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Meta-analysis

Transcatheter Aortic Valve Replacement Across Hemodynamic Subtypes of Severe Aortic Valve Stenosis: A Network Meta-analysis

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ABSTRACT

Background: Studies assessing outcomes of transcatheter aortic valve replacement (TAVR) in patients with severe aortic valve stenosis (AS) with hemodynamic subtypes have demonstrated mixed results with respect to outcomes and periprocedural complications. This study aimed to assess the outcomes of TAVR in patients across various hemodynamic subtypes of severe AS.

Methods: PubMed, Embase, and Cochrane databases were searched through September 2023 to identify all observational studies comparing outcomes of TAVR in patients with paradoxical low flow low gradient (pLFLG), classic LFLG, and high gradient AS (HGAS). The primary outcome was major adverse cardiovascular events (MACE). The secondary outcomes were components of MACE (mortality, myocardial infarction [MI], stroke). A bivariate, influential, and frequentist network meta-analysis model was used to obtain the net odds ratio (OR) with a 95% CI.

Results: A total of 21 studies comprising 17,298 (8742 experimental and 8556 HGAS) patients were included in the quantitative analysis. TAVR was associated with a significant reduction in the mean aortic gradient, and an increase in the mean aortic valve area irrespective of the AS type. Compared with HGAS, TAVR in classic LFLG had a significantly higher (OR, 1.68; 95% CI, 1.04-2.72), while pLFLG (OR, 0.98; 95% CI, 0.72-1.35) had a statistically similar incidence of MACE at a median follow-up of 1-year. TAVR in LFLG also had a significantly higher need for surgery (OR, 3.57; 95% CI, 1.24-10.32), and a greater risk of periprocedural (OR, 2.00; 95% CI, 1.17-3.41), 1-month (OR, 1.69; 95% CI, 1.08-2.64), and 12-month (OR, 1.41; 95% CI, 1.05-1.88) mortality compared with HGAS. The incidence of MI, major bleeding, vascular complications, paravalvular leak, pacemaker implantation, and rehospitalizations was not significantly different between all other types of AS (HGAS vs LFLG, pLFLG).

Conclusions: TAVR is an effective strategy in severe AS irrespective of the hemodynamic subtypes. Relatively, pLFLG did not have significantly different risk of periprocedural complications compared with HGAS, while classical LFLG AS had higher risk of MACE, primarily driven by the greater mortality risk.

Introduction

Transcatheter aortic valve replacement (TAVR) is a widely utilized treatment strategy for patients with severe symptomatic aortic stenosis (AS). The American and European guidelines identify severe AS as an aortic valve area (AVA) <1.0 cm^2 and maximum aortic jet velocity (Vmax) $\geq$4 m/s or mean pressure gradient (MG) $\geq$40 mm Hg.[1,2] However, more than 30% of TAVR recipients exhibit discordant AS grading criteria, where a calculated AVA of <1.0 cm^2 can be seen with an MG $<$40 mm Hg or Vmax $<$4 m/s (low gradient [LG]).[3] Another important hemodynamic parameter is the presence of low left ventricular (LV) outflow (stroke volume index [SVi] $<$ 35 mL/m^2) defined as a low flow (LF) state. The low flow low gradient (LFLG) state is commonly a result of LV dysfunction characterized by reduced ejection fraction (EF) ($<$40%) and is termed classic LFLG AS. However, in up to 20% of patients with LFLG, severe AS (AVA <1.0 cm^2) is observed in combination with preserved LVEF ($>$50%), this discrepancy is known as paradoxical low flow low gradient (pLFLG) AS.[4] The pLFLG is due to diastolic dysfunction either

Abbreviations: AVA, aortic valve area; EF, ejection fraction; HG, high gradient; LBBB, left bundle branch block; LF, low flow; LG, low gradient; MACE, major adverse cardiovascular events; SVI, stroke volume index; TAVR, transcatheter aortic valve replacement.

Keywords: aortic stenosis; discordant hemodynamics; transcatheter aortic valve replacement.

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due to myocardial fibrosis, or increased afterload due to any reason. Depending upon the distribution of MG, SVi, and EF, severe AS can be classified as HGAS (MG $\geq$40 mm Hg, AVA $<$1 cm^2), LFLG (SVi $<$35 mL/m^2, MG $<$40 mm Hg, EF $<$50%), and pLFLG (SVi $<$35 mL/m^2, MG $<$40 mm Hg, EF $\geq$50%). The benefits of TAVR in patients with HGAS have previously been well demonstrated in the literature. However, current data describing outcomes of TAVR in patients with other hemodynamic AS subtypes are conflicting and limited to small studies.

The American College of Cardiology (ACC) and American Heart Association (AHA) 2014 guidelines on the management of valvular heart disease previously recommended aortic valve replacement in symptomatic patients with HGAS as class I, and pLFLG AS as class IIa indication.[1] The recent ACC/AHA updated guidelines (2022) upgraded TAVR to class I indication for all symptomatic patients with low gradients (LFLG and pLFLG) regardless of the hemodynamic subtypes if severe AS was the most likely explanation for symptoms.[5] However, these guidelines recognized the lack of randomized data, and recommendations were based on expert consensus and smaller studies. Given the paucity of large-scale data, our current study sought to pool all observational data, to investigate the hemodynamic, procedural, and clinical benefits of TAVR in patients in all hemodynamic subtypes.

Methods

The Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist[6] was followed to conduct the current NMA.

Search strategy

PubMed, Cochrane, and Embase databases were queried until September 2023 to identify all relevant articles. Various medical subject headings were combined using Boolean operators. Using the EndNote library, overall results were screened at the level of title and abstract; potentially relevant studies underwent a full-text appraisal and data extraction. References of the included studies were also assessed to identify items missed on the initial screening (backward citation chasing). The detailed search strategy and search map are given in the Supplemental Material.

Selection criteria

The inclusion criteria were (1) all studies comparing the outcomes of TAVR, (2) in patients with severe aortic valve (AV) stenosis, and (3) have at least 1 efficacy end point. Studies with duplicate populations, non-TAVR populations, insufficient data, review articles, conference papers, and case reports were excluded. The selection criteria of individual studies are given in Supplemental Table S1.

