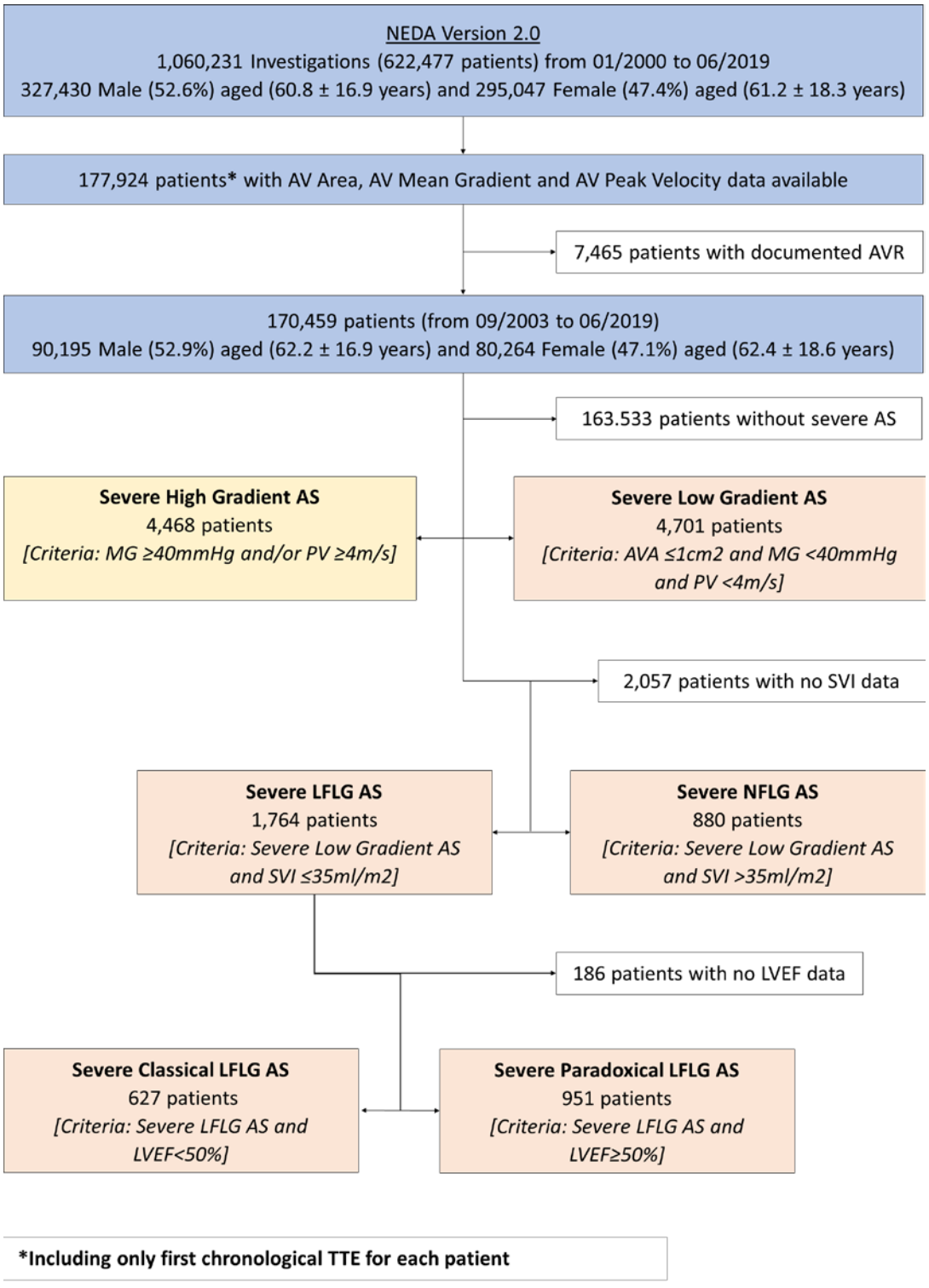

Figure S4 – Distribution of severe aortic stenosis subtypes – Results from second sensitivity analysis (see Figure S3).

