TAVR outcome after reclassification of aortic valve stenosis by using a hybrid continuity equation that combines computed tomography and echocardiography data

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Abstract

**Background:** In the continuity equation, assumption of a round-shaped left ventricular outflow tract (LVOT) leads to underestimation of the true aortic valve area in two-dimensional echocardiography. The current study evaluated whether inclusion of the LVOT area, as measured by computed tomography (CT), reclassifies the degree of aortic stenosis (AS) and assessed the impact on patient outcome after transcatheter aortic valve replacement (TAVR).

**Methods and Results:** Four hundred and twenty-two patients with indexed aortic valve area index (AVAi) of <0.6 cm²/m², assessed by using the classical continuity equation (mean age: 81.5 ± 6.1 years, 51% female, mean left ventricular ejection fraction: 53.2 ± 13.6%), underwent TAVR and were included. After inclusion of the CT measured LVOT area into the continuity equation, the hybrid AVAi led to a reclassification of 30% (n = 128) of patients from severe to moderate AS. Multivariate predictors for reclassification were male sex, lower mean aortic gradient, and lower annulus/LVOT ratio (all p < .01). Reclassified patients had significantly higher sST2 at baseline and higher NT-proBNP values at baseline and 6 months follow-up compared to non-reclassified patients. Acute kidney injury was experienced more frequently after TAVR by reclassified patients, but no significant mortality difference occurred during 2 years of follow-up.

**Conclusion:** The hybrid AVAi reclassifies a significant portion of low-gradient severe AS patients into moderate AS. Reclassified patients showed increased fibrosis and heart failure markers at baseline compared to non-reclassified patients.

**Abbreviations:** AS, aortic valve stenosis; AV, aortic valve; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BSA, body surface area; LF-HG, low flow, high gradient; LF-LG, low flow, low gradient; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MDCT, multidetector computed tomography; MPG, mean pressure gradient; NF-HG, normal flow, high gradient; NF-LG, normal flow, low gradient; NYHA, New York Heart Association; SVi, indexed stroke volume; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography; VTI, velocity time integral.
1 | INTRODUCTION

According to the ESC guidelines from 2012 and actual recommendations on the echocardiographic assessment of aortic valve stenosis, a severe aortic stenosis (AS) is defined by an aortic valve area index (AVAi) of <0.6 cm²/m² as calculated in the continuity equation.

However, in some patients with normal flow (stroke volume index ≥35 ml/m²) and a mean gradient <40 mmHg, deciding whether the AS is still moderate or already severe can be challenging.

This type of discordance raises uncertainty about the proper therapeutic management, especially when the patient is suffering from certain comorbidities, such as chronic obstructive pulmonary disease. The combination of an AVAi <0.6 cm²/m² as calculated by the continuity equation formula and an inconsistent low mean gradient (<40 mmHg) accounts for up to 30% of AS cases. One explanation for this discrepancy is that the assumption of a circular shape of the left ventricular outflow tract (LVOT) in the continuity equation leads to underestimation of the aortic valve area (AVA) in two-dimensional (2D) echocardiography. This can be explained by the fact that the LVOT has an elliptical shape and transthoracic echocardiography (TTE) usually measures the smaller, anterior–posterior diameter. Previous imaging studies with three-dimensional imaging modalities, such as multidetector computed tomography (MDCT), showed an oval shaped LVOT, and integration in the continuity equation improves congruence of AS severity, whereas the classical continuity equation with use of the 2D echocardiography-derived LVOT diameter underestimates AVA.

The clinical impact of daily, routine AVAi underestimation using 2D echocardiography, has not yet been fully elucidated. The current study evaluated whether a hybrid continuity equation with LVOT area as evaluated by CT reclassifies the degree of aortic valve stenosis compared to the regular calculation of AVA with LVOT measurement derived by 2D echocardiography and assessed the impact of a reclassification of the AS severity on patient parameters and outcome.

2 | METHODS

2.1 | Patients

Patients with symptomatic severe AS (indexed aortic valve area [AVAi] of <0.6 cm²/m², derived by TTE) and indication for transcatheter aortic valve replacement (TAVR) were included in the study. Impaired left ventricular ejection fraction (LVEF) was not an exclusion criterion. Before TAVR, transthoracic and transesophageal echocardiography as well as coronary angiography and MDCT were performed. Dependent on risk scores and comorbidities patients were allocated to TAVR by the local multidisciplinary heart team. Data were prospectively collected by the “Bonn TAVR registry” with informed consent. Clinical follow-up was conducted up to 2 years after TAVR.

