The robustness of the flow-gradient classification of severe aortic stenosis

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Bart J. J. Velders, MD,[a] Michiel D. Vriesendorp, MD, PhD,[a] Federico M. Asch, MD,[b]
Michael G. Moront, MD,[c] Francois Dagenais, MD,[d] Michael J. Reardon, MD,[e] Joseph F. Sabik III, MD,[f]
Rolf H. H. Groenwold, MD, PhD,[g] and Robert J. M. Klautz, MD, PhD[a]
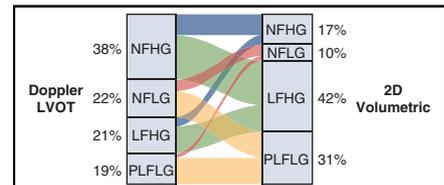
ABSTRACT

Objectives: A flow-gradient classification is used to determine the indication for intervention for patients with severe aortic stenosis (AS) with discordant echocardiographic parameters. We investigated the agreement in flow-gradient classification by stroke volume (SV) measurement at the left ventricular outflow tract (LVOT) and at the left ventricle.

Methods: Data were used from a prospective cohort study and patients with severe AS (aortic valve area index ≤ 0.6 cm^2/m^2) with preserved ejection fraction ($>50\%$) were selected. SV was determined by an echocardiographic core laboratory at the LVOT and by subtracting the 2-dimensional left ventricle end-systolic from the end-diastolic volume (volumetric). Patients were stratified into 4 groups based on SV index (35 mL/m^2) and mean gradient (40 mm Hg). The group composition was compared and the agreement between the SV measurements was investigated using regression, correlation, and limits of agreement. In addition, a systematic LVOT diameter overestimation of 1 mm was simulated to study flow-gradient reclassification.

Results: Of 1118 patients, 699 were eligible. The group composition changed considerably as agreement on flow state occurred in only 50% of the measurements. LVOT SV was on average 15.1 mL (95% limits of agreement −24.9:55.1 mL) greater than volumetric SV. When a systematic 1-mm LVOT diameter overestimation was introduced, the low-flow groups halved.

Conclusions: There was poor agreement in the flow-gradient classification of severe AS as a result of large differences between LVOT and volumetric SV. Furthermore, this classification was sensitive to small measurement errors. These results stress that parameters beyond the flow-gradient classification should be considered to ensure accurate recommendations for intervention. (JTCVS Open 2023;16:177-88)

HG/LG, High/low-gradient; *NF/PLF*, normal/paradoxical low-flow; *LVOT*, left ventricular outflow tract.

CENTRAL MESSAGE

There was poor agreement in the flow-gradient classification of severe aortic stenosis (AS) as a result of large differences between LVOT and volumetric echocardiographic measurements of stroke volume.

PERSPECTIVE

A flow-gradient classification is used to determine the indication for intervention for patients with severe AS with discordant echocardiographic parameters. Our results stress that the heart team should consider multiple hemodynamic, anatomical, and clinical parameters beyond this classification to diagnose severe AS and ensure accurate recommendations for intervention for this challenging clinical entity.

AS	=	aortic stenosis
AVA	=	aortic valve area
AVAi	=	aortic valve area index
CI	=	confidence interval
CT	=	computed tomography
LFHG	=	low-flow, high-gradient
LV	=	left ventricle
LVOT	=	left ventricular outflow tract
NFHG	=	normal-flow, high-gradient
NFLG	=	normal-flow, low-gradient
PLFLG	=	paradoxical low-flow, low-gradient
SV	=	stroke volume
SVi	=	stroke volume index

The diagnosis of severe aortic stenosis (AS) is challenging when echocardiographic parameters such as the mean pressure gradient (MPG) and the aortic valve area (AVA) are discordant. Even in case of preserved left ventricular ejection fraction (LVEF), flow alterations are thought to play a crucial role in explaining this discrepancy.[1] Hence, a classification based on flow-gradient patterns was proposed.[2] Patients with an MPG $\leq$40 mm Hg are still considered to have severe AS in case of a small aortic valve area index (AVAi) and low-flow state (stroke volume index [SVi] $\leq$35 mL/m^2). This classification is important to the heart team, as it determines the indication for aortic valve replacement (AVR) in the guidelines.[3,4]

The main pitfall for this classification is stroke volume (SV) measurement, determined at the left ventricular outflow tract (LVOT).[1,2,5] Therefore, corroboration with volumetric echocardiographic methods such as the Simpson's rule was initially advised.[2,5] Although fair agreement between these SV methods was reported by some studies,[6,7] several other studies found poor agreement.[8-10] The consequences for the flow-gradient classification, which are directly relevant to clinical practice, are still unclear.

Hence, this study aimed to investigate the agreement in flow-gradient classification by LVOT and volumetric SV for patients with severe AS with preserved LVEF. The secondary aim was to study the agreement between the SV measurements themselves. The overarching goal is to provide information to improve decision-making by the heart team for patients with AS with discordant echocardiographic parameters.

METHODS
Study Data
Data from the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve (www.clinicaltrials.gov, NCT02088554) were used. The PERIGON Pivotal Trial is a single-armed prospective observational follow-up study to examine the safety and performance of the Avalus bioprosthesis (Medtronic). The design of the trial was formerly outlined in detail.[11] In the PERIGON Pivotal Trial, patients with a clinical indication for AVR due to moderate or severe AS or aortic regurgitation were enrolled. More than mild mitral or tricuspid regurgitation was an exclusion criterion. Specifically for the current study, patients with aortic regurgitation or a mixed primary indication with more than mild regurgitation were also excluded. Moreover, only the patients with an AVAi $\leq$0.6 cm^2/m^2 and preserved LVEF (>50%) were selected. The study was conducted at 38 centers across North America and Europe, at which local institutional review boards or ethics committees provided study approval (see supplementary files from Klautz and colleagues[12] for approval number and date per center). Furthermore, written informed consent for publication of study data was obtained for all patients represented in these analyses. All deaths and valve-related events were adjudicated by an independent clinical events committee (Baim Institute for Clinical Research).

Two-Dimensional and Doppler Echocardiography
An independent core laboratory (MedStar Health Research Institute) assessed all echocardiograms. MPG and AVA were determined using the simplified Bernoulli equation and the continuity equation, respectively. SV was calculated according to 2 independent methods. The first was the LVOT method (SV$_{LVOT}$), in which the velocity–time integral was multiplied by the LVOT cross-sectional area under the assumption of a circular shape. The second was the volumetric method (SV$_{volumetric}$), in which the 2D left ventricle (LV) end-systolic volume was subtracted from the LV end-diastolic volume using biplane data, conforming to the modified Simpson's rule. When 2 orthogonal views were not adequate for measurement, a single plane measurement was used. LVEF was also calculated from the LV end-systolic and end-diastolic volume, conforming to the modified Simpson's rule. When this continuous parameter was not available (which was the case in 21%), a categorical variable was used that indicated whether LVEF was good (>50%), moderate (31%-50%), poor (21%-30%), or very poor ($\leq$20%) based on visual inspection. Indexed parameters were calculated by dividing them by body surface area (according to the DuBois formula[13]).

