



# Efficacy and Safety of Transcatheter vs. Surgical Aortic Valve Replacement in Low-to-Intermediate-Risk Patients: A Meta-Analysis

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Lou Y, Gao Y, Yu Y, Li Y, Xi Z, Swe KNC, Zhou Y, Nie X and Liu W (2020) Efficacy and Safety of Transcatheter vs. Surgical Aortic Valve Replacement in Low-to-Intermediate-Risk Patients: A Meta-Analysis. Front. Cardiovasc. Med. 7:590975. doi: 10.3389/fcvm.2020.590975 **Background:** The efficacy and safety of transcatheter aortic-valve replacement (TAVR) vs. surgical aortic valve replacement (SAVR) for low- to intermediate-surgical risk patients remains uninvestigated.

**Objectives:** We aimed to investigate the efficacy and safety of transcatheter aortic-valve replacement (TAVR) vs. surgical aortic valve replacement (SAVR) for low-intermediate surgical risk patients.

**Methods:** PubMed, Cochrane Library, and Embase databases were searched to identify potential references. Only randomized controlled trials (RCTs) or observational studies using propensity score matching were eligible for screening. The primary endpoint was all-cause death. The secondary outcomes were bleeding, stroke, myocardial infarction (MI), and other complications of aortic-valve replacement. In addition, we performed subgroup analysis based on surgical risk and study type.

**Results:** Eight RCTs and 13 observational studies covering 12,467 patients were included in the current meta-analysis. For patients with low-surgical risk, compared with SAVR, TAVR was found to be associated with a lower mortality at a follow-up period of 1 year (odds ratio, OR: 0.66, 95% CI: [0.46, 0.96], P = 0.03). This benefit disappeared when the follow-up was extended to 2 years (OR: 0.89, 95% CI: [0.61, 1.30], P = 0.56). For patients with intermediate-surgical risk, TAVR showed to have similar mortality with SAVR regardless of follow-up period (30-day, 1-year, or 2-year). TAVR could reduce the incidence of bleeding, AF, and AKI. For complications, such as MI and stroke, TAVR exhibited to have similar safety with SAVR. However, TAVR was found to be associated with a higher incidence of reintervention, major vascular complication, paravalvular leak, and PPI.

**Conclusion:** For patients with a low-to-intermediate surgical risk, TAVR has at least an equivalent clinical effect to SAVR for 2 years after the procedure.

Keywords: transcatheter aortic-valve replacement, TAVR, surgical aortic valve replacement, SAVR, meta-analysis

# INTRODUCTION

Severe aortic stenosis (AS) is associated with a high mortality rate (1), and the most effective treatment for severe AS is aortic valve replacement (AVR) (2). The 2017 Joint American College of Cardiology and American Heart Association guidelines for the management of patients with valvular heart disease recommend surgical AVR (SAVR) as the first-line AVR method (2). Another alternative is transcatheter AVR (TAVR), which is a novel treatment strategy comprising a minimally invasive procedure to replace a narrowed aortic valve that fails to open properly (aortic valve stenosis) (2, 3). TAVR and SAVR share the same efficacy and safety in high-surgical-risk patients (2, 4, 5). However, although TAVR is not recommended as the optimal treatment in lowand intermediate-surgical-risk patients (2), ~90% of patients requiring AVR are considered low and intermediate surgical risk (6). Additionally, the prevalence of TAVR is increasing in lowand intermediate-surgical-risk patients (7). Hence, it is essential to investigate the efficacy and safety of TAVR vs. SAVR in patients with low-to-intermediate surgical risk.

# MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the recommendations of the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (8, 9).

### **Search Strategy**

The PubMed, Cochrane Library, and Embase databases were searched from inception until February 28, 2020, to identify potentially relevant references using MESH words and keywords (title/abstract). We also performed a manual search of relevant references. All studies comparing TAVR with SAVR, including randomized controlled trials (RCTs) and observational studies, were identified using the filters presented in Harvard Countway Library. The search details are listed in the **Supplementary Materials**.

### **Inclusion Criteria**

- 1. RCTs or observational studies using propensity score matching (PSM) that compared TAVR and SAVR in patients classified as having a low or intermediate surgical risk.
- 2. Risk stratification reported in the article.

# **Exclusion Criteria**

- 1. Minimally invasive SAVR.
- 2. Patients with a history of failed surgical aortic bioprosthesis implantation.
- 3. For observational studies, the Society of Thoracic Surgeons (STS) score or European System for Cardiac Operative Risk Evaluation (EuroSCORE) significantly differed between the TAVR and SAVR groups after PSM.
- 4. Being a single-arm prospective study.

# Definitions of Low and Intermediate Surgical Risks

Low surgical risk was defined as a mean STS score of <4% and/or a logistic EuroSCORE of <10%. Intermediate surgical risk was defined as a mean STS score of 4–8% and/or a logistic EuroSCORE of 10–20%.

### **Data Extraction**

Two authors (Lou and Yu) independently screened eligible studies and evaluated the study quality. Another two authors (Xi and Swe) independently extracted the baseline and outcome data. Disagreements were resolved by another two authors (Zhou and Li). Incomplete data were obtained by contacting the corresponding authors or browsing other published articles.