2.2 | Imaging analysis

2.2.1 | Echocardiography

Preinterventional patient screening included transthoracic as well as transesophageal echocardiography to confirm the diagnosis, define the aortic valve morphology, and measure the aortic valve annular diameter. Follow-up echocardiography was performed after the procedure and at a 6-month follow-up. We used commercially available ultrasound scanners (Vivid 7, GE Healthcare, Waukesha, WI; iE33, Philips Medical Systems, Best, The Netherlands). For the calculation of LVEF, the endocardial border of the LV was manually traced in the apical four-chamber and two-chamber views in end-diastole and end-systole and calculated by using the biplane Simpson's method. From the LV apical long-axis or five-chamber views, continuous-wave (CW) Doppler spectral recordings through the aortic valve were obtained, and the highest aortic valve velocity was obtained systematically in all patients. The LVOT area was derived from the LVOT diameter measured on a zoomed parasternal long-axis view, 5 mm below the aortic annulus. Spectral pulsed-wave (PW) Doppler recordings of the LVOT were measured from the LV apical long-axis or five-chamber views with the sample volume located 5 mm below the aortic annulus. In case of atrial fibrillation, a minimum of three beats was recorded and a mean value was calculated. AVAi was calculated using the continuity equation according to current echocardiography guidelines and then indexed to body surface area (BSA). The maximum pressure gradient across the restrictive orifice was evaluated using the modified Bernoulli equation (4v²). Indexed stroke volume (SVi) was assessed by velocity time integral (VTI) of pulsed-wave Doppler recordings of the LVOT and TTE-derived LVOT diameter and was calculated as follows: 

\[ SV_i = \frac{LVOT \text{area} \times VTI \times 2.5}{BSA} \]

Depending on transaortic gradient and SVi values, patients were divided into four groups: normal flow, high gradient (NF-HG, SVi > 35 ml/m² and mean pressure gradient [MPG] ≥40 mmHg), low flow, high gradient (LF-HG, SVi ≤35 ml/m² and MPG ≥40 mmHg), normal flow, low gradient (NF-LG, SVi > 35 ml/
m² and MPG < 40 mmHg), and low flow, low gradient (LF-LG, SVI ≤ 35 ml/m² and MPG < 40 mmHg). In case of LF-LG AS with reduced LVEF, we performed a low dose dobutamine stress echocardiography to rule out pseudo-severe AS.

### 2.2.2 Multidetector computed tomography (MDCT)

MDCT scans were performed using a 64-detector row computed tomography scanner (Philips Brilliance TM CT 64, Philips Medical Systems). A bolus of 60–90 ml of nonionic contrast agent (Ultravist 370 mg/ml; Schering AG, Berlin, Germany) followed by 50 ml of normal saline were injected intravenously using a two-phase injection protocol at a rate of 5 ml/s. Using retrospective electrocardiogram gating, routine reconstructions at 75% (diastolic phase) and 30–40% (systolic phase) of the RR interval were performed. The CT scans were analyzed, in consensus, by two experienced interventional cardiologists using a dedicated workstation (3mensio® Structural Heart 7.1 SP 1, 3mensio Medical Imaging, Bilthoven, The Netherlands). From the contrast-enhanced data set, the three multiplanar reformation planes were aligned on the standard orthogonal coronal and sagittal views to obtain a double-oblique transverse view of the aortic valve. The LVOT area was measured by planimetry, 5 mm below the predefined aortic annulus level in diastolic phase. The annulus/LVOT area ratio was obtained by dividing annulus area by LVOT area. By combining hemodynamic echocardiographic data and LVOT area measured on contrast-enhanced MDCT, the hybrid AVAi was calculated, introducing the MDCT-derived LVOT area into the continuity equation:

\[
AVAi = \frac{CT \text{ LVOT area} \times \text{Echo PW LVOT}}{\text{Echo CW aortic valve} \times \text{Body surface area}}
\]

