# Near and medium term outcomes of transcatheter aortic valve replacement in elderly patients with aortic stenosis: A meta-analysis

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Abstract: It proves that transcatheter aortic valve replacement (TAVR) is effective in aortic valve stenosis (AS), but its efficacy and safety in elder patients are controversial. We compared the near and medium-term (2 years after surgery) all-cause mortality and complications in older AS patients who underwent TAVR versus surgical aortic valve replacement (SAVR). We searched the literature on TAVR in elderly patients with AS from PubMed, Embase, and Web of Science by computer. The search period is up to August 2023. We performed a meta-analysis in the RevMan 5.3 software. We selected 16 cohort studies with 18,183 patients (9,809 received TAVR and 8,374 received SAVR). Through meta analysis, we found that in comparison with the SAVR, 1-year postoperative stroke rate of the TAVR was lower [OR=0.65, 95%CI(0.54, 0.79), P<0.001], the 2-year re-hospitalization on rate in the TAVR group was higher[OR=1.27, 95%CI(1.11, 1.46), P=0.0005], and the 2-year bleeding rate was lower [ $I^2$ =18%, FEM; OR=0.55, 95%CI(0.40, 0.77), P=0.0004]. The permanent pacemaker implantation (PPI) rate at 2 years after surgery of the TAVR was higher [OR=3.03, 95%CI (1.70, 5.39), P=0.0002] and the rate of New-onset Atrial Fibrillation (NOAF) 2 years after surgery was lower [OR=0.57, 95%CI(0.40, 0.83), P=0.004]. Therefore, we conclude that the near - and medium-term efficacy of TAVR in elderly patients with AS is generally better than that of SAVR, but with a higher risk of re-hospitalization and PPI 2 years after surgery.

# **1. Introduction**

Aortic valve stenosis (AS) is a valvular heart disease, which is common in the elderly population, mainly manifested by limited aortic valve opening, reduced effective valve opening area, increased transvalvular blood flow resistance, resulting in left ventricular hypertrophy, arrhythmia, and even left heart failure. Conservative treatment after the onset of clinical symptoms is ineffective, and the 5-year survival rate is only 15% to 50%<sup>[1]</sup>. With the progress of the global population aging, the number of elderly AS patients has been increasing in recent decades. AS has become a disease with high morbidity and mortality<sup>[2]</sup>, which seriously affects survival and life and increases the global

economic burden.

Surgical operation is the gold standard for severe AS treatment. However, about 30% of patients lose the opportunity for surgical operation due to old age, left heart dysfunction, and multiple complications<sup>[3]</sup>. Since 2002, transcatheter aortic valve replacement (TAVR) has gradually turned into one of the best treatment options for medium-high risk AS patients, with rapid development and popularity, and become the preferred surgery for elderly AS patients<sup>[4]</sup>. However, in assessing the risk of cardiac surgery, the European Heart Surgery Risk Score (EuroSCORE II) and the American Society of Thoracic Surgeons (STS) score for elderly AS are poor<sup>[5]</sup>. There is no evidence that the elderly should not be contraindicated for TAVR, but whether elderly AS patients can truly benefit from TAVR remains questionable<sup>[6]</sup>.

Therefore, we conducted this study to evaluate the near - and medium-term efficacy and safety of TAVR in elderly AS patients.

# 2. Material and Methods

# 2.1. Study inclusion and Exclusion

The types of studies were randomized controlled trials (RCTS) and cohort studies comparing clinical outcomes after TAVR. For the document, the language is English, and the publication time is not limited. The subjects were patients aged 60 years or older who had been diagnosed with AS based on cardiac ultrasound and CT. The treatment is TAVR or SAVR, and there are no restrictions on the type of valve selected during TAVR surgery (balloon dilated, self-dilated) or delivery route (apical, transfemoral, etc.). Outcome measures included all-cause mortality, stroke rate, myocardial infarction rate, re-hospitalization rate, incidence of bleeding events (including major or fatal bleeding events), PPI rate, and incidence of NOAF 1 or 2 years after surgery.

The following conditions were excluded: (1) case-control studies, case reports, conference abstracts, reviews and editorials; (2) Too much research data is lost or unavailable; (3) Lack of full text; (4) Duplicate published studies.