Study subjects and comparison strategies

The patients were categorized into 3 hemodynamic subgroups. High gradient AS (HGAS) (MG $>$40 mm Hg), LFLG (SVi $<$35 mL/m^2, MG $<$40 mm Hg, EF $<$50%), and pLFLG (SVi $<$35 mL/m^2, MG $<$40 mm Hg, EF $>$50%). The common control group for direct comparisons was HGAS.

Study outcomes

The echocardiographic findings before and after the TAVR procedure were compared within the same type of AS. For comparison between different types of AS, the primary clinical outcome was major adverse cardiovascular events (MACE). MACE was a composite of all-cause mortality, nonfatal myocardial infarction (MI), and nonfatal stroke that were extracted from the included studies. Secondary end points included individual components of MACE, myocardial infarction (MI), all-cause hospitalizations, heart failure (HF) related readmissions, left bundle branch block (LBBB), vascular complications, paravalvular leak, need for permanent pacemaker (PPM) implantation and conversion to open AV surgical procedure. The study-level definition of outcomes is given in Supplemental Table S2.

Statistical analysis

Statistical analysis was performed using conventional and network meta-analytic approaches. For the former, standardized mean differences (SMD) were calculated using the Hedges' g equation. For network analysis, a frequentist random effect model was fitted in a splitwise manner to simultaneously analyze mixed treatment comparisons (mixture of direct and indirect treatment comparisons). The prerequisites of analysis (similarity and transitivity) were satisfied by detailed scrutinization of study-level methodology. The transitivity was statistically validated by measuring the loop and global consistency of the summary estimates. P value $>$ .05 suggested no evidence of inconsistency. A quadratic heatmap was constructed to visually assess design-level consistency. The design- and study-level estimates were graphically illustrated using interval and network forest plots. Direct evidence plots were obtained to show the contribution of direct and indirect estimates at the level of each comparison. To determine the relative superiority of a strategy (ie, probability of a strategy being the best, second best, or worst for each end point), the magnitude of the effect size was plotted using the p-score. A p-score closer to 1 indicated the highest performance of the treatment strategy. Estimates were reported with its 95% CI, keeping the allowable threshold for alpha error at 5% ($P \leq$05 was significant). The effect size between comparison groups was considered similar for outcomes where it did not reach the threshold of statistical significance, and thus there was insufficient evidence to declare a difference between groups, without taking into account the necessary power to detect a difference. Analysis was performed using Stata version 16 (StataCorp LLC), and R version 4.01 (R Foundation for Statistical Computing).

Results

Search results

The preliminary literature search identified a total of 4198 records, reduced to 2031 after the removal of duplicates (2167). After screening titles and abstracts for relevance, 1531 studies were further excluded. The remaining 496 articles were read in full-text form, and 21 observational studies qualified for data extraction and quantitative analysis. The flow diagram is shown in Supplemental Figure S1.

Demographics and baseline comorbidities

A total of 21 studies comprising 17,298 (8742 experimental and 8556 HGAS) were included in the quantitative analysis.[7–26] The mean age of the included population was 82.3 years, with an average of 42.9% males (Table 1). The cardiovascular comorbidities of the direct comparison between pLFLG and LFLG vs HGAS are presented in Figure 1. Most of the traditional risk factors were equally distributed, with the highest prevalence of hypertension (pLFLG 84.6% vs HGAS 84.6%; LFLG 86.7% vs HGAS 84%). The mean STS score was 6.45 $\pm$ 6, and approximately 70% of the overall cohort had NYHA class 3 or 4 symptoms. The design-level and study-level detailed comorbidities are presented in Table 1 and Supplemental Tables S3 and S4, respectively.

Table 1. Pooled baseline echocardiographic and procedural characteristics of summative patient population stratified into hemodynamic subgroups based on comparisons made in included trials.

	pLFLG vs HGAS		LFLG vs HGAS	
	pLFLG	HGAS	LFLG	HGAS
Demographics and baseline comorbidities				
Sample size (mean)	2517	7972	236	853
Age, y (mean)	81.0	81.0	81.9	82.7
Male sex, %	46.8	44.8	46.0	56.3
Hypertension, %	84.6	84.6	86.8	84.0
Diabetes mellitus, %	34.5	60.9	29.0	28.5
Hyperlipidemia, %	65.2	68.9	44.5	37.0
CAD/Prior MI, %	44.4	59.6	14.8	15.0
Prior PCI, %	28.0	23.0	34.4	26.2
Prior CABG, %	20.2	30.2	15.0	20.0
Chronic obstructive pulmonary disease, %	29.0	25.3	17.4	17.3
End-stage renal disease, %	32.0	45.4	45.0	34.2
Valve surgery, %	3.50	3.80	17.7	16.8
Peripheral vascular disease, %	27.3	22.4	32.4	22.1
Cerebrovascular accident, %	15.8	14.2	12.9	17.6
Smoking, %	18.9	17.9	26.0	18.0
Prior PPM/ICD, %	18.6	13.1	NR	NR
NYHA class III-IV, %	69.7	71.0	74.5	75.2
Atrial fibrillation/flutter, %	44.3	37.9	48.8	33.1
Echocardiographic findings				
LVEF, % (mean)	58.0	57.7	41.6	52.0
AV mean gradient, mm Hg	30.8	50.9	31.6	52.1
LVOT VTI (mean)	18.3	22.1	NR	NR
AV peak velocity, m/sec (mean)	12.9	19.7	3.7	4.9
SVI, mL/m^2 (mean)	27.9	39.5	28.1	40.6
Aortic valve area, cm^2 (mean)	0.6	0.6	0.6	0.6
Mitral regurgitation				
Severe, %	12.5	14.6	6.5	5.5
Moderate, %	18.0	16.3	NR	NR
Mild, %	50.5	62.0	NR	NR
None, %	17.0	13.5	NR	NR
Laboratory results				
Serum creatinine, mg/dL	1.2	1.2	1.3	1.5
NT-proBNP, pg/mL	598.2	488.4	252.5	152.1
Serum sodium, mEq/L	139.0	140.0	NR	NR
Hemoglobin, g/dL	11.9	11.9	NR	NR
Albumin, g/dL	3.97	3.89	NR	NR
International normalized ratio	1.1	1.2	NR	NR
Type of valves				
SAPIEN, %	66.4	69.2	39.8	56.3
Evolut, %	39.8	42.8	13.5	18.8
LOTUS, %	2.0	1.0	NR	NR
Procedural access				
Transfemoral, %	75.7	75.9	76.2	75.0
Transaortic, %	7.8	8.9	14.8	14.6
Transapical, %	20.7	23.0	12.3	20.7
Axillary, %	1.9	0.9	NR	NR