### 2.3 Statistical analysis

Exploratory data analysis was performed, and Bonferroni adjustments were made for multiple tests. Normal distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Continuous data are expressed as the mean ± SD. Noncontinuous data are expressed in quartiles 1–3. Two-tailed \( p \) values were calculated and considered to be significant if <.05. Comparisons between two groups were performed using Student's \( t \) tests for paired samples or pairwise comparisons with Wilcoxon's signed-rank tests for paired continuous variables. Pairwise comparisons of noncontinuous data were tested with Mann–Whitney \( U \) test. For categorical data, Fisher's exact tests or Pearson's chi-square test were performed. Survival curves were constructed using Kaplan–Meier estimates, while comparisons relied on the log-rank test. Correlation testing was performed by Pearson's correlation coefficient. The multivariable model was built by selecting baseline variables of clinical interest and/or satisfaction of the entry criterion of \( p < .1 \) in the univariable analysis: STS score, logistic EuroScore, LVEF, BNP, age, gender, AV MPG, annulus/LVOT ratio, and coronary artery disease (CAD).

### 3 RESULTS

Four hundred and twenty-two patients were included in our study (mean age: 81.5 ± 6.1 years, 50.1% female). Echocardiographic AVAi was 0.35 ± 0.11 cm²/m², mean pressure gradient = 41.5 ± 15.6 mmHg, maximal transaortic velocity = 4.23 ± 0.73 m/s, SVi = 36.33 ± 13.52 ml/m², and LVEF = 53.24 ± 13.64%.

Patients were classified into four groups according to flow (stroke volume index of <35 or ≥35 ml/m²) and transaortic gradient (mean transaortic pressure gradient of <40 or ≥40 mmHg): NF-HG \( n = 114, 27\% \), LF-HG \( n = 86, 20\% \), NF-LG \( n = 91, 22\% \), and LF-LG \( n = 131, 31\% \).

Table S1 presents the demographic and clinical characteristics of the four patient groups. The groups were comparable concerning age, BSA, CT-derived LVOT area, STS score, NT-pro BNP, baseline creatinine, and New York Heart Association (NYHA) classification. The LF-LG group showed a significantly higher logistic EuroSCORE and lower baseline LVEF compared to other groups (Table S1). Both LG groups showed a significantly higher prevalence of CAD. The LF-LG group showed a significantly higher rate of atrial fibrillation compared to the NF-HG group (52% vs. 28%, \( p < .01 \)). In the LF-LG group, baseline sST2 was significantly higher compared to both NF groups. Furthermore, in LG patients, the annulus/LVOT area ratio was significant smaller in comparison to both HG groups.

### 3.1 Baseline and echocardiographic characteristics after CT fusion

Integration of CT-derived LVOT area into the continuity equation (Figure 1) led to a significantly higher \( \text{AVA}_\text{hybrid} \) compared to the classical echocardiography-based AVA calculation (\( \text{AVA}_\text{hybrid}/\text{BSA}: 0.52 ± 0.17 \) vs. \( \text{AVA}_\text{classical}/\text{BSA}: 0.35 ± 0.11, \( p < .01 \)) with only moderate correlation (\( \rho = 0.59, p < .01 \)). Patients in the LG groups had a significantly
higher AVA compared to the normal-gradient groups (Hybrid AVA: LF-LG: 1.01 ± 0.3 cm² and NF-LG: 1.19 ± 0.33 cm² vs. NF-HG: 0.87 ± 0.21 cm² and LF-HG: 0.79 ± 0.25 cm², p < .01, Table S1) after recalculation of the AVA by using CT-derived LVOT measurements instead of echocardiographic LVOT assessment. However, the CT-derived LVOT area itself was not different between the four groups.

With the use of the CT-derived hybrid AVAi, 59% (n = 54) of the patients with NF-LG and 37% (n = 48) of the patients with LF-LG were reclassified into moderate AS (hybrid AVAi ≥ 0.6 cm²). Among NF-HG patients, only 13% (n = 26) of patients were reclassified. Detailed baseline characteristics of these groups after recalculation of AVAi are shown in Table 1 and Figure 2. Patients with reclassified AS were significantly younger, more frequently male (66.4% vs. 41.5%, p < .01), and showed higher BSA (1.89 ± 0.19 m² vs. 1.82 ± 0.21 m², p < .01). Risk scores such as logistic EuroSCORE and STS-PROM were similar in both groups, whereas prevalence of CAD was significantly higher (69.5% vs. 62.9%, p < .05) and ejection fraction was significantly lower (48.99 ± 14.62% vs. 55.09 ± 12.78%, p < .01) in the reclassified AS group.