#### Outcomes

The primary outcome was all-cause mortality. The secondary outcomes were bleeding, stroke, myocardial infarction (MI), atrial fibrillation (AF), reintervention, major vascular complication, paravalvular leak, permanent pacemaker implantation (PPI), and acute kidney injury (AKI). All outcomes were assessed at 30 days, 1 year, and 2 years after AVR.

#### **Risk of Bias**

For RCTs, the risk of bias was evaluated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). For observational studies, the study quality was assessed using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) tool (10).

### **Statistical Analysis**

All statistical analyses were performed using Review Manager (RevMan) 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 15.1 (Stata Corp., College Station, TX, USA) software.

The odds ratio (OR) and 95% confidence interval (CI) were used to compare the clinical outcomes of TAVR vs. SAVR. The I<sup>2</sup> statistic was used to test the heterogeneity across studies. The Mantel–Haenszel random-effects model was employed to calculate the OR and 95% CI given the possible heterogeneity across PSM studies and RCTs. In addition, subgroup analyses were carried out based on the data source (RCT or observational study) and surgical risk (low or intermediate). Sensitivity analysis was undertaken by the sequential exclusion of one trial. Publication bias was assessed using a visual funnel plot and Begg's test.

# RESULTS

### **Study Selection**

The initial search identified 7,515 potentially relevant articles. A total of 2,218 duplicates, 847 reviews, 325 case reports, 986 abstracts, 854 non-RCTs, and 2,150 studies with nonrelevant topics were excluded. The full-text versions of the remaining 135 articles were assessed. A final total of 21 studies with 12,467 patients were eligible for meta-analysis after the exclusion of studies that did not report the risk stratification and/or had

significant differences in STS scores between the TAVR and SAVR groups. Of the 21 eligible studies, eight were RCTs, and 13 were observational studies (**Figure 1**).

#### **Characteristics of Eligible Studies**

Of the 12,467 patients, 6,329 (50.7%) received TAVR and 6,138 (49.3%) received SAVR. Furthermore, 4,123 of 6,329 (65.1%) patients who underwent TAVR were from RCTs and 3,932 of 6,138 (64.1%) patients who received SAVR were from RCTs. The number of patients in each study ranged from 60 to 2,032. Patients' baseline data are listed in **Table 1**.

# **Primary Endpoint**

The primary endpoint of the present meta-analysis was all-cause mortality at 30 days, 1 year, and 2 years after AVR; the analysis of mortality at each of the timepoints was performed using data from 19, 14, and six studies, respectively. As shown in Figure 2, TAVR and SAVR provided similar clinical benefits at 30 days (OR: 0.90, 95% CI: [0.71, 1.14], P = 0.38), 1 year (OR: 0.90, 95% CI: [0.79, 1.04], P = 0.16), and 2 years (OR: 0.91, 95% CI: [0.79, 1.06], P = 0.22). Subgroup analysis showed that lowrisk patients undergoing TAVR had a lower 1-year mortality rate than those undergoing SAVR (OR: 0.66, 95% CI: [0.46, 0.96], P = 0.03), while this advantage disappeared when the followup was extended to 2 years (OR: 0.89, 95% CI: [0.61, 1.30], P = 0.56). For intermediate-risk patients, the mortality rate did not significantly differ between patients undergoing TAVR and SAVR at any timepoint (30-day mortality (OR: 1.04, 95% CI: [0.79, 1.36], P = 0.81; 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95% CI: [0.79, 1.36], P = 0.81); 1-year mortality (OR: 0.93, 95\%) (OR: 0.93, 95\%) (OR: 0.93, 95\%) 1.11], *P* = 0.43); and 2-year mortality (OR: 0.91, 95% CI: [0.79, 1.06], P = 0.30) (Figure 3). The subgroup analysis based on data source did not find any significant difference between RCTs and PSM studies (Figure 4).

### **Secondary Endpoints**

The secondary endpoints were bleeding, MI, stroke, AF, reintervention, major vascular complication, paravalvular leak, PPI, and AKI. TAVR significantly reduced bleeding events compared with SAVR during 30 days of follow-up (OR: 0.34, 95% CI: [0.18, 0.64], P = 0.001), even if the follow-up was extended to 1 and 2 years. TAVR was associated with lower incidences of AF and AKI than SAVR at each of the follow-up timepoints. Compared with SAVR, TAVR reduced the incidences of AF and AKI by 51 and 80%, respectively. The incidences of MI and stroke were similar in patients undergoing TAVR and SAVR. The 2-year postoperative incidences of stroke in the TAVR and SAVR groups were 6.8 and 8.1% (P = 0.09), respectively, and the incidence of MI was low in both groups, at approximately 3.0%. Compared with SAVR, TAVR increased the risks of reintervention, major vascular complication, paravalvular leak, and PPI at each of the follow-up timepoints; the corresponding OR and 95% CI for these variables were 3.23 [1.64, 6.38], 2.25 [1.02, 4.94], 14.69 [5.32, 40.60], and 2.52 [1.20, 5.25], respectively (Figure 5).

# **Publication Bias and Quality Assessment**

No substantial publication bias was noted in the funnel plot. The risk of bias in RCTs was mainly related to blinding, which could

not be avoided. The detailed study quality assessment results are listed in the **Supplementary Materials**.