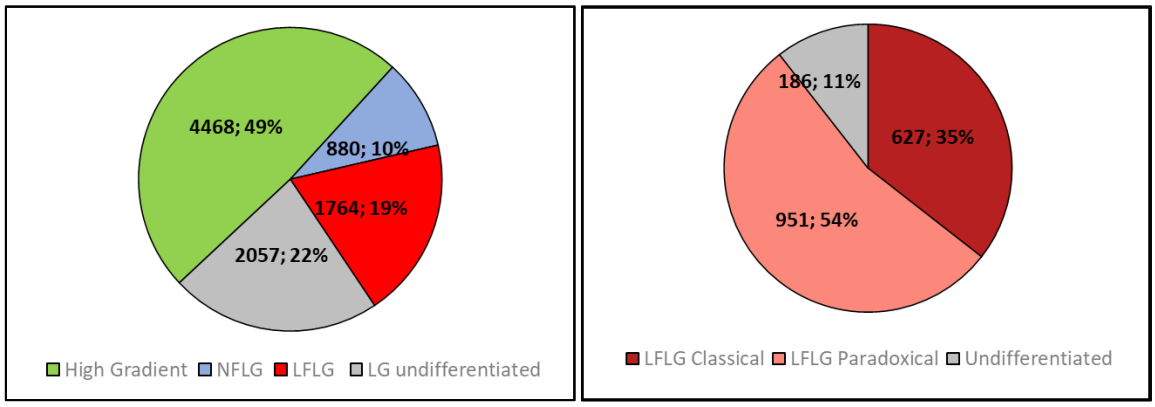

Figure S5 – Results of additional Cox regression analyses for main cohort (included covariates: patient age, sex, Body Surface Area and LV Mass) – Showing Kaplan-Meier curves for 1-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) with adjusted HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

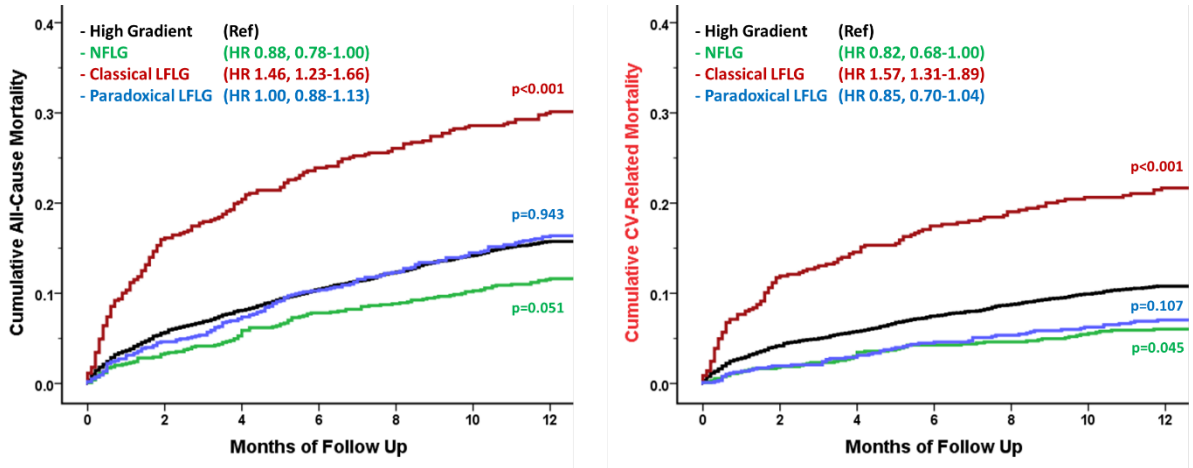

Figure S6 – Results of additional Cox regression analyses for main cohort (included covariates: patient age, sex, Body Surface Area and LV Mass) – Showing Kaplan-Meier curves for 5-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) with adjusted HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