After reclassification, AV mean gradient (33.4 ± 12.1 mmHg vs. 44.99 ± 15.6 mmHg, p < .01) and AV maximum velocity (3.83 ± 0.65 m/s vs. 4.40 ± 0.70 m/s, p < .01) were significantly lower, leading to a significantly higher classical, indexed AVA (0.42 ± 0.09 cm² vs. 0.32 ± 0.1 cm², p < .01) in the reclassified AS group (Table 1).

### TABLE 1  Baseline parameters and group subdivision after CT fusion

|                    | All patients (n = 422) | Reclassified AS (n = 128) | True severe AS (n = 294) | p value |
|--------------------|------------------------|---------------------------|--------------------------|---------|
| Normal flow, high gradient, n (%) | 114 (27) | 13 (10) | 101 (34) | <.01 |
| Normal flow, low gradient, n (%) | 91 (22) | 54 (42) | 37 (13) | <.01 |
| Low flow, high gradient, n (%) | 86 (20) | 13 (10) | 73 (25) | <.01 |
| Low flow, low gradient, n (%) | 131 (31) | 48 (38) | 83 (28) | <.01 |
| Age (years)       | 81.5 ± 6.1             | 80.5 ± 6.1               | 82 ± 6.1                 | <.05   |
| Female gender, n (%) | 215 (50.9%) | 43 (33.6%) | 172 (58.5%) | <.01 |
| BSA (m²)          | 1.84 ± 0.2             | 1.89 ± 0.19              | 1.82 ± 0.21              | <.01   |
| STS-PROM (%)      | 7.12 ± 5.39            | 7.55 ± 5.62              | 6.93 ± 5.28              | ns     |
| Logistic EuroSCORE (%) | 22.17 ± 15.16 | 24 ± 16.52 | 21.38 ± 14.49 | ns     |
| CAD, n (%)        | 274 (64.9%)            | 89 (69.5%)               | 185 (62.9%)              | <.05   |
| AF (%)            | 170 (40.3%)            | 58 (45.3%)               | 112 (38.1%)              | ns     |
| LVEF (%)          | 53.24 ± 13.64          | 48.99 ± 14.62            | 55.09 ± 12.78            | <.01   |
| Pressure mean gradient (mmHg) | 41.48 ± 15.58 | 33.4 ± 12.06 | 44.99 ± 15.64 | <.01 |
| Peak aortic valve velocity (m/s) | 4.22 ± 0.73   | 3.83 ± 0.65             | 4.40 ± 0.70              | <.01   |
| Calculated aortic valve area (cm²) | 0.65 ± 0.22 | 0.78 ± 0.19            | 0.59 ± 0.2               | <.01   |
| Indexed calculated aortic valve area (cm²) | 0.35 ± 0.11 | 0.42 ± 0.09            | 0.32 ± 0.11              | <.01   |
| Pulmonary artery pressure (mmHg) | 38.28 ± 19.82 | 39.62 ± 20.82 | 37.72 ± 19.4            | ns     |
| Creatinine (mg/dl) | 1.37 ± 0.64           | 1.46 ± 0.67             | 1.33 ± 0.63              | ns     |
| Troponin I (ng/ml) | 0.08 ± 0.27           | 0.07 ± 0.12             | 0.08 ± 0.31              | ns     |
| NT-pro BNP, Q2 (Q1/Q3) (ng/ml) | 2.692 (1,047/7,036) | 3.716 (1,159/9,825) | 2.516 (1,018/5,986) | <.05   |
| sST2 (ng/ml)      | 25.56 ± 21.99          | 29.65 ± 27.33            | 23.52 ± 18.51            | <.05   |
| NYHA class        | 3.1 ± 0.5              | 3.1 ± 0.5                | 3.1 ± 0.5                | ns     |
| NYHA class > 2, n (%) | 394 (93.3)            | 119 (92.9)               | 275 (93.5)               | ns     |
| Follow-up (days)  | 956 ± 615              | 939 ± 638                | 963 ± 607                | ns     |
| Indexed planimetric aortic valve area (cm²) | 0.39 ± 0.12 | 0.39 ± 0.12            | 0.39 ± 0.11              | ns     |
| SVi (ml/m²)       | 36.33 ± 13.52          | 37.85 ± 12.6             | 35.67 ± 13.88            | ns     |
| CT anulus area (mm²) | 469.4 ± 95.7     | 518.9 ± 98.5             | 447.8 ± 86               | <.01   |
| TTE LVOT area (mm²) | 303.71 ± 83.43   | 317.07 ± 80.59           | 297.89 ± 84.1            | <.05   |
| CT LVOT area (mm²) | 456.89 ± 126.21 | 542.29 ± 127.55          | 419.72 ± 106.14          | <.01   |
| Anulus/LVOT ratio | 1.06 ± 0.18           | 0.97 ± 0.14              | 1.09 ± 0.18              | <.01   |
| Hybrid indexed AVA (cm²) | 0.52 ± 0.17   | 0.77 ± 0.12             | 0.43 ± 0.1               | <.01   |