## **2.2. Retrieval strategy**

We searched PubMed, Embase, and Web of Science on the computer. The date of publication was limited to August 2023 at the latest. In addition, we reviewed meeting proceedings and references to the included literature for additional studies not identified in the initial database search. If data from included studies were incomplete, we contacted the authors to obtain unpublished data. English subject term include "transcatheter aortic valve replacement", "TAVR", "surgical aortic valve replacement", "SAVR", "aortic valve stenosis", "AS", etc. English free term include "curative effect", "security", "all-cause mortality", "stroke", "myocardial infarction", "rehospitalization", "bleeding", "permanent pacemaker implantation", "new onset atrial fibrillation", "PPI", "NOAF", etc. We adopted the search strategy of subject term + free term and adjusted the search strategy according to the database. The specific search strategy were used: "transcatheter aortic valve replacement"[TIAB] OR "TAVR"[TIAB] OR "TAVI"[TIAB] AND "surgical aortic valve replacement"[TIAB] OR "SAVR"[TIAB] AND "aortic valve stenosis"[TIAB] OR "AS"[TIAB] AND "curative effect"[TIAB] OR "security"[TIAB] OR "all-cause mortality"[TIAB] OR "stroke"[TIAB] OR "myocardial infarction"[TIAB] OR "rehospitalization"[TIAB] OR "bleeding"[TIAB] OR "permanent pacemaker implantation"[TIAB] OR "new onset atrial fibrillation"[TIAB] OR "PPI"[TIAB] OR "NOAF"[TIAB].

# 2.3. Literature screening and data extraction

In strict accordance with the inclusion and exclusion of the study, two researchers were responsible for independently searching the title and screening after reading the abstract. We then carefully reviewed the selected research literature to determine inclusion.

Data extraction for included studies were as follows: First author, year of publication, number of patients enrolled, baseline population data, postoperative complications [including all-cause mortality, stroke, myocardial infarction, rehospitalization, bleeding events, permanent pacemaker implantation (PPI), and New-onset Atrial Fibrillation (NOAF)], and quality assessment information. Two researchers extracted data and collected them in a pre-standardized data table.

#### 2.4. Methodological quality evaluation of included studies

Researchers applied the Cochrane Collaboration's Bias Risk tool<sup>[7]</sup> to comprehensively measure bias risk. We applied the Newcastle-Ottawa Scale (NOS)<sup>[8]</sup> to assess the cohort study quality, including patient selection (including 4 items and rated 4 points), comparability between groups (including 1 item and rated 2 points), and result measurement (including 3 items and rated 3 points). There are 8 items in 3 parts. The full score is 9 points. The higher the evaluation score is, the higher the research quality is. The range  $\geq$ 7, 5-6, and  $\leq$ 4 were separately rated as high-quality, medium-quality, and low-quality research. Two researchers assessed the included studies' bias risk and cross-checked them.

### **2.5. Statistical analysis**

We applied RevMan 5.3 software line system evaluation and meta-analysis. The odds ratio (OR) of 95% confidence interval (CI) was the effect size for categorical variables.

Meta-analysis: We used the  $\chi^2$  test and I<sup>2</sup> to quantify the heterogeneity between studies. For those with no significant heterogeneity (I<sup>2</sup><50%), we applied the fixed effects model (FEM). For those with heterogeneity (I<sup>2</sup> $\geq$ 50%), we adopted the random effects model (REM) and explored heterogeneity sources by parallel sensitivity analysis.

At different follow-up times and different types of events, we performed subgroup analyses according to pre-set criteria to uncover more potential information. We also excluded heterogeneity and performed funnel plot analysis. For those with a high publication bias risk (there were studies in the funnel plot intersected with or even beyond the funnel slash), we applied sensitivity analysis (that is, performed meta-analysis again after excluding literature with a high publication bias risk). P < 0.05 is considered to have a significant difference.

# **3. Results**

# 3.1. The final selection of literature and its information

In our initial search, we found 3,288 potentially eligible studies. Finally, 16 clinical studies<sup>[9-24]</sup> met the inclusion criteria. We show the retrieval and screening process in Figure 1.

The meta-analysis included 18,183 patients (9809 TAVR and 8374 SAVR). Basic information about the included literature, such as study baseline characteristics, STS score, EuroSCORE II, and NOS quality assessment, is shown in Table 1.



