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Background: Previous reports of longer-term outcomes of transcatheter aortic valve implantation (TAVI) focus on higher risk patients and suggest potential temporal changes.

Aims: To evaluate the longer-term and temporal performances of TAVI compared to surgical aortic valve replacement (SAVR).

Methods: Randomized controlled trials reporting outcomes with at least 1-year follow-up. The primary outcome was the composite of all-cause death or disabling stroke.

Results: We included 8 trials with 8,749 patients. TAVI was associated with a higher risk of longer-term (5-year) primary outcome compared to SAVR among higher-risk [odds ratio (OR), 1.25; 95% CI, 1.07–1.47] but not lower-risk participants [1.0 (0.77–1.29)]. However, a significant temporal interaction was detected in both risk profiles. TAVI with balloon-expandable valves was associated with a higher risk of longer-term primary outcome compared to SAVR [1.38 (1.2–1.6)], whereas no statistical difference was found with self-expanding valves [1.03 (0.89–1.19)]. There was a significant interaction between the two valve systems, and a temporal interaction was detected in both systems. Overall landmark analysis revealed a lower risk in TAVI within the initial 30 days [0.76 (0.6, 0.96)], comparable between 30 days to 2 years [1.04 (0.85, 1.28)], and higher beyond 2 years [1.36 (1.15–1.61)]. Analysis for all-cause death generated largely similar results.

Conclusions: TAVI was associated with a higher longer-term risk of primary outcome compared to SAVR in higher-risk patients and with balloon-expandable valves. However, a characteristic temporal interaction was documented in all subgroups. Future studies are warranted to test these findings.

KEYWORDS

aortic stenosis, TAVI, SAVR, longer-term, randomized controlled trials (RCT)

1 Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a popular treatment for patients with severe aortic stenosis, surpassing surgical procedures in some countries (1). We previously indicated a potential higher mortality associated with TAVI compared to surgical aortic valve replacement (SAVR) at 5-year follow-up (2), mainly in high risk patients (3–5). The longer-term performance of TAVI vs. SAVR in patients with lower risk remains uncertain. Additionally, the temporal changes in TAVI performance at different timepoints have yet to be determined. Given the expansion of TAVI to low-risk patients with increased life expectancy, this assessment holds critical clinical importance.

The 5-year follow-up data from nearly all registered comparative randomized controlled trials (RCTs) of TAVI vs. SAVR have recently been published (6–9). We therefore are able to assess the longer-term outcomes of TAVI and conduct a landmark analysis to identify the timepoint at which the performance of TAVI might diverge from SAVR, as indicated in some studies (5). The aim of our study was to evaluate the longer-term and temporal performances of TAVI compared to SAVR, both overall and within important subgroups.

2 Methods

We reported the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Supplementary Table S1).

2.1 Data sources and searches

PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, and major conference proceedings were systematically searched from inception through October 25, 2023, an update of our previous meta-analysis (2). The computer-based searches combined terms and keywords which included transcatheter aortic valve implantation, transcatheter aortic valve replacement, TAVI, TAVR, and randomized trial (Supplementary Materials). Two investigators independently hand-searched the references of identified studies and relevant reviews to identify any additional relevant trials.

2.2 Study selection

Two reviewers conducted independent screening of titles and abstracts to determine eligibility of the studies. Full-text articles were retrieved for studies that were deemed potentially relevant. In cases where discrepancies arose, a third investigator resolved the discrepancies. Eligible studies had to be RCTs evaluating TAVI vs. SAVR in patients with severe aortic stenosis, and reporting outcomes of interest with at least 1-year follow-up. Nonrandomized observational studies, studies comparing different types of TAVI devices, and studies with less than 1-year follow-up were excluded.

2.3 Outcome measures

The primary outcome was the composite of all-cause death and disabling stroke. Secondary outcomes included all-cause death, cardiovascular death, myocardial infarction, stroke, transient ischemic attack (TIA), major bleeding, major vascular complications (MVC), permanent pacemaker implantation (PPM), new-onset atrial fibrillation, aortic-valve reintervention, rehospitalization, and moderate or severe paravalvular leak (PVL).

2.4 Data extraction and quality assessment

Two investigators independently extracted the data using a pre-specified form. Whenever possible, data from the intentionto-treat analysis were extracted; otherwise, data from the astreated analysis were extracted. The same investigators also assessed the risk of bias in the included RCTs using the Cochrane Risk of Bias 2.0 tool.

2.5 Statistical analysis

Summary measures were reported as odds ratios (ORs) and pooled using random-effects models (DerSimonian-Laird method). Data were analyzed separately for different time points, including data within 30 days, 1 year, 2 years, and 5 years (one trial reported 4-year outcome and was used), and categorized as early, short-term, midterm, and longer-term outcomes, respectively. Landmark analysis was also conducted for intervals within 1 year, between 1 year and 2 years, and beyond 2 years. Events occurring within 1 year were further divided into events within 30 days and events between 30 days and 1 year to further explore the timing of performance change. For trials in which only one of the arms had no events, the 0.5 continuity correction was applied. Stratified analyses were performed based on surgical risks (higher and lower risks) and TAVI systems [balloon-expandable valves (BEV) and selfexpanding valves (SEV)]. The higher-risk group included trials involving patients with extreme, high, and intermediate-to-high surgical risk, while the lower-risk group included trials involving patients with low and low-to-intermediate risk, as determined by the evaluation using the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score. Between-subgroup differences were assessed using the χ^2 -test for heterogeneity. Sensitivity analysis was performed for the outcomes using Hartung-Knapp-Sidik-Jonkman primary variance correction, and by removing an individual trial each time. Heterogeneity was evaluated using the Q and I2 statistics. All meta-analyses were performed using Stata software version 16.0, and the Review Manager version 5.3. A 2-tailed p value <0.05 was considered statistically significant.

Abbreviations

MVC, major bleeding, major vascular complication; PPM, permanent pacemaker implantation; PVL, paravalvular leak; RCT, randomized controlled trials; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

3 Results

3.1 Study selection and characteristics

We included 8 trials and 14 secondary reports that provided eligible data from these trials (3–23), involving a total of 8,749 patients (Supplementary Figure S1). All 8 trials reported outcomes at 30 days and 1 year, 7 reported 2-year outcomes, one reported 4-year outcomes (8), and 6 reported 5-year outcomes (3–6, 9, 20). The mean age was 79.2 years and 57.4% were male. Based on STS-PROM risk score, 4 trials were categorized as lower-risk trials (mean STS PROM 1.9%–3.0%), while the other 4 categorized as higher-risk trials (mean STS PROM 4.5%–11.7%). BEV was used in 3 trials, SEV in 4 trials, and a mixed TAVI system in one trial. Baseline characteristics are presented in Supplementary Tables S2, S3. Blinding of participants and personnel was not feasible in any of the trials (Supplementary Table S4).

3.2 Primary outcome

TAVI demonstrated a lower rate of primary outcome compared to SAVR at 30 days [odds ratio (OR), 0.76 (95% CI 0.6–0.96)] and 1 year [0.83 (0.72–0.96)]. However, at longer-term follow-up, TAVI was associated with a higher risk [1.17 (1.01–1.36)] (Figure 1). Landmark analysis indicated a significant benefit of TAVI within the first year, comparable events between 1 year and 2 years [1.19 (0.95–1.49)], but a significant disadvantage beyond 2 years [1.36 (1.15–1.61)], with a significant temporal interaction (p for interaction<0.0001) (Figure 2). The most notable benefit of TAVI was observed within the initial 30 days, whereas no significant difference was found between 30 days and 1 year [0.9 (0.74–1.08)] (Supplementary Table S5).

