



Systematic Review

# Surgical Versus Transcatheter Aortic Valve Replacement in Low-Flow, Low-Gradient Aortic Stenosis: Results From 1900 Patients

Xander Jacquemyn<sup>1,2</sup>, Rohit Ganduboina<sup>3</sup>, Michel Pompeu Sá<sup>4</sup>, Irsa Hasan<sup>1,2</sup>, Takuya Ogami<sup>1,2</sup>, Derek Serna-Gallegos<sup>1,2</sup>, Dustin Kliner<sup>2</sup>, Catalin Toma<sup>2</sup>, Amber Makani<sup>2</sup>, Ibrahim Sultan<sup>1,2,\*</sup>

<sup>1</sup>Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA

<sup>2</sup>UPMC Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

<sup>3</sup>Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

<sup>4</sup>Heart, Vascular & Thoracic Institute, Cleveland Clinic Florida, Weston, FL 33331, USA

\*Correspondence: [sultani@upmc.edu](mailto:sultani@upmc.edu) (Ibrahim Sultan)

Academic Editors: Tadahisa Sugiura and Toshihiro Fukui

Submitted: 4 November 2025 Revised: 23 December 2025 Accepted: 31 December 2025 Published: 23 April 2026

## Abstract

**Background:** Low-flow, low-gradient (LFLG) aortic stenosis (AS) is associated with high-risk physiology and poor outcomes; however, the optimal intervention strategy, surgical aortic valve replacement (SAVR) versus transcatheter aortic valve replacement (TAVR), remains uncertain. **Methods:** A systematic review and pooled meta-analysis of studies reporting Kaplan-Meier outcomes after SAVR and TAVR in patients with LFLG AS, published through June 2025, was performed. Individual patient data were reconstructed from published curves. Analyses included Cox frailty models, restricted mean survival time (RMST), and two-stage meta-analyses. Adjusted analyses accounted for baseline differences, including age, comorbidities, and echocardiographic parameters. **Results:** Five studies comprising 1940 patients (721 SAVR and 1219 TAVR) were included. Patients undergoing TAVR were older and had higher rates of peripheral arterial disease, while other comorbidities and echocardiographic parameters were similar between groups. In unadjusted analyses, TAVR was associated with higher mortality compared with SAVR (hazard ratio (HR) 1.36, 95% confidence interval (CI) 1.11–1.65;  $p = 0.003$ ). The estimated 5-year survival was 67% for SAVR versus 49% for TAVR, with an RMST of 0.64 years in favor of SAVR. Despite risk adjustment, TAVR was associated with higher mortality (HR 1.42, 95% CI 1.17–1.73), with a reduction in RMST of 1.06 years. Two-stage meta-analyses yielded consistent findings with low-to-moderate heterogeneity. **Conclusion:** SAVR was associated with significantly lower mortality in patients with LFLG AS than TAVR, both before and after risk adjustment. While these findings suggest a potential survival benefit, the data are observational and hypothesis-generating, and residual confounding cannot be excluded.

**Keywords:** aortic stenosis; surgical aortic valve replacement; transcatheter aortic valve replacement

## 1. Introduction

Patients with severe aortic stenosis (AS) may present with a low transvalvular pressure gradient despite possessing a severely reduced aortic valve area (AVA), a condition termed low-flow, low-gradient (LFLG) AS [1]. This condition can occur with reduced left ventricular ejection fraction (LVEF; classical LFLG) or preserved ejection fraction (paradoxical LFLG), each reflecting distinct underlying pathophysiologies [2]. Classical LFLG typically results from impaired systolic function due to afterload mismatch or concomitant ischemic heart disease, whereas paradoxical LFLG arises from impaired diastolic filling, ventricular remodeling, or other comorbidities. In addition, patients commonly present with concomitant atrial fibrillation and mitral regurgitation, which contribute to low stroke volume index.

Gradient alone is insufficient to capture disease severity, as low flow can mask the hemodynamic burden of severe stenosis [3–5]. Consequently, stroke volume, flow status, and valve area provide complementary information that

is critical for clinical decision-making [6,7]. Current guidelines recommend aortic valve replacement (AVR) for symptomatic patients with severe LFLG AS; however, the optimal choice of intervention, surgical AVR (SAVR) versus transcatheter AVR (TAVR), remains uncertain [2,8]. TAVR offers a less invasive alternative with potential hemodynamic advantages; meanwhile, SAVR provides durable outcomes, lower rates of paravalvular leak and conduction disturbances, and facilitates concomitant procedures such as coronary revascularization [9,10].

Nonetheless, evidence directly comparing SAVR and TAVR in LFLG AS remains limited, as most available studies are often retrospective, small, or heterogeneous in patient characteristics [11]. Therefore, the impact of procedural choice on long-term survival in this high-risk population remains unclear. To address this gap, this study aimed to pool available data comparing mortality after TAVR versus SAVR in patients with LFLG AS to provide evidence for guiding individualized treatment decisions.



## 2. Materials and Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Ethical approval was not required for this study-level meta-analysis.

### 2.1 Search Strategy

A structured literature search was performed in the MEDLINE, Embase, and Web of Science databases to identify studies published through June 1st, 2025. The search was guided by the PICO framework: Population: patients with low-flow, low-gradient aortic stenosis; Intervention: transcatheter aortic valve replacement (TAVR); Comparison: surgical aortic valve replacement (SAVR); Outcomes: all-cause mortality. Key search terms included “low gradient”, “paradoxical low flow low gradient”, “classical low flow low gradient”, “normal flow low gradient”, and “aortic stenosis”, combined using Boolean operators and tailored to each database. Moreover, reference lists of included studies and relevant reviews were also screened to ensure completeness. Two reviewers (X.J., M.P.S.) independently screened titles, abstracts, and full texts according to predefined eligibility criteria. Studies were included if the analysis enrolled patients with LFLG AS undergoing TAVR or SAVR and reported relevant outcomes with extractable data. Exclusion criteria included reviews, case reports, single-arm studies, and studies with patients without LFLG AS. When multiple reports from overlapping populations were identified, the most recent or most comprehensive study was retained.