Figure 1: Flowchart of studies screening process.

	Country	Year	Number of cases (cases)		Average age (years)		Male			STS-PROM scores		Euro	NYHA class III or IV		Follow-up	NOG
The first author									Artificial			Score				NOS
autioi			TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	valve	TAVR	SAVR	П	TAVR	SAVR	visit(years)	
Leon [9]	The United States	2021	496	454	73.3	±5.8	69.3%		Balloon dilated type	1.9%		NR	NR	NR	2	8
Søndergaard [10]	Denmark, Sweden	2016	142	134	79.2	±4.9	53.	2%	Self-expand ing type	3.0±	1.7%	8.6±4.8 %	NR	NR	2	8
Reardon [11]	Netherlands, Germany, Switzerland, the United States	2016	202	181	81.5±7.6	81.2±6.6	57.9%	55.8%	Self-expand ing type	5.3%(4.3 %-6.1%)	5.3% (4.1%-5.9 %)	NR	NR	NR	2	8
Popma [12]	Australia, Canada, France, Japan, Netherlands	2019	734	734	74.1±5.8	73.6±5.9	65.	1%	Self-expand ing type	1.9±0.7	NR	NR	NR	NR	2	7
Yakubov [13]	England	2020	197	197	79.1	±6.2	40.6%	41.1%	Self-expand ing type	4.0±1.5	3.9±1.3%	NR	NR	NR	2	8
Thyregod [14]	The United States	2015	145	135	79.2±4.9	79.0±4.7	53.	2%	Self-expand ing type	3.0±1.7	NR	NR	NR	47.1%	1	7
Smith [15]	The United States, Canada, Germany	2011	348	351	83.6±6.8	84.5±6.4	57.8%	56.7%	Balloon dilated type	NR	NR	29.25%	94.3%	94.0%	1	8
Leon [16]	The United States, Canada	2016	1011	1021	81.5±6.7	81.7±6.7	54.2%	54.8%	Self-expand ing type	5.8±2.0	NR	NR	77.3%	76.1%	2	8
Reardon [17]	England	2017	864	796	79.9±6.2	79.7±6.1	57.6%	55.0%	Self-expand ing type	4.4±1.5	4.5±1.6%	NR	60.2%	58.1%	2	7
Amrane [18]	The United States	2019	864	791	79.9±6.2	79.7±6.1	1.5%	55.0%	Self-expand ing type	$4.4 \pm 1.5\%$	4.5±1.6%	NR	NR	NR	1	8
Baron [19]	The United States	2019	2071	944	81.7±6.7	$81.6 \pm 6.8$	58%	55%	Balloon dilated type	5.6% ±1.7 %	5.8 ± 1.9%	NR	NR	NR	2	7
Thyregod [20]	Denmark, Sweden	2016	121	109	78.1±4.9	76.6±4.5	58.4%	54.1%	Balloon dilated type	2.6±1.4%	2.7±1.4%	NR	NR	NR	2	8
Reardon [21]	England	2015	391	359	83.2±7.1	83.3±6.3	52.9%	52.4%	Self-expand ing type	7.3±3.0%	7.5±3.3%	NR	42.7%	43.5%	2	7
Durko [22]	Europe, the United States, Canada	2018	864	796	79.3±7.2	80.0±6.5	54.0%	56.5%	Self-expand ing type	4.4±1.7%	4.5±1.6%	11.2±8. 45%	60.19%	58.2%	1	8
Chen [23]	the United States, Canada	2018	1011	1021	80.5±6.7	81.0±6.4	54.2%	548%	not limited	6.0±2.1%	6.0±1.9%	NR	77.3%	76.0%	2	8
Kodali [24]	England	2017	348	351	84.1	±6.6	NR	NR	not limited	NR	NR	NR	94.	1%	2	7

Table 1: Basic information of the included literature

# 3.2. Meta-analysis

# **3.2.1.** All-cause mortality

Nine studies<sup>[9, 13-18, 22, 24]</sup> reported 1-year all-cause mortality. It was insignificant in 1-year all-cause mortality between the TAVR and SAVR difference [ $I^2$ =0%, FEM; OR=0.93, 95%CI(0.81,

1.07), P=0.29], with a small of publication bias risk (Figure 2, 4A).