Note: All p values are with regard to the reclassified AS group.

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; CAD, coronary artery disease; CT, computed tomography; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; ns, not significant; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons–Predicted Risk of Mortality; SVi, stroke volume index; TTE, transthoracic echocardiography.
vs. 297.89 ± 84.1 mm², \( p < .05 \)) or CT (542.29 ± 127.55 mm² vs. 419.72 ± 106.14 mm², \( p < .05 \)), was significantly larger in the reclassified AS group.

When calculating the ratio of annulus to LVOT area, the mean quotient in the reclassified AS group was significantly lower (0.97 ± 0.14 vs. 1.09 ± 0.18, \( p < .01 \), Table 1, Figure 3) compared to patients with true severe AS. In patients with a true severe AS, the LVOT shape looks like a trumpet, whereas in patients with reclassified AS the LVOT looks more funnel-shaped (Figure 3). Furthermore, we found a moderate correlation between LVEF and annulus/LVOT area ratio (\( r = .36, p < .01 \)).

### 3.2 Clinical discrimination after CT reclassification

Baseline troponin and creatinine levels showed no relevant differences between the groups, whereas patients with reclassified AS had significantly higher sST2 and NT-pro BNP values at baseline (29.65 ± 27.33 ng/ml vs. 23.52 ± 18.51 ng/ml, \( p < .05 \); 3,716 ng/ml [1,159/9,825] vs. 2,516 ng/ml [1,018/5,986], \( p < .05 \)) compared to patients with true severe AS.

Significantly higher NT-proBNP values were documented 6 months after TAVR (3,249.1 ± 4,188.4 vs. 2,912.2 ± 7,050.3, \( p < .05 \)) in the group with reclassified AS. Despite higher NT-proBNP follow-up values, no significant mortality difference was seen up to 2 years after TAVR (\( p = .3 \), Table 2, Figure 4b). In the LF-LG group, we observed a trend (\( p = .055 \)) toward worse survival 2 years after TAVR.

![Figure 2](https://wileyonlinelibrary.com) Composition of flow and gradient groups after CT fusion. CT, computed tomography; LF-HG, low flow, high gradient; LF-LG, low flow, low gradient; NF-HG, normal flow, high gradient; NF-LG, normal flow, low gradient [Color figure can be viewed at wileyonlinelibrary.com]

![Figure 3](https://wileyonlinelibrary.com) Illustration of the different LVOT types. LVOT, left ventricular outflow tract
compared to the other flow-gradient groups (Figure 4a). However, when comparing patients with an annulus/LVOT ratio \(\leq 1\) versus \(> 1\), we found no mortality difference 2 years after TAVR (Figure 4d).

Regarding major adverse cardiovascular and cerebrovascular event (incidence of stroke, myocardial infarction, as well as vascular complications) between the groups (Table 2). In contrast, periprocedural acute kidney injury occurred more often in the reclassified AS group (23.6% vs. 12.1%, \(p < .01\)).