### 2.2 Data Extraction, Quality Assessment, and Statistical Analysis

Two reviewers (X.J., M.P.S.) independently extracted patient characteristics, and Kaplan-Meier curves from each study were digitized using Web Plot Digitizer software; individual patient data (IPD) were reconstructed from these plots, including the total number of patients, total events, and the number at risk at each time point for each treatment group [13]. The methodological quality and risk of bias were also independently evaluated by the same reviewers using the Cochrane Risk of Bias tool. Time-to-event outcomes were analyzed using a Cox frailty model with robust standard errors to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Between-study heterogeneity was accounted for by including a  $\gamma$ -frailty term and modeling studies as random effects. Proportional hazards assumptions were verified using the Grambsch–Therneau test and Schoenfeld residual plots, and were satisfied in all analyses. In addition, the restricted mean survival time (RMST) was calculated for each study arm to quantify differences in life expectancy. Then, a conventional two-step meta-analysis was performed using the DerSimonian–Laird random-effects model, and pooled estimates were visual-

ized with forest plots. Heterogeneity was quantified using the Cochran Q statistic and  $I^2$  metric. All statistical comparisons were two-sided with a significance level of 5%. All analyses were conducted in R Statistical Software (version 4.4.0, Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1 Study Selection

Our initial search yielded 1146 unique citations, of which 10 publications were potentially relevant (Fig. 1). From these, five studies were included, encompassing 1940 patients, with 721 undergoing SAVR and 1219 undergoing TAVR (Table 1) [11,14–17]. Study periods ranged from 2002 to 2023. The included studies were conducted across multiple countries, including Austria, Canada, Switzerland, the United States, the United Kingdom, and multinational cohorts. Study designs were primarily retrospective observational analyses; one study reported a post hoc analysis of the Placement of Aortic Transcatheter Valves (PARTNER) 2A randomized trial and the PARTNER 2 SAPIEN 3 intermediate- and high-risk registry. All studies employed statistical adjustment methods to account for baseline differences, including multivariable regression, inverse probability of treatment weighting (IPTW), and propensity score weighting. Fig. 2 presents the qualitative assessment of the included studies using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool, highlighting most concerns due to residual confounding, which was moderate in most studies. Overall, however, the risk of bias was judged to be low.

Baseline characteristics for the patients in the individual studies are reported in Table 2 (Ref. [11,14–17]). Patients undergoing TAVR were generally older than those undergoing SAVR, with mean ages ranging from 66 to 82.5 years (mean difference (MD) +8.96 years, 95% CI +5.26 to +12.66;  $p < 0.001$ ). Body mass index (BMI) was slightly lower in TAVR patients, ranging from 26.4 to 31.1 kg/m<sup>2</sup> (MD -1.87, 95% CI -0.98 to -2.76;  $p < 0.001$ ). In contrast, sex distribution was similar between groups, with males ranging from 33% to 78% (odds ratio (OR) 0.94, 95% CI 0.70–1.26;  $p = 0.688$ ). Regarding comorbidity status, the prevalence of hypertension (OR 1.41, 95% CI 0.53–3.70;  $p = 0.493$ ), diabetes (OR 0.98, 95% CI 0.75–1.30;  $p = 0.893$ ), and coronary artery disease (OR 1.96, 95% CI 0.75–5.26;  $p = 0.173$ ) was similar between the two groups. In contrast, patients undergoing TAVR had a higher prevalence of peripheral arterial disease, ranging from 3% to 36% (OR 4.35, 95% CI 2.22–8.33;  $p < 0.001$ ). When evaluating echocardiographic status, AVA (MD -0.05, 95% CI -0.109 to 0.009;  $p = 0.096$ ), mean gradient (MD 0.35, 95% CI -1.43 to 2.12;  $p = 0.702$ ), and LVEF (MD -2.21, 95% CI -7.15 to 2.72;  $p = 0.380$ ) were also comparable between groups.

**Table 1. Characteristics of studies that reported patient outcomes for low-flow, low-gradient aortic stenosis.**

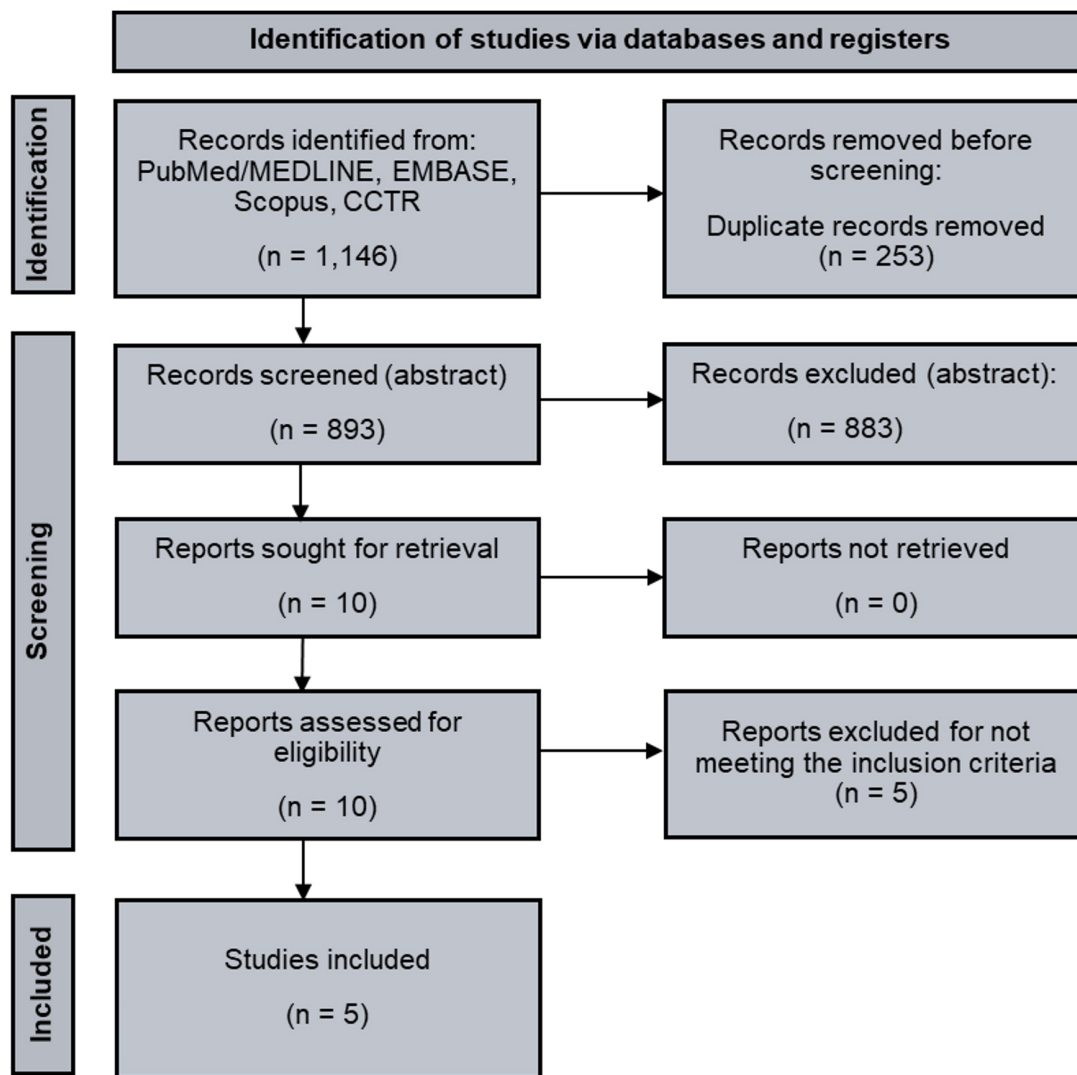
Study	Country	Study design	Period	Total sample, n	SAVR, n	TAVR, n	Adjustment for confounders
Annabi <i>et al.</i> , 2020 [17]	Austria and Canada	Retrospective from Prospective Registry	2002–2016	274	176	98	Multivariable and IPTW
Brown <i>et al.</i> , 2025 [15]	United States	Retrospective observational	2010–2023	248	131	117	Multivariable adjustment
O’Sullivan <i>et al.</i> , 2015 [11]	Switzerland	Retrospective observational	2005–2012	160	52	108	Multivariable adjustment
Patel <i>et al.</i> , 2023 [14]	United Kingdom	Retrospective observational	2015–2020	322	102	220	Propensity score weighting
Salaun <i>et al.</i> , 2020 [16]	Multiple	Post hoc RCT	2012–2014*	936	260	676	Multivariable adjustment