Ten studies<sup>[9-12, 16, 17, 20, 21, 23, 24]</sup> reported 2-year all-cause mortality. It was insignificant in 2-year all-cause mortality between the TAVR and SAVR difference [I<sup>2</sup>=88%, REM; OR=1.19, 95%CI(0.81, 1.75), P=0.37] (Figure 3A). The 2-year all-cause mortality funnel plot showed studies with a higher bias risk. Sensitivity analysis showed that the difference was still not significant (P=0.27) (Figures 3B, 4B, and 4C).



Figure 2: Forest map of 1-year comparative meta-analysis of all-cause mortality.



A: Before sensitivity analysis. B: After sensitivity analysis.

Figure 3: Forest map of 2-year comparative meta-analysis of all-cause mortality.



A: 1-year all-cause mortality. B: 2 years before sensitivity analysis of all-cause mortality. C: After 2-year sensitivity analysis of all-cause mortality.

Figure 4: Funnel plot of a meta-analysis comparing all-cause mortality.

## 3.2.2. Stroke rate

Nine studies<sup>[9, 13-18, 22, 24]</sup> reported stroke rates one year after surgery. It was insignificant in stroke rates between the TAVR and SAVR difference [I<sup>2</sup>=62%, REM; OR=0.85, 95%CI(0.63, 1.15), P=0.29], with funnel plots showing studies with a higher risk of bias (Figure 5A, 6A). Sensitivity analysis suggested a lower stroke rate of TAVR [I<sup>2</sup>=0%, FEM; OR=0.65, 95%CI(0.54, 0.79), P<0.001] (Figure 5B, 6B).

Eight studies<sup>[9, 10, 16, 17, 20, 21, 23, 24]</sup> reported stroke rates of 2 years after surgery. It was insignificant between the TAVR and SAVR difference [I<sup>2</sup>=35%, FEM; OR=0.94, 95%CI(0.80, 1.10), P=0.41] (Figure 7).



A: Before sensitivity analysis. B: After sensitivity analysis.

Figure 5: Forest map of 1-year stroke rate comparative meta-analysis.



Figure 6: Funnel plot of a meta-analysis comparing 1-year stroke rates.





## **3.2.3. Myocardial infarction rate**

Four studies<sup>[14, 16, 17, 24]</sup> reported myocardial infarction rate 1 year after surgery. It was insignificant between the TAVR and SAVR difference [I<sup>2</sup>=0%, FEM; OR=0.86, 95%CI(0.57, 1.28), P=0.45], and their funnel plots showed studies with a higher risk of unbias (Figure 8A, 9A).

Five studies<sup>[14, 16, 17, 21, 24]</sup> reported the rate of myocardial infarction 2 years after surgery. It was insignificant between the two operations' difference [I<sup>2</sup>=0%, FEM; OR=0.90, 95%CI(0.64, 1.25), P=0.53], whose funnel plots showed studies with a higher risk of unbias (Figure 8B, 9B).



A: 1 year after surgery. B: 2 years after surgery.

Figure 8: Forest map of myocardial infarction rate comparison meta-analysis.



Figure 9: Funnel plot of comparative meta-analysis of myocardial infarction rate.

# 3.2.4. Rehospitalization rate

Five studies<sup>[9, 12, 16, 17, 24]</sup> reported a re-hospitalization rate one year after surgery. It was insignificant between the TAVR and SAVR difference [I<sup>2</sup>=27%, FEM; OR=1.03, 95%CI(0.87, 1.21), P=0.72] (Figure 10).

Five studies<sup>[9, 16, 17, 23, 24]</sup> reported re-hospitalization rates two years after surgery. It was insignificant between the TAVR and SAVR difference [I<sup>2</sup>=54%, REM; OR=1.17, 95%CI(0.96, 1.43), P=0.12] (Figure 11A, 12A). Sensitivity analysis suggested a higher re-hospitalization rate of TAVR [I<sup>2</sup>=0%, FEM; OR=1.27, 95%CI(1.11, 1.46), P=0.0005] (Figure 11B, 12B).



Figure 10: A meta-analysis of 1-year readmission rates.



A: Before sensitivity analysis. B: After sensitivity analysis.

Figure 11: Forest map for comparison of 2-year readmission rates in meta-analysis.



Figure 12: Funnel plot of a meta-analysis comparing 2-year readmission rates.