Patients were stratified by flow-gradient pattern according to the criteria of Dumesnil and colleagues[2]; low flow was defined as SV $\leq$35 mL/m^2 and low gradient as MPG $\leq$40 mm Hg. This resulted in 4 groups: normal-flow, high-gradient (NFHG); normal-flow, low-gradient (NFLG); low-flow, high-gradient (LFHG); and paradoxical low-flow, low-gradient (PLFLG).

Statistical Analysis
Numerical data were presented either as mean $\pm$ standard deviation or median [interquartile range] depending on their distribution, and categorical data were presented as counts (percentages). Missing baseline data were present only for SV$_{volumetric}$ (in 20%) and were assumed to be missing at random.[14] Therefore, multiple imputation was performed based on all available patient characteristics, preoperative echocardiographic parameters, and survival status using predictive mean matching with 50 iterations to create 10 imputed datasets. Estimates and corresponding variances were pooled according to Rubin's rules.[14] To pool correlation coefficients, a Fisher Z transformation was used.[15] A sensitivity analysis was carried out in patients with complete data.

First, the proportion of patients per flow-gradient group was determined according to each SV method. Subsequently, the agreement between these methods was investigated using linear regression and the Pearson correlation coefficient. Furthermore, the mean difference between the SV measurements, including 95% limits of agreement, was illustrated in a Bland–Altman plot.[16] Two Kaplan–Meier analyses were executed

according to flow-gradient patterns determined by each SV method to investigate whether potential differences in group composition affected the corresponding survival rates. Follow-up started at the day of surgery and lasted until death, withdrawal, or stay in the study until the data pull, whichever came first.

Lastly, the clinical implication of measurement error in SV_{LVOT} was studied. An overestimation of the LVOT diameter by 1 mm was simulated, after which the SV and AVA were recalculated and the consequences for the flow-gradient classification were assessed.

All analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing; www.r-project.org).

RESULTS

Patient Characteristics According to Flow-Gradient Patterns

Of 1118 patients in the PERIGON Pivotal Trial, 699 were eligible (Figure E1). The baseline characters are presented according to flow-gradient patterns determined by SV_{LVOT} (Table 1). The low-flow groups comprised more male patients. The LFHG group had the lowest median Society of Thoracic Surgeons Predicted Risk of Mortality, whereas

TABLE 1. Baseline characteristics of patients with severe aortic stenosis by flow-gradient patterns based on LVOT SV measurement

Characteristic	NFHG N = 267 (38%)	NFLG N = 156 (22%)	LFHG N = 148 (21%)	PLFLG N = 128 (19%)
Patient characteristics				
Age, y	71.3 ± 8.3	70.8 ± 8.1	70.0 ± 7.0	70.7 ± 7.6
Male	188 (70%)	110 (71%)	116 (78%)	96 (75%)
Body surface area, m^2	1.93 ± 0.19	1.98 ± 0.22	2.07 ± 0.21	1.99 ± 0.20
Body mass index, kg/m^2	28.6 ± 4.8	29.9 ± 5.0	30.6 ± 5.4	30.1 ± 5.6
STS score, %	1.54 [1.06, 2.46]	1.68 [1.10, 2.38]	1.43 [0.98, 2.13]	1.77 [1.15, 2.45]
Diabetes mellitus	56 (21%)	51 (33%)	61 (41%)	42 (33%)
Hypertension	200 (75%)	130 (83%)	116 (78%)	95 (74%)
Chronic obstructive pulmonary disease	28 (10%)	15 (10%)	18 (12%)	11 (9%)
Coronary artery disease	106 (40%)	76 (49%)	57 (39%)	65 (51%)
Concomitant CABG	76 (28%)	62 (40%)	35 (24%)	56 (44%)
Atrial fibrillation	24 (9%)	9 (6%)	14 (9%)	17 (13%)
New York Heart Association class III/IV	116 (43%)	68 (44%)	66 (45%)	53 (41%)
Stroke	13 (5%)	7 (4%)	7 (5%)	4 (3%)
Peripheral vascular disease	16 (6%)	13 (8%)	11 (7%)	11 (9%)
Renal insufficiency	30 (11%)	13 (8%)	14 (9%)	18 (14%)
Echocardiography				
Peak aortic jet velocity, ms^{-1}	4.7 ± 0.5	3.8 ± 0.4	4.6 ± 0.4	3.6 ± 0.4
Mean pressure gradient, mm Hg	55 ± 13	33 ± 6	55 ± 10	31 ± 7
Aortic valve area, cm^2	0.71 ± 0.15	0.90 ± 0.14	0.57 ± 0.11	0.74 ± 0.15
Aortic valve area index, cm^2/m^2	0.37 ± 0.07	0.46 ± 0.07	0.28 ± 0.05	0.37 ± 0.08
Doppler velocity index	0.23 ± 0.08	0.29 ± 0.08	0.20 ± 0.08	0.25 ± 0.08
LVOT SV, mL	84.9 ± 15.2	83.0 ± 12.9	63.2 ± 8.1	61.0 ± 9.4
LVOT SV index, mL/m^2	44.0 ± 7.0	42.1 ± 5.5	30.6 ± 3.0	30.6 ± 3.5
Volumetric SV, mL	62.9 ± 18.8	62.6 ± 18.7	61.8 ± 17.6	53.5 ± 17.3
Volumetric SV index, mL/m^2	32.4 ± 8.7	31.8 ± 8.1	30.0 ± 7.9	26.8 ± 7.4
Heart rate, bpm	65 ± 10	64 ± 11	71 ± 12	70 ± 12
LV end-diastolic volume index, mL/m^2	52.0 ± 13.4	51.7 ± 13.4	49.4 ± 12.8	43.6 ± 11.7
LV end-systolic volume index, mL/m^2	19.9 ± 6.3	20.0 ± 6.4	19.5 ± 6.4	16.2 ± 5.6
Left ventricular ejection fraction, %	62 ± 6	62 ± 5	61 ± 6	62 ± 6
Left ventricular hypertrophy	120 (45%)	42 (27%)	63 (43%)	43 (34%)
Mild mitral regurgitation	100 (37%)	54 (35%)	58 (39%)	26 (20%)
Mild tricuspid regurgitation	101 (38%)	43 (28%)	38 (26%)	39 (30%)

Data are either presented as mean ± standard deviation, median [interquartile range], or counts (percentages). *NFHG*, Normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient; *STS*, Society of Thoracic Surgeons; *CABG*, coronary artery bypass grafting; *LVOT*, left ventricular outflow tract; *SV*, stroke volume; *LV*, left ventricle.

the PLFLG had the highest. The average AVA and AVAi were smallest in the LFHG group and largest in the NFLG group. There were large discrepancies in SV_{LVOT} and $SV_{volumetric}$, and patients in the PLFLG group had the smallest average indexed left ventricular end-diastolic volume. Mild mitral regurgitation was relatively uncommon in the PLFLG group. Coronary artery disease and concomitant coronary artery bypass grafting were more common in the low-gradient groups as compared with the high-gradient groups. Lastly, atrial fibrillation was frequently present in patients in the PLFLG group.