AV, aortic valve; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; HGAS, high gradient aortic stenosis; ICD, implantable cardioverter-defibrillator; LFLG, low flow low gradient; LVEF, left ventricle ejection fraction; LVOT, left ventricle outflow tract; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association classification; PCI, primary coronary intervention; pLFLG, paradoxical low flow low gradient; PPM, permanent pacemaker; SVI, stroke volume index; VTI, velocity time integral.

Baseline echocardiographic and labs parameter

The baseline pre-TAVR mean echocardiographic parameters were compared between the intervention and comparison strategies (Supplemental Table S5). The mean pre-TAVR LVEF was 58.7% in the low flow group and 51.1% in the HGAS group. While all patient had AVA <1.0 cm^2 the mean AV gradient was variable (30.9 mm Hg in the low flow group and 48.4 mm Hg in the HGAS group). The mean SVi was 23.5 mL/m^2 for the low flow group and 35.5 mL/m^2 for the HGAS group. The mean creatinine level was approximately 1.4 mg/dL in the low flow group and 1.2 in patients with HGAS. Similarly, the mean serum NT-pro-brain natriuretic peptide was 1051.25 pg/mL, and 947 pg/mL in low flow and HGAS group, respectively. The baseline echocardiographic and laboratory parameters stratified into subgroups are given in Table 1.

Procedural characteristics

The most common valve type used was SAPIEN (Edwards Lifesciences) in ~63% of patients. Other common valves used in studies include Evolut (Medtronic) (35%) and LOTUS (Boston Scientific) (2%) (Supplemental Figure S2).

Echocardiographic outcomes

The echocardiographic benefits of TAVR in patients with various severe AS hemodynamic subtypes are summarized in Figure 2. TAVR was associated with a significant increase in the AVA in patients with HGAS (SMD, –3.32; 95% CI, –4.13 to –2.52; $P < .001$), LFLG (SMD, –2.79; 95% CI, –3.41 to 2.18; $P = .01$), and pLFLG (SMD, –2.31; 95% CI, –2.78 to –1.84; $P < .001$) (Supplemental Figure S3). Similarly, there was a significant reduction in the MG across all types of AS (SMD, 3.64; 95% CI, 3.25 to 4.04; $P < .001$) (Supplemental Figure S4). The SVi improved for pLFLG after TAVR (SMD, –0.5; 95% CI, –0.77 to –0.22; $P < .001$). The increase in the SVi in patients with LFLG (SMD, –0.14; 95% CI, –0.42 to 0.15) and HGAS (SMD, –0.01; 95% CI, –0.17 to 0.15) did not reach the threshold of statistical signifcance (Supplemental Figure S5). In patients with LFLG, TAVR was associated with a significant increase in EF (SMD, –1.11; 95% CI, –1.75 to –0.47; $P < .001$) (Supplemental Figure S6).

Primary clinical outcomes

Patients undergoing TAVR for AS with pLFLG (OR, 0.98; 95% CI, 0.72-1.35), had a similar, while LFLG had a significantly higher (OR, 1.68; 95% CI, 1.04-2.72) risk of MACE compared with HGAS at a median follow-up of 1-year (Figure 3, Central Illustration). The contributions of direct and indirect comparisons are presented in Supplemental Figure S7 and Supplemental Table S6.

Secondary clinical outcomes

TAVR in pLFLG had a similar risk of periprocedural (OR, 0.92; 95% CI, 0.64-1.31), 1-month (OR, 1.15; 95% CI, 0.86-1.52), 6-month (OR, 0.95; 95% CI, 0.74-1.22), and 12-month (OR, 1.08; 95% CI, 0.90-1.29) mortality compared with HGAS. However, TAVR in LFLG was associated with a significantly higher risk of periprocedural (OR, 2.00; 95% CI, 1.17-3.41), 1-month (OR, 1.69; 95% CI, 1.08-2.64), and 12-month (OR, 1.41; 95% CI, 1.05-1.88) mortality compared with HGAS. Compared with TAVR in HGAS, the need for surgery was also significantly higher in LFLG (OR, 3.57; 95% CI, 1.24-10.32). The incidence of MI, major bleeding, vascular complications, paravalvular leak, pacemaker implantation, and rehospitalizations was not significantly different between all other types of AS (HGAS vs LFLG or pLFLG). Similarly, there was no difference in the incidence of periprocedural, 1-month, and 12-month stroke rates between TAVR in HGAS vs all other types of AS (Supplemental Figure S8).

Ranking of treatment strategies

The p-score plotting and ranking of treatment preferences are plotted in Supplemental Figure S9. TAVR had the best performance in the pLFLG (p-score, 0.78) and HGAS (p-score, 0.71) for reducing MACE.