# **3.2.5. Bleeding**

Seven studies<sup>[11, 14, 16, 17, 19, 21, 24]</sup> reported the bleeding rate two years after surgery. The TAVR showed a higher bleeding rate [I<sup>2</sup>=98%, REM; OR=0.42, 95%CI(0.19, 0.92), P=0.03], and the funnel plot revealed higher bias risk studies (Figure 13A, 14A). Sensitivity analysis disclosed a lower bleeding rate of TAVR [I<sup>2</sup>=18%, FEM; OR=0.55, 95%CI(0.40, 0.77), P=0.0004] (Figure 13B, 14B).

		TAVR g	roup	SAVR g	group		Odds Ratio		Odds Ratio			
Α.	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	M-H, Rand	om. 95% Cl		
	Baron 2019	141	2071	438	944	15.2%	0.08 [0.07, 0.10]		•			
	Kodali 2017	60	348	95	351	14.9%	0.56 [0.39, 0.81]					
	Leon 2016	169	1011	471	1021	15.2%	0.23 [0.19, 0.29]		-			
	Reardon 2015	69	391	140	359	15.0%	0.34 [0.24, 0.47]		-			
	Reardon 2016	44	202	67	181	14.6%	0.47 [0.30, 0.74]					
	Reardon 2017	105	864	74	796	15.0%	1.35 [0.99, 1.85]			-		
	Thyregod 2015	5	145	3	135	10.0%	1.57 [0.37, 6.71]					
	Total (95% CI)		5032		3787	100.0%	0.42 [0.19, 0.92]		-			
	Total events	593		1288								
	Heterogeneity: Tau <sup>2</sup> =	1.03; Chi <sup>2</sup>	= 245.1	3, df = 6 (	P < 0.00	0001); l <sup>2</sup> =	98%				400	
	Test for overall effect:	Z = 2.18 (F	P = 0.03	5)				0.01	U.1 TAV/P group	SAVP group	100	
									TAVIN gloup	SAVIN gloup		
		TAVR gr	oup	SAVR g	roup		Odds Ratio		Odds	Ratio		
R-	Study or Subgroup	TAVR gr Events	oup Total	SAVR g Events	roup Total	Weight	Odds Ratio M-H, Random, 95% CI		Odds M-H, Rando	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019	TAVR gr Events 141	oup Total 2071	SAVR g Events 438	roup Total 944	Weight 0.0%	Odds Ratio <u>M-H. Random, 95% Cl</u> 0.08 [0.07, 0.10]		Odds M-H, Rando	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017	TAVR gr Events 141 60	oup <u>Total</u> 2071 348	SAVR g Events 438 95	roup Total 944 351	Weight 0.0% 54.6%	Odds Ratio <u>M-H, Random, 95% CI</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81]		Odds M-H, Rando	Ratio om, 95% Cl		
B-	<u>Study or Subgroup</u> Baron 2019 Kodali 2017 Leon 2016	TAVR gr Events 141 60 169	oup Total 2071 348 1011	SAVR g Events 438 95 471	roup <u>Total</u> 944 351 1021	Weight 0.0% 54.6% 0.0%	Odds Ratio <u>M-H, Random, 95% CI</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29]		Odds <u>M-H, Rando</u> - <del>■</del> -	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015	TAVR gr Events 141 60 169 69	oup Total 2071 348 1011 391	SAVR g Events 438 95 471 140	roup <u>Total</u> 944 351 1021 359	Weight 0.0% 54.6% 0.0% 0.0%	Odds Ratio <u>M-H. Random, 95% Cl</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47]		Odds <u>M-H, Rando</u> - <del>_</del> -	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2016	TAVR gr Events 141 60 169 69 44	Total 2071 348 1011 391 202	SAVR g Events 438 95 471 140 67	roup 944 351 1021 359 181	Weight 0.0% 54.6% 0.0% 0.0% 40.4%	Odds Ratio M-H. Random, 95% CI 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47] 0.47 [0.30, 0.74]		Odds <u>M-H, Rando</u>	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2016 Reardon 2017	TAVR gr Events 141 60 169 69 44 105	Total 2071 348 1011 391 202 864	SAVR g Events 438 95 471 140 67 74	roup 944 351 1021 359 