In Table E1, the baseline characteristics per flow-gradient group are presented, stratified by SV method. When $SV_{volumetric}$ was used, the normal-flow groups comprised more male patients than the low-flow groups. Furthermore, the lowest Society of Thoracic Surgeons Predicted Risk of Mortality was observed for the NFHG group, and the largest discrepancies in SV were present in the low-flow groups. Except for these differences, the group characteristics remained rather similar to the scenario using SV_{LVOT}.

The Agreement in Flow-Gradient Classification and SV Measurement

Using SV_{LVOT}, the NFHG group comprised 267 (38%) patients, the NFLG group 156 (22%), the LFHG group 148 (21%), and the PLFLG group 128 (19%). The group composition changed when $SV_{volumetric}$ was used (Figure E2); the NFHG group consisted of 111 (17%) patients, the NFLG group of 53 (10%), the LFHG group of 227 (42%), and the PLFLG group of 168 (31%). Both SV methods agreed on low-flow in 31% and normal-flow in 19%, whereas they disagreed in the other 50% (Figure 1). Furthermore, an increase in LVOT SVi of 1 mL/m² resulted on average in an increase in volumetric SVi of 0.22 mL/m² (95% confidence interval [CI], 0.14-0.29 mL/m²). The correlation between the SV methods was 0.33 (95% CI, 0.26-0.40). SV_{LVOT} was on average 15.1 mL greater than $SV_{volumetric}$ with 95% limits of agreement ranging from −24.9 to 55.1 mL (Figure 2). For the entire cohort, the median follow-up time was 1785 days. The discrepancy in flow-gradient classification also yielded alterations in survival (Figure 3). If SV was obtained via the LVOT method, the patients in NFHG showed the worst survival, with a Kaplan–Meier survival rate of 87% (95% CI, 82%-91%) at 5 years of follow-up. However, when using volumetric SV, the LFHG group had the worst survival (Kaplan–Meier survival rate 88%, 95% CI 84%-93%), and the survival curves for all patient groups changed.

The results of the aforementioned analyses based on partly imputed data were similar to the results of the sensitivity analysis in patients with complete data (Table E2, Figures E3 and E4).
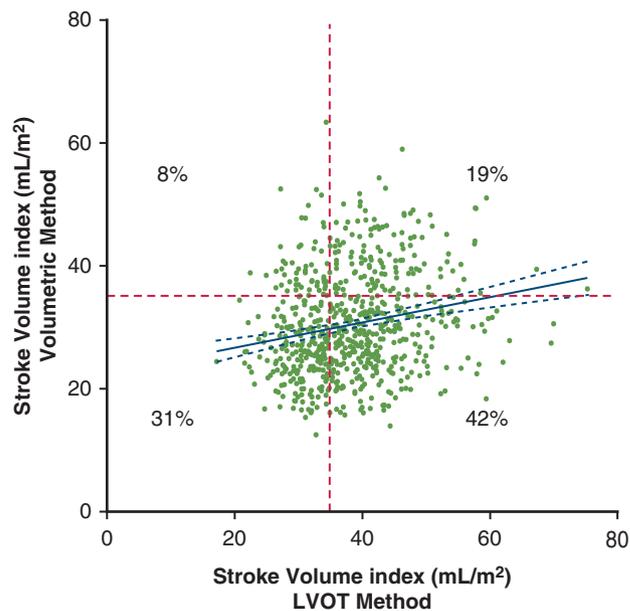

FIGURE 1. Agreement between the LVOT and the volumetric method to determine indexed stroke volume in patients with severe aortic stenosis. The *blue line* displays the relation using linear regression, including corresponding 95% confidence intervals. The *horizontal* and *vertical dashed red lines* are placed at the threshold for low flow. *LVOT*, Left ventricular outflow tract.

Clinical Implication of Measurement Error in LVOT SV

A 1-mm overestimation of the LVOT diameter resulted in an increase in mean SV_{LVOT} index from 38.3 to 42.7 mL/m² and in mean AVAi from 0.37 to 0.43 cm². Consequently, although 40% were originally in low flow, only 20% remained in this state after the introduction of the 1-mm overestimation (Figures 4 and E5). In absolute numbers, the
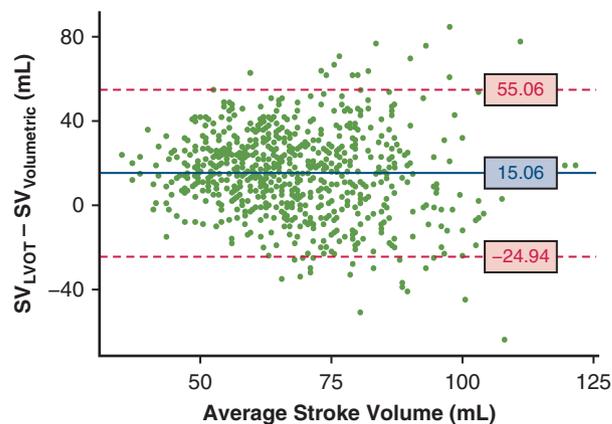