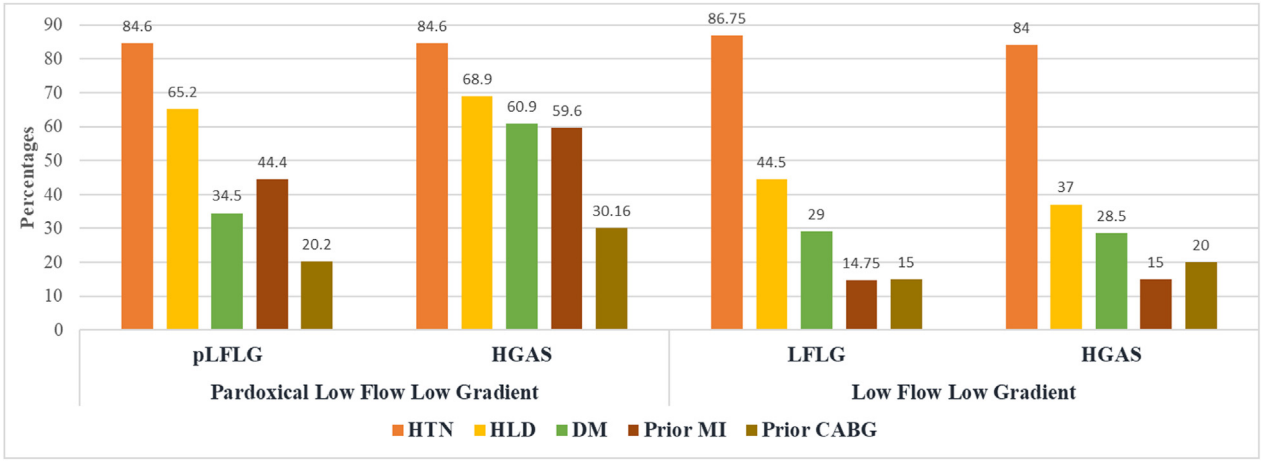


Figure 1.
Baseline cardiovascular comorbidities between different aortic stenosis subtypes in patients undergoing TAVR based on comparisons made in included trials. CABG, coronary artery bypass graft; DM, diabetes mellitus; HGAS, high gradient aortic stenosis; HLD: hyperlipidemia, HTN, hypertension; MI, myocardial infarction; TAVR, transcatheter aortic valve replacement.

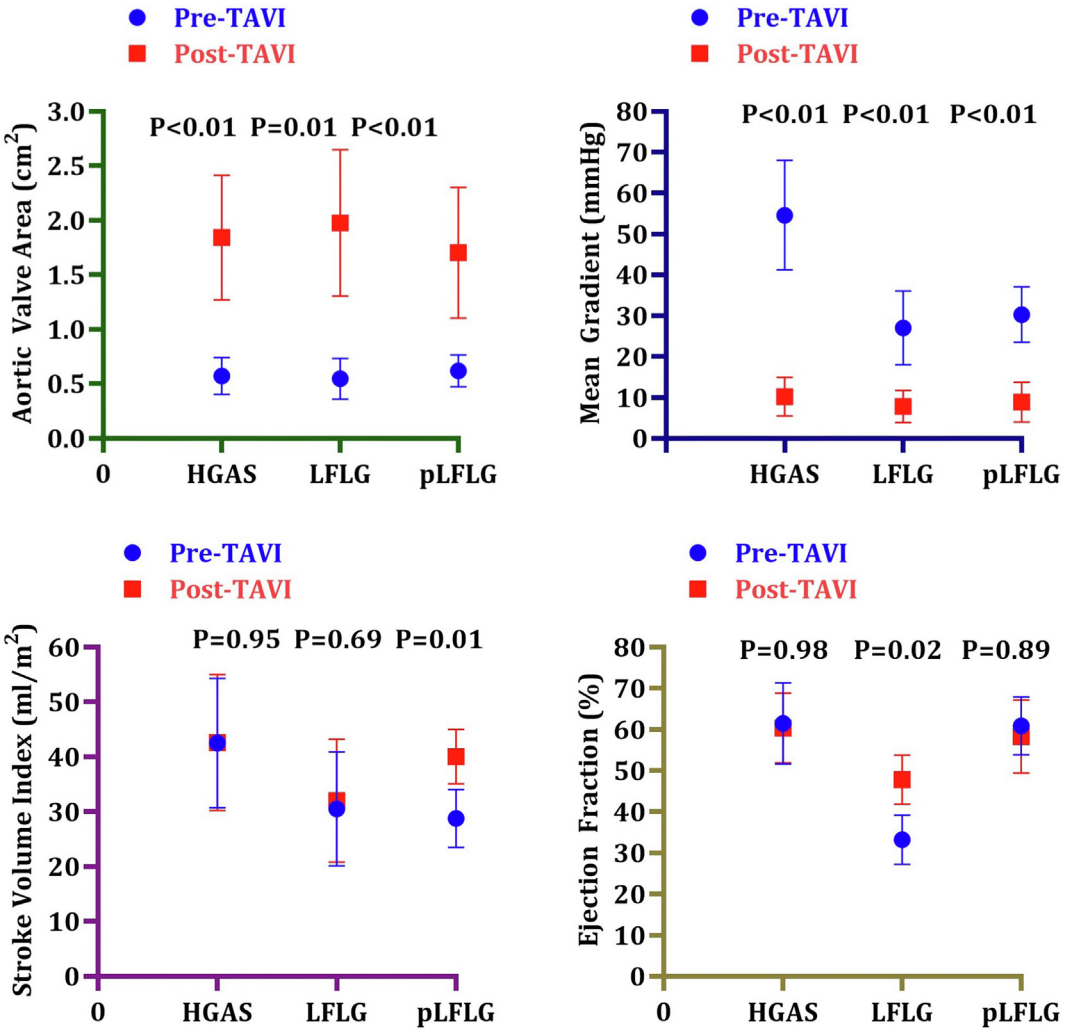


Figure 2.
Echocardiographic outcomes between different types of discordant aortic stenosis undergoing TAVR. HGAS, high gradient aortic stenosis; LFLG, low flow low gradient; pLFLG, paradoxical low flow low gradient; TAVR, transcatheter aortic valve replacement.