Subgroup analysis revealed a higher risk of longer-term primary outcome in TAVI compared to SAVR among participants with higher risk [1.25 (1.07–1.47)], but no statistical difference was found in patients with lower risk [1.00 (0.77–1.29)]. The higher risk of TAVI in higher-risk patients was primarily attributed to events occurring beyond 2 years [1.45 (1.24–1.7)] (p for interaction<0.0001) (Figure 2; Supplementary Table S6). The lower risk of TAVI over SAVR in lower-risk patients within 1 year [0.67 (0.49–0.93)] was not observed at longer-term follow-up, and a significant temporal interaction was detected (p for interaction = 0.01) (Supplementary Table S7).

Subgroup analysis demonstrated a higher risk of longer-term primary outcome in TAVI using BEV compared to SAVR [1.38 (1.2–1.6)], but no statistical difference was found with SEV [1.03 (0.89–1.19)] (Figure 3). A significant interaction was observed between two valve systems (p for interaction = 0.005, Supplementary Table S8). The higher risk of TAVI with BEV was primarily attributed to events occurring beyond 2 years [1.57 (1.32–1.86)] (p for interaction = 0.004) (Figure 4; Supplementary Table S9). The benefit of TAVI with SEV over SAVR within 1 year [0.75 (0.6–0.94)] was not observed at longer-term follow-up

[1.21 (0.93-1.56)], and a significant temporal interaction was detected (p for interaction = 0.015) (Supplementary Table S10).

3.3 Other outcomes

Overall and subgroup analysis for all-cause death generated largely similar results with the primary outcome (Supplementary Figures S2, S3). At longer-term follow-up, TAVI was found to have a numerically higher risk of cardiovascular death, a significantly higher risk of TIA, MVC, PPM, reintervention, rehospitalization, and moderate to severe PVL, compared to SAVR. However, TAVI showed a significantly lower risk of major bleeding and new-onset atrial fibrillation, and a comparable risk of stroke and myocardial infarction (Table 1).

The increased risk of TAVI on cardiovascular death was primarily attributed to events occurring beyond 2 years, rehospitalization attributed to events beyond 1 year, while TIA, MVC, and reintervention were primarily associated with events within 1 year. The benefits of TAVI on major bleeding and new-onset atrial fibrillation were mainly attributed to lower events occurring within 1 year. The risk of PPM at longer-term follow-up was primarily attributed to higher events occurring within 1 year in TAVI, with the risk attenuating but still higher in TAVI between 1 year and 2 years and beyond 2 years (Supplementary Table S5).

In subgroup analysis, a statistically higher risk of longer-term reintervention and rehospitalization was observed in TAVI compared to SAVR among participants at higher risk, while no statistical difference was found in patients at lower risk (Supplementary Table S11). Significant interaction was detected between the two risk groups (both p for interaction <0.0001). The lower risk of rehospitalization in TAVI over SAVR in lower-risk patients within the first year was not observed during longer-term follow-up (Supplementary Table S7). Subgroup analysis indicated a statistically higher risk of longer-term PPM in TAVI compared to SAVR, regardless of participants' higher or lower risk. The SEV showed a higher risk than the BEV, with a significant difference (p for interaction <0.0001) (Supplementary Table S8).

3.4 Heterogeneity, publication bias, and sensitivity analyses

There was minimal heterogeneity observed across trials for both the primary outcomes and all death outcomes across all follow-up durations, as detailed in corresponding figures and tables. Several tests for publication bias were conducted for the primary outcome, and no significant results were found (not shown). However, the assessment of publication bias was limited by the relatively small number of trials, potentially affecting the ability to detect small-study effects. The analysis of primary outcome using the Hartung-Knapp-Sidik-Jonkman variance correction and excluding each trial one time revealed largely similar findings (Supplementary Figures S4–S7).