FIGURE 2. Bland–Altman plot: agreement between LVOT and the volumetric stroke volume measurements in patients with severe aortic stenosis. The *lines* represent the mean difference between the 2 measurements, including the 95% limits of agreement. *SV*, Stroke volume; *LVOT*, left ventricular outflow tract.
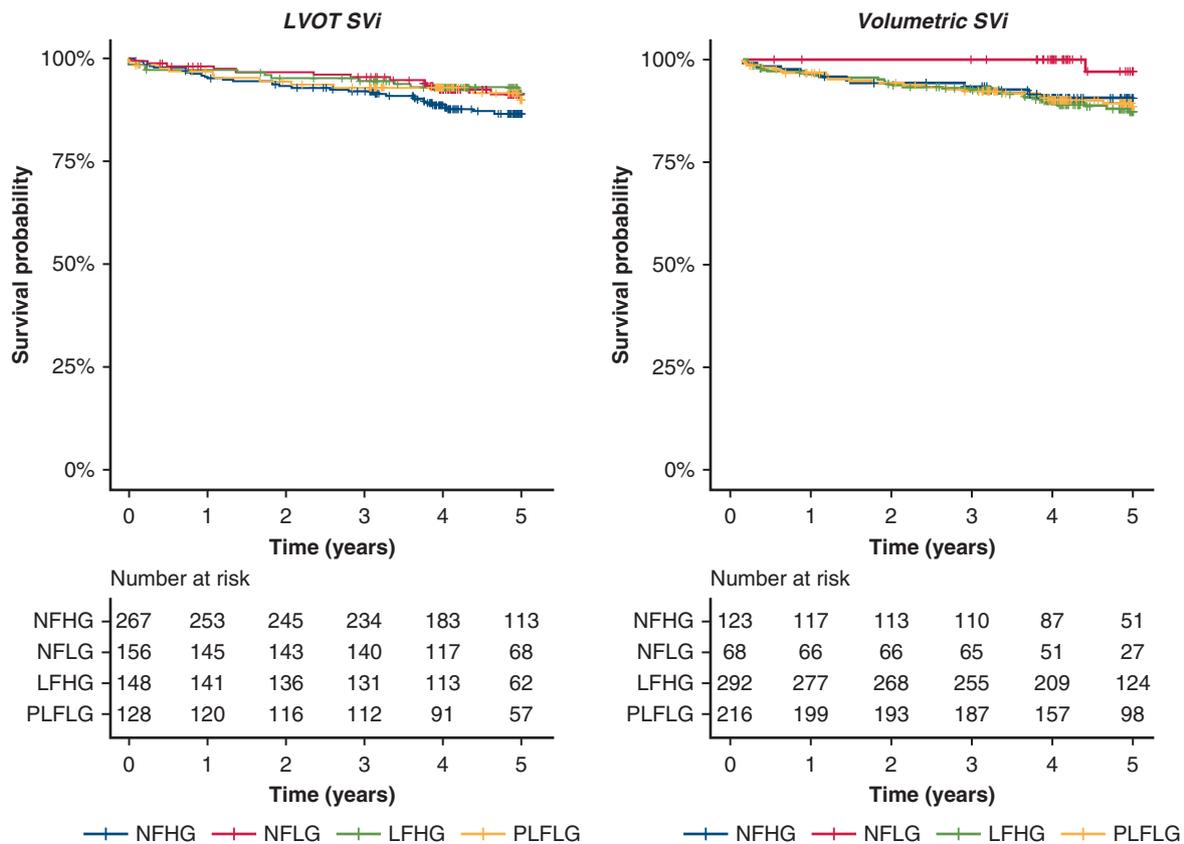
FIGURE 3. Kaplan–Meier survival analysis according to flow-gradient patterns of patients who underwent aortic valve replacement. Censoring is indicated by the "+" sign. For the *left* Kaplan–Meier analysis, the survival rates were 86.5% (95% CI, 82.3%-91.0%) for NFHG, 91.4% (95% CI, 86.7%-96.2%) for NFLG, 91.5% (95% CI, 86.7%-96.6%) for LFHG, and 90.0% (95% CI, 84.4%-96.0%) for PLFLG. For the *right* Kaplan–Meier analysis, the survival rates were 90.7% (95% CI, 85.4%-96.4%) for NFHG, 96.3% (95% CI, 89.4%-100%) for NFLG, 88.1% (95% CI, 83.5%-92.9%) for LFHG, and 89.8% (95% CI, 85.2%-94.7%) for PLFLG. *LVOT*, Left ventricular outflow tract; *SVi*, stroke volume index; *NFHG*, normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient; *CI*, confidence interval.

LFHG group decreased from 148 to 79 patients and the PLGLG group from 128 to 64, ie, the low-flow groups almost halved. Furthermore, 43 (6%) patients were reclassified to moderate AS due to an AVAi >0.6 cm^2/m^2.

DISCUSSION

In this analysis of 699 patients with severe AS with preserved LVEF, there were large differences in flow-gradient classification as a result of poor agreement between LVOT and volumetric SV measurement (Figure 5). SV$_{volumetric}$ was systematically lower than SV$_{LVOT}$. Furthermore, SV$_{LVOT}$ was very sensitive to small measurement error; when a systematic 1-mm LVOT diameter overestimation was simulated, the low-flow groups halved.

The flow-gradient classification was proposed to enhance the confirmation of severe AS, specifically for patients with discordant echocardiographic parameters.[2] The patient characteristics that distinguish the flow-gradients patterns are moderately understood, and the reported features are

quite heterogeneous.[17] Bavishi and colleagues[18] reported high incidences of coronary artery disease in the low-flow groups and frequent atrial fibrillation and a small indexed left ventricular end-diastolic volume in patients in the PLFLG group. For the LFHG group, Eleid and colleagues[19] found that the AVA and AVAi was smallest and that the incidence of diabetes mellitus was relatively high. In our study, we identified similar characteristics.

Previous studies have stated that SV corroboration with other methods is essential for accurate flow-gradient classification.[2,5] In the first study concerning PLF severe AS, the SVs derived from the LVOT and the Simpson's method were comparable,[6] which was also found in a more recent study comprising patients with mild-to-severe AS.[7] Conversely, a significantly lower SV by the biplane Simpson's method was observed by Stähli and colleagues,[8] by Iwataki and colleagues,[9] and by the World Alliance of Societies of Echocardiography[10] in 1450 healthy adult volunteers. In the current study, SV$_{volumetric}$ was expected to
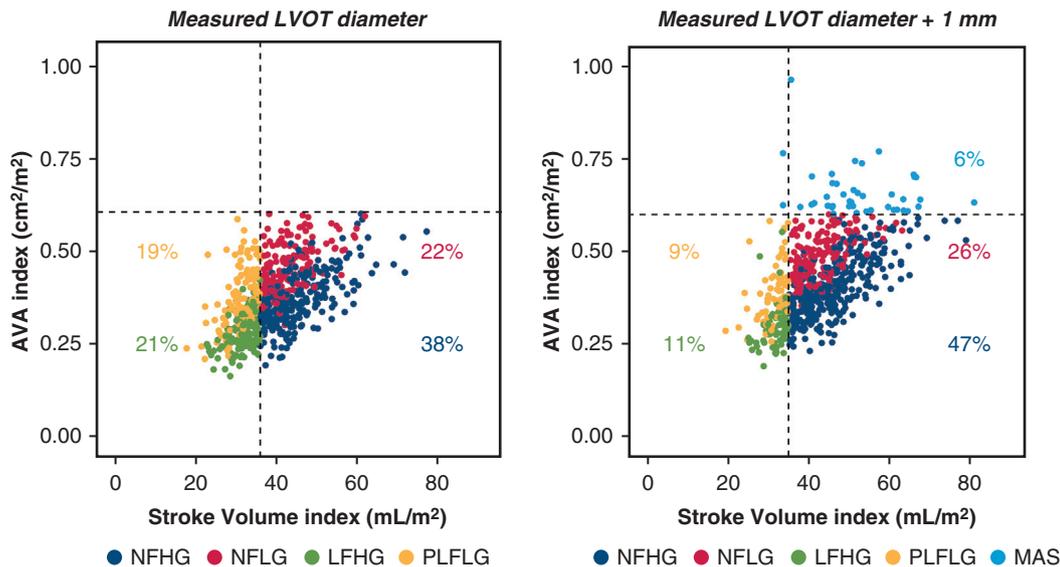
FIGURE 4. Clinical implication of overestimation of LVOT diameter by 1 mm for the flow-gradient classification of severe aortic stenosis. The *vertical line* represents the threshold for low flow and the *horizontal line* for severe aortic stenosis. *LVOT,* Left ventricular outflow tract; *AVA,* aortic valve area; *NFHG,* normal-flow, high-gradient; *NFLG,* normal-flow, low-gradient; *LFHG,* low-flow, high-gradient; *PLFLG,* paradoxical low-flow, low-gradient; *MAS,* moderate aortic stenosis.