Legend: Data include study design, country, study period, total sample size, number of patients undergoing surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR), and methods used to adjust for confounders. \*For the PARTNER 2 Registry, data collection continued through 2017. Abbreviations: SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; IPTW, inverse probability of treatment weighting; RCT, randomized controlled trial.

**Table 2. Patient characteristics in the included studies.**

Study	Age, years	Male, %	BMI, kg/m <sup>2</sup>	HTN, %	DM, %	CAD, %	PAD, %	COPD, %	AVA, cm <sup>2</sup>	MG, mmHg	Vmax, m/s	LVEF, %	Classical LFLG, %
Annabi <i>et al.</i> , 2020 [17]	71 ± 10/80 ± 7	127 (72)/64 (66)	28.3 ± 5.8/26.5 ± 4.7	118 (67)/87 (90)	61 (35)/36 (37)	63 (36)/73 (75)	4 (2)/18 (19)	46 (27)/35 (38)	0.76 ± 0.17/0.76 ± 0.22	28 ± 8/27 ± 8	3.5 ± 1.8/3.4 ± 1.8	35 [25–60]/30 [25–40]	115 (65)/74 (76)
Brown <i>et al.</i> , 2025 [15]	66 [59–73]/79 [76–84]	103 (78.6)/97 (82.9)	31.1 [26.0–35.1]/28.4 [25.6–31.6]	109 (83.2)/105 (89.7)	43 (32.8)/39 (33.3)	38 (29)/68 (58.1)	10 (7.6)/27 (23.1)	NA	0.8 [0.7–1.0]/0.7 [0.6–0.9]	32 [27–36]/32 [27–36]	NA	45 [33–58]/48 [35–60]	81 (61.8)/59 (50.4)
O’Sullivan <i>et al.</i> , 2015 [11]	78.4 ± 4.1/82.5 ± 4.4	33 (63)/63 (58)	26.4 ± 4.6/25.4 ± 4.8	43 (83)/87 (81)	17 (33)/35 (32)	40 (77)/80 (74)	6 (12)/29 (27)	7 (13)/17 (16)	0.73 ± 0.23/0.74 ± 0.21	29.26 ± 9.54/28.57 ± 10.29	3.32 ± 0.60/3.24 ± 0.61	38.90 ± 11.95/34.52 ± 11.38	NA
Patel <i>et al.</i> , 2023 [14]	71 ± 11/81 ± 9	72 (71)/155 (71)	NA	82 (80)/153 (70)	33 (32)/62 (28)	52 (51)/103 (47)	NA	NA	0.8 [0.6–0.9]/0.7 [0.6–0.8]	28 [22–36]/31 [24–35]	NA	NA	102 (100)/220 (100)
Salaun <i>et al.</i> , 2020* [16]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Legend: Reported parameters include demographic characteristics, comorbidities, functional status, echocardiographic indices, and operative details. Continuous variables are expressed as the mean ± standard deviation or median (Q25–Q75), respectively. Values are presented as “SAVR/TAVR” unless otherwise indicated. \*Salaun *et al.* [16] reported baseline characteristics only by flow status (classical low-flow low-gradient (LFLG), paradoxical low-flow low-gradient), without stratification by treatment group (SAVR vs. TAVR), which precluded inclusion in this table. Abbreviations: BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; AVA, aortic valve area; MG, mean gradient; Vmax, maximal aortic velocity; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; LFLG, low-flow low-gradient.



**Fig. 1. Study flowchart.** Legend: PRISMA flow diagram of included studies. Abbreviations: CCTR, Cochrane Controlled Trials Register; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

### 3.2 Overall Outcomes

Four studies were included, comprising 618 patients who underwent SAVR and 998 who underwent TAVR, with a median follow-up of approximately 2 years (Q25–Q75: 1–3) and a total follow-up of 5 years. Patients treated with TAVR had a higher risk of mortality than those treated with SAVR (HR 1.36, 95% CI 1.11–1.65;  $p = 0.003$ ). Estimated survival for SAVR patients was 82% (95% CI 79–85) at 1 year, 77% (95% CI 73–80) at 2 years, and 67% (95% CI 62–73) at 5 years, compared with 75% (95% CI 73–78), 64% (95% CI 61–67), and 49% (95% CI 41–58), respectively, for TAVR patients (Fig. 3A). RMST analysis indicated that TAVR was associated with a reduction in expected survival of 7.5 months compared with SAVR (RMST difference –0.64 years, 95% CI –0.88 to –0.40;  $p < 0.001$ ). A two-stage meta-analysis confirmed these findings, yielding a pooled hazard ratio of 1.55 (95% CI 1.08–2.23;  $p = 0.018$ ) and moderate heterogeneity ( $I^2 = 59\%$ ;  $p = 0.062$ ) (Fig. 3B).