181 796	Weight 0.0% 54.6% 0.0% 0.0% 40.4% 0.0%	Odds Ratio <u>M-H. Random, 95% CI</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47] 0.47 [0.30, 0.74] 1.35 [0.99, 1.85]		Odds <u>M-H. Rando</u>	Ratio om, 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2016 Reardon 2017 Thyregod 2015	TAVR gr Events 141 60 169 69 44 105 5	oup Total 2071 348 1011 391 202 864 145	SAVR g Events 438 95 471 140 67 74 3	roup 944 351 1021 359 181 796 135	Weight 0.0% 54.6% 0.0% 40.4% 0.0% 5.0%	Odds Ratio <u>M-H, Random, 95% Cl</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47] 0.47 [0.30, 0.74] 1.35 [0.99, 1.85] 1.57 [0.37, 6.71]		Odds <u>M-H. Rando</u>	Ratio om. 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2017 Thyregod 2015 Total (95% CI)	TAVR gr Events 141 60 169 69 44 105 5	oup Total 2071 348 1011 391 202 864 145 695	SAVR g Events 438 95 471 140 67 74 3	roup <u>Total</u> 944 351 1021 359 181 796 135 667	Weight 0.0% 54.6% 0.0% 40.4% 0.0% 5.0% 100.0%	Odds Ratio M-H. Random, 95% Cl 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47] 0.47 [0.30, 0.74] 1.35 [0.99, 1.85] 1.57 [0.37, 6.71] 0.55 [0.40, 0.77]		Odds M-H. Rando 	Ratio pm. 95% Cl		
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2016 Reardon 2017 Thyregod 2015 Total (95% CI) Total events	TAVR gr Events 141 60 169 69 44 105 5 5	oup Total 2071 348 1011 391 202 864 145 695	SAVR g Events 438 95 471 140 67 74 3 165	roup 944 351 1021 359 181 796 135 667	Weight 0.0% 54.6% 0.0% 40.4% 0.0% 5.0% 100.0%	Odds Ratio <u>M-H. Random. 95% C1</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.34 [0.24, 0.47] 0.34 [0.24, 0.47] 1.35 [0.39, 1.85] 1.57 [0.37, 6.71] 0.55 [0.40, 0.77]		Odds M-H. Rando	Ratio om, 95% Cl		
B-	Study or Subgroup   Baron 2019   Kodali 2017   Leon 2016   Reardon 2015   Reardon 2016   Reardon 2017   Thyregod 2015   Total (95% CI)   Total events   Heterogeneity: Tau <sup>2</sup> = (	TAVR gr <u>Events</u> 141 60 169 69 44 105 5 109 0.02; Chi <sup>2</sup> :	oup <u>Total</u> 2071 348 1011 391 202 864 145 695 = 2.44, c	SAVR g Events 438 95 471 140 67 74 3 165 if = 2 (P =	roup <u>Total</u> 944 351 1021 359 181 796 135 667 = 0.29); I	Weight   0.0%   54.6%   0.0%   0.0%   0.0%   5.0%   100.0%   ² = 18%	Odds Ratio <u>M-H. Random. 95% Ci</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.23 [0.19, 0.29] 0.34 [0.24, 0.47] 1.35 [0.30, 0.74] 1.35 [0.99, 1.85] 1.57 [0.37, 6.71] 0.55 [0.40, 0.77]	0.01	Odds M-H, Rando	Ratio 	100	
B-	Study or Subgroup Baron 2019 Kodali 2017 Leon 2016 Reardon 2015 Reardon 2015 Reardon 2017 Thyregod 2015 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect. 2	TAVR gr <u>Events</u> 141 60 69 44 105 5 109 0.02; Chi <sup>2</sup> = 2 = 3.53 (P	oup <u>Total</u> 2071 348 1011 391 202 864 145 695 = 2.44, c	SAVR g Events 438 95 471 140 67 74 3 165 df = 2 (P = 04)	Total 944 351 1021 359 181 796 135 667 = 0.29); 1	Weight   0.0%   54.6%   0.0%   0.0%   5.0%   100.0%   ² = 18%	Odds Ratio <u>M-H. Random. 95% CI</u> 0.08 [0.07, 0.10] 0.56 [0.39, 0.81] 0.34 [0.2, 0.47] 0.34 [0.2, 0.47] 0.47 [0.30, 0.74] 1.35 [0.99, 1.85] 1.57 [0.37, 6.71] 0.55 [0.40, 0.77]	0.01	Odds M-H, Rando	Ratio om. 95% CI	100	

A: Before sensitivity analysis. B: After sensitivity analysis.