approximate the forward SV_{LVOT} since patients with more than mild mitral or tricuspid regurgitation were excluded. However, a lower SV was observed using the volumetric method. In the absence of substantial backward flow, it is difficult to physiologically explain this discrepancy.

Moreover, in a post-hoc analysis, we excluded patients who underwent concomitant CABG to rule out the potential influence of LV wall motion abnormalities and the results (which are not reported) remained unchanged. Since both methods require multiple measurements
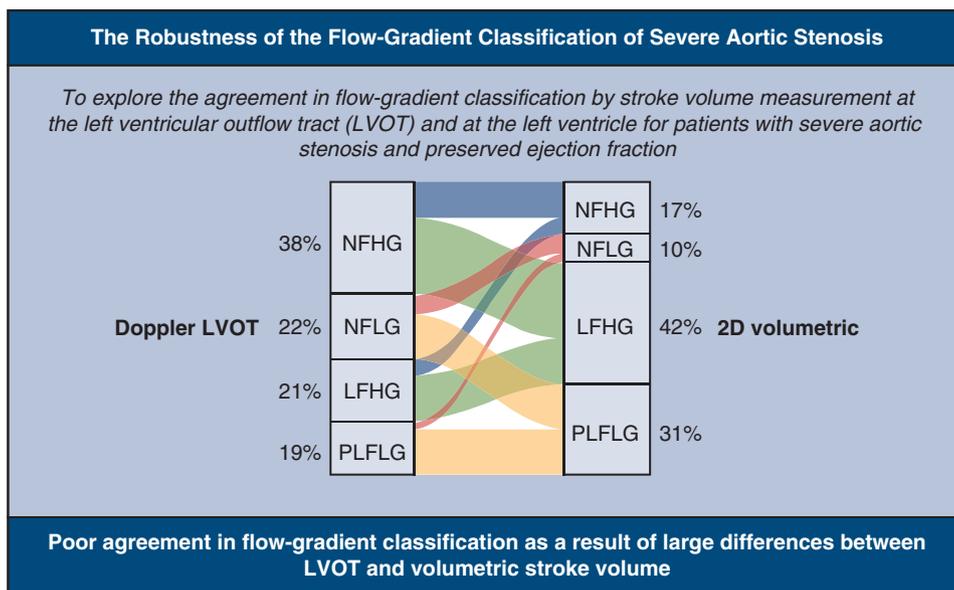

FIGURE 5. Graphical abstract: The robustness of the flow-gradient classification of severe aortic stenosis. *NFHG,* Normal-flow high-gradient; *NFLG,* normal-flow, low-gradient; *LFHG,* low-flow, high-gradient; *PLFLG,* paradoxical low-flow, low-gradient.

and geometrical assumptions, measurement errors are a likely cause.

Derivation of $SV_{volumetric}$ via the biplane Simpson's method demands capturing the complex LV geometry in 2-dimensional images. Errors could arise in tracing the endocardial borders, from the inability to track the entire LV volume, for example, due to anatomical constraints, geometrical assumptions, and (apical) foreshortening.[10,20] Small variability in 2-dimensional measurements can lead to larger distortions when translated to the volumetric scale. Foreshortening happens when the echo beam does not capture the true apex and results in underestimation of the LV volume. This problem arises from the image acquisition and cannot be solved by image analysis despite the use of an experienced core lab. Hence, foreshortening could contribute to the SV discrepancy in our study.

Although the LVOT method is most commonly applied, this measurement is also susceptible to measurement error. The velocity–time integral across the LVOT could be mismeasured due to probe malalignment or due to a spatially nonuniform velocity profile,[21] whereas the LVOT area is often underestimated as a result of the assumption of a circular shape.[1] Considering the latter, SV_{LVOT} would increase; hence, the apparent difference would even be larger. The sensitivity to small errors in the LVOT diameter is a drawback of the LVOT method. To exemplify, a 1-mm overestimation of the LVOT diameter resulted in a reduction in the proportion of low-flow patients of approximately 50% in our simulation. This has important implications not only for scientific research, in which patients could be misclassified to incorrect flow-gradient groups, but also for clinical practice since recommendations for intervention exist only for specific flow-gradient groups.[3,4]

From our data, we cannot conclude that $SV_{volumetric}$ is a systematic underestimation of the SV_{LVOT} or vice versa. Although this was not the aim of this study, the optimal SV method for the flow-gradient classification of severe AS is hard to determine due to the lack of a gold standard for noninvasive SV measurement. However, as studies including imaging modalities such as 3-dimensional echocardiography,[10,22] computed tomography (CT),[8] or cardiovascular magnetic resonance[7,23] also indicate different (usually larger) SVs, it seems that neither method is completely interchangeable. To avoid ambiguity, we encourage guideline authors to at least specify the SV measurement method in recommendations for interventions based on specific flow-gradient patterns. Furthermore, more consideration of the clinical relevance of using echocardiographic SV to categorize patients with AS might be needed. Theoretically, it makes sense to assess SV when a low gradient is observed. However, the benefit of correctly identifying low-flow patients who would benefit from AVR

needs to be weighed against the harms of misclassification due to measurement variability and error.