### 3.3 Adjusted Outcomes

Four studies were included in the adjusted analysis, comprising 668 patients who underwent SAVR and 641 who underwent TAVR, with a median follow-up of 1.89 years (Q25–Q75: 0.17–2.37) and a total follow-up of 5 years. Even after adjustment for baseline covariates, TAVR was associated with a significantly higher risk of mortality compared with SAVR (HR 1.42, 95% CI 1.17–1.73;  $p < 0.001$ ). Estimated survival among SAVR patients was 79% (95% CI 76–82) at 1 year, 73% (95% CI 69–76) at 2 years, and 64% (95% CI 58–69) at 5 years, compared with 64% (95% CI 60–68), 54% (95% CI 50–59), and 44% (95% CI 37–52), respectively, for TAVR patients (Fig. 4A). RMST analysis indicated that TAVR patients experienced a reduction in expected survival of approximately 1.06 years compared with SAVR patients (RMST difference –1.02 years, 95% CI –1.35 to –0.69;  $p < 0.001$ ). A two-stage meta-analysis confirmed these findings, yielding a pooled hazard

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Annabi et al, 2020	-	+	+	+	+	+	+	+
Brown et al, 2025	-	+	+	+	+	+	+	+
O'Sullivan et al, 2015	-	+	+	+	+	+	+	+
Patel et al, 2023	-	+	+	+	?	+	+	+
Salaun et al, 2020	+	+	+	+	+	+	+	+

Domains:  
D1: Bias due to confounding.  
D2: Bias due to selection of participants.  
D3: Bias in classification of interventions.  
D4: Bias due to deviations from intended interventions.  
D5: Bias due to missing data.  
D6: Bias in measurement of outcomes.  
D7: Bias in selection of the reported result.

Judgement  
- Moderate  
+ Low  
? No information

**Fig. 2. Risk of bias assessment for the included studies.** Legend: Risk of bias was evaluated with the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool.

ratio of 1.42 (95% CI 1.17–1.72;  $p < 0.001$ ) and no significant heterogeneity between studies ( $I^2 = 0\%$ ;  $p = 0.969$ ) (Fig. 4B).

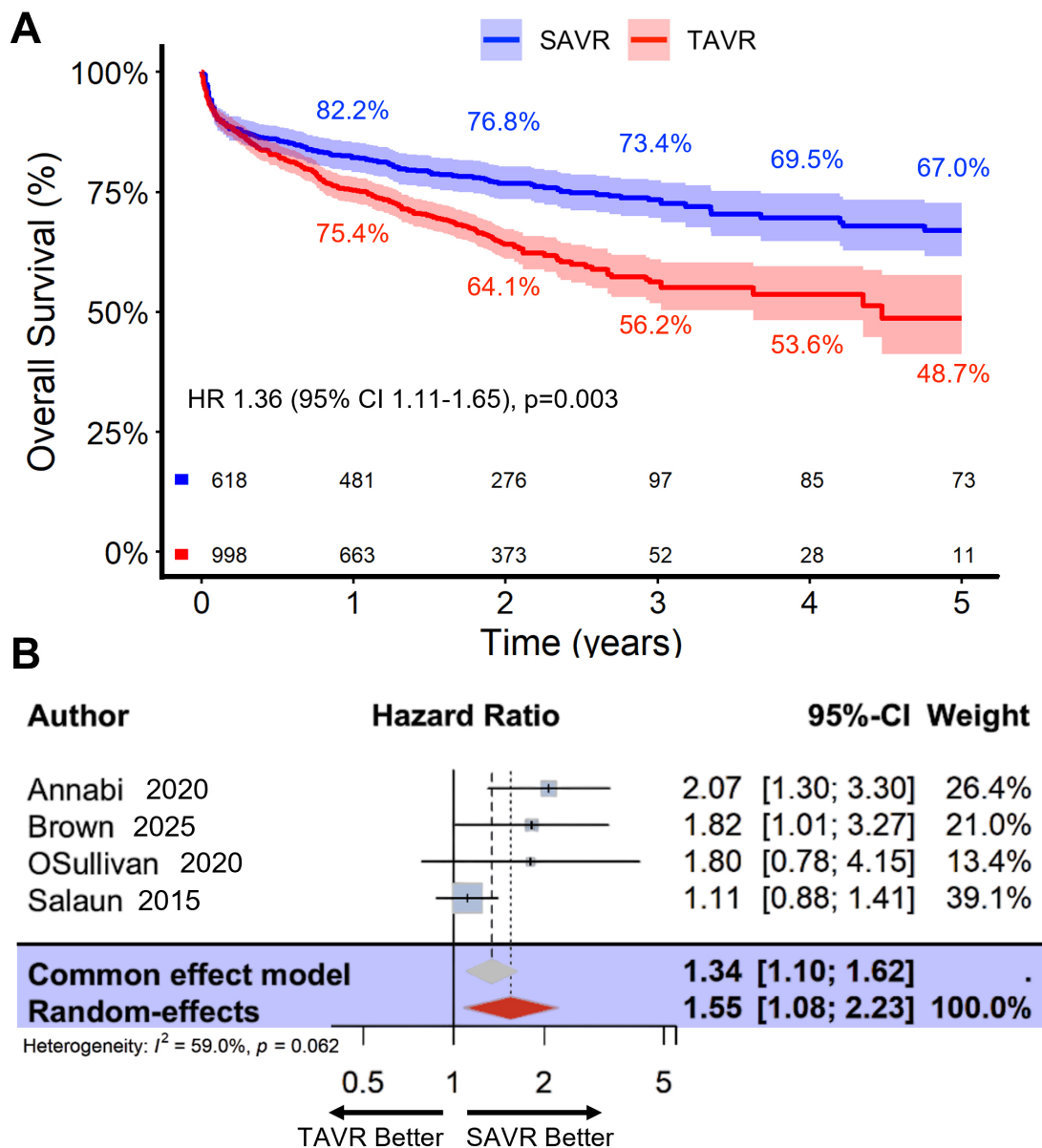
#### 4. Discussion

In this meta-analysis of patients with LFLG AS, our findings suggest that TAVR was associated with significantly higher mortality than SAVR in both the unadjusted (HR 1.36, 95% CI 1.11–1.65) and adjusted analyses (HR 1.42, 95% CI 1.18–1.72). Survival at 1, 2, and 5 years was consistently higher among SAVR patients, and RMST analyses indicated an average loss of approximately one year of life expectancy over 5 years for those who underwent TAVR. However, these associations should be interpreted cautiously, given the observational nature of the included studies and the potential for residual confounding. Patients who underwent TAVR were generally older and had a higher prevalence of peripheral arterial disease, whereas most other comorbidities and echocardiographic parameters were similar. Overall, these results reflect associations rather than causal effects and highlight the need for individualized heart-team decision-making.

The importance of this work lies in recognizing that patients with LFLG AS constitute a distinct clinical entity compared with those with normal-flow, high-gradient AS. These patients have historically demonstrated poorer survival, even when LVEF is preserved. Importantly, this population is not rare, as LFLG AS accounts for approximately 5–10 percent of patients undergoing isolated, first-time

AVR. Within this group, two subtypes are recognized: classical LFLG, characterized by reduced LVEF, and paradoxical LFLG, where LVEF is preserved. Classical LFLG is more common, whereas paradoxical LFLG is frequently associated with the worst outcomes among patients with AS. In addition to LVEF, low transvalvular flow has been identified as a strong predictor of outcomes following valve replacement. Although current guidelines recommend AVR for patients with severe symptomatic LFLG AS [2,8], the optimal choice of intervention, SAVR or TAVR, remains an area of active investigation [18].