**TABLE 2**  Clinical follow-up

|                              | All patients (n = 422) | Reclassified AS (n = 128) | True severe AS (n = 294) | \(p\) value |
|------------------------------|------------------------|---------------------------|--------------------------|-------------|
| 6-month mortality n (%)      | 59 (14%)               | 19 (14.8%)                | 40 (13.6%)               | ns          |
| 12-month mortality n (%)     | 79 (18.7%)             | 25 (19.5%)                | 54 (18.4%)               | ns          |
| 24-month mortality n (%)     | 121 (28.7%)            | 41 (32%)                  | 80 (27.2%)               | ns          |
| 6-month NT-pro BNP, Q2 (Q1/Q3) [ng/ml] | 1,109 (519/3,059) | 1,647 (774/4,903) | 1,041 (498/2,902) | <.05 |
| 6-month LVEF (%)             | 57.8 ± 11.04           | 57.01 ± 11.56             | 58.09 ± 10.86            | ns          |
| Acute kidney injury 30d, n (%) | 65 (15.6%)            | 30 (23.6%)                | 35 (12.1%)               | <.01 |
| Myocardial infarction 30d, n (%) | 2 (0.5%)              | 0 (0%)                    | 2 (0.7%)                 | ns          |
| Stroke 30d, n (%)            | 9 (2.1%)               | 2 (1.6%)                  | 7 (2.4%)                 | ns          |
| Major vascular complication 30d, n (%) | 21 (4.9%)         | 7 (5.4%)                  | 14 (4.7%)                | ns          |

Abbreviations: AS, aortic stenosis; LVEF, left ventricular ejection fraction; ns, not significant.

**FIGURE 4**  Kaplan-Meier survival analysis after TAVR for (a) flow-gradient groups (log rank: \(p = .055\)), (b) reclassified versus true severe AS, (c) reclassified versus true severe AS in NF-LG group, and (d) annulus/LVOT ratio \(\leq 1\) versus annulus/LVOT ratio \(> 1\). AS, aortic stenosis; LF-HG, low flow, high gradient; LF-LG, low flow, low gradient; LVOT, left ventricular outflow tract; NF-HG, normal flow, high gradient; NF-LG, normal flow, low gradient; TAVR, transcatheter aortic valve replacement [Color figure can be viewed at wileyonlinelibrary.com]
In univariate analysis, age, BSA, male sex, CAD, LVEF, AV mean gradient, sST2, and annulus/LVOT area ratio were predictive for incidence of reclassified AS. In a multivariate analysis, independent parameters for incidence of reclassified AS were male sex (Odds ratio (OR): 2.09, p = .003), AV mean gradient (OR: 1.06, p < .001), and annulus/LVOT area ratio (OR per 0.1: 6.12, p < .001, Table 3).

4 | DISCUSSION

Our study reveals that after recalculations of the AVA by the continuity equation with inclusion of CT-based LVOT area, 30% of patients were reclassified from severe to moderate AS. The relative proportion of reclassified patients was higher among LG (MPG < 40 mmHg) patients who had a transcardiographic-based continuity equation to underestimate the true anatomical AVA. Almost 50% of LG patients were downgraded. One reason could be the inverse annulus/LVOT area ratio which was pronounced in the reclassified AS patients because a larger LVOT area from CT scan—inserted into the hybrid continuity equation (Figure 1)—leads to a higher AVAi. Reclassified patients had a higher comorbidity burden, without impact on clinical endpoints such as mortality, myocardial infarction, or cerebrovascular complications; this can be probably explained by sample size and follow-up time. However, reclassification was associated with higher sST2 and NT-pro BNP values at baseline and higher NT-pro BNP at the 6-month follow-up in the downgraded AS group.

4.1 | Allocation of patients regarding flow and gradient status

Compared to other studies, it should be emphasized that in our study one-third of the patients are in the LF-LG group and, even more important, that 50% of the patients had a low gradient, which can be predominately explained by the additional inclusion of patients with reduced LVEF. Kamperidis et al recently published a TAVR-cohort in which 22% of the patients had LF-LG status and altogether 46% an LG pattern. In another cohort published by Mehrotra et al, 46% of patients with severe AS had a low-gradient stenosis. However, in these studies, patients with reduced LVEF (<50%) were excluded, which might be an explanation for lower percentages of LG patients, as gradient and flow is dependent on left ventricular function. Therefore, our patients better reflect real-world data, and reduced LV function could also be a sign of an advanced stage of AS in our cohort.