Recent research endeavors suggest shifting the focus to the myocardium to optimize diagnostic pathways and the timing of intervention.[24] The main idea is to intervene before structural components of the heart are irreversibly damaged. Modern echocardiographic parameters such as global longitudinal strain and myocardial work indices but also multimodality imaging like fibrosis assessment using cardiovascular magnetic resonance could be helpful to achieve this; however, robust evidence on their superiority is needed before these will be part of standard clinical practice. For now, the results of this analysis reinforce the guideline recommendations[3,4] that for the confirmation of true severe AS, an integrated approach is crucial. Especially in cases of conflicting primary parameters, other echocardiographic measurements, such as Doppler velocity index, functional status, and anatomical parameters like valvular calcification on CT should also point in the direction of severe AS.[3,4]

Strengths and Limitations

The study population consisted of patients who were at low surgical risk, which could reduce the generalizability of the observed differences in SV to patients with high-risk severe AS who are scheduled for transcatheter AVR. Nevertheless, although all patients had a primary indication for valve replacement based on their AVAi, common concomitant procedures like CABG were allowed, which boosts overall representativeness to the entire severe AS population. In addition, the study was executed in an international multicenter setting with prospective data gathering. The current analysis included relatively large patient groups, especially the LFHG and PLFLG group when compared with previous studies.[18] Unfortunately, no information on anatomical AS severity such as valve calcification was present due to the lack of routine CT assessments.

Differences between SV_{LVOT} and $SV_{volumetric}$ have been described before[6-10]; however, we directly related these to the flow-gradient classification of AS, which is essential to decision-making by the heart team. For this classification, we also demonstrated the sensitivity to small measurement errors. The outline of these implications for clinical practice is the novelty of the current study.

CONCLUSIONS

In this analysis, there were large differences in flow-gradient classification as a result of poor agreement between LVOT and volumetric SV measurement. Furthermore, this classification was sensitive to small measurement errors. These results stress that the heart team should

consider multiple hemodynamic, anatomical, and clinical parameters beyond the flow-gradient classification to ensure accurate recommendations for intervention for patients with AS with discordant echocardiographic parameters.

Conflict of Interest Statement

B.V.: institutional research grant and speaker's honorarium paid to his department from Medtronic. M.V.: institutional research grant and reimbursement of travel expenses from Medtronic. F.A.: no personal conflicts of interest, but his organization receives grants or research contracts from Medtronic, Abbott, Edwards Lifesciences, Boston Scientific, Biotronik, Corcym, and HLT Medical. M.M.: trainer and consultant for Medtronic; a trainer and speaker for AtriCure; and a speaker and consultant for Haemonetics. F.D.: proctor and speaker for Medtronic and Cook Medical. M.R.: consultant to Medtronic, Abbott Medical, Boston Scientific, Gore Medical, and Transverse Medical; the fees are paid to his department. J.S.: Principal Investigator, PERIGON Pivotal Trial for Medtronic. R.K.: research support, consultation fees, and Principal Investigator, PERIGON Pivotal Trial for Medtronic. All other authors reported no conflicts of interest.