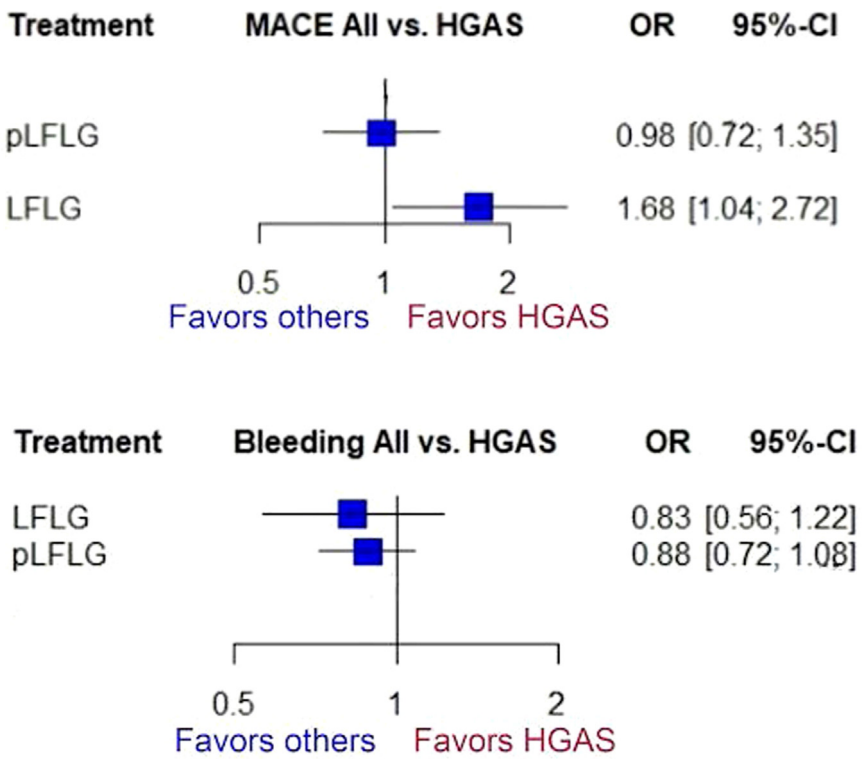


Figure 3.
Network forest plot for MACE (top) and major bleeding (bottom). The comparison control group is TAVR in HGAS having direct comparisons with LFLG and pLFLG AS. HGAS, high gradient aortic stenosis; LFLG, low flow low gradient; MACE, major adverse cardiovascular events, pLFLG: paradoxical low flow low gradient.

Patients undergoing TAVR for LFLG had the worst ranking for reducing MACE and mortality (p-score 0.01).

Net clinical benefit on bivariate analysis

The net clinical benefit was graphically illustrated with a bivariate outcome plot for MACE and major bleeding end points in Figure 4. In relative terms, TAVR in pLFLG derived the maximum benefit as indicated by its left lower position on the bivariate plot. Patients with LFLG had worse MACE compared with HGAS, without increasing the risk of major bleeding resulting in its rightward position on the plot.

Network consistency and heterogeneity

On NMA, there was no evidence of total (global), within-, and between-design (loop) inconsistency in MACE and major bleeding ($P \geq .05$) (Supplemental Table S7). The heatmap graphically illustrated a minimal inconsistency in the comparisons (Supplemental Figure S10).

Discussion

The current network meta-analysis is the most contemporaneous evidence on the utility of TAVR in patients with severe AS (AVA <1 cm^2) and different hemodynamic subtypes. The net estimates revealed that TAVR is beneficial in terms of increasing the AVA area and reducing the MG across all hemodynamic subtypes of AS, irrespective of the flow and gradient across the aortic valve. Moreover, in patients with classic LFLG, TAVR resulted in a significant increase in the postprocedure LVEF. TAVR in patients with pLFLG AS had a similar risk of MACE compared with HGAS, while those patients with LFLG had a 68% higher risk of MACE events. Analysis of the individual components of MACE revealed that it was entirely driven by the significantly greater incidence of post-TAVR mortality, which is consistent with the overall mortality risk conferred by a reduced LVEF. Apart from this, there was no significant difference in MI, major bleeding, stroke, paravalvular leak, vascular complications, new onset LBBB, need for rehospitalization, or requirement for PPM in patients undergoing TAVR for HGAS vs any other type of AS (LFLG, pLFLG).

The clinical, echocardiographic, and procedural benefits of TAVR are well established in patients with high gradient AS (our control group). The pivotal clinical trials (PARTNER and SURTAVI) that first demonstrated the safety of TAVR in patients with severe AS primarily included patients with high gradients (HG) (MG $>$ 40 mm Hg or Vmax $>$ 4 m/s).[27–31] A subgroup analysis of patients with severe AS based on the mean LVEF (above vs below 55%) did not reveal any significant difference in mortality.[24] This indirectly suggested that TAVR in all patients with severe AS might obtain similar survival benefits regardless of LVEF. However, this observation was based on the assumption that LVEF $>$55% is a true surrogate indicator of a normal flow state, which can be misleading. Moreover, the aforementioned trials excluded patients with low gradient (MG $<$40 mm Hg) AS, questioning the safety and efficacy of TAVR in patients with severe AS (AVA <1 cm^2) with discordant hemodynamics (LFLG and pLFLG states).

Among all the hemodynamic subtypes of severe AS, LFLG AS is the most common and carries the worst prognosis. In ~80% of these patients, the low flow state is due to systolic dysfunction, dilated cardiomyopathy, or failure of pump function leading to reduced stroke volume and LVEF $<$50% (classic LFLG or stage D2).[4] In the remaining 20% of patients, where the LVEF $>$50%, the underlying mechanism of the low flow state is theorized to be multifactorial due to: (1) increased stiffness of the left ventricle presumably secondary to myocardial fibrosis which decreases overall contractility; (2) impaired relaxation and filling of the left ventricle in diastole; and (3) prominent left ventricular remodeling due to chronically high afterload which decreases the chamber size as measured by valvulo-arterial impedance, and ultimately reduces stroke