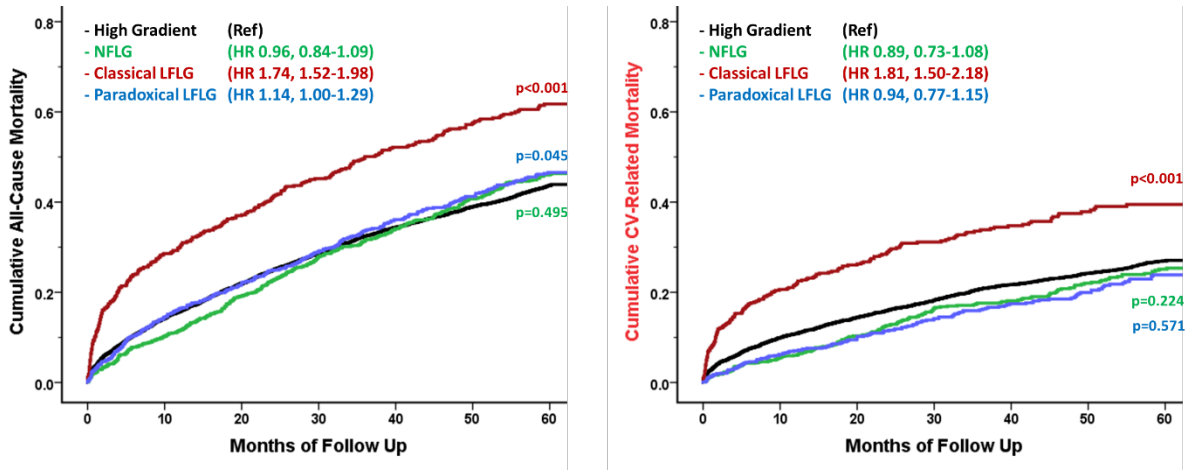

Figure S7 – Results from first sensitivity analysis (Figure S1) – Showing Kaplan-Meier curves for 1-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

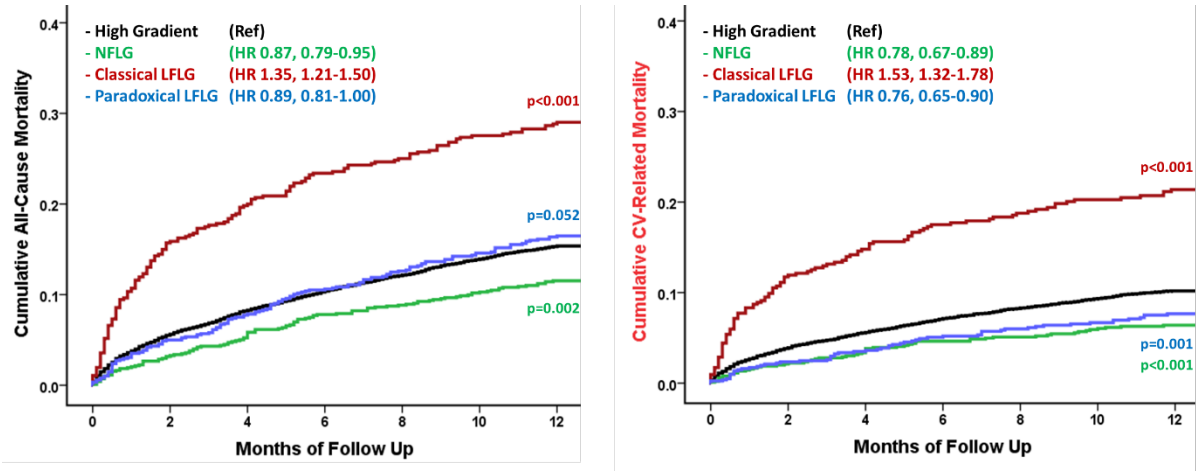

Figure S8 – Results from first sensitivity analysis (Figure S1) – Showing Kaplan-Meier curves for 5-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

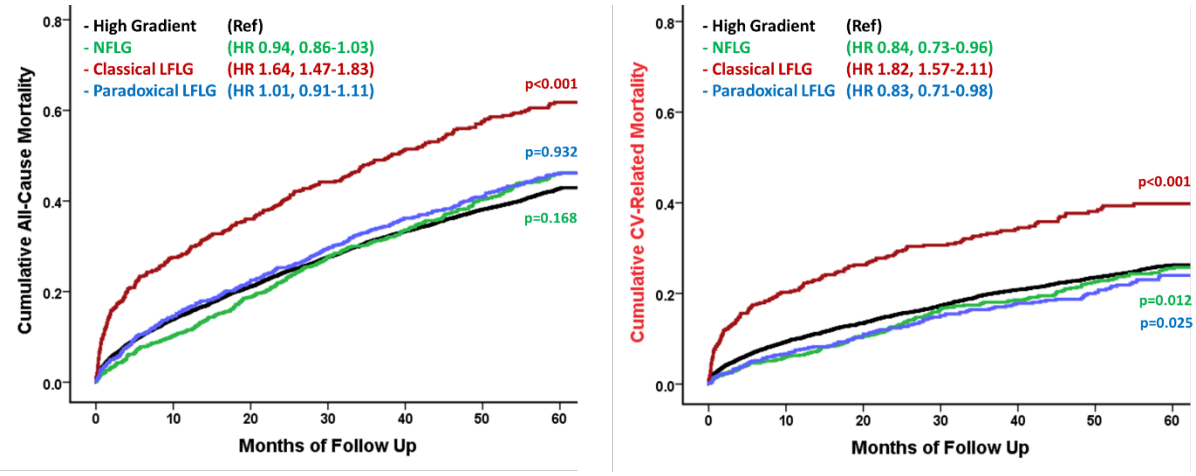

Figure S9 – Results from second sensitivity analysis (Figure S3) – Showing Kaplan-Meier curves for 1-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