Study or Subgroup	TAVR Events Total	SAVR Events Total	Weight I	Odds Ratio V, Random, 95% CI	Odds Ratio IV, Random, 95% Cl
3.5.1 Higher risk		80-day follow-	-	.,	
1PARTNER	24 348	28 351		0.85 [0.48, 1.51]	
2SURTAVI	24 864	31 796	16.8%	0.71 [0.41, 1.21]	
3U.S. CoreValve 4PARTNER 2A	23 390 62 1011	24 357 80 1021	14.4% 37.1%	0.87 [0.48, 1.57] 0.77 [0.54, 1.08]	
Subtotal (95% CI)	133 2613	163 2525	83.8%	0.79 [0.62, 1.08]	
Heterogeneity: $Tau^2 = 0$	00; Chi ² = 0.37	, df = 3 (P = 0.	95); $I^2 = 0$		•
Test for overall effect: Z	= 2.00 (P = 0.0)	5)			
3.5.2 Lower risk					
6Evolut Low Risk Trial	6 734	18 734	6.1%	0.33 [0.13, 0.83]	
7PARTNER 3 8UK TAVI	2 496 14 458	6 454 11 455	2.1% 8.1%	0.30 [0.06, 1.51] 1.27 [0.57, 2.83]	
Subtotal (95% CI)	22 1688	35 1643	16.2%	0.55 [0.20, 1.54]	
Heterogeneity: $Tau^2 = 0$			06); $I^2 = 6!$	5%	
Test for overall effect: Z					
Total (95% CI)	155 4301	198 4168	100.0%	0.76 [0.60, 0.96]	•
Total events Heterogeneity: Tau ² = 0.	01° Chi ² = 6.44	df = 6 (P = 0)	$(38) \cdot 1^2 = 79$	%	
Test for overall effect: Z			50), 1 = 17		
Test for subgroup different	ences: $Chi^2 = 0$	42, df = 1 (P =	0.52), I ² =	0%	
3.6.1 Higher risk	В. 1	-year follow-u	р		
1PARTNER	92 348	93 351	•	1.00 [0.71, 1.40]	+
2SURTAVI	66 864	66 796	15.7%	0.91 [0.64, 1.31]	+
3U.S. CoreValve	63 390	79 357	14.7%	0.68 [0.47, 0.98]	-1
4PARTNER 2A Subtotal (95% CI)	145 1011 366 2613	160 1021 398 2525	32.6% 80.5%	0.90 [0.71, 1.15] 0.88 [0.75, 1.03]	
Heterogeneity: $Tau^2 = 0$					•
Test for overall effect: Z					
3.6.2 Lower risk					
5NOTION	16 145	21 135	4.1%	0.67 [0.34, 1.35]	
6Evolut Low Risk Trial 7PARTNER 3	18 734 5 496	29 734 13 454	5.6% 1.9%	0.61 [0.34, 1.11] 0.35 [0.12, 0.98]	
8UK TAVI	30 458	35 455	7.8%	0.84 [0.51, 1.39]	
Subtotal (95% CI)	69 1833	98 1778	19.5%	0.67 [0.49, 0.93]	◆
Heterogeneity: $Tau^2 = 0$			49); $I^2 = 0$	6	
Test for overall effect: Z Total (95% CI)	= 2.43 (P = 0.0 435 4446	496 4303	100.0%	0.83 [0.72, 0.96]	
Heterogeneity: $Tau^2 = 0$					•
Test for overall effect: Z					
Test for subgroup differ	ences: $Chi^2 = 2$.	14, df = 1 (P = 1	$0.14), I^2 =$	53.3%	
3.7.1 Higher risk	C. 2	-year follow-u	р		
1PARTNER	127 348		17.1%	1.12 [0.82, 1.53]	- <u>+</u> -
2SURTAVI 3U.S. CoreValve	108 864 93 390	97 796 113 357	19.1% 15.9%	1.03 [0.77, 1.38] 0.68 [0.49, 0.93]	
4PARTNER 2A	192 1011	202 1021	32.7%	0.95 [0.76, 1.18]	
Subtotal (95% CI)	520 2613	531 2525	84.8%	0.93 [0.77, 1.13]	+
Heterogeneity: $Tau^2 = 0$			13); $I^2 = 43$	7%	
Test for overall effect: Z 3.7.2 Lower risk	= 0.69 (P = 0.4)	9)			
5NOTION	23 145	25 135	4.4%	0.83 [0.45, 1.55]	
6Evolut Low Risk Trial	32 734	39 734	7.4%	0.81 [0.50, 1.31]	
7PARTNER 3	15 496	17 454	3.4%	0.80 [0.40, 1.62]	
Subtotal (95% CI)	70 1375	81 1323	15.2%	0.81 [0.58, 1.14]	
Heterogeneity: Tau ² = 0. Test for overall effect: Z			$(00); 1^{2} = 0$	70	
Total (95% CI)	= 1.20 (P = 0.2 590 3988	612 3848	100.0%	0.92 [0.81, 1.05]	•
Heterogeneity: $Tau^2 = 0$					1
Test for overall effect: Z			o. 461 - 2		
Test for subgroup differ				0%	
3.8.1 Higher risk		-year follow-u	-	1 50 51 15 2 5	
1PARTNER 2SURTAVI	236 348 255 864	200 351 217 796		1.59 [1.17, 2.17]	-
3U.S. CoreValve	255 864 216 390	193 357	19.6% 14.8%	1.12 [0.90, 1.38] 1.05 [0.79, 1.41]	
4PARTNER 2A	456 1011	388 1021	22.5%	1.34 [1.12, 1.60]	-
Subtotal (95% CI)	1163 2613	998 2525	70.6%	1.25 [1.07, 1.47]	♦
Heterogeneity: $Tau^2 = 0$.			15); $I^2 = 44$	4%	
Test for overall effect: Z 3.8.2 Lower risk	= 2.78 (P = 0.0	(סט			
5NOTION	55 145	49 135	7.4%	1.07 [0.66, 1.74]	
6Evolut Low Risk Trial	76 734	90 734	13.0%	0.83 [0.60, 1.14]	- +
7PARTNER 3	55 496	41 454	9.0%	1.26 [0.82, 1.92]	+ - -
Subtotal (95% CI)	186 1375	180 1323	29.4%	1.00 [0.77, 1.29]	+
Heterogeneity: $Tau^2 = 0$.			29); $I^2 = 20$)%	
Test for overall effect: Z Total (95% CI)		9) 1178 3848	100.0%	1.17 [1.01, 1.36]	
Heterogeneity: $Tau^2 = 0$					0.01 0.1 1 10 100
Test for overall effect: Z	= 2.09 (P = 0.0)	4)			Favours TAVR Favours SAVR
Test for subgroup differ	ences: Chi ² = 2.	14, df = 1 (P =	$0.14), I^2 =$	53.3%	

Study or Subaroun	TAVE		SAV		Waight	Odds Rati			Odds Ratio		
Study or Subgroup	Events		Vithin 1		weight	V, Random, 9	5% CI		IV, Random, 95% C		
3.6.1 Higher risk	0.2			-	17 50/	1 00 [0 71	1 401				
	92	348	93	351	17.5%	1.00 [0.71	-		I		
	66	864	66	796	15.7%	0.91 [0.64					
3U.S. CoreValve	63	390	79	357	14.7%	0.68 [0.47	-		-		
4PARTNER 2A		1011		1021	32.6%	0.90 [0.71					
Subtotal (95% CI)		2613		2525	80.5%	0.88 [0.75	1.03]				
Heterogeneity: Tau ² = 0 Fest for overall effect: Z 3.6.2 Lower risk	,			$(\mathbf{P}=0.$	$(47); 1^{-} = 0;$	ő					
5NOTION	16	145	21	135	4.1%	0.67 [0.34	1.351				
5Evolut Low Risk Trial	18	734	29	734	5.6%	0.61 [0.34					
PARTNER 3	5	496	13	454	1.9%	0.35 [0.12					
BUK TAVI	30	458	35	455	7.8%	0.84 [0.51	-				
Subtotal (95% CI)		1833		1778	19.5%	0.67 [0.49]					
Heterogeneity: $Tau^2 = 0$							0.551				
Test for overall effect: Z				(F = 0.	(+9), 1 = 0	0					
				4202	100.0%	0 92 [0 72	0.061				
Fotal (95% CI)		4446			100.0%	0.83 [0.72	0.96]				
Heterogeneity: $Tau^2 = 0$				(P=0.	$(42); 1^2 = 25$	%					
Test for overall effect: Z					a						
Test for subgroup differ	ences: Ch	$11^2 = 2.$	14, df =	1 (P =	$(0.14), I^2 =$	53.3%					
8.11.1 Higher risk		B. E	Betweer	n 1 yea	r and 2 ye	ars					
LPARTNER	35	348	26	351	17.6%	1.40 [0.82	2.381		∔∎		
2SURTAVI	42	864	31	796	22.0%	1.26 [0.78	-				
3U.S. CoreValve	30	390	34	357	18.8%	0.79 [0.47	-				
4PARTNER 2A		1011		1021	27.4%	1.14 [0.74	-				
Subtotal (95% CI)		2613		2525							
Heterogeneity: $Tau^2 = 0$						1.13 [0.88	1.43]				
				(P=0.	(45), T = 0	6					
Test for overall effect: Z	= 0.96 (F	r = 0.3	4)								
3.11.2 Lower risk											
5NOTION	7	145	4	135	3.2%	1.66 [0.48	5.81]				
6Evolut Low Risk Trial	14	734	10	734	7.4%	1.41 [0.62	3.19]		- -		
7PARTNER 3	10	496	4	454	3.6%	2.31 [0.72	7.43]			-	
Subtotal (95% CI)		1375		1323	14.2%	1.66 [0.92	2.99]				
Heterogeneity: Tau ² = 0	.00; Chi ²	= 0.47	, df = 2	(P=0.	79); $I^2 = 0$	6					
Fest for overall effect: Z	= 1.68 (F	P = 0.0	9)								
Fotal (95% CI)		3988			100.0%	1.19 [0.95	1.49]		•		
Heterogeneity: Tau ² = 0	.00; Chi ²	= 4.56	, df = 6	(P = 0.	60); $I^2 = 0$	6					
Fest for overall effect: Z Fest for subgroup differ				1 (P =	0.23), l ² =	29.9%					
3.12.1 Higher risk		C F	Retween	2 and	5 years						
•	100				•	1 52 51 00	2 1 2 1				
	109	348	81	351	15.0%	1.52 [1.09	-				
2SURTAVI	147	864	120	796	19.7%	1.15 [0.89	-		1		
3U.S. CoreValve	123	390	80	357	15.5%	1.60 [1.15					
4PARTNER 2A		1011		1021		1.59 [1.28					
Subtotal (95% CI)		2613			74.0%	1.45 [1.24	1.70]		•		
Heterogeneity: Tau ² = 0 Fest for overall effect: Z 3.12.2 Lower risk				(P = 0.	27); l ² = 24	4%					
5NOTION	32	145	24	135	6.6%	1.31 [0.73	2.36]		+-		
Evolut Low Risk Trial	44	734	51	734	11.3%	0.85 [0.56	-				
7PARTNER 3	40	496	24	454	8.1%	1.57 [0.93	-				
Subtotal (95% CI)		1375		1323		1.17 [0.79	-		-		
Heterogeneity: $Tau^2 = 0$							-		Ť		
Fest for overall effect: Z Fotal (95% CI)	= 0.78 (F 759	P = 0.4 3988	3) 566	3848	100.0%	1.36 [1.15	1.61]		•		
Heterogeneity: $Tau^2 = 0$.02; Chi ²	= 9.84	, df = 6	(P=0.	13); $I^2 = 39$	9%		0.01 0	+ .1 1	10	100
Test for overall effect: Z									.1 I vours TAVR Favours S		10(
Fest for subgroup differ	ences: Ch	$i^2 = 1.$	03, df =	1 (P =	0.31), $I^2 =$	2.7%		rd	VOUIS FAVIL FAVOUIS		
Fest for subgroup differ											
URE 2								rgical risks.			