# **Sensitivity Analysis**

A sensitivity analysis performed after the exclusion of one study revealed that our results were robust.

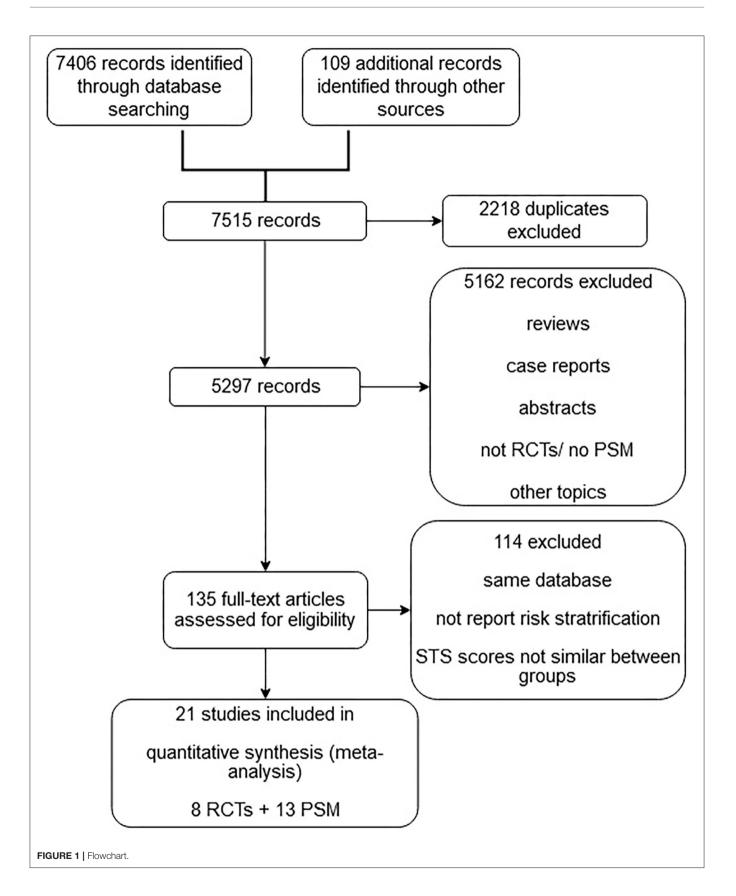
# DISCUSSION

To the best of our knowledge, the present meta-analysis is the largest one to compare the efficacy and safety of TAVR vs. SAVR in the low-to-intermediate-surgical-risk population. For patients with a low surgical risk, TAVR was associated with a lower mortality rate within 1 year than SAVR; however, this positive influence disappeared when the follow-up period was extended to 2 years. For patients with an intermediate surgical risk, SAVR and TAVR resulted in similar mortality rates. Compared with SAVR, TAVR reduced the incidences of bleeding, AF, and AKI but increased the incidences of reintervention, major vascular complication, paravalvular leak, and PPI. The incidences of MI and stroke were similar after TAVR and SAVR.

At present, observational studies show that patients with an intermediate surgical risk have a similar mortality rate after either TAVR or SAVR (25, 27). However, as this result is based on studies with small sample sizes and few RCTs, it is hard to definitively conclude that TAVR is as safe as SAVR. Our metaanalysis included three RCTs and nine observational studies and confirmed the safety of TAVR in patients with a low-to-intermediate surgical risk.

For patients classified as having a low surgical risk, it remains controversial whether TAVR benefits patients more than SAVR. Vipparthy and Levett found that TAVR reduces the mortality rate of low-surgical-risk patients compared with SAVR (32, 33), while Witberg et al. drew the opposite conclusion that low-surgicalrisk patients have a higher mortality rate after TAVR than SAVR (34). The most recent RCTs showed that the 1-year mortality rate does not significantly differ between patients undergoing TAVR vs. SAVR (14, 16). Our subgroup analysis of eight studies found that TAVR was associated with a lower mortality rate in the first year of follow-up, but this benefit disappeared when the followup period was extended to 2 years. Witberg et al. drew their conclusion by analyzing data from four studies with different follow-up periods, ranging from several weeks to 3 years. In contrast, we synthesized our data using studies with same followup periods, which may cause less bias; furthermore, the sample size of our meta-analysis is almost twice that in the study by Witberg et al. These factors may suggest that our conclusion is more reliable than that of Witberg et al.

For patients with a low surgical risk, TAVR was superior to SAVR during a follow-up period of 30 days or 1 year, whereas the benefit disappeared when the follow-up was extended to 2 years. Another study found that TAVR and SAVR result in similar mortality rates during 30 days of follow-up, but TAVR results in a much lower 3-year survival rate than SAVR (35). As low-risk patients may be younger than patients with a higher surgical risk, they have a longer anticipated life. Thus, the long-term efficacy of TAVR should be evaluated in low-risk patients. Moreover, the