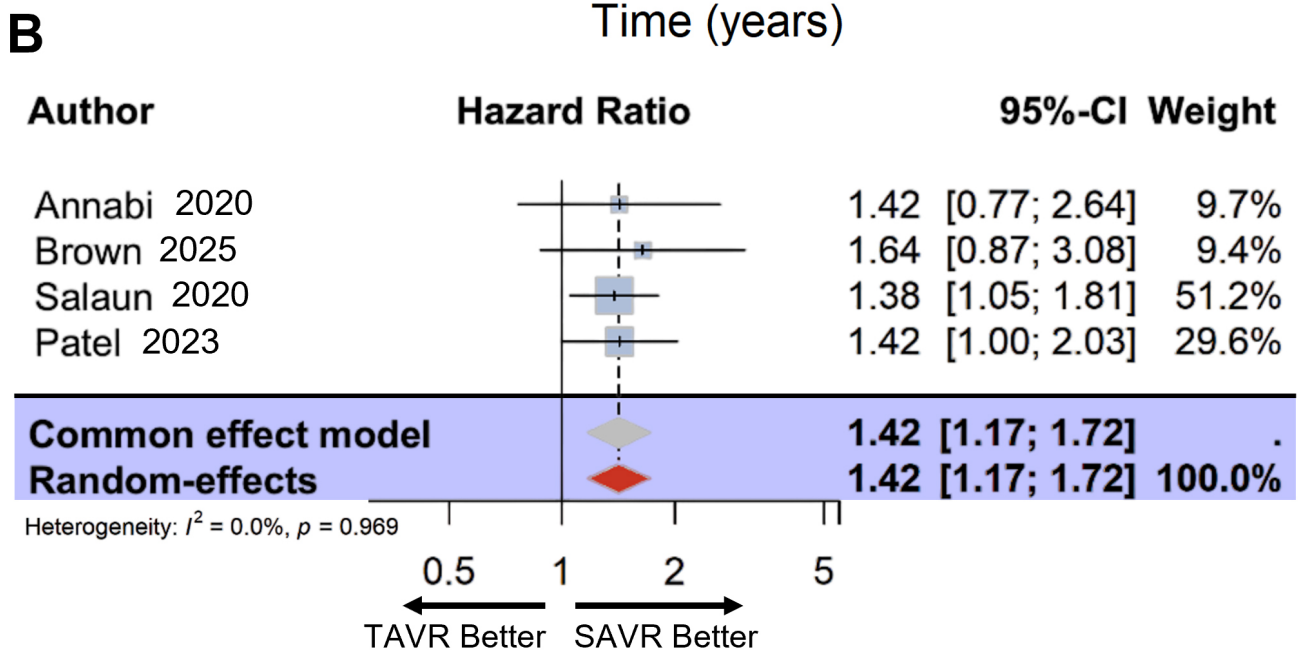
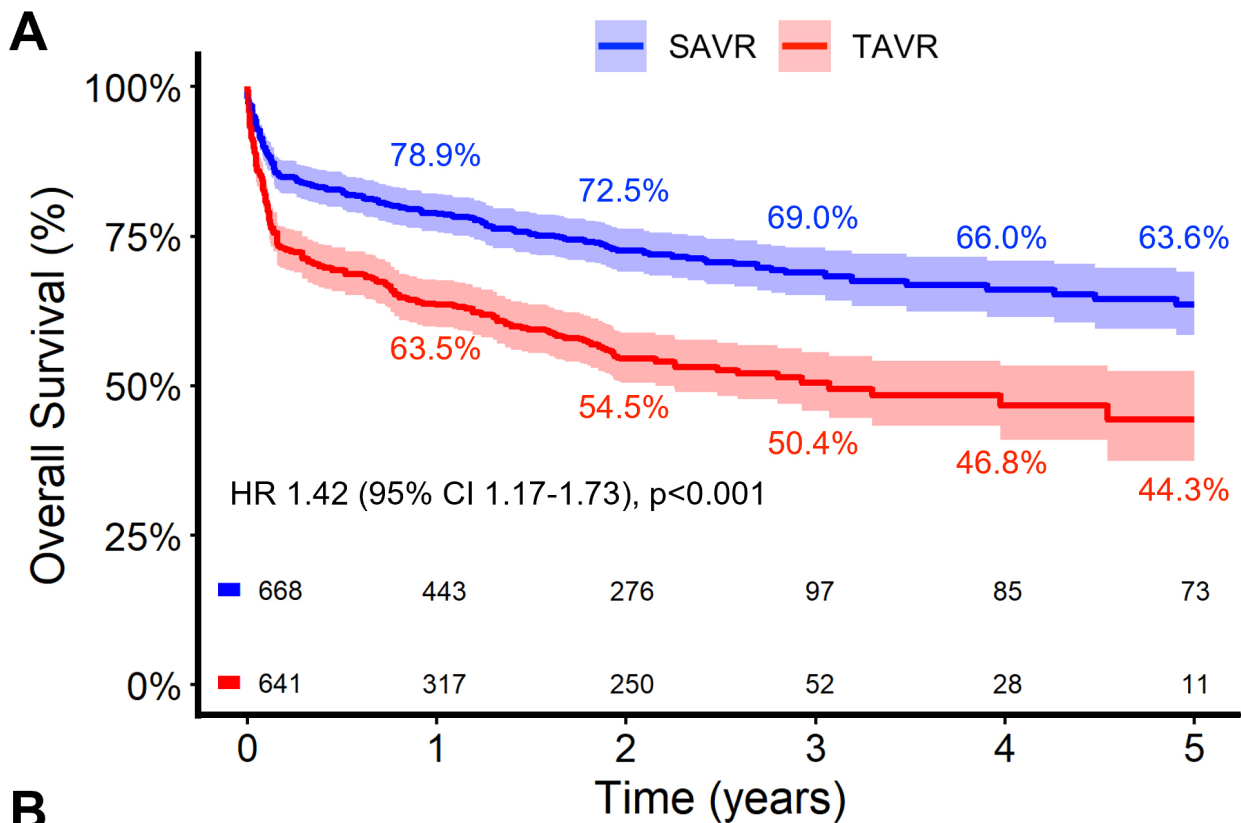
In a multicenter cohort of 204 patients with LFLG AS and concomitant coronary artery disease treated between 2005 and 2012, both SAVR and TAVR were associated with significantly improved survival compared with medical therapy (adjusted HR 0.16 and 0.30, respectively). While there were no significant differences in all-cause mortality between the two procedures, SAVR patients were more likely to undergo complete revascularization (35% vs. 8%). Notably, this finding is relevant, as patients with incomplete revascularization had more than a 2-fold increase in 1-year cardiovascular mortality [11]. In contrast, the PARTNER high-risk substudy found no statistically significant difference in mortality between TAVR and SAVR at 2 years among 105 patients with classical LFLG AS [16]. Furthermore, at the opposite end of the risk spectrum, the TOPAS registry reported significantly lower mortality with transfemoral TAVR compared with SAVR (HR 0.28, 95% CI 0.11–0.72) at 36 months [17]. Lastly, in a contemporary