	TAVE		SAV		Weight	Odds Ratio IV, Random, 95% (Odds Ratio CI IV, Random, 95% CI
Study or Subgroup 4.2.1 Balloon-expanda			A. 30-c		-	IV, Kanuom, 95%	
1PARTNER	24	348	A. 30-C 28	351	26.0%	0.85 [0.48, 1.5	11 -
4PARTNER 2A		1011		1021	70.7%	0.77 [0.54, 1.0	
7PARTNER 3	2	496	6	454	3.2%	0.30 [0.06, 1.5	
Subtotal (95% CI)		1855			100.0%	0.77 [0.57, 1.0]	
Heterogeneity: $Tau^2 = 0$							•
Test for overall effect: Z	= 1.80 (P = 0.0	7)				
4.2.2 Self-expanding v	alves						
2SURTAVI	24	864	31	796	42.0%	0.71 [0.41, 1.2	1] — — — — — — — — — — — — — — — — — — —
3U.S. CoreValve	23	390	24	357	38.0%	0.87 [0.48, 1.5	
6Evolut Low Risk Trial	6	734	18	734	20.1%	0.33 [0.13, 0.8	3]
Subtotal (95% CI)		1988			100.0%	0.65 [0.41, 1.0	5] 🔶
Heterogeneity: $Tau^2 = 0$).06; Chi ²	= 3.05	, $df = 2$	(P=0.	22); $I^2 = 3$	34%	
Test for overall effect: Z							
Test for subgroup differ	rences: Ch	$ni^{2} = 0.$	31, df =	1 (P =	0.57), l ² :	= 0%	
4.1.1 Balloon-expanda		c	В. 1-уе	ar foll	ow-up		
1PARTNER	101e valve 92	3 348	-	351			01
4PARTNER 2A			93		40.2% 51.9%	1.00 [0.71, 1.4	
4PARTNER 2A 7PARTNER 3	145 5	1011 496	160	1021 454	51.9% 7.9%	0.90 [0.71, 1.1 0.35 [0.12, 0.9	
Subtotal (95% CI)		1855			7.9% 100.0%	0.35 [0.12, 0.9	
Heterogeneity: $Tau^2 = 0$							
Test for overall effect: Z							
4.1.2 Self-expanding v		0.5	-/				
2SURTAVI	66	864	66	796	39.2%	0.91 [0.64, 1.3	11 🚽
3U.S. CoreValve	63	390	79	357	36.7%	0.68 [0.47, 0.9	-
5NOTION	16	145	21	135	10.2%	0.67 [0.34, 1.3	-
6Evolut Low Risk Trial	18	734	29	734	13.9%	0.61 [0.34, 1.1	-
Subtotal (95% CI)		2133			100.0%	0.75 [0.60, 0.9	
Heterogeneity: $Tau^2 = 0$	0.00; Chi ²	= 2.03	df = 3	(P = 0.	57); $I^2 = ($		· ·
Test for overall effect: Z	. = 2.52 (P = 0.0	1)				
Test for subgroup differ	rences: Ch	$ni^2 = 0.$	57. df =	1 (P =	0.45), l ² :	= 0%	
4.3.1 Balloon-expanda			С. 2-уе		•		
1PARTNER	127	348	119	351	31.4%	1.12 [0.82, 1.5	
4PARTNER 2A		1011		1021	62.5%	0.95 [0.76, 1.1	-
7PARTNER 3 Subtotal (95% CI)	15	496 1855	17	454	6.1% 100.0%	0.80 [0.40, 1.6 0.99 [0.83, 1.1]	
Heterogeneity: $Tau^2 = 0$							8]
		- 1.00		(i – 0.	50), 1 – (J /0	
Test for overall effect [.] 7		P = 0.9	1)				
Test for overall effect: Z	z = 0.11 (F)	P = 0.9	1)				
4.3.2 Self-expanding v	2 = 0.11 (F valves			700	20 50/	1 0 2 10 77 1 2	
4.3.2 Self-expanding v 2SURTAVI	2 = 0.11 (F valves 108	864	97	796	38.5%	1.03 [0.77, 1.3	
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve	2 = 0.11 (F valves 108 93	864 390	97 113	357	33.3%	0.68 [0.49, 0.9	3] —
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION	2 = 0.11 (F valves 108 93 23	864 390 145	97 113 25	357 135	33.3% 10.8%	0.68 [0.49, 0.9 0.83 [0.45, 1.5	3] - 5]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial	2 = 0.11 (F valves 108 93 23 32	864 390 145 734	97 113 25 39	357 135 734	33.3% 10.8% 17.3%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3	3] 5] 1]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI)	2 = 0.11 (F valves 108 93 23 32 256	864 390 145 734 2133	97 113 25 39 274	357 135 734 2022	33.3% 10.8% 17.3% 100.0%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0	3] 5] 1]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0	Z = 0.11 (F) valves 108 93 23 23 256 0.01; Chi ²	864 390 145 734 2133 = 3.61	97 113 25 39 274 , df = 3	357 135 734 2022	33.3% 10.8% 17.3% 100.0%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0	3] 5] 1]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z	2 = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² 2 = 1.62 (F	864 390 145 734 2133 = 3.61 P = 0.1	97 113 25 39 274 , df = 3 1)	357 135 734 2022 (P = 0.	33.3% 10.8% 17.3% 100.0% 31); I ² = 1	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17%	3] 5] 1]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ	2 = 0.11 (F valves 108 93 23 256 0.01; Chi ² 2 = 1.62 (F rences: Ch	$864 \\ 390 \\ 145 \\ 734 \\ 2133 \\ = 3.61 \\ P = 0.1 \\ ni2 = 1.$	97 113 25 39 274 , df = 3 1) 40, df =	357 135 734 2022 (P = 0. 1 (P =	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² =	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17%	3] 5] 1]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda	2 = 0.11 (F valves 108 93 23 256 0.01; Chi ² 2 = 1.62 (F rences: Ch ble valve	$864 390 145 734 2133 = 3.61 P = 0.1 ni^2 = 1.s$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye	357 135 734 2022 (P = 0. 1 (P = ar follo	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² =	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17%	3] 5] 1] 4]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch uble valve 236	$864 390 145 734 2133 = 3.61 P = 0.1 ni^2 = 1.s348$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200	357 135 734 2022 (P = 0. 1 (P = ar follo 351	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 1 0.24), I ² = 1 0.24), I ² = 1	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6%	3] 5] 1] 4] 7]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A	2 = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² 2 = 1.62 (F rences: Ch ble valve 236 456	$864 390 145 734 2133 = 3.61 P = 0.1 ni^2 = 1.s3481011$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021	33.3% 10.8% 17.3% 100.0% $31); I^{2} = 3$ $0.24), I^{2} = 3$ 21.9% 66.6%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6	3] 5] 1] 4] 7] 0]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3	2 = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² 2 = 1.62 (F rences: Ch ble valve 236 456 55	$864 390 145 734 2133 = 3.61 P = 0.1 ni^2 = 1.s3481011496$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 5w-up 21.9% 66.6% 11.5%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI)	z = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 456 55 747	$864 390 145 734 2133 = 3.61 P = 0.1 ni^2 = 1.s34810114961855$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 0w-up 21.9% 66.6% 11.5% 100.0%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6]	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ²	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11	97 113 25 39 274 , df = 3 1) 40, df = 200 388 41 629 , df = 2	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 0w-up 21.9% 66.6% 11.5% 100.0%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6]	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda IPARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11	97 113 25 39 274 , df = 3 1) 40, df = 200 388 41 629 , df = 2	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 0w-up 21.9% 66.6% 11.5% 100.0%	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6]	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves	864 390 145 734 2133 = 3.61 $P = 0.1$ $hi^2 = 1.$ s 348 1011 496 1855 = 1.11 $P < 0.0$	97 113 25 39 274 , df = 3 1) 40, df = 200 388 41 629 , df = 2 001)	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0.	33.3% 10.8% 17.3% 100.0% 31); I ² = 1 0.24), I ² = 5 0w-up 21.9% 66.6% 11.5% 100.0% 58); I ² = 0	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6	3] 5] 1] 4] 7] 0] 2] 0] •