Figure 13: Forest map of comparative meta-analysis of bleeding rates two years after surgery.



Figure 14: Funnel plot of meta-analysis comparing bleeding rates two years after surgery.

## **3.2.6. PPI rate**

Eight studies<sup>[10,11,16,17, 19-21,24]</sup> reported PPI rates two years after surgery. It showed a higher PPI rate of TAVR [I<sup>2</sup>=93%, REM; OR=3.03, 95%CI(1.70, 5.39), P=0.0002], with higher bias risks (Figure 15).



Figure 15: A meta-analysis of PPI rates two years after surgery.

# **3.2.7. NOAF rate**

Five studies<sup>[10, 11, 13, 14, 21]</sup> reported the NOAF rate two years after surgery. It showed a lower NOAF rate of TAVR [I<sup>2</sup>=85%, REM; OR=0.38, 95%CI(0.22, 0.65), P=0.0003], with higher bias risks (Figure 16A, 17A). Sensitivity analysis disclosed a still lower NOAF rate of TAVR [I<sup>2</sup>=58%, REM; OR=0.57, 95%CI(0.40, 0.83), P=0.004] (Figure 16B, 17B).



A: Before sensitivity analysis. B: After sensitivity analysis.





Figure 17: Funnel plot of meta-analysis comparing NOAF rates two years after surgery.

#### 4. Discussion

TAVR is a new type of surgery for high-risk AS patients who cannot tolerate surgery. However, elderly patients with AS often have lower EuroSCORE II and STS scores and are at high risk of disease development and death<sup>[25]</sup>. The clinical efficacy and safety of TAVR in elderly AS patients remain doubtful. Therefore, it is necessary to systematically analyze the feasibility of TAVR implementation in elderly AS.

We applied a meta-analysis to compare patients treated with TAVR and SAVR. Statistically, we found that TAVR to elderly AS patients still had a risk of death in the near and medium term, but there was little difference in the risk of death compared with SAVR, which was clinically acceptable. It is different from the results of Dowling et al.<sup>[26]</sup>, which may be related to the age difference of the included patients, suggesting that TAVR in the elderly population may increase

the risk of near-to-medium-term death, which sufficient clinical evidence is needed to prove. Compared with SAVR, TAVR involves more instruments and consumables, including artificial valves, dilating balloons of various sizes, arterial sheath tubes, various types of catheters, special wires, and vascular suture devices. Nevertheless, before surgery, the TAVR team and guidance experts jointly checked the materials, discussed the surgical plan, further confirmed the patient's condition and surgical indications, and ensured the safety of TAVR. In addition, the initial development of TAVR is inseparable from the efforts of vascular and cardiac surgery support, catheter room, or hybrid operating room equipped with extracorporeal circulation membrane oxygenation device (ECMO), which is also a reassurance for TAVR doctors<sup>[27]</sup>. Our further study data proved that compared with SAVR, elderly patients with AS also had more complications after TAVR. However, the risk of some complications was different from SAVR. The 1-year risk of stroke was lower in the TAVR. Histopathological studies have shown that embolus components include thrombus, calcification, aortic valve, myocardial tissue and foreign bodies in the catheter and valve delivery system<sup>[28]</sup>. The insertion of the TAVR valve damages endothelial cells, leading to platelet activation and activation of the clotting pathway, leading to thrombosis. The pro-coagulation state induced by TAVR devices may also activate platelet aggregation and clotting pathways to promote thrombosis<sup>[29]</sup>. The decrease in the incidence of stroke after TAVR may be attributed to the increased experience of the operator, the reduction of equipment size and the improvement of design<sup>[30]</sup>. In addition, stroke is associated with high thromboembolism, including the prevalence of atherosclerosis and atrial fibrillation<sup>[31]</sup>. TAVR probably lower the thromboembolism risks and thus reduce stroke risk. Imaging and histopathological studies have shown that most strokes after TAVR result from embolism or thrombosis<sup>[32]</sup>. At present, stroke prevention measures after TAVR mainly include the intraoperative use of cerebral protection devices (CPD), which can reduce the risk of stroke by reducing the entry of embolic substances into the cerebral arteries during surgery. Specifically, these devices are placed and positioned at the beginning of the procedure to maximize coverage of the three large branch entrances of the aortic arch, namely the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery, preventing emboli from entering the cerebral circulation by trapping or diverting them into the peripheral circulation<sup>[33]</sup>.