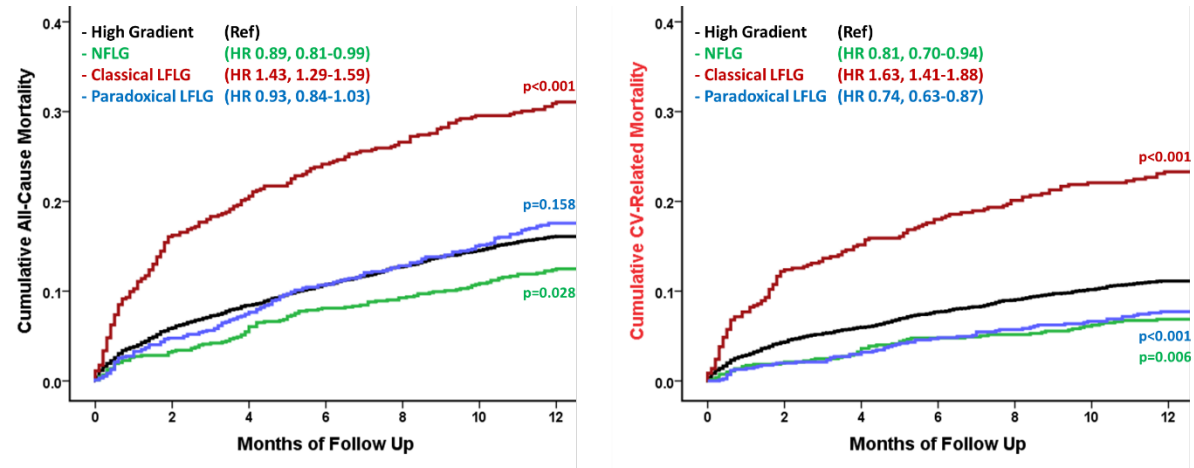

Figure S10 – Results from second sensitivity analysis (Figure S3) – Showing Kaplan-Meier curves for 5-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

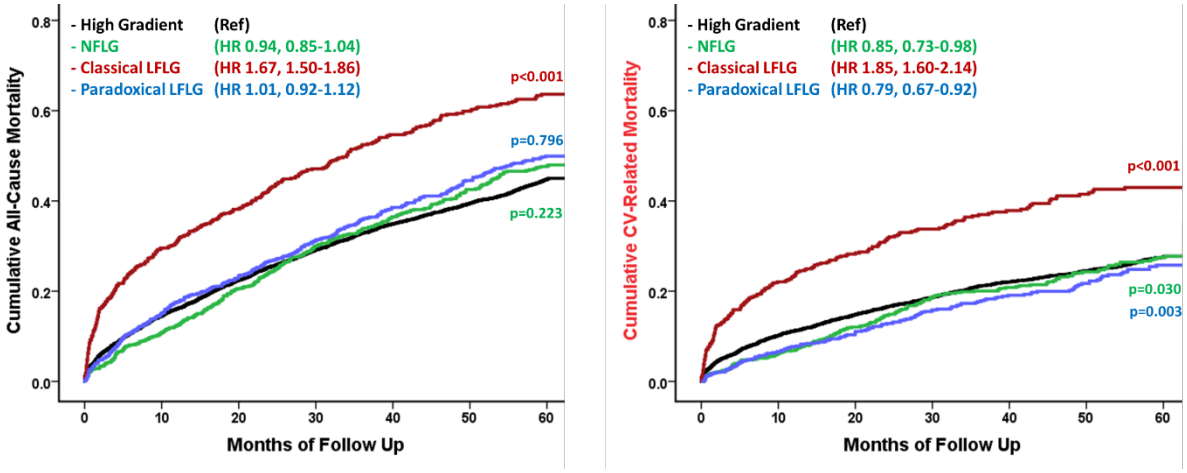

Figure S11 – Results from third sensitivity analysis (see Table S2) – Showing Kaplan-Meier curves for 1-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