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI	z = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255	864 390 145 734 2133 = 3.61 $P = 0.1$ $hi^2 = 1.$ s 348 1011 496 1855 = 1.11 $P < 0.0$ 864	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 31); \ l^2=3\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5$ 0.24), \ l^2=5 0.24), \ l^2	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6] % 1.12 [0.90, 1.3	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11 P < 0.0 864 390	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217 193	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357	33.3% 10.8% 17.3% 100.0% 31); l ² = : 0.24), l ² = : 0.25), l ² = : 0.25, l ² = :	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6)% 1.12 [0.90, 1.3 1.05 [0.79, 1.4	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION	$\begin{array}{c} z = 0.11 \ (F \\ \mbox{valves} \\ 108 \\ 93 \\ 23 \\ 32 \\ 256 \\ 0.01; \ Chi^2 \\ z = 1.62 \ (F \\ rences: \ Ch \\ \mbox{valves} \\ 236 \\ 456 \\ 55 \\ 747 \\ 0.00; \ Chi^2 \\ z = 4.38 \ (F \\ \mbox{valves} \\ 255 \\ 216 \\ 55 \\ \end{array}$	864 390 145 734 2133 = 3.61 0 = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11 0 < 0.0 864 390 145	97 113 25 39 274 , df = 3 1) 40, df = 200 388 41 629 , df = 2 001) 217 193 49	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 331); \ l^2=1\\ 0.24), \ l^2=2\\ 0.24, \ $	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6)% 1.12 [0.90, 1.3 1.05 [0.79, 1.4 1.07 [0.66, 1.7	3]
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch 266 456 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216 55 76	$\begin{array}{c} 864\\ 390\\ 145\\ 734\\ 2133\\ = 3.61\\ 0 = 0.1\\ 01^2 = 1.\\ \mathbf{s}\\ 348\\ 1011\\ 496\\ 1855\\ = 1.11\\ 0 < 0.0\\ 864\\ 390\\ 145\\ 734\\ \end{array}$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 308 41 629 , df = 2 001) 217 193 49 90	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135 734	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 311); 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24), 1^2 = 1\\ 0.24, 1$	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6] 0% 1.12 [0.90, 1.3 1.05 [0.79, 1.4 1.07 [0.66, 1.7 0.83 [0.60, 1.1]	3] 5] 1] 4] 7] 0] 2] 0] 8] 1] 4] 4] 4] 4] 4] 4] 4] 4] 5] 5] 5] 5] 5] 5] 5] 5] 5] 5
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI)	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216 55 76 602	$\begin{array}{c} 864\\ 390\\ 145\\ 734\\ 2133\\ = 3.61\\ 2 = 0.1\\ 10^2 = 1.\\ \mathbf{s}\\ 348\\ 1011\\ 496\\ 1855\\ = 1.11\\ 2 < 0.0\\ 864\\ 390\\ 145\\ 734\\ 2133\\ \end{array}$	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217 193 49 90 549	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135 734 2022	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 31); \ l^2=1\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 10.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 000\%$	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6] 3.05 [0.79, 1.4 1.07 [0.66, 1.7 0.83 [0.60, 1.1] 1.03 [0.89, 1.1]	3] 5] 1] 4] 7] 0] 2] 0] 8] 1] 4] 4] 4] 4] 4] 4] 4] 4] 5] 5] 5] 5] 5] 5] 5] 5] 5] 5
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0	z = 0.11 (F valves 108 93 23 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216 55 76 602 0.00; Chi ²	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11 P < 0.0 864 390 145 734 2133 = 2.38	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217 193 49 900 549 5, 49 9, 549 5, 45 5, 45 1, 5, 56 1, 56 1, 57 1, 57 1	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135 734 2022	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 31); \ l^2=1\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 0.24), \ l^2=5\\ 10.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 100.0\%\\ 000\%$	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6] 3.05 [0.79, 1.4 1.07 [0.66, 1.7 0.83 [0.60, 1.1] 1.03 [0.89, 1.1]	3] 5] 1] 4] 7] 0] 8] 1] 4] 4] 5] 7] 0] 6] 7] 0] 6] 7] 0] 7] 0] 7] 0] 7] 0] 0] 1] 1] 1] 1] 1] 1] 1] 1
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z	z = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216 55 76 602 0.00; Chi ² z = 0.44 (F	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11 P < 0.0 864 390 145 734 2133 = 2.38 P = 0.6 200 200 200 200 200 200 200 20	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217 193 49 90 549 5, df = 3 6)	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135 732 202 (P = 0.	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 31); \ l^2 = 1\\ 0.24), \ l^2 = 1\\ 0.24, \ l^2 =$	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6 0% 1.12 [0.90, 1.3 1.05 [0.79, 1.4 1.07 [0.66, 1.7 0.83 [0.60, 1.1 1.03 [0.89, 1.1] 0%	3] 5] 1] 4] 7] 0] 2] 0] 8] 1] 4] 4] 4] 4] 4] 4] 4] 5] 1] 4] 4] 4] 4] 4] 4] 4] 4] 4] 4
4.3.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ 4.4.1 Balloon-expanda 1PARTNER 4PARTNER 2A 7PARTNER 3 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 4.4.2 Self-expanding v 2SURTAVI 3U.S. CoreValve 5NOTION 6Evolut Low Risk Trial Subtotal (95% CI) Heterogeneity: Tau ² = 0	z = 0.11 (F valves 108 93 23 32 256 0.01; Chi ² z = 1.62 (F rences: Ch ble valve 236 456 55 747 0.00; Chi ² z = 4.38 (F valves 255 216 55 76 602 0.00; Chi ² z = 0.44 (F	864 390 145 734 2133 = 3.61 P = 0.1 ni ² = 1. s 348 1011 496 1855 = 1.11 P < 0.0 864 390 145 734 2133 = 2.38 P = 0.6 200 200 200 200 200 200 200 20	97 113 25 39 274 , df = 3 1) 40, df = D. 5-ye 200 388 41 629 , df = 2 001) 217 193 49 90 549 5, df = 3 6)	357 135 734 2022 (P = 0. 1 (P = ar follo 351 1021 454 1826 (P = 0. 796 357 135 732 202 (P = 0.	$\begin{array}{c} 33.3\%\\ 10.8\%\\ 17.3\%\\ 100.0\%\\ 31); \ l^2 = 1\\ 0.24), \ l^2 = 1\\ 0.24, \ l^2 =$	0.68 [0.49, 0.9 0.83 [0.45, 1.5 0.81 [0.50, 1.3 0.84 [0.68, 1.0 17% = 28.6% 1.59 [1.17, 2.1 1.34 [1.12, 1.6 1.26 [0.82, 1.9 1.38 [1.20, 1.6 0% 1.12 [0.90, 1.3 1.05 [0.79, 1.4 1.07 [0.66, 1.7 0.83 [0.60, 1.1 1.03 [0.89, 1.1] 0%	3] 5] 1] 4] 7] 0] 8] 1] 4] 4] 5] 7] 0] 6] 7] 0] 6] 7] 0] 7] 0] 7] 0] 7] 0] 0] 1] 1] 1] 1] 1] 1] 1] 1