#### TABLE 1 | Baseline characteristics of included studies.

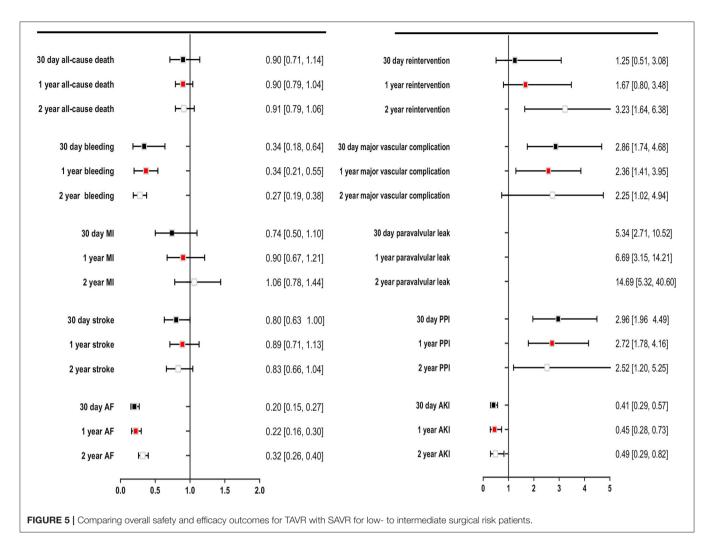
Study ID	Study design	Data source	Follow-up	Sample size (TAVR/SAVR)	Age (years)	DM	Hypertension	COPD	CAD	PCI	STS score	Valve for TAVR	AVG (mmHg)	AVA (cm <sup>2</sup> )
Makkar, (2020) (11)	RCT	PARTNER 2	5 year	1011/1021	82/82	38/34	. /	31.8/30.0	) 69/67	27/28	5.8/5.8	Edwards Lifesciences SAPIEN XT heart-valve system	45/45	0.7/0.7
Reardon, (2017) (12)	RCT	SURTAVIC	2 year	864/796	80/80	34/35	93/90	/	63/64	21/21	4.4/4.5	84% CoreValve bioprosthesis/16% Evolut R bioprosthesis	/	/
Thyregod et al. (2019) (13)	RCT	NOTION	5 year	145/135	79/79	18/21	71/76	12/12	/	8/9	2.9/3.1	Medtronic CoreValve System(TM)	/	/
Mack et al. (2019) (14)	RCT	PARTNER 3	2 year	496/454	73/74	31/30	/	5/6	28/28	/	1.9/1.9	SAPIEN 3 system	49/48	0.8/0.8
Popma, (2019) (15)	RCT	Evolut Low Risk Trial	1 year	725/678	74/73	31/31	85/83	15/18		14/13	1.9/1.9	3.6% CoreValve/74.1% Evolut R/22.3% Evolut PRO	47/47	0.8/0.8
Toff (2020) (16)	RCT	UK TAVI	1 year	458/455	81/81	23/25	72/72	/	30/32	12/9	2.6/2.7	SAPIEN/CoreValve/Evolut/others	/	0.7/0.7
Nielsen, (2012) (17)	RCT	STACCATO	1 year	34/36	80/82	3/8	/	3/3		/	3.1/3.4	Edwards Lifesciences SAPIEN	/	0.7/0.7
Gleason, (2018) (18)	RCT	US-CoreValve High Risk Study	5 year	390/357	83/83	35/45	95/96	/	75/76	34/38	7.3/7.5	CoreValve self-expanding prosthesis	/	/
Fusari, (2012) (19)	PSM	Italy, 2008–2009	1 year	30/30	81/78	23/7	93/77	30/33	37/33	/	6.6/6.1	/	53/52	0.7/0.7
Virtanen, (2019) (20)	PSM	FinnValve registry	3 year	304/304	78/78	22/22	/		19/19	17/16	2.1/2.1	/	/	/
Latib, (2012) (21)	PSM	Italy, 2003–2008	1 year	111/111	81/80	19/22	70/69	26/23	40/46	/	4.6/4.6	58.3% EdwardsSAPIEN, Edwards-SAPIEN XT/ 41.7% CoreValve		
Tamburino, (2015) (22)	PSM	OBSERVANT, 2010–2012, Italy	1 year	650/650	81/80	25/25	/	22/22	/	15/13	9.5/10.2 (LES)	SAPIEN/CoreValve	51/51	0.7/0.7
Schaefer, (2019) (23)	PSM	University Heart Center Hamburg, Hamburg, Germany	30 day	109/109	76/74	16/22	/	/	30/30	/	2.0/2.0 (LES 2)		44/42	0.8/0.8
Tzamalis et al. (2020) (24)	PSM	TAVI Karlsruhe registry	6 year	216/216	78/78	/	/	/	48/48	/	8.7/8.8 (LES)	SAPIEN/CoreValve	/	/
Castrodeza et al. (2016) (25)	PSM	Hospital Clínico Universitario de Valladolid, Valladolid, Spain, 2009–2014	1 year	70/70	79/78	37/26	64/73	30/16	/	/	4.6/4.3	SAPIEN/CoreValve	50/50	0.6/0.7
Auffret, (2017) (26)	PSM	Québec Heart and Lung Institute, Québec, Canada, and Rennes University Hospital, Rennes, France, 2007–2015	1 year	71/71	74/73	/	/	/	44/61	/	4.4/4.4	SAPIEN/CoreValve	44/37	/
Piazza et al. (2013) (27)	PSM	SURTAVI-PSM	1 year	255/255	81/80	31/24	87/81	19/16	62/61	/	17.3/17.6 (LES)	/	/	/
Osnabrugge, (2012) (28)	PSM	TAVR or SAVR at the Erasmus MC, Rotterdam, Netherlands	1 year	42/42	79/79	26/19	/	24/19	48/48	/	12.9/12.5 (LES)	/	/	/
Kawashima, (2017) (29)	PSM	OCEAN-TAVI registry	30 day	166/166	86/85	/	81/74	21/21	/	25/28	7.1/6.2	SAPIEN XT	46/51	0.6/0.6
Sponga, (2017) (30)	PSM	University Hospital of Udine, Italy	30 day	40/40	88/87	15/15	70/80	30/23	38/58	/	3.2/3.2 (EuroScore II)	SAPIEN/CoreValve	44/46	0.6/0.7
Repossini, (2017) (31)	PSM	7 European cardiac centers, 2010–2014	30 day	142/142	76/76	29/30	61/59	/	/	/	7.2/6.7	/	48/49	0.7/0.7