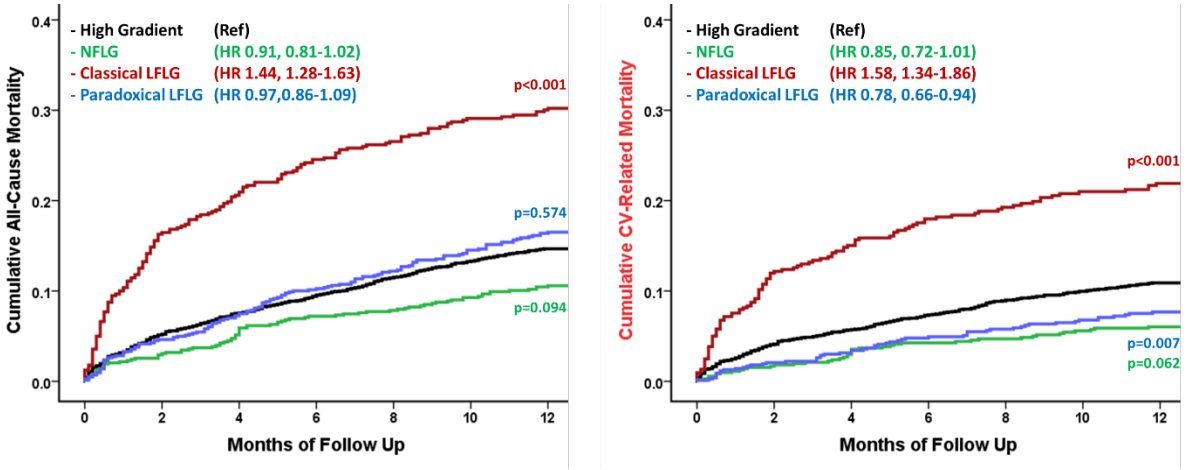

Figure S12 – Results from third sensitivity analysis (see Table S2) – Showing Kaplan-Meier curves for 5-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.

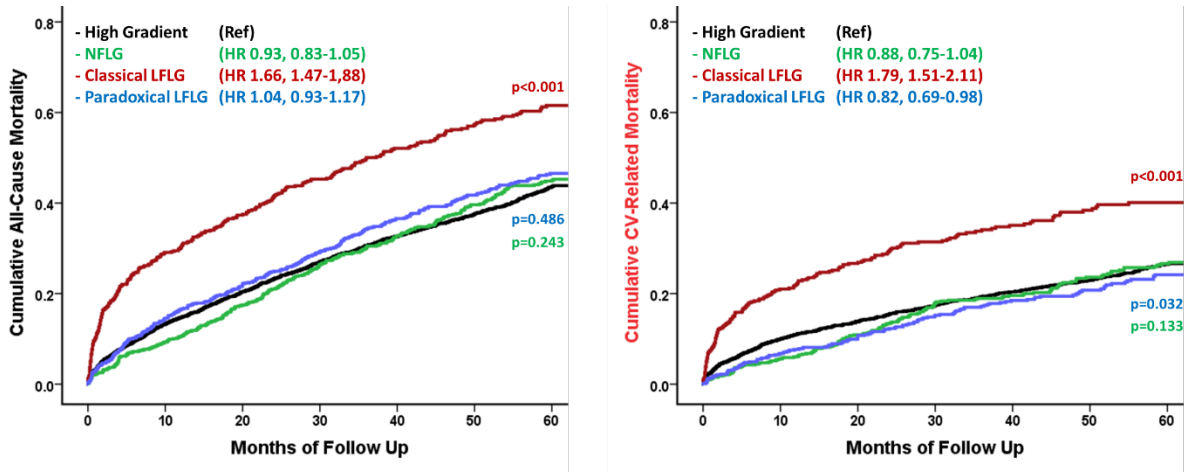

Figure S13 – Results from fourth sensitivity analysis, including only main cohort patients without recorded AVR during follow-up – Showing Kaplan-Meier curves for 5-year all-cause mortality (LHS) and cardiovascular-related mortality (RHS) and results of Cox regression analyses (included covariates: patient age and sex) with HR (± 95% CI) and p-values comparing to high-gradient severe AS subgroup.