	TAVR	SAVR		Odds Ratio	Odds Ratio
Study or Subgroup			-	/, Random, 95% CI	IV, Random, 95% Cl
4.1.1 Balloon-expandal		A. Within 1 y			
1PARTNER	92 348	93 351	40.2%	1.00 [0.71, 1.40]	
4PARTNER 2A	145 1011	160 1021	51.9%	0.90 [0.71, 1.15]	
7PARTNER 3	5 496	13 454	7.9%	0.35 [0.12, 0.98]	
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0$.	$242 \ 1855$	$266 \ 1826$		0.87 [0.64, 1.18] ∞	
Test for overall effect: Z			10), 1 = 45	70	
4.1.2 Self-expanding va	-	0)			
2SURTAVI	66 864	66 796	39.2%	0.91 [0.64, 1.31]	
3U.S. CoreValve	63 390	79 357	36.7%	0.68 [0.47, 0.98]	
5NOTION	16 145	21 135	10.2%	0.67 [0.34, 1.35]	
6Evolut Low Risk Trial	18 734	29 734	13.9%	0.61 [0.34, 1.11]	
Subtotal (95% CI)	163 2133	195 2022		0.75 [0.60, 0.94]	
Heterogeneity: $Tau^2 = 0$.					•
Test for overall effect: Z					
Test for subgroup differe			$(0.45), ^2 =$	0%	
4.5.1 Balloon-expandal		B. Between 1	-	2	
1PARTNER	35 348	26 351	36.2%	1.40 [0.82, 2.38]	L
4PARTNER 2A	47 1011	42 1021	56.3%	1.14 [0.74, 1.74]	
7PARTNER 3	10 496	4 454	7.5%	2.31 [0.72, 7.43]	
Subtotal (95% CI)	92 1855	72 1826		1.29 [0.94, 1.78]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: $Tau^2 = 0$.			50 ; $I^2 = 0\%$		
Test for overall effect: Z		2)			
4.5.2 Self-expanding va					
2SURTAVI	42 864	31 796	42.8%	1.26 [0.78, 2.03]	
3U.S. CoreValve	30 390	34 357	36.6%	0.79 [0.47, 1.32]	
5NOTION	7 145	4 135	6.2%	1.66 [0.48, 5.81]	
6Evolut Low Risk Trial Subtotal (95% CI)	14 734 93 2133	10 734 79 2022	14.4%	1.41 [0.62, 3.19] 1.10 [0.81, 1.50]	
Heterogeneity: $Tau^2 = 0$.				1.10 [0.01, 1.50]	•
Test for overall effect: Z					
Test for subgroup differe			(0.48) $I^2 =$	0%	
rest for subgroup unien	= 0.	, .			
4.6.1 Balloon-expandal	ole valves	C. Between 2	and 5 yea	irs	
1PARTNER	109 348	81 351	25.5%	1.52 [1.09, 2.13]	-
4PARTNER 2A	264 1011	186 1021	64.0%	1.59 [1.28, 1.96]	
7PARTNER 3	40 496	24 454	10.5%	1.57 [0.93, 2.65]	
Subtotal (95% CI)	413 1855	291 1826		1.57 [1.32, 1.86]	•
Heterogeneity: $Tau^2 = 0$.	,	, .	$98); 1^2 = 0\%$		
Test for overall effect: Z		0001)			
4.6.2 Self-expanding va		100 765	24.000	1 1 5 10 00 1	L
2SURTAVI	147 864	120 796	34.8%	1.15 [0.89, 1.50]	
3U.S. CoreValve	123 390	80 357	28.9%	1.60 [1.15, 2.21]	
5NOTION	32 145	24 135	14.0%	1.31 [0.73, 2.36]	
6Evolut Low Risk Trial Subtotal (95% CI)	44 734 346 2133	51 734 275 2022	22.3% 100.0%	0.85 [0.56, 1.30] 1.21 [0.93, 1.56]	
Heterogeneity: $Tau^2 = 0$.					
Test for overall effect: Z					0.01 0.1 1 10 100
Test for subgroup differe			0.09). $I^2 =$	64.4%	Favours TAVR Favours SAVR
		,			
SURE 4					