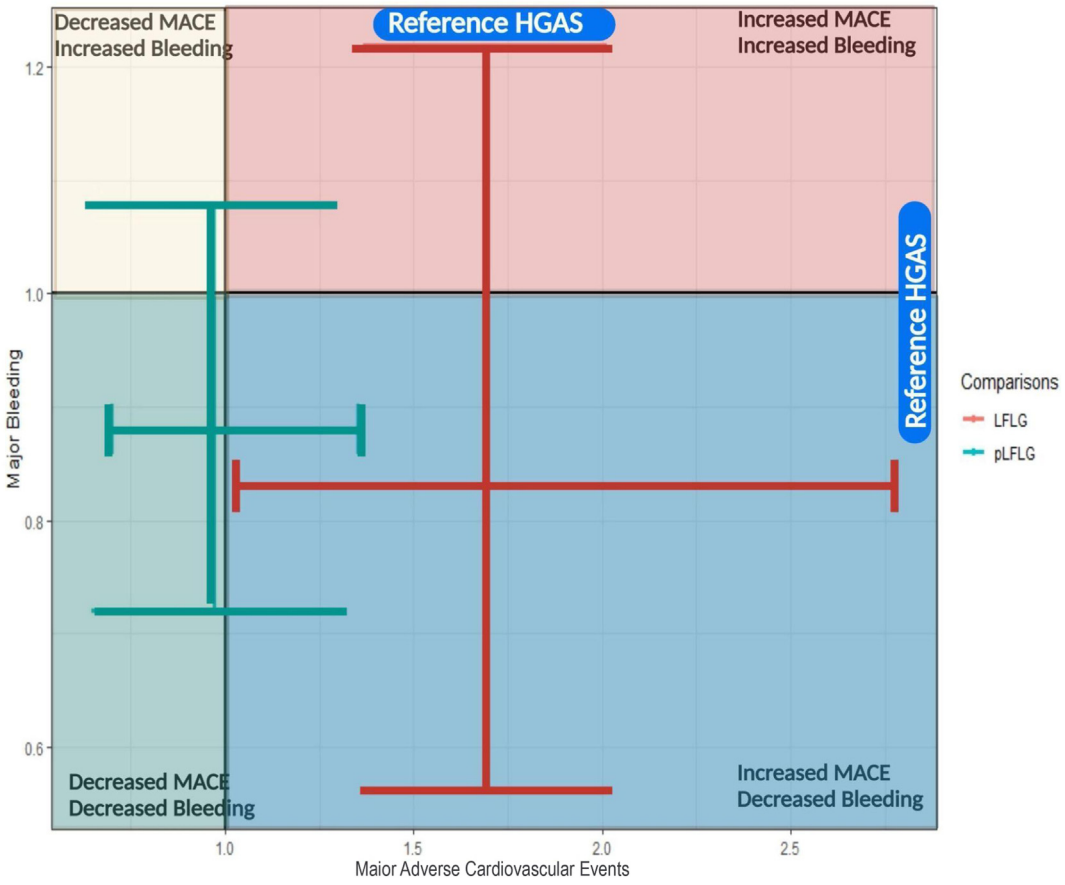


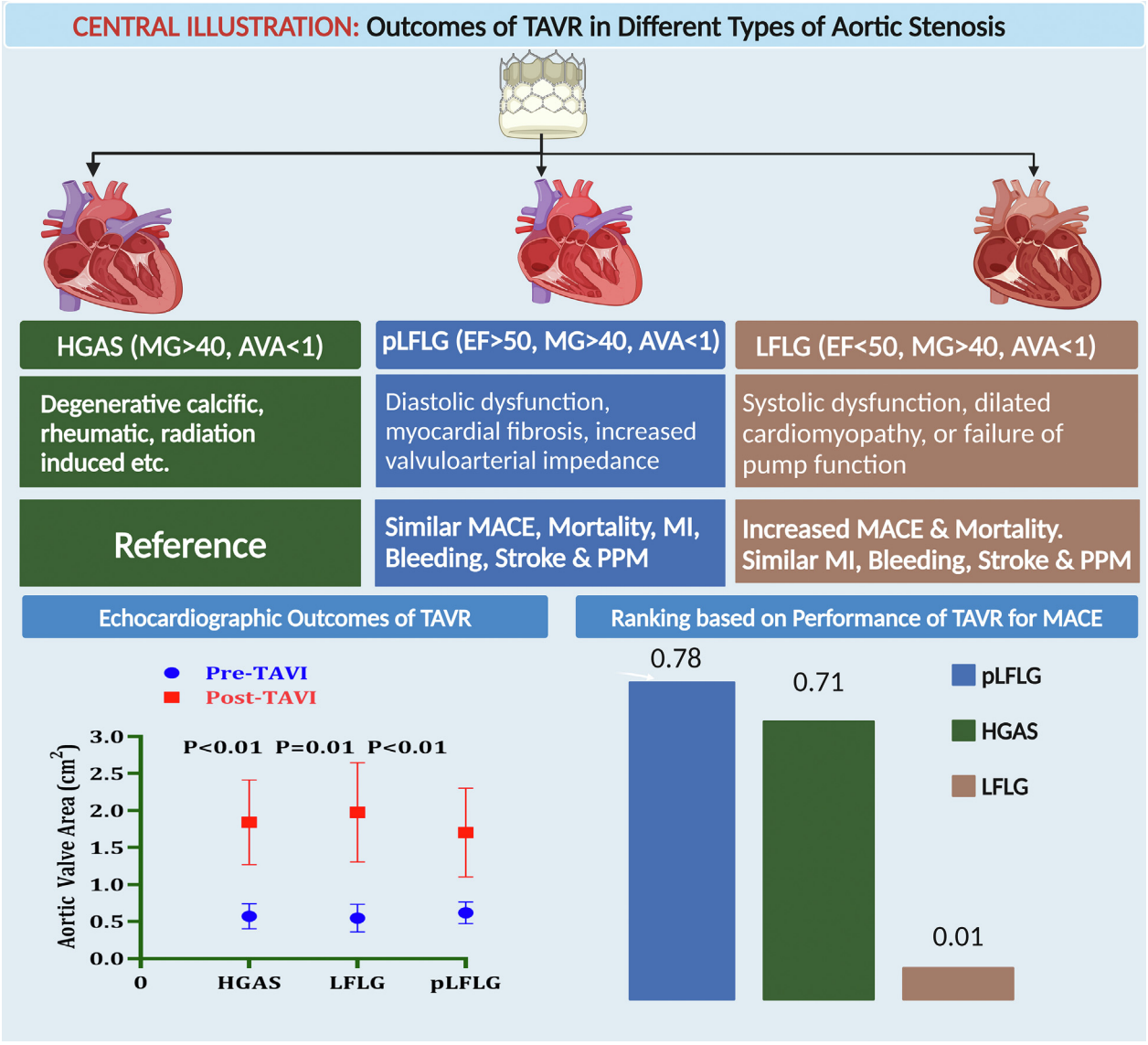
Figure 4.
Bivariate plot showing risk ratios of major bleeding and major adverse cardiovascular events (MACE) in HGAS (reference) with its associated 95% CIs. MACE is plotted on the x-axis against major bleeding on the y-axis. The left lower quadrant is the best strategy, while right upper is the worst. pLFLG occupied the left lower quadrant (best net performance). LFLG occupied the right lower quadrant indicating worst performance mostly due to high MACE. HGAS, high gradient aortic stenosis; LFLG, low flow low gradient; pLFLG, paradoxical low flow low gradient.