4.2 | Reclassification of aortic valve stenosis severity after combination of computed tomography-derived LVOT and echocardiographic-assessed continuity equation

Introduction of CT-derived LVOT area into the continuity equation and recalculation of AVA from this value leads to a significant portion of patients being downgraded from severe to moderate AS (n = 128, 30%). In our study, especially patients with low transvalvular gradient were very likely to be reclassified to moderate AS (n = 102, 46%). A study by De Vecchi et al showed a systematic underestimation of transthoracic echocardiographic-derived LVOT area in comparison to CT-derived LVOT area that results in a lower AVAi value. These factors lead to a systematic error, which causes an underestimation of AVAi. O’Brien et al showed in 51 patients a reclassification of AS patients in 25% of the cases from severe to moderate AS after including true CT-derived LVOT area into the continuity equation, independent of the underlying LVEF. Kamperidis et al additionally analyzed mean gradient and flow component and showed that especially NF-LG patients are prone to be downgraded to moderate aortic valve stenosis after CT fusion. This downgrading could be observed in 52% of NF-LG patients, whereas only 12% of LF-LG patients were reclassified. Pronounced downgrading in NF-LG patients might be caused by low gradient and high LVOT area in this subgroup (Table S1), which both lead to higher AVA after putting into continuity equation. As previously mentioned, Kamperidis et al included only patients with LVEF > 50% in their analysis. In our study, mean LVEF was 52% and one-third of all patients had an impaired LVEF (<50%). This might explain the downgrading of 59% (n = 54) of patients with NF-LG and 37% (n = 48) of patients with LF-LG AS. Especially the NF-LG group is important, because ESC/EACTS guidelines propose that in this constellation severe AS is unlikely.

The ESC/EACTS recommendation is mainly based on three publications but the evidence for symptomatic AVS patients in these studies is lacking. The prospective study, Simvastatin and Ezetimibe in Aortic Stenosis (SEAS), which only included asymptomatic AS patients, found that low gradient patients showed the same outcome as patients with moderate AS. In contrast, in our study, all patients were symptomatic. The second study of Mehrotra retrospective compared LF-LG patients (n = 38, NYHA I: 55%) against NF-LG patients (n = 75, NYHA I: 75%) and those with moderate AS (n = 70, NYHA I: 84%). The LF-LG group showed the worst survival compared to both other groups, which showed almost equal results. Three points should be mentioned. First, patients with aortic valve replacement during follow-up were not excluded and indication for AVR was chosen by the local heart team. Second, most patients were asymptomatic, and third, all patients had at least a preserved LVEF. The third
study, by Tribouilloy et al, compared LG AS patients with moderate AS patients without a difference in outcome between the groups after medical therapy in most cases during a mean follow-up period of 39 months. Only NF-HG patients showed lower survival rates compared to patients with moderate AS, whereas only 15.8% of all patients were symptomatic (NYHA III-IV).

All three studies included predominantly asymptomatic patients with preserved LVEF and featured a relatively short follow-up period. Our study revealed that both NF groups and the NF-LG group showed almost the same survival rate, with nearly 75% survival 2 years after TAVR, whereas the LF-LG group had a 2-year survival rate of approximately 65%. This difference in mortality failed to gain statistical significance (p = .055, Figure 4a). The missing difference in survival between the flow and gradient groups might be caused by the compensating therapeutic effect of TAVR. An important difference from our data compared to the three above-mentioned studies is that we elucidated survival after TAVR and the others mainly analyzed survival until treatment of AS. A randomized comparison of symptomatic LF-LG and NF-LG patients with versus without AS therapy has not yet been realized. In this context, Zusman et al showed recently in an observational study a survival benefit of TAVR and SAVR in NF-LG patients, compared to using a conservative treatment strategy. The above-mentioned discrepancies among the studies may be explained by the fact that NF-LG AS is a highly heterogeneous entity and represents a moderate-to-severe form of AS. To gain evidence in the treatment of patients with symptomatic NF-LG and moderate AS, randomized trials and substantially higher numbers of cases would be required. The randomized TAVR Unload Trial (NCT02661451), which compares TAVR via a transfemoral approach in heart failure patients with moderate AS with optimal heart failure therapy, will enlighten this field and first results are expected in the year 2022.

4.3 Predictors for the probability of reclassification

Following multivariate analysis, independent predictors for incidence of reclassification of AS were male sex, low gradient, and low annulus/LVOT area ratio (all p < .01).

4.3.1 Gender

Due to the continuity equation, a larger LVOT area leads to a larger AVA. Because men generally have a larger LVOT area compared to women, this could be one important reason for the relatively high proportion of reclassified men. Even though we indexed AVA for BSA, this did not reduce the rate of reclassified men (66%, Table 1). In the literature, male patients suffer almost twice as often from CAD and have reduced mean LVEF. Lower LVEF is associated with lower gradients, as described by Kamperidis et al. But surprisingly, LVEF—in contrast to low gradient, male gender, or low annulus/LVOT ratio—was not an independent predictor for reclassification.