utudy or Subgroup .1.1 30 days .uffret,2017 usari,2012 Gleason,2018	Events	Total	Evonte				
uffret,2017 Jusari,2012			Lvenis	Iotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
usari,2012							
and the second s	2	71	4	71	1.8%	0.49 [0.09, 2.74]	
ileason,2018	0	30	2	30	0.6%	0.19 [0.01, 4.06]	
	13	390	16	357	9.3%	0.73 [0.35, 1.55]	
awashima,2017	3	166	2	166	1.7%	1.51 [0.25, 9.15]	
atib,2012	2	111	2	111	1.4%	1.00 [0.14, 7.23]	
lack,2019	2	496	5	454	2.0%	0.36 [0.07, 1.88]	
lakkar,2020	39	1011	41	1021	22.9%	0.96 [0.61, 1.50]	
lielsen,2012	2	34	0	36	0.6%	5.62 [0.26, 121.32]	
iazza, 2013	20	255	18	255	11.6%	1.12 [0.58, 2.17]	
opma,2019	4	725	9	678	3.9%	0.41 [0.13, 1.35]	
Reardon,2017	19	864	14	796	10.6%	1.26 [0.63, 2.52]	
Repossini,2017	9	142	3	142	3.1%	3.14 [0.83, 11.83]	
chaefer,2019	2	109	1	109	1.0%	2.02 [0.18, 22.60]	
ponga,2017	4	40	3	40	2.2%	1.37 [0.29, 6.56]	
amburino,2015	20	650	24	650	13.7%	0.83 [0.45, 1.51]	
hyregod,2019	3	145	5	135	2.6%	0.55 [0.13, 2.34]	
off,2020	8	458	4	455	3.7%	2.00 [0.60, 6.70]	- <b> </b>
zamalis,2020	3	216	4 9	216	3.1%	0.32 [0.09, 1.21]	<del></del>
	3	304	9 11	304	3.1% 4.1%		<del>_</del>
/irtanen,2019 Subtotal (95% CI)	4	304 6217	11		4.1%	0.36 [0.11, 1.13]	
	450	0211	470	0020	100.0%	0.90 [0.71, 1.14]	٦
otal events	159	40.7	173	(D 0	443 12 4	0/	
leterogeneity: Tau <sup>2</sup> = 0 est for overall effect: 2				6 (P = 0.	.41); 1- = 4	%	
.1.2 1 year							
uffret,2017	10	71	10	71	2.1%	1.00 [0.39, 2.57]	
astrodeza,2016	8	70	5	70	1.4%	1.68 [0.52, 5.41]	
usari,2012	1	30	5	30	0.4%	0.17 [0.02, 1.58]	· · · · · · · · · · · · · · · · · · ·
Bleason,2018	55	390	67	357	12.6%	0.71 [0.48, 1.05]	
atib,2012	7	111	9	111	1.8%	0.76 [0.27, 2.13]	
lack,2019	, 5	496	11	454	1.7%	0.41 [0.14, 1.19]	
lakkar,2020	123	1011	124	1021	27.1%	1.00 [0.77, 1.31]	+
	7	42	5	42	1.3%		
Snabrugge,2012						1.48 [0.43, 5.10]	
Piazza, 2013	42	255	43	255	8.8%	0.97 [0.61, 1.55]	
opma,2019	17	725	20	678	4.5%	0.79 [0.41, 1.52]	
Reardon,2017	56	864	52	796	12.6%	0.99 [0.67, 1.47]	<u> </u>
amburino,2015	83	650	82	650	18.0%	1.01 [0.73, 1.41]	T
hyregod,2019	7	145	10	135	1.9%	0.63 [0.23, 1.72]	
off,2020	21	458	30	455	5.8%	0.68 [0.38, 1.21]	
ubtotal (95% CI)		5318		5125	100.0%	0.90 [0.79, 1.04]	•
otal events	442		473				
leterogeneity: Tau² = 0 est for overall effect: 2				(P = 0	.65); I² = 0	%	
.1.3 2 year							
Bleason,2018	85	390	99	357	19.9%	0.73 [0.52, 1.01]	
lack,2019	12	496	14	454	3.6%	0.78 [0.36, 1.70]	
lakkar,2020	166		170		40.4%	0.98 [0.78, 1.24]	<b>+</b>
opma,2019	33	725	31	678	40.4 <i>%</i> 8.8%	1.00 [0.60, 1.64]	
						and the second sec	- <b>-</b> -
Reardon,2017	98	864	92	796	24.2%	0.98 [0.72, 1.32]	<b>_</b>
hyregod,2019 Subtotal (95% CI)	11	145 <b>3631</b>	13	135 <b>3441</b>	3.1% <b>100.0%</b>	0.77 [0.33, 1.78] <b>0.91 [0.79, 1.06]</b>	•
otal events	405		419				
leterogeneity: Tau <sup>2</sup> = 0 est for overall effect: 2				P = 0.73	8); I² = 0%		
							0.02 0.1 1 10 50
							Favours [TAVR] Favours [SAVR]