4 Discussion

This present meta-analysis, including comprehensive data from all available trials comparing TAVI with SAVR, with >8,000 patients and longer-term follow-up data from nearly all trials, yields several important conclusions (Central Illustration). First, TAVI was associated with a higher risk of longer-term primary outcome compared to SAVR among participants with higher risk, but not among those with lower risk. However, a significant temporal interaction was detected in both risk profiles. Second, TAVI with BEV was associated with a higher risk of longer-term primary outcome compared to SAVR, whereas no statistical difference was found with SEV. There was a significant interaction between the two valve systems, and a temporal interaction was observed in both TAVI systems. Third, landmark analysis revealed a lower risk of primary outcome in TAVI compared to SAVR within the initial 30 days, comparable between 30 days and 2 years, and a significant higher risk beyond 2 years. Fourth, overall analysis showed that TAVI was associated with a higher longer-term risk of all-cause death, TIA, MVC, PPM, reintervention, rehospitalization, and moderate to severe PVL, a comparable risk of stroke and myocardial

TABLE 1 Outcomes at different durations of follow-up for TAVI compared to SAVR.

Outcome or subgroup	Trials	TAVI	SAVR	OR (95% CI)	P value
All-cause death					
30-day	8	100/4,446	116/4,303	0.83 (0.61, 1.12)	0.23
1-year	8	366/4,446	401/4,303	0.88 (0.75, 1.02)	0.09
2-year	7	514/3,988	522/3,848	0.95 (0.83, 1.08)	0.43
Longer-term	7	1,268/3,988	1,101/3,848	1.18 (1.03, 1.36)	0.02
Cardiovascular death					
30-day	8	89/4,446	93/4,303	0.93 (0.69, 1.25)	0.633
1-year	8	233/4.446	257/4,303	0.87 (0.73, 1.05)	0.151
2-year	7	320/3,988	329/3,848	0.94 (0.79, 1.1)	0.427
Longer-term	7	755/3,988	675/3,848	1.11 (0.99, 1.26)	0.078
Myocardial infarction		-	· · ·	,	
30-day	8	42/4,446	55/4,303	0.72 (0.48, 1.09)	0.122
1-year	8	78/4,446	83/4,303	0.91 (0.66, 1.25)	0.556
2-year	7	94/3,988	96/3,848	0.96 (0.72, 1.29)	0.805
Longer-term	7	198/3,988	157/3,848	1.12 (0.79, 1.59)	0.514
-				(-//), 10//	0.011
Stroke	0	160/4 446	184/4 202	0.95 (0.62, 1.16)	0.201
0-day	8	160/4,446	184/4,303	0.85 (0.62, 1.16)	0.301
-year	8	240/4,446	246/4,303	0.96 (0.7, 1.3)	0.777
2-year	6	265/3,988 339/3,254	280/3,848	0.9 (0.7, 1.15)	0.407
onger-term	0	339/3,254	325/3,114	0.99 (0.84, 1.18)	0.955
Fransient ischemic attack					
30-day	7	34/3,988	23/3,848	1.45 (0.83, 2.52)	0.190
l-year	7	84/3,988	60/3,848	1.35 (0.97, 1.89)	0.078
2-year	6	99/3,254	64/3,114	1.49 (1.08, 2.06)	0.014
Longer-term	5	128/2,758	94/2,660	1.32 (1, 1.73)	0.046
Najor bleeding					
30-day	8	427/4,446	980/4,303	0.35 (0.18, 0.69)	0.003
1-year	6	408/3,437	944/3,372	0.36 (0.23, 0.56)	< 0.0001
2-year	4	384/2,483	769/2,463	0.46 (0.25, 0.84)	0.012
Longer-term	2	207/738	247/708	0.71 (0.57, 0.89)	0.003
Major vascular complications					
30-day	8	286/4,446	118/4,303	2.74 (1.74, 4.31)	< 0.0001
1-year	6	236/3,437	115/3,372	2.31 (1.48, 3.6)	< 0.0001
2-year	4	181/2,483	101/2,463	2.03 (1.2, 3.41)	0.008
Longer-term	2	68/738	21/708	3.39 (2.05, 5.6)	< 0.0001
Permanent pacemaker implantation	n		· · · · · · · · · · · · · · · · · · ·		-
30-day	8	652/4,446	248/4,303	2.66 (1.64, 4.31)	< 0.0001
1-year	7	495/3,582	244/3,507	2.29 (1.42, 3.7)	0.001
2-year	7	746/3,988	319/3,848	2.57 (1.54, 4.27)	< 0.001
Longer-term	7	852/3,988	395/3,848	2.37 (1.53, 3.68)	<0.0001
	· ·	352, 5, 500			.5.0001
New-onset atrial fibrillation	7	201/2 000	1 226/2 0 40	0.22 (0.14, 0.2)	-0.0001
30-day	7	381/3,988	1,236/3,848	0.22 (0.16, 0.3)	<0.0001
l-year	6	332/3,124	936/3,052	0.27 (0.18, 0.41)	<0.0001
2-year	4	246/2,042	627/1,967	0.26 (0.16, 0.41)	<0.0001
onger-term	4	330/2,386	804/2,344	0.28 (0.2, 0.38)	<0.0001
Moderate to severe paravalvular le					
0-day	7	166/3,438	14/3,465	11.4 (6.69, 19.5)	<0.0001
-year	7	115/3,040	15/2,494	5.67 (3.25, 9.88)	< 0.0001
l-year	6	127/1,976	16/1,707	7.97 (2.21, 28.8)	0.002
Longer-term	6	49/1,695	3/1,449	7.9 (3.12, 20.22)	< 0.0001
Reintervention					
30-day	5	22/4,098	6/3,952	2.85 (1.16, 7)	0.022
1-year	6	54/4,098	19/3,952	2.48 (1.45, 4.23)	0.001
2-year	4	47/2,906	14/2,763	2.92 (1.3, 6.55)	0.009
Longer-term	6	82/3,640	42/3,497	1.86 (1.05, 3.28)	0.032

(Continued)

TABLE 1 Continued

Outcome or subgroup	Trials	TAVI	SAVR	OR (95% CI)	P value
Rehospitalization					
30-day	5	130/3,453	153/3,356	0.78 (0.56, 1.1)	0.157
1-year	6	393/3,843	378/3,713	0.97 (0.74, 1.27)	0.828
2-year	6	528/3,843	450/3,713	1.12 (0.88, 1.43)	0.371
Longer-term	6	825/3,843	658/3,713	1.23 (1.0, 1.5)	0.047

Overall				OR (95% CI)	interaction
	30-day –			0.76 (0.60, 0.96)	
	1-year			0.83 (0.72, 0.96)	
	2-year	_∎∔		0.92 (0.81, 1.05)	
	5-year	-		1.17 (1.01, 1.36)	
Overall	within 1 year			0.83 (0.72, 0.96)	<0.0001
	1-to-2 year	+	-	1.19 (0.95, 1.49)	
	2-to-5 year		-	1.36 (1.15, 1.61)	
Higher-risk	within 1 year	_ _		0.88 (0.75, 1.03)	<0.0001
	1-to-2 year	-+		1.13 (0.88, 1.43)	
	2-to-5 year			1.45 (1.24, 1.70)	
Lower risk	within 1 year			0.67 (0.49, 0.93)	0.011
	1-to-2 year	+		1.66 (0.92, 2.99)	
	2-to-5 year			1.17 (0.79, 1.72)	
BES	within 1 year		_	0.87 (0.64, 1.18)	0.004
	1-to-2 year	+		1.29 (0.94, 1.78)	
	2-to-5 year	ļ		1.57 (1.32, 1.86)	
SES	within 1 year -			0.75 (0.60, 0.94)	0.015
	1-to-2 year			1.10 (0.81, 1.50)	
	2-to-5 year	+	-	1.21 (0.93, 1.56)	
	l .25	1		I 4	
		TAVR	Favors SAVR	-	

infarction, but a lower risk of major bleeding and new-onset atrial fibrillation.