The higher rate of re-hospitalization 2 years after TAVR may be related to the higher rate of PPI in this patient, and the patient needs to be re-hospitalized after PPI surgery. It can be seen that TAVR is inferior to SAVR in reducing PPI, which is consistent with Ding et al.<sup>[34]</sup>. High-grade atrioventricular block and new left bundle branch block are often associated with TAVR and require PPI. Studies have shown that PPI increases hospitalization costs after TAVR and is associated with higher cardiac mortality and re-hospitalization for heart failure within 1 year<sup>[35]</sup>. Auffret et al.<sup>[36]</sup> found that the proportion of patients who underwent PPI after TAVR was related to valve insertion depth, left ventricular septal thickness, preoperative conduction abnormalities, non-calcified aortic valve and other factors. It is suggested that although TAVR has a higher risk of PPI, strict control of its risk factors may reduce the possibility of PPI and make TAVR more feasible. However, when analyzing the PPI rate, most of the included studies had publication bias, so there was a lot of uncertainty about the postoperative PPI risk of TAVR.

After systematic analysis, we also found that the 2-year bleeding risk of TAVR therapy was lower. Most of the bleeding events after TAVR occurred within 30 days after surgery, and about half of the bleeding events reported were related to the surgical path. Compared with the transapical approach, the incidence of bleeding increased by 83%. Non-femoral approach, female, chronic kidney disease, and peripheral artery disease were risk factors for bleeding events<sup>[37]</sup>. In addition, bleeding after TAVR may also be associated with postoperative antiplatelet and anticoagulant therapy. From this, we can infer that for the patients undergoing TAVR, the clinicians should strictly control bleeding events occurrence. However, at present, there is no uniform standard for the optimal antithrombotic treatment after TAVR. We confirmed that the 2-year risk of NOAF was lower in patients undergoing TAVR, further suggesting the feasibility of TAVR in elderly patients

with AS. NOAF refers to new atrial fibrillation after TAVR. At present, the mechanism of NOAF after TAVR is unclear. However, a large number of studies have revealed that the predictors of NOAF after TAVR include age, New York Heart Association cardiac function grade III or IV, previous cerebrovascular events, decreased left ventricular ejection fraction, chronic lung disease, increased left atrial volume and so on<sup>[38]</sup>. Predictors associated with surgical procedures include balloon aortic valvuloplasty, general anesthesia, transfemoral route, hemodynamic instability, and perioperative complications<sup>[39]</sup>. With the gradual deepening of the research, the influencing factors of NOAF after TAVR are constantly discovered and make the clinical intervention strategy clear, increasing the practical application value of TAVR.

There are some limitations in our study: as there is no published RCTS, the study was only included in the cohort study for analysis, which may cause some bias. Due to the lack of data at the individual patient, we did not perform subgroup meta-analyses for certain measures, nor did we analyze other relevant outcomes such as renal impairment, valve type, or delivery path. Analysis of long-term outcomes is lacking. Therefore, after our study, new research should make up for the above shortcomings to support the reliability of the results of this study.

## **5.** Conclusion

The results suggest that TAVR does not increase all-cause mortality and myocardial infarction rate, and has advantages in reducing stroke, bleeding events, and NOAF, but the risk of re-hospitalization and PPI should be vigilant. We suggest that elderly patients receiving TAVR should be comprehensively evaluated by the cardiac team, including imaging, anaesthesia, surgical intervention, ultrasound and nursing, so as to strictly control the occurrence of postoperative complications and maximize surgical benefits. Although statistical data suggest that patients receiving TAVR have higher rates of rehospitalization and PPI than those receiving SAVR, this difference should be clinically surmountable as technology improves. These data support the cardiac team's comprehensive assessment of the near - and medium-term safety and efficacy of TAVR in older AS patients. To a certain extent, our study can provide reference for the treatment decision of clinical elderly AS.

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