FIGURE 2 | All-cause mortality of TAVR vs. SAVR in low-intermediate surgical risk patients at 30 days, 1 year, and 2 years.

#### All cause death 30-day TAVR SAVR Odds Ratio Odds Ratio Study or Subgroup M-H, Random, 95% CI M-H. Random, 95% CI Events Total Weight Events Total 2.1.1 low surgical risk Mack,2019 Nielsen,2012 Popma,2019 Schaefer,2019 0.36 [0.07, 1.88] 5.62 [0.26, 121.32] 0.41 [0.13, 1.35] 2.02 [0.18, 22.60] 496 2 2 6% 5 454 496 34 725 109 454 36 678 109 2.6% 0.8% 4.9% 1.2% 3.3% 09 2 4 2 3 5 4 9 11 0.55 [0.13, 2.34] Thyregod,2019 Toff,2020 145 135 0.35 [0.13, 2.34] 2.00 [0.60, 6.70] 0.32 [0.09, 1.21] 0.36 [0.11, 1.13] 0.62 [0.34, 1.13] 8 458 455 4 7% Toff,2020 Tzamalis,2020 Virtanen, 2019 Subtotal (95% CI) 455 216 304 2387 4.7% 3.9% 5.1% **26.4%** 34 216 304 Subtraction (55% Cl)2467Total events28Heterogeneity: Tau² = 0.18; Chi² = 9.23, dTest for overall effect: Z = 1.55 (P = 0.12) 44 = 9.23, df = 7 (P = 0.24); $l^2 = 24\%$ 2.1.2 intermediate surgical risk 0.49 [0.09, 2.74] 0.19 [0.01, 4.06] 0.73 [0.35, 1.55] 1.51 [0.25, 9.15] 1.00 [0.14, 7.23] 0.96 [0.61, 1.50] 1.12 [0.58, 2.17] 1.26 [0.63, 2.52] 3.14 [0.83, 11 83] Auffret,2017 Fusari,2012 Gleason,2018 71 30 357 2.4% 0.8% 10.9% 30 16 2 2 390 13 Kawashima.2017 166 111 1011 255 864 32 166 2.2% 106 111 1021 255 796 142 Latib,2012 Makkar,2020 Piazza, 2013 Reardon,2017 1.8% 23.3% 13.3% 12.2% 3.9% 2.9% 29 20 19 ∠ 41 18 14 Repossini,2017 9 4 142 з 3.14 [0.83, 11.83] Sponga,2017 Subtotal (95% CI) з 40 1.37 [0.29, 6.56] 40 2989 3080 73.6% Total events 111 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 6.16, dt Test for overall effect: Z = 0.24 (P = 0.81) 105 df = 9 (P = 0.72); l<sup>2</sup> = 0% Total (95% CI) 5567 5376 100.0% 0.91 [0.69, 1.19] 0.01 0.1 1 10 Favours [TAVR] Favours [SAVR] 100 1-year TAVR SAVR Odds Ratio Odds Ratio M-H. Random. 95% CI Study or Subgroup Events Total Events Total Weight M-H. Random, 95% Cl 2.2.1 low surgical risk Mack,2019 0.41 [0.14, 1.19] 0.79 [0.41, 1.52] 0.63 [0.23, 1.72] 0.68 [0.38, 1.21] **0.66 [0.46, 0.96]** 5 17 2.1% 496 11 454 Popma.2019 725 20 678 5.4% Thyregod,2019 Toff,2020 Subtotal (95% CI) 2.4% 7.1% **17.0%** 145 10 135 455 21 30 1824 1722 50 71 Total events Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 1.07, df = 3 (P = 0.78); l<sup>2</sup> = 0% Test for overall effect: Z = 2.16 (P = 0.03) 2.2.2 intermediate surgical risk Auffret,2017 Castrodeza,2016 2.6% 1.7% 0.5% 71 70 1.00 [0.39, 2.57] 1.68 [0.52, 5.41] 10 10 70 8 5 5 0.17 [0.02, 1.58] 0.71 [0.48, 1.05] 0.76 [0.27, 2.13] Fusari.2012 30 30 Gleason,2018 Latib,2012 55 7 67 9 357 111 15.4% 2.2% 390 Makkar,2020 123 124 1021 1011 33.0% 1.00 [0.77, 1.31] Osnabrugge,2012 Piazza, 2013 Reardon,2017 5 43 52 1.48 [0.43, 5.10] 0.97 [0.61, 1.55] 0.99 [0.67, 1.47] 0.93 [0.79, 1.11] 7 42 42 1.5% 10.8% 15.3% 83.0% 42 56 255 864 255 796 2753 Subtotal (95% CI) 2844 Total events 309 320 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 6.18, df = 8 (P = 0.63); l<sup>2</sup> = 0% Test for overall effect: Z = 0.79 (P = 0.43) Total (95% Cl) 4668 4475 100.0% Total events 359 391 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 9.95, df = 12 (P = 0.62); I<sup>2</sup> = 0% 4475 100.0% 0.88 [0.76, 1.03] 0.01 0.1 1 10 Favours [TAVR] Favours [SAVR] 100 Test for subaroup differences: Chi<sup>2</sup> = 2.69. df = 1 (P = 0.10). $I^2 = 62.9\%$ 2-year TAVR SAVR Odds Ratio Odds Ratio Events Total Events Total Weight M-H, Random, 95% Cl Study or Subgroup M-H. Random, 95% CI 2.3.1 low surgical risk 0.78 [0.36, 1.70] 1.00 [0.60, 1.64] 0.77 [0.33, 1.78] **0.89 [0.61, 1.30]** Mack,2019 12 496 14 454 3.6% Popma,2019 33 725 31 678 8.8% Thyregod,2019 Subtotal (95% CI) 11 145 13 135 3.1% 1366 1267 15.6% 56 58 Total events Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.42, df = 2 (P = 0.81); I<sup>2</sup> = 0% Test for overall effect: Z = 0.59 (P = 0.56) 2.3.2 intermediate surgical risk Gleason,2018 Makkar,2020 19.9% 40.4% 0.73 [0.52, 1.01] 0.98 [0.78, 1.24] 85 166 390 90 357 1011 170 1021 Reardon,2017 98 864 92 796 24.2% 0.98 [0.72, 1.32] Subtotal (95% CI) 2265 2174 84.4% 0.91 [0.76, 1.09] 349 361 Total events Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 2.39, df = 2 (P = 0.30); l<sup>2</sup> = 16% Test for overall effect: Z = 1.03 (P = 0.30) Total (95% CI) 3631 3441 100.0% 0.91 [0.79, 1.06] Total events 405 419 Total events 405 + 405 + 419Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 2.82, df = 5 (P = 0.73); l<sup>2</sup> = 0% Test for overall effect: Z = 1.23 (P = 0.22) Test for subaroup differences: Chi<sup>2</sup> = 0.01. df = 1 (P = 0.93). l<sup>2</sup> = 0% 0.01 100 0.1 Favours [TAVR] Favours [SAVR] FIGURE 3 | Subgroup analysis of all-cause mortality based on surgical risk stratification (low/intermediate).