We conducted a comprehensive search on PubMed to identify relevant meta-analyses comparing the longer-term outcomes of TAVI and SAVR. However, these meta-analyses included 3–4 trials with 5-year follow-up data, focusing exclusively on patients with higher risks (2, 24, 25). In contrast, our meta-analysis incorporated a larger dataset, comprising 7 trials with longer-term follow-up data, encompassing both higher- and lower-risk patients. It is important to note that our study utilized longer-term data from nearly all registered large RCTs. One of the identified metaanalyses employed a network meta-analysis approach but considered 1-to-2-year follow-up as long-term (26). Another metaanalysis included only 3 RCTs but supplemented them with 7 propensity-score matching observational studies, which were limited by inadequate adjustment for important confounding (27). We also performed several additional analyses. Firstly, we conducted a landmark analysis to assess the differences in TAVI outcomes within specific time intervals, revealing significant temporal variations in the effect of TAVI. Secondly, we conducted subgroup analyses based on TAVI systems and surgical risks, revealing noteworthy distinctions between subgroups.

None of the trials included were specifically designed to have sufficient statistical power to detect a significant reduction in allcause death. However, our meta-analysis revealed a significant higher risk of longer-term mortality associated with TAVI. This finding aligns with the temporal trend observed in primary outcome. Further subgroup analysis indicated a significantly higher risk of all-cause death in TAVI among higher-risk patients and with BEV, but no significant difference was observed in lower-risk patients or with SEV. Importantly, the temporal trend was also only evident in the former two subgroups. A separate meta-analysis of 7 propensity matched studies corroborated our findings by showing a significantly higher risk of mortality at 5-year follow-up (27).

TAVI demonstrated initial superiority over SAVR within the first year but lost this advantage thereafter in lower risk patients. Given that lower risk patients typically have good life expectancy, this temporal interaction warrants intensive and close attention. In the PARTNER 3 trial, Kaplan-Meier event curves for the primary outcome crossed around the 2- to 3-year mark, thereafter favoring SAVR, while in the Evolut Low Risk trial, the curves remained parallel, favoring TAVI (8, 9). Although there were some differences, the pooled analysis of longer-term data from these lower-risk trials did not show substantial heterogeneity ($I^2 = 20\%$). A large real-world registry including 42,586 patients who underwent isolated SAVR and meeting the inclusion and exclusion criteria for the PARTNER 3 and Evolut Low Risk trials, revealed excellent survival rates in low-risk patients following SAVR, with all-cause mortality of 7.1% at 5 years and 12.4% at 8 years (28). Similar findings were observed in other large registries (29). Determining whether TAVI can achieve such excellent long-term outcomes as SAVR will require robust evidence from follow-up periods exceeding 10 years. The recommendation of TAVI in these patients is pending this evidence.

We showed a higher longer-term risk of primary outcome and all-cause death in TAVI compared to SAVR among higher-risk patients. These observations seem a paradox, i.e., patients with a higher surgical risk actually had better longer-term outcomes when they underwent surgery instead of opting for TAVI. Notably, the short-term risk of all-cause death was not decreased in TAVI in higher risk patients. This observation was similar to several meta-analyses with higher-risk patients (2, 24). Unfortunately, no randomized trials in high-risk patients using newer-generation valves have been conducted thus far. There have been some propensity-matched studies that shed light on this topic. For instance, a study involving 72 pairs of high-risk patients, although utilizing mixed generations of TAVI valves, showed a lower in-hospital mortality rate but a higher risk of allcause death at 5-year follow-up in the TAVI group (30). Another propensity-matched analysis of 783 pairs of intermediate-risk patients (mean age: 81.7 years, mean STS score: 5.5) using newer-generation SAPIEN 3 valves demonstrated a comparable risk of death or disabling stroke at 5 years compared to SAVR (31). Further studies are warranted to evaluate the performance of TAVI with newer-generation valves compared to SAVR in the context of higher-risk patients.

An interesting finding of our analysis was the significant interaction between BEV and SEV regarding the primary outcome and all-cause death at longer-term follow-up. A temporal interaction was observed in BEV for both the primary outcome and all-cause death, while in SEV, it was observed only for the primary outcome. These temporal trends closely align with those reported in the PARTNER 2A trial (5), which compared earlygeneration BEV TAVI with SAVR in higher surgical risk patients, and the PARTNER 3 trial (9), which compared newer-generation BEV TAVI with SAVR in lower surgical risk patients. Landmark analyses of clinical events between 2 and 5 years in both trials demonstrated higher rates of all-cause death and the primary outcome in TAVI compared to SAVR. Similarly, in another trial of BEV TAVI, the Kaplan-Meier event curves for all-cause death converged at 2 years (4). In contrast, trials comparing SEV TAVI to SAVR showed Kaplan-Meier event curves for the primary endpoint that remained parallel, favoring TAVI in the Evolut Low Risk trial (8), nearly overlapped in the SURTAVI (6) and NOTION (20) trials, and converged until the 5-year mark in the U.S. CoreValve trial (3). Longer-term data from head-to-head comparisons of BEV with SEV TAVI have been reported in only one RCT (32). In this trial, with 241 high-risk patients randomly assigned to early generation BEV and SEV, all-cause mortality (53.4% vs. 47.6%) and cardiovascular mortality (31.6% vs. 21.5%) at 5 years were numerically higher in the BEV group compared with the SEV group, consistent with our findings. These differences might be attributed to better forward flow hemodynamics and less structural valve deterioration in SEV compared to BEV (32). Several propensity-matched studies showed varied findings, but these conclusions were limited by residual confounders that could not be fully accounted for, such as patients' anatomical suitability. It is likely that more patients with extensive outflow tract calcifications, low implanted coronary arteries, or complex and small femoral access received SEV (33). We found no significant difference between BEV and SEV at short-term follow-up, which is also consistent with findings from other RCTs (34, 35).

Our analysis had several strengths. Firstly, we incorporated the largest number of RCTs with longer-term follow-up outcomes, ensuring a comprehensive evaluation of the data. Additionally, the trials included in our analysis had nearly identical follow-up durations, enabling landmark analyses and mitigating the potential impact of variations in follow-up durations on the outcomes.

However, it is important to acknowledge some limitations. Firstly, our analysis was based on trial-level rather than patientlevel data. Although we performed subgroup analyses based on clinically relevant subgroups, we were unable to conduct more detailed meta-regression analyses to account for potential confounding factors beyond the subgroup variables. Secondly, concomitant procedures were performed in both TAVI and SAVR groups in original trials, which could potentially influence the evaluation of isolated TAVI vs. isolated SAVR. Thirdly, our assessment of publication bias was limited by the relatively small number of trials, potentially affecting the ability to detect small-study effects.

5 Conclusions

TAVI was associated with a higher longer-term risk of primary outcome compared to SAVR in higher-risk patients and with balloon-expandable valves. However, a characteristic temporal interaction was documented in all subgroups. Long-term followup data from low-risk trials and large trials comparing TAVI with balloon-expandable and self-expanding valves are warranted to test these findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

YW: Data curation, Formal analysis, Investigation, Writing -XiaZ: Conceptualization, Data original draft. curation. Methodology, Writing review editing. & XinZ: Conceptualization, Formal analysis, Methodology, Validation, Writing - review & editing. WX: Conceptualization, Resources, Supervision, Writing - review & editing.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2025. 1479200/full#supplementary-material

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