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Key Words: flow-gradient classification, severe aortic stenosis, stroke volume, low flow
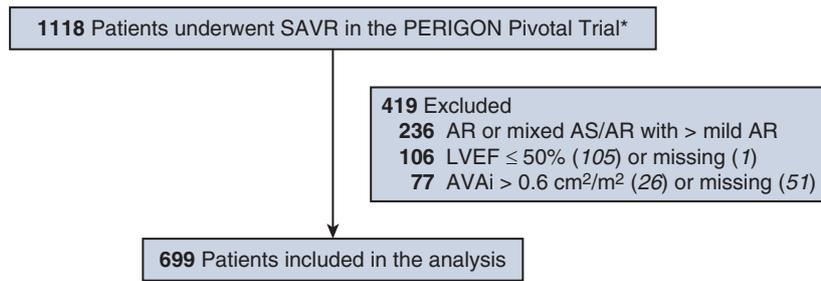
FIGURE E1. CONSORT diagram for patients with severe aortic stenosis and preserved ejection fraction. *Data were from the PERIcardial SurGical AOrtic Valve ReplacemeNt (*PERIGON*) Pivotal Trial for the Avalus valve (Medtronic). *SAVR*, Surgical aortic valve replacement; *AR*, aortic regurgitation; *AS*, aortic stenosis; *LVEF*, left ventricular ejection fraction; *AVAi*, aortic valve area index; *CONSORT*, Consolidated Standards of Reporting Trials.
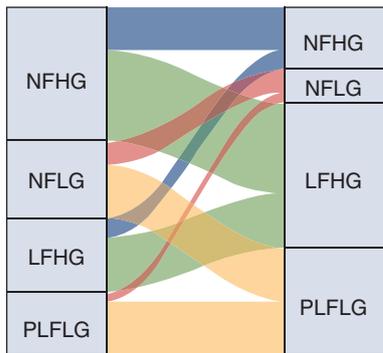
FIGURE E2. Concordance in flow-gradient classification of patients with severe aortic stenosis between left ventricular outflow tract (*left*) and volumetric stroke volume index measurements (*right*). *NFHG*, Normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient.
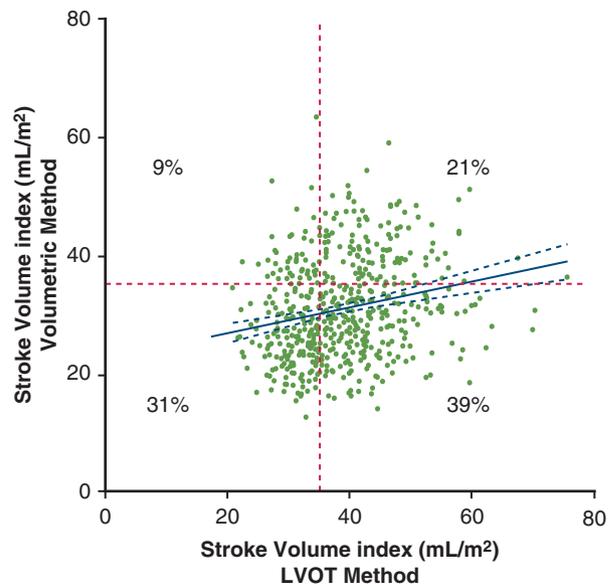
FIGURE E3. Agreement between the LVOT and the volumetric methods to determine indexed stroke volume in patients with severe aortic stenosis and complete data. The *solid blue* line displays the relation using linear regression. The *dashed blue lines* represent the corresponding 95% confidence intervals. The *horizontal and vertical dashed red lines* are placed at the threshold value of 35 mL/m^2 for low flow. The *green filled circles* represent patient values. *LVOT*, Left ventricular outflow tract.
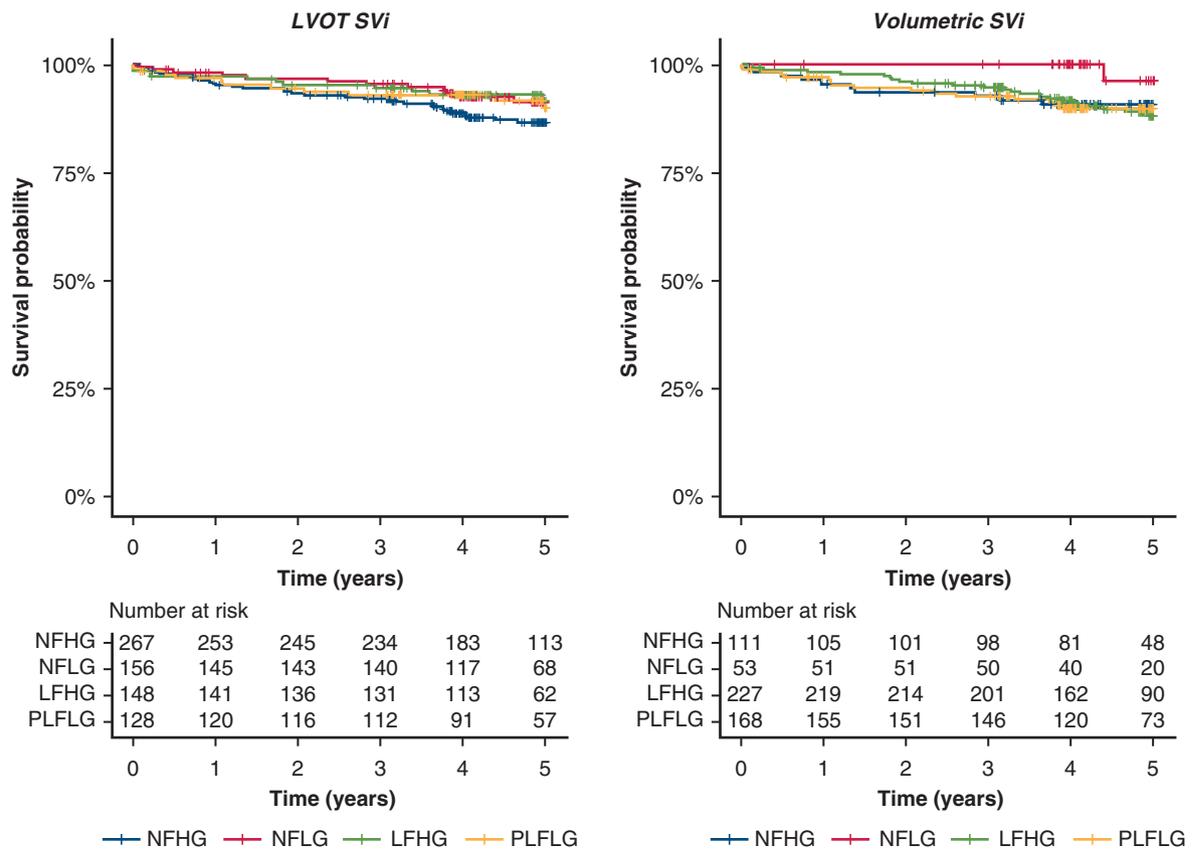
FIGURE E4. Kaplan–Meier survival analysis according to flow-gradient patterns of patients who underwent aortic valve replacement and had complete data. Censoring is indicated by the "+" sign. *LVOT*, Left ventricular outflow tract; *SVi*, stroke volume index; *NFHG*, Normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient.
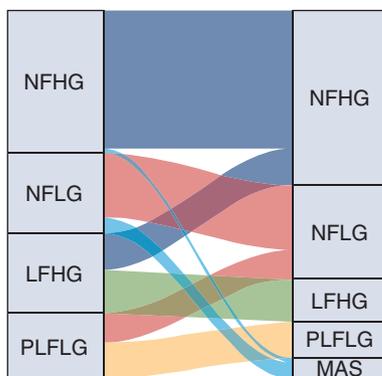
FIGURE E5. Concordance in flow-gradient classification after introduction of a 1-mm overestimation of LVOT diameter (*right*) to the actual situation (*left*). *NFHG*, Normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient; *MAS*, moderate aortic stenosis; *LVOT*, left ventricular outflow tract.

TABLE E1. Baseline characteristics of patients with severe aortic stenosis by flow-gradient patterns using LVOT or volumetric stroke volume