Bitly or Categoria         TAVE         EAVE         Outs Ratio         Didta Ratio           Bitly or Categoria         13 3000         10 344         200%         0.37 [0.35, 1.50]         0.44 Bandom 952.CL           Meck.2010         13 300         10 344         200%         0.36 [0.51, 1.50]         0.44 Bandom 952.CL           Meck.2010         13 2000         10 444         1024         22.0%         0.36 [0.51, 1.50]           Meck.2017         13 2000         14 445         32.0%         0.34 [0.53, 1.52]         0.44 [0.53, 1.52]           Permator.2017         13 2000         14 455         32.0%         0.34 [0.56, 1.57]         0.44 [0.56, 1.27]           Test sector         13 2 [0.53, 2.51]         14 44 132         0.30 [0.51, 4.66]         0.44 [0.56, 1.27]           Test sector         13 2 [0.53, 2.51]         13 2 [0.56, 2.61]         14 44 132         0.30 [0.51, 4.66]           Test sector         13 2 [0.56, 2.61]         13 3 [0.56, 2.61]         14 44 132         0.30 [0.71, 1.13]           Test sector         13 2 [0.56, 2.61]         13 3 [0.56, 2.61]         13 3 [0.56, 2.61]         14 44 132           Test sector         13 2 [0.56, 2.61]         13 3 [0.56, 2.61]         14 44 132         0.30 [0.71, 1.13]           Test sector <td< th=""><th>- - R]</th></td<>	- - R]
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$\frac{P \circ Print, 2019}{T more and 2019} = \frac{1}{12} \frac{728}{48} + \frac{9}{48} \frac{9}{48} \frac{778}{48} - \frac{3}{48} \frac{9}{48} + \frac{9}{48} \frac{578}{48} - \frac{3}{48} \frac{9}{48} - \frac{9}{48} \frac{9}{$	- 100 RJ
$\frac{1}{3} \frac{1}{12} \frac{1}{2} 1$	
Substate (95% C) 4123 3932 65.6% 0.91 [0.06, 1.27] Total events Tart = 0.02 (0) = 7.55. (f = 7 (P = 0.37); P = 7% Test for overall effect 2 = 0.54 (P = 0.57); P = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 7% Test for overall effect 2 = 0.54 (P = 0.57); T = 0.56 Sponga. 2013 2 2 111 2 2 111 1.4% 1.00 [0.14, 7.23] Paraces. 2013 2 0 285 18 255 11.6% 1.12 [0.56, 1.13] Sponga. 2017 2 14 4 0 3 40 2.2% 1.20 [0.66, 1.51] Sponga. 2017 2 14 4 0 3 40 2.2% 1.20 [0.66, 1.51] Sponga. 2017 3 2 0 650 12 4 660 13.7% 0.035 [0.46, 1.51] Test for overall effect 2 = 0.68 (P = 0.30) T = 117% Test for overall effect 2 = 0.68 (P = 0.30) T = 10 (P = 0.34); P = 13% Test for overall effect 2 = 0.68 (P = 0.30) T = 10 (P = 0.34); P = 13% Test for overall effect 2 = 0.68 (P = 0.30) T = 10 (P = 0.34); P = 15% Test for overall effect 2 = 0.68 (P = 0.30) T = 10 (P = 0.34); P = 15% Test for overall effect 2 = 0.68 (P = 0.30) T = 10 (P = 0.34); P = 4% Test for overall effect 2 = 0.68 (P = 0.30) d = 1 (P = 0.87); P = 0.65 Test for overall effect 2 = 0.68 (P = 0.30) d = 1 (P = 0.87); P = 0.65 Test for overall effect 2 = 0.68 (P = 0.30) d = 1 (P = 0.87); P = 0.65 Test for overall effect 2 = 0.68 (P = 0.30) d = 1 (P = 0.87); P = 0.65 Test