**Fig. 3. Comparative outcomes of TAVR versus SAVR in patients with LFLG AS.** Legend: (A) Kaplan-Meier survival curves up to 5 years for patients who underwent TAVR versus SAVR, with survival estimates indicated at key time points. (B) Results of a two-stage meta-analysis summarizing the pooled effect of TAVR versus SAVR on long-term survival.

low-risk cohort, early outcomes, including 30-day mortality, stroke, and pacemaker rates, were comparable between SAVR and TAVR; however, paravalvular leak was more common with TAVR, and survival at 1 year was numerically higher with SAVR, consistent with trends observed in our pooled analysis [15]. In that study, the higher incidence of paravalvular leakage may partially explain these findings, as even mild leaks have been associated with adverse long-term outcomes following TAVR [19]. Another potential explanation for the observed differences in outcomes between TAVR and SAVR is the impact of patient-prosthesis mismatch (PPM), particularly in the LFLG population [20]. Although severe PPM is more frequent after SAVR, the impact of this condition is primarily observed in TAVR pa-

tients with low-flow physiology, in whom PPM is linked to higher cardiac mortality and rehospitalization [20–22]. Overall, these data suggest a possible survival benefit and more durable hemodynamic performance with SAVR in appropriately selected patients; however, the limited number of studies and risk of confounding prevent definitive conclusions. For example, smaller sample sizes in prior studies may have obscured a true survival benefit with SAVR. Conversely, up to 70% of the excess mortality observed with TAVR may reflect residual confounding from older age, higher comorbidity burden among TAVR recipients, differences in valve types, or an era effect [23]. This is particularly important because most studies were judged to have at least a moderate risk of bias in the domain of residual



**Fig. 4. Adjusted comparative outcomes of TAVR versus SAVR in patients with LFLG AS.** Legend: (A) Kaplan-Meier survival curves up to 5 years for patients who underwent TAVR versus SAVR, adjusted for confounders, with survival estimates shown at key time points. (B) Results of a two-stage meta-analysis summarizing the pooled, adjusted effect of TAVR versus SAVR on long-term survival.

confounding, a key limitation for interpreting these pooled estimates.

Recent evidence further refines our understanding of factors influencing outcomes following TAVR in patients with LFLG AS. Observational studies have examined the impact of valve type, balloon-expandable versus self-

expanding. While 30-day mortality was similar between groups, self-expanding valves were associated with lower mean gradients but higher rates of paravalvular leak. In contrast, balloon-expandable valves were associated with a reduced risk of heart failure readmission over a median follow-up of approximately 2.5 years [24]. The supra-

annular design of many self-expanding valves contributes to lower post-TAVR gradients, especially in patients with small annuli or low-flow states, potentially improving left ventricular (LV) unloading [25,26]. Similarly, annular size has been evaluated as a potential determinant of post-TAVR outcomes. In a cohort of 1866 patients, individuals with small annuli had higher mean gradients and a greater incidence of structural valve deterioration; however, intermediate-term mortality and heart failure rehospitalization were comparable to those with larger annuli across all flow-gradient subgroups, including classical and paradoxical LFLG AS [27]. Extending this to surgical practice, valve size has not been associated with either in-hospital or mid-term mortality, even for prostheses smaller than 21 mm [28]. TAVR valves typically achieve larger effective orifice areas and lower gradients at equivalent sizes, thereby potentially favoring hemodynamic effects on ventricular remodeling and early clinical outcomes. Sutureless surgical valves, which offer hemodynamics comparable to TAVR while maintaining lower rates of paravalvular leak, may represent an alternative strategy for selected patients with LFLG AS; however, prospective studies are needed to confirm these potential benefits [29,30].

In patients with LFLG AS, recent advances in imaging have enabled computed tomography-derived aortic valve calcium (AVC) scoring to complement traditional functional assessments, particularly when dobutamine stress echocardiography (DSE) is inconclusive or not feasible [6,31]. However, recent evidence shows that AVC has limited discriminatory power in this population, with low sensitivity (44.3%) and specificity (56.5%) for identifying true severe AS [32]. While DSE remains the reference standard, the use of this technique can be limited by arrhythmias, patient tolerance, and availability [33]. Thus, although AVC provides a noninvasive and reproducible measure of valve calcification, current Agatston score cutoffs cannot reliably replace DSE and should be applied with caution in clinical decision-making for these patients. Lastly, despite advances in both new-generation TAVR devices and SAVR techniques, clinical outcomes for patients with LFLG AS remain suboptimal [33]. These findings emphasize that AVR alone may not be sufficient to fully address the elevated risk in this vulnerable population [33]. Optimizing long-term outcomes will likely require a comprehensive, multidisciplinary strategy that combines valve replacement with intensive medical therapy, close management of comorbid conditions, and structured cardiac rehabilitation to enhance functional recovery and survival [7,34].

### *Limitations*

This meta-analysis has several important limitations. Most of the included studies were retrospective observational cohorts; only one was a post hoc analysis of a randomized trial, in which flow status was not specifically accounted for. Therefore, residual confounding from un-

measured patient characteristics, procedural selection, and center-specific practices cannot be excluded despite statistical adjustments. Critical baseline variables, including frailty and surgical risk scores, were inconsistently reported across the included studies. These factors are particularly relevant, as patients undergoing TAVR in real-world practice are often at higher baseline risk than those receiving SAVR. Additionally, heterogeneity in LFLG subtypes (classical versus paradoxical), baseline comorbidities, and valve selection may have influenced outcomes. Given the important differences between LFLG subtypes, a formal subgroup analysis would be valuable. However, most studies did not report outcomes separately for classical and paradoxical LFLG AS, precluding such an analysis. Additionally, TAVR technology has evolved substantially over the study period, and earlier studies may not reflect contemporary practice, which could influence observed outcomes. Moreover, reconstruction of individual patient data from digitized Kaplan-Meier curves, although validated, may introduce minor inaccuracies relative to the original datasets. In addition, the use of varying adjustment methods across studies (IPTW, propensity scores, or multivariable regression) may have introduced further heterogeneity in the estimated effects. Finally, follow-up was limited to a maximum of 5 years, thereby limiting conclusions regarding long-term survival and valve durability. Despite these limitations, this analysis offers meaningful insights into the differential impact of TAVR versus SAVR in high-risk LFLG patients; meanwhile, prospective randomized controlled trials are awaited to provide more definitive evidence.