volume and cardiac index. This is called pLFLG (or stage D3).[5] To date, there has been no randomized direct or indirect comparison of patients undergoing TAVR for severe AS in the setting of different hemodynamic subtypes, and with attention to flow state based on the recommended stroke volume index (SVi <35 mL/m^2) rather than on EF.

Prior studies assessing the clinical and echocardiographic outcomes of TAVR in patients with pLFLG AS had conflicting results adding to the ambiguity around its management. Some data demonstrated a higher incidence of cardiovascular collapse and an increased need for PPM implantation with TAVR in pLFLG. The former was hypothesized to be due to a sudden correction of afterload in patients with impaired contractility and diastolic filling leading to outflow hemodynamic obstruction, the so-called "suicide left ventricle."[9] The higher incidence of PPM was linked with the augmentation of myocardial fibrosis-induced conduction abnormalities by TAVR-related mechanical pressures on the AV nodal pathway.[7] Other studies such as the OCEAN-TAVI registry and data from Mangner et al[16] demonstrated higher mortality in patients undergoing TAVR for pLFLG compared with HGAS.[20] This could be attributed to the use of older-generation TAVR prostheses or alternative access routes that are known to have worse outcomes. By contrast, the GARY trial, and analysis by Rodriguez-Gabella et al[9] and Debry et al[17] showed comparable post-TAVR survival rates and periprocedural complications between patients with pLFLG vs those with HG.[25] A meta-analysis by Takagi et al[32] showed no difference in the early and midterm mortality between LFLG and pLFLG patients after TAVR. Given the conflicting evidence in prior studies, our large-scale evidence brings consensus on the topic by demonstrating that patients with pLFLG AS derive the same degree of echocardiographic and clinical benefit from TAVR as patients with any other type of AS. Whether this favorable shift is due to the use of contemporary TAVR devices, careful elimination of patient-prosthesis mismatch, procedural refinement, improvement in operator skills, or better patient selection, requires further investigation.

In patients classic LFLG, the 2-year post TAVR mortality is as high as 33%. A post hoc analysis of the PARTNER trial showed that a low flow state was the strongest predictor of mortality after TAVR irrespective of the baseline LVEF.[24] These observations of relatively higher mortality in the classic LFLG state were confirmed by our pooled NMA analysis. However, we postulate that this difference in mortality was not entirely driven by the low flow state, as there remained a significantly higher risk of mortality in patients with classic LFLG AS compared with a similar cohort of low flow state, but having normal EF (pLFLG), as well as those with high gradients (HGAS).

In congruence with the prior studies, patients with LFLG in our analysis had a numerically higher need for HF-related readmissions and a statistically greater need for conversion to surgery; this could have translated into higher mortality. The other plausible mechanisms could be frailty and a higher burden of comorbidities including a history of prior MI, risk of repeat coronary interventions, chronic kidney disease, and need for concomitant procedures.[12] Together, the culmination of these factors might not only explain the 2-times relatively higher odds of periprocedural mortality but also the 1.41-1.69 fold increase in the follow-up mortality (at 1-12 months) seen in our TAVR cohort of LFLG AS



Central Illustration.
Outcome of transcatheter aortic valve replacement (TAVR) in different types of aortic stenosis. AVA, aortic valve area; EF, ejection fraction; HGAS, high gradient aortic stenosis; LFLG, low flow low gradient; MACE, major adverse cardiovascular events; MG, mean pressure gradient; MI, myocardial infarction; pLFLG, paradoxical low flow low gradient; PPM, permanent pacemaker.

compared with pLFLG and HGAS. Despite this, the overall absolute post-TAVR mortality risk in LFLG remained lower than 5%, and a significant increase in AVA and LVEF attests to the efficacy of TAVR in these patients.

Limitations

The major limitation of our study is the lack of randomized control trials on the topic. Our study is therefore constrained by the limitations of the included observational studies. Some of the included studies lacked data on diagnostic modalities such as right heart catheterization and imaging to evaluate for true vs pseudo LFLG states. The inclusion criteria, matching thresholds, and follow-up duration of the included studies were variable. The lack of adjusted analysis limits our ability to definitively attribute the observed clinical benefit solely to the TAVR procedure. The lack of patient-level data precluded our ability to perform adjusted analyses based on differing baseline characteristics that could serve as potential effect modifiers. There remains a possibility of pooling of bias and errors from study-level variables. Immeasurable confounders like operator expertise, physician discretion, and patient preference for the procedure could not be accounted for. Quality of life measures could not be analyzed due to heterogeneity in reporting and lack of granular data. Despite this, our study represents the largest evidence on the topic that sheds light on the real-world challenges in the management of these patients that can serve as a springboard for future randomized trials on the topic.