| Characteristic	NFHG		NFLG		LFHG		PLFLG	
	LVOT N = 267 (38%)	Volumetric N = 108 (18%)	LVOT N = 156 (22%)	Volumetric N = 51 (10%)	LVOT N = 148 (21%)	Volumetric N = 234 (42%)	LVOT N = 128 (19%)	Volumetric N = 166 (30%)
Demography								
Age, y	71.4 ± 8.3	70.1 ± 7.6	70.9 ± 8	70.2 ± 8.9	69.8 ± 7.0	70.9 ± 7.5	70.8 ± 8.0	70.4 ± 7.5
Male	188 (70%)	88 (81%)	109 (71%)	43 (84%)	118 (78%)	172 (74%)	95 (75%)	116 (70%)
Body surface area, m^2	1.9 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
Body mass index, kg/m^2	28.6 ± 4.8	29.3 ± 4.1	29.8 ± 5.0	29.3 ± 4.7	30.6 ± 5.4	28.7 ± 5.0	30.2 ± 5.6	29.5 ± 5.3
STS-PROM, %	1.54 [1.06, 2.45]	1.42 [0.99, 2.15]	1.66 [1.10, 2.38]	1.60 [1.02, 2.11]	1.41 [0.97, 2.09]	1.48 [1.05, 2.30]	1.81 [1.15, 2.44]	1.78 [1.16, 2.40]
Diabetes mellitus	58 (22%)	32 (30%)	50 (33%)	19 (37%)	63 (42%)	66 (28%)	39 (31%)	47 (28%)
Hypertension	203 (76%)	85 (79%)	125 (82%)	42 (82%)	117 (77%)	173 (74%)	95 (75%)	121 (73%)
COPD	29 (11%)	17 (16%)	14 (9%)	4 (8%)	19 (13%)	22 (9%)	12 (9%)	17 (10%)
Coronary artery disease	106 (40%)	42 (39%)	76 (50%)	24 (47%)	54 (36%)	88 (38%)	64 (50%)	81 (49%)
Concomitant CABG	75 (28%)	31 (29%)	62 (41%)	20 (39%)	33 (22%)	62 (26%)	54 (43%)	69 (42%)
Atrial fibrillation	24 (9%)	7 (6%)	9 (6%)	2 (4%)	15 (10%)	27 (12%)	19 (15%)	18 (11%)
NYHA III/IV	115 (43%)	48 (44%)	67 (43%)	19 (37%)	67 (45%)	96 (41%)	53 (42%)	75 (45%)
Stroke	13 (5%)	5 (5%)	7 (5%)	3 (6%)	8 (5%)	13 (6%)	5 (4%)	6 (4%)
Peripheral vascular disease	16 (6%)	7 (6%)	13 (8%)	3 (6%)	12 (8%)	14 (6%)	11 (9%)	18 (11%)
Renal insufficiency	31 (12%)	10 (9%)	13 (8%)	2 (4%)	20 (13%)	29 (12%)	18 (14%)	17 (10%)
Echocardiography								
V_{max}, ms^{-1}	4.7 ± 0.5	4.7 ± 0.5	3.8 ± 0.4	3.9 ± 0.3	4.6 ± 0.4	4.6 ± 0.5	3.6 ± 0.4	3.6 ± 0.4
MPG, mm Hg	54.7 ± 12.7	55.4 ± 12.2	32.8 ± 6.1	34.3 ± 4.9	54.3 ± 10.1	54.3 ± 11.4	31.1 ± 6.5	31.0 ± 6.6
AVA, cm^2	0.71 ± 0.1	0.69 ± 0.2	0.9 ± 0.1	0.87 ± 0.2	0.57 ± 0.1	0.65 ± 0.1	0.73 ± 0.1	0.8 ± 0.2
AVAi, cm^2/m^2	0.37 ± 0.1	0.35 ± 0.1	0.46 ± 0.1	0.43 ± 0.1	0.28 ± 0.1	0.33 ± 0.1	0.37 ± 0.1	0.41 ± 0.1
DVI	0.23 ± 0.1	0.21 ± 0.1	0.29 ± 0.1	0.27 ± 0.1	0.20 ± 0.1	0.22 ± 0.1	0.25 ± 0.1	0.27 ± 0.1
VTI AV, cm^2	116.3 ± 16.9	117.0 ± 16.6	88.9 ± 11.4	89.6 ± 10.1	110.3 ± 16.4	113.2 ± 17	82.6 ± 13.2	85.0 ± 13.3
VTI LVOT, cm^2	26.0 ± 4.6	24.0 ± 4.6	25.3 ± 4.2	23.9 ± 4.9	21.5 ± 3.6	24.4 ± 4.8	20.3 ± 3.5	22.5 ± 4.4
CO, L/min	5.49 ± 1.2	5.16 ± 1.4	5.29 ± 1.1	5.08 ± 1.2	4.42 ± 0.9	5.04 ± 1.2	4.25 ± 1	4.63 ± 1.2
LVOT SV, mL	85.1 ± 15.3	82.1 ± 18.9	82.9 ± 12.8	80.2 ± 14.3	62.8 ± 8.4	75.2 ± 16.9	60.7 ± 9	70.2 ± 15.5
LVOT SVi, mL/m^2	44.1 ± 7.1	41.3 ± 9.5	42.1 ± 5.4	40.0 ± 7.4	30.6 ± 3.1	38.6 ± 8.9	30.5 ± 3.5	36.1 ± 7.5
Volumetric SV, mL	62.7 ± 18.9	82.8 ± 12.6	62.0 ± 18.1	82.7 ± 12.7	60.9 ± 17.7	52.5 ± 11.6	53.0 ± 17	50.2 ± 11.5
Volumetric SVi, mL/m^2	32.3 ± 8.7	41.4 ± 5.1	31.6 ± 8.1	41.0 ± 4.9	29.7 ± 7.9	26.7 ± 5	26.6 ± 7.3	25.7 ± 5
Heart rate, bpm	65 ± 10	63 ± 10	64 ± 11	63 ± 11	71 ± 12	68 ± 11	70 ± 12	67 ± 12
LVEDVi, mL/m^2	52.1 ± 13.5	65.4 ± 9.7	51.2 ± 13.1	65.4 ± 9.2	50.3 ± 13.3	45.3 ± 9.5	44.4 ± 12.3	42.9 ± 8.9
LVESVi, mL/m^2	20.1 ± 6.5	24.0 ± 7.2	19.8 ± 6.2	24.4 ± 6.4	20.7 ± 8.1	18.6 ± 6.4	17.8 ± 7.1	17.2 ± 5.8
LVEF, %	61.8 ± 6.7	63.9 ± 7.0	61.6 ± 5.5	63.1 ± 5.7	59.6 ± 7.7	59.6 ± 6.8	60.3 ± 7.8	60.4 ± 6.8
LVH	119 (44%)	49 (45%)	40 (26%)	16 (31%)	65 (43%)	104 (44%)	40 (31%)	42 (25%)
Mild mitral regurgitation	100 (37%)	36 (33%)	51 (33%)	12 (24%)	60 (40%)	91 (39%)	27 (21%)	51 (31%)
Mild tricuspid regurgitation	100 (37%)	37 (34%)	40 (26%)	19 (37%)	39 (26%)	83 (35%)	40 (32%)	49 (30%)

Data are presented as either mean $\pm$ standard deviation, median [interquartile range], or counts (percentages). *NFHG*, Normal-flow, high-gradient; *NFLG*, normal-flow, low-gradient; *LFHG*, low-flow, high-gradient; *PLFLG*, paradoxical low-flow, low-gradient; *LVOT*, left ventricular outflow tract; *STS-PROM*, Society of Thoracic Surgeons Predicted Risk of Mortality; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass grafting; *NYHA*, New York Heart Association; V_{max}, peak aortic jet velocity; *MPG*, mean pressure gradient; *AVA*, aortic valve area; *AVAi*, aortic valve area index; *DVI*, Doppler velocity index; *VTI*, velocity–time integral; *AV*, aortic valve; *CO*, cardiac output; *SV*, stroke volume; *SVi*, stroke volume index; *LVEDVi*, left ventricular end-diastolic volume index; *LVESVi*, left ventricular end-systolic volume index; *LVEF*, left ventricular ejection fraction; *LVH*, left ventricular hypertrophy.

TABLE E2. Agreement between stroke volume methods in main analysis and in patients with complete data

Method	Main analysis using multiple imputations	Complete-case analysis
Linear regression	Volumetric SVi = 22.1 + 0.22 × LVOT SVi	Volumetric SVi = 22.3 + 0.22 × LVOT SVi
Correlation	0.33	0.33
Average difference $SV_{LVOT} - SV_{Volumetric}$	15.1 mL (95% limits of agreement −24.9, 55.1 mL)	14.8 mL (95% limits of agreement −25.6, 55.3 mL)

SVi, Stroke volume index; *LVOT*, left ventricular outflow tract; *SV*, stroke volume.