## **5. Conclusion**

In patients with LFLG AS, SAVR was associated with significantly lower mortality than TAVR, both before and after adjustment for baseline characteristics. Across studies, TAVR patients experienced a reduction in expected survival of approximately 1 year over follow-up periods of up to 5 years. These findings represent observed associations rather than causal effects, and residual confounding cannot be excluded. Accordingly, these data are hypothesis-generating and should not be interpreted as definitive evidence of SAVR superiority, highlighting the need for careful procedural selection and individualized management in this high-risk population.

## **Availability of Data and Materials**

All data reported in this paper will be shared by the corresponding author upon request.

## **Author Contributions**

XJ, GR, and MPS contributed to the conception and design of the study, performed the research, and drafted the manuscript. IH, TO, DS-G, DK, CT, and AM contributed to data interpretation and critically revised the manuscript

for important intellectual content. IS contributed to the conception and design of the study, contributed to data interpretation and critically revised the manuscript, and provided overall supervision. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

The authors declare no conflict of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-4o in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/HSF47967>.

## References

- [1] Orwat S, Kaleschke G, Kerckhoff G, Radke R, Baumgartner H. Low flow, low gradient severe aortic stenosis: diagnosis, treatment and prognosis. *EuroIntervention*. 2013; 9: S38–S42. <https://doi.org/10.4244/EIJV9SSA8>.
- [2] Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin III JP, *et al.* 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *JACC*. 2021; 77: e25–e197. <https://doi.org/10.1016/j.jacc.2020.11.018>.
- [3] Mosleh W, Amer MR, Ding Y, Megaly M, Mather JF, McMahon S, *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. *Circulation. Cardiovascular Interventions*. 2021; 14: e010042. <https://doi.org/10.1161/CIRCINTERVENTIONS.120.010042>.
- [4] Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, *et al.* Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. *Journal of the American College of Cardiology*. 2008; 51: 1466–1472. <https://doi.org/10.1016/j.jacc.2007.10.067>.
- [5] Mogensen NSB, Ali M, Carter-Storch R, Annabi MS, Grenier-Delaney J, Møller JE, *et al.* Dobutamine Stress Echocardiography in Low-Gradient Aortic Stenosis. *J Am Soc Echocardiogr*. 2024;37:1023–1033. <https://doi.org/10.1016/j.echo.2024.06.017>.
- [6] Clavel MA. Therapeutic Management of Low-Gradient Aortic Stenosis: First Assess the State of the Schrödinger Cat Before Making a Decision. *Circulation. Cardiovascular Interventions*. 2017; 10: e005320. <https://doi.org/10.1161/CIRCINTERVENTIONS.117.005320>.
- [7] Tribouilloy C, Rusinaru D, Maréchaux S, Castel AL, Debry N, Maizel J, *et al.* Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. *Journal of the American College of Cardiology*. 2015; 65: 55–66. <https://doi.org/10.1016/j.jacc.2014.09.080>.
- [8] Praz F, Borger MA, Lanz J, Marin-Cuartas M, Abreu A, Adamo M, *et al.* 2025 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). *European Heart Journal*. 2025; 46: 4635–4736. <https://doi.org/10.1093/eurheartj/ehaf194>.
- [9] Baudo M, Leone PP, Sicouri S, Magouliotis DE, Yamashita Y, Cabrucci F, *et al.* Transcatheter or Surgical Strategy for Aortic Stenosis and Coronary Artery Disease: A Kaplan-Meier-Derived Meta-Analysis. *Am J Cardiol*. 2026;260:80–88. <https://doi.org/10.1016/j.amjcard.2025.11.018>.
- [10] Jacquemyn X, Sá MP, Rega F, Verbrugge P, Meuris B, Serna-Gallegos D, *et al.* Transcatheter versus surgical aortic valve replacement for severe aortic valve stenosis: Meta-analysis with trial sequential analysis. *The Journal of Thoracic and Cardiovascular Surgery*. 2025; 169: 1214–1225.e5. <https://doi.org/10.1016/j.jtcvs.2024.04.007>.
- [11] O’Sullivan CJ, Englberger L, Hosek N, Heg D, Cao D, Stefanini GG, *et al.* Clinical outcomes and revascularization strategies in patients with low-flow, low-gradient severe aortic valve stenosis according to the assigned treatment modality. *JACC. Cardiovascular Interventions*. 2015; 8: 704–717. <https://doi.org/10.1016/j.jcin.2014.11.020>.
- [12] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*. 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>.
- [13] Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology*. 2021; 21: 111. <https://doi.org/10.1186/s12874-021-01308-8>.
- [14] Patel KP, Vandermolen S, Cooper J, Pugliese F, Ozkor M, Kennon S, *et al.* Comparing Outcomes Between Surgical and Transcatheter Aortic Valve Replacement in Classical Low-Flow Low-Gradient Aortic Stenosis. *The American Journal of Cardiology*. 2023; 192: 206–211. <https://doi.org/10.1016/j.amjcard.2023.01.020>.
- [15] Brown JA, Ashwat E, Warraich N, Iyanna N, Serna-Gallegos D, Kliner D, *et al.* Outcomes of surgical versus transcatheter aortic valve replacement in patients with low-flow, low-gradient aortic stenosis. *The Journal of Thoracic and Cardiovascular Surgery*. 2025; 170: 1392–1401. <https://doi.org/10.1016/j.jtcvs.2025.04.034>.
- [16] Salaun E, Clavel MA, Hahn RT, Jaber WA, Asch FM, Rodriguez L, *et al.* Outcome of Flow-Gradient Patterns of Aortic Stenosis After Aortic Valve Replacement: An Analysis of the PARTNER 2 Trial and Registry. *Circulation. Cardiovascular Interventions*. 2020; 13: e008792. <https://doi.org/10.1161/CIRCINTERVENTIONS.119.008792>.