Conclusion

Patients with severe AS and different hemodynamic subtypes benefited from TAVR regardless of the flow and gradient characteristics. In terms of hard clinical outcomes, patients with pLFLG derived similar benefits as HGAS, while patients with LFLG had a higher risk of mortality translating into greater incidence of MACE. Further studies are needed to decide on the expansion of indications of TAVR to populations with different subtypes of AS.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

The study was exempted from ethics committee approval and informed consent as data were collected from published articles.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the Journal of the Society for Cardiovascular Angiography & Interventions at 10.1016/j.jscai.2023.101255.

References

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(22):2438–2488.
2. Vahanian A, Beyersdorf F, Praz F, et al. ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J. 2021*. 2022;43(7):561–632.
3. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J*. 2008;29(8):1043–1048. https://doi.org/10.1093/eurheartj/ehm543
4. Lauten J, Rost C, Breithardt OA, et al. Invasive hemodynamic characteristics of low gradient severe aortic stenosis despite preserved ejection fraction. *J Am Coll Cardiol*. 2013;61(17):1799–1808. https://doi.org/10.1016/j.jacc.2013.02.009
5. Isselbacher EM, Preventza O, Hamilton Black III J, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;80(24):e223–e393.
6. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA*. 2000;283(15):2008–2012.
7. Thakker P, Husaini M, Thangam M, et al. Transcatheter aortic valve replacement (TAVR) in patients with paradoxical low-flow low-gradient aortic stenosis. *Struct Heart*. 2020;4(4):312–319.
8. Mosleh W, Amer MR, Ding Y, et al. Benefit of transcatheter aortic valve replacement in patients with paradoxical low-flow low-gradient versus high-gradient aortic stenosis and preserved left ventricular function. *Circ Cardiovasc Interv*. 2021;14(3):e010042.
9. Rodriguez-Gabella T, Nombela-Franco L, Auffret V, et al. Transcatheter aortic valve implantation in patients with paradoxical low-flow, low-gradient aortic stenosis. *Am J Cardiol*. 2018;122(4):625–632.
10. Schewel J, Schewel D, Frerker C, Wohlmuth P, Kuck KH, Schäfer U. Invasive hemodynamic assessments during transcatheter aortic valve implantation: comparison of patient outcomes in higher vs. lower transvalvular gradients with respect to left ventricular ejection fraction. *Clin Res Cardiol*. 2016;105(1):59–71.
11. Nara Y, Kataoka A, Watanabe Y, et al. Prognostic impact of postprocedure stroke volume in patients with low-gradient aortic stenosis. *Open Heart*. 2019;6(1):e000988.
12. Stähli BE, Nguyen-Kim TD, Gebhard C, et al. Calcification characteristics of low-flow low-gradient severe aortic stenosis in patients undergoing transcatheter aortic valve replacement. *Cardiol Res Pract*. 2015;2015, 802840.
13. Carreras ET, Kaneko T, Ramirez-Del Val F, et al. Impact of flow, gradient, and left ventricular function on outcomes after transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2018;91(4):798–805. March 1.
14. Fischer-Rasokat U, Renker M, Liebetrau C, et al. 1-year survival after TAVR of patients with low-flow, low-gradient and high-gradient aortic valve stenosis in matched study populations. *JACC Cardiovasc Interv*. 2019;12(8):752–763.
15. Zbroński K, Huczek Z, Gawalko M, et al. Paradoxical low-flow aortic stenosis – baseline characteristics, impact on mortality. *Adv Interv Cardiol*stępy w *Kardiologii Interwencyjnej*. 2019;15(1):13–19.
16. Mangner N, Stachel G, Woitek F, et al. Predictors of mortality and symptomatic outcome of patients with low-flow severe aortic stenosis undergoing transcatheter aortic valve replacement. *J Am Heart Assoc*. 2018;7(8):e007977.
17. Debry N, Sudre A, Amr G, et al. Transcatheter aortic valve implantation for paradoxical low-flow low-gradient aortic stenosis patients. *Catheter Cardiovasc Interv*. 2016;87(4):797–804.
18. Salaun E, Clavel MA, Hahn RT, et al. Outcome of flow-gradient patterns of aortic stenosis after aortic valve replacement: an analysis of the PARTNER 2 trial and registry. *Circ Cardiovasc Interv*. 2020;13(7):e008792.
19. O'Sullivan CJ, Stortecky S, Heg D, et al. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013;34(44):3437–3450.
20. Kataoka A, Watanabe Y, Kozuma K, et al. Prognostic impact of low-flow severe aortic stenosis in small-body patients undergoing TAVR: the OCEAN-TAVI registry. *JACC Cardiovasc Imaging*. 2018;11(5):659–669.
21. Le Ven F, Freeman M, Webb J, et al. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2013;62(9):782–788.
22. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Sénéchal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2012;60(14):1259–1267.
23. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115(22):2856–2864.
24. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic transcatheter Valves (PARTNER) trial analysis. *Circulation*. 2013;127(23):2316–2326.
25. Lauten A, Figulla HR, Möllmann H, et al. TAVI for low-flow, low-gradient severe aortic stenosis with preserved or reduced ejection fraction: a subgroup analysis from the German Aortic Valve Registry (GARY). *EuroIntervention*. 2014;10(7):850–859.
26. Reinthaler M, Schwabe A, Landmesser U, et al. 'Paradoxical' low-flow, low-gradient severe aortic valve stenosis: an entity with limited improvement following transcatheter aortic valve implantation. *J Heart Valve Dis*. 2014;23(4):441–449.
27. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187–2198.
28. Carabello BA. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *Curr Cardiol Rep*. 2011;13(3):173–174.
29. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609–1620.
30. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695–1705.
31. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321–1331.
32. Takagi H, Hari Y, Kawai N, Kuno T, Ando T, ALICE. A meta-analysis of impact of low-flow/low-gradient aortic stenosis on survival after transcatheter aortic valve implantation. *J Cardiovasc Med (Hagerstown)*. 2019;20(10):691–698.