4.3.2 AV gradient

Previous studies of Kamperidis and Maes also detected lower gradients in the reclassified AS patients. Kamperidis et al additionally detected CAD and LVEF to be predictive for low gradient by using univariate analysis. The reason for the high number of reclassifications in the low-gradient group might be due to the fact that calculated AVA of low-gradient patients is often situated in the “gray zone,” that is between 0.8 and 1.0 cm², as previously described by Tarantini et al and Minners et al. CT fusion with inclusion of the larger LVOT area into the continuity equation might lead to AVA enlargement above 1 cm² or 0.6 cm²/m² in these borderline patients. Lowering the threshold to 0.8 cm² has been discussed many times but robust data dealing with this issue are missing. As previously discussed, low gradient patients are part of a highly heterogeneous entity and represent a moderate-to-severe form of AS.

4.3.3 LVOT/annulus ratio

Lower AV gradients correlate weakly with larger LVOT area (r = −.16, p < .01), which is seen in our cohort with numerically larger mean LVOT area in the low gradient groups (Table S1). Especially in the reclassified AS group, we saw significantly larger LVOT areas compared to the true severe AS group. The creation of the annulus/LVOT ratio is based on observations that reclassified AS patients have a larger LVOT area than annulus area and true severe AS patients have the opposite (Figure 3). This ratio has not been described before, but it might be an interesting parameter to describe LVOT geometry. A funnel-like, “tapered” LVOT in the direction to the annulus could be a sign of pathological LV remodeling, whereas a larger annulus compared to LVOT area is caused by LV hypertrophy and shows a trumpet-like LVOT geometry (Figure 3). We observed a positive correlation between LVEF and the annulus/LVOT area ratio (r = .36, p < .01) but a mortality difference was not found when comparing annulus/LVOT ratio of ≥1 and <1 (Figure 4d).

4.4 Clinical impact of reclassification

Reclassified AS patients had higher baseline sST2 values as well as significantly higher NT-pro BNP values at baseline and 6 months after TAVR. This might be explained by lower baseline LVEF of the reclassified compared to the true severe AS group, but the higher NT-proBNP values might also be a sign for less clinical improvement in reclassified AS patients, indicating that these patients already suffer from a more advanced disease state. However, a difference in mortality between both groups after reclassification was not observed until
2 years after TAVR (Figure 4b), which might indicate that both groups benefit from TAVR in a similar way. Thus, one of the principal findings of this study is that reclassification has no impact on mortality. This important finding is in line with a study by Clavel et al who found no difference in mortality rate after CT reclassification in patients with medically treated severe AVS.16 Furthermore, we saw no mortality difference in the NF-LG group (Figure 4a) that is often put on a level with moderate AVS.

Our study is the first to investigate clinical outcome after TAVR and AS reclassification with CT-derived LVOT area. Reclassified patients showed enhanced sST2 at baseline, increased numbers of postinterventional acute kidney injury, as well as higher NT-pro BNP values at baseline and 6 months after TAVR; however, there was not a significant impact on mortality up to 2 years after aortic valve replacement. According to these results, routine assessment of hybrid AVAi might not be helpful to improve further risk stratification of TAVR patients.

5 | CONCLUSION

The hybrid AVAi reclassifies a significant portion of low-gradient severe AS into moderate AS by providing the true cross-sectional LVOT area. Reclassified patients showed enhanced sST2 at baseline, increased numbers of postinterventional acute kidney injury, as well as higher NT-pro BNP values at baseline and 6 months after TAVR; however, there was not a significant impact on mortality up to 2 years after aortic valve replacement. According to these results, routine assessment of hybrid AVAi seems not to improve further risk stratification of TAVR patients, and low gradient AS patients still present diagnostic and therapeutic challenges.

5.1 | Limitations

This observational study is a retrospective analysis of prospectively collected data. The prognostic implications of fusion AVAi need to be demonstrated in larger prospective studies. A control—or even better, randomized—group of hybrid moderate AS patients with conservative management would help to understand the impact of this phenomenon. In the current analysis, the AVA was indexed to BSA to correct for different anatomic conditions. However, in obese or cachectic patients, the grade of miscalculation of the AVAi may be larger. Sample size and the monocentric character are additional limitations of this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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