- [17] Annabi MS, Côté N, Dahou A, Bartko PE, Bergler-Klein J, Burwash IG, *et al.* Comparison of Early Surgical or Transcatheter Aortic Valve Replacement Versus Conservative Management in Low-Flow, Low-Gradient Aortic Stenosis Using Inverse Probability of Treatment Weighting: Results From the TOPAS Prospective Observational Cohort Study. *Journal of the American Heart Association.* 2020; 9: e017870. <https://doi.org/10.1161/JAHA.120.017870>.
- [18] Ueyama H, Kuno T, Harrington M, Takagi H, Krishnamoorthy P, Sharma SK, *et al.* Impact of Surgical and Transcatheter Aortic Valve Replacement in Low-Gradient Aortic Stenosis: A Meta-Analysis. *JACC. Cardiovascular Interventions.* 2021; 14: 1481–1492. <https://doi.org/10.1016/j.jcin.2021.04.038>.
- [19] Sá MP, Jacquemyn X, Van den Eynde J, Tasoudis P, Erten O, Sicouri S, *et al.* Impact of Paravalvular Leak on Outcomes After Transcatheter Aortic Valve Implantation: Meta-Analysis of Kaplan-Meier-derived Individual Patient Data. *Structural Heart: the Journal of the Heart Team.* 2023; 7: 100118. <https://doi.org/10.1016/j.shj.2022.100118>.
- [20] Abbas AE, Ternacle J, Pibarot P, Xu K, Alu M, Rogers E, *et al.* Impact of Flow on Prosthesis-Patient Mismatch Following Transcatheter and Surgical Aortic Valve Replacement. *Circulation. Cardiovascular Imaging.* 2021; 14: e012364. <https://doi.org/10.1161/CIRCIMAGING.120.012364>.
- [21] Herrmann HC, Daneshvar SA, Fonarow GC, Stebbins A, Vemulapalli S, Desai ND, *et al.* Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. *J Am Coll Cardiol.* 2018;72:2701-2711. <https://doi:10.1016/j.jacc.2018.09.001>.
- [22] Sá MP, Jacquemyn X, Van den Eynde J, Chu D, Serna-Gallegos D, Ebels T, *et al.* Impact of prosthesis-patient mismatch after surgical aortic valve replacement: systematic review and meta-analysis of reconstructed time-to-event data of 122 989 patients with 592 952 patient-years. *Journal of the American Heart Association.* 2024; 13: e033176. <https://doi.org/10.1161/JAHA.123.033176>.
- [23] Feldman DR, Romashko MD, Koethe B, Patel S, Rastegar H, Zhan Y, *et al.* Comorbidity Burden and Adverse Outcomes After Transcatheter Aortic Valve Replacement. *Journal of the American Heart Association.* 2021; 10: e018978. <https://doi.org/10.1161/JAHA.120.018978>.
- [24] Warraich N, Brown JA, Sultan A, Kliner D, Serna-Gallegos D, Toma C, *et al.* Balloon-Expandable Versus Self-Expanding Valves in Low-Flow, Low-Gradient Aortic Stenosis: Does Valve Type Matter? *Catheter Cardiovasc Interv.* 2026; 23. <https://doi.org/10.1002/ccd.70529>.
- [25] Yamamoto M, Ryzaki T, Hioki H, Kagase A, Shirai S, Ohno Y, *et al.* Intra- versus supra-annular self-expanding transcatheter heart valves in small aortic annuli. *EuroIntervention.* 2025;21:e749-e757. <https://doi:10.4244/EIJ-D-24-00966>.
- [26] Chetcuti SJ, Deeb GM, Popma JJ, Yakubov SJ, Grossman PM, Patel HJ, *et al.* Self-Expanding Transcatheter Aortic Valve Replacement in Patients With Low-Gradient Aortic Stenosis. *JACC. Cardiovascular Imaging.* 2019; 12: 67–80. <https://doi.org/10.1016/j.jcmg.2018.07.028>.
- [27] Besir B, Ramu SK, Lomaia T, Ali Majeed-Saidan MM, Rajendran J, Motairek I, *et al.* Outcomes of Patients With a Small and Large Aortic Annulus Following Balloon-Expandable Transcatheter Aortic Valve Replacement Across Flow-Gradient Patterns. *Structural Heart: the Journal of the Heart Team.* 2025; 9: 100456. <https://doi.org/10.1016/j.shj.2025.100456>.
- [28] Lopez-Marco A, Miller H, Youhana A, Ashraf S, Zaidi A, Bhatti F, *et al.* Low-flow low-gradient aortic stenosis: surgical outcomes and mid-term results after isolated aortic valve replacement. *European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery.* 2016; 49: 1685–1690. <https://doi.org/10.1093/ejcts/ezv449>.
- [29] Sá MP, Jabagi H, Dokollari A, Awad AK, Van den Eynde J, Malin JH, *et al.* Early and late outcomes of surgical aortic valve replacement with sutureless and rapid-deployment valves versus transcatheter aortic valve implantation: Meta-analysis with reconstructed time-to-event data of matched studies. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions.* 2022; 99: 1886–1896. <https://doi.org/10.1002/ccd.30162>.
- [30] Grubb KJ, Tom SK, Sultan I, Sá MP. Overcoming prosthesis-patient mismatch with transcatheter aortic valve replacement. *Annals of Cardiothoracic Surgery.* 2024; 13: 236–243. <https://doi.org/10.21037/acs-2024-aae-27>.
- [31] Pawade T, Sheth T, Guzzetti E, Dweck MR, Clavel MA. Why and how to measure aortic valve calcification in patients with aortic stenosis. *JACC: Cardiovascular Imaging.* 2019; 12: 1835–1848. <https://doi.org/10.1016/j.jcmg.2019.01.045>.
- [32] Adrichem R, Hokken TW, Bouwmeester S, Abdelkarim O, Vogel B, Blusztajn DI, *et al.* Diagnostic Value of Aortic Valve Calcification Levels in the Assessment of Low-Gradient Aortic Stenosis. *JACC. Cardiovascular Imaging.* 2024; 17: 847–860. <https://doi.org/10.1016/j.jcmg.2024.03.014>.
- [33] Mengi S, Nombela-Franco L, Cepas-Guillén P, Lerakis S, Makkar R, Chakravarty T, *et al.* Temporal Trends in Transcatheter Aortic Valve Replacement Outcomes in Patients With Low-Flow, Low-Gradient Aortic Stenosis: Insights From the TOPAS-TAVI Registry. *The Canadian Journal of Cardiology.* 2025; 41: 1503–1514. <https://doi.org/10.1016/j.cjca.2025.04.015>.
- [34] Sukul D, Albright J, Thompson MP, Villablanca P, Keteyian SJ, Yaser J, *et al.* Predictors and Variation in Cardiac Rehabilitation Participation After Transcatheter Aortic Valve Replacement. *JACC. Advances.* 2023; 2: 100581. <https://doi.org/10.1016/j.jacadv.2023.100581>.