for overall effect 2 = 0.78 (P = 0.30); T = 0.65 Test for overall effect 2 = 0.68 (P = 0.30) d = 1 (P = 0.87); P = 0.65 Test for overall effect 2 = 0.68 (P = 0.30); T = 0.65; P = 0.50 Test for overall effect 2 = 0.68 (P = 0.30); P = 0.65; P = 0.57 Test for overall effect 2 = 0.78 (P = 0.77); P = 0.56 Test for overall effect 2 = 0.16 (P = 0.37); P = 0.56 Test for overall effect 2 = 0.01 (P = 0.05); P = 0.56; P = 0.57; P = 0.56 Test for overall effect 2 = 0.01 (P = 0.05); P = 0.56; P = 0.57; P	- 100 RJ
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Lib.2012 2 2 111 1 2 111 1.4% 1.00 [0.14, 7.23] Plazas 2017 2 2 106 1 109 1.0% 3.20 [0.16, 7.23] Scheeter, 2019 2 106 1 109 1.0% 3.20 [0.16, 7.20] Scheeter, 2019 2 106 1 109 1.0% 3.20 [0.16, 7.20] Scheeter, 2019 2 106 1 109 1.0% 3.20 [0.16, 7.20] Scheeter, 2019 2 106 1 109 1.0% 3.20 [0.16, 7.20] Temburing, 2019 2 204 7 2044 4.4% 0.38 [0.51, 113] Subtrail (9% CI) 204 7 2044 4.4% 0.38 [0.51, 113] Subtrail (9% CI) 6 217 6026 100.0% 0.39 [0.71, 1.14] Total (9% CI) 6 217 6026 100.0% 0.90 [0.71, 1.14] Total events 159 173 Test for overall effect: $Z = 0.69 (P = 0.50)$ Total (9% CI) 6 217 6026 100.0% 0.90 [0.71, 1.14] Total events 159 173 Test for auboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.47); P = 0% Test for auboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.47); P = 0% Test for auboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.47); P = 0% Test for auboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.47); P = 0% Test for auboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.47); P = 0% Total (9% CI) 7 10 7 10 71 2.1% 1.00 [0.39, 2.57] Glessen, 2019 7 142 5 43 20 71 0.48, 1.68 [0.52, 5.41] Auffred; 2017 6 8 264 52 796 12.6% 0.99 [0.67, 1.47] Three oreal effect: Z = 1.75 (P = 0.68); B = 0% Total (9% CI) 8 318 0 1 30 4.40 0.68 [0.52, 1.12] Auffred; 2017 10 71 10 71 2.1% 1.00 [0.39, 2.57] Castrodeza, 2016 8 70 5 70 1.4% 1.68 [0.52, 5.41] Auffred; 217 1.75 (P = 0.05]; F = 0% Test for overall effect: Z = 1.75 (P = 0.65); F = 0% Test for overall effect: Z = 1.32 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.65); F = 0% Test for overall effect: Z = 1.42 (P = 0.57); P = 0% Test for overall effect: Z = 1.42 (P	- 100 RJ
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Virturene. 2019 4 304 11 304 4.1% 0.36 [0.11, 113] Titation (6% c) 0 70 204 44.4% 0.36 [0.51, 12] Total (6% c) 0 60 (0* c) 70 204 44.4% 0.36 [0.51, 12] Total (6% c) 0 70 204 44.4% 0.36 [0.50, 1.20] Total events 150 100 (0* c) 0.000 (0.71, 1.14) Total events 150 173 0026 100.0% 0.90 [0.71, 1.14] Total events 150 173 0026 11 044 1.05] Makkan 2020 123 1011 124 1021 27.1% 1.00 [0.77, 1.31] Popma.2019 17 755 20 676 4.5% 0.79 [0.41, 1.52] Reardon,2017 56 864 52 756 12.6% 0.99 [0.67, 1.47] Thyregod (21) 458 314 65 5.8% 0.68 [0.33, 1.21] Total events 114 114 1021 27.1% 1.00 [0.37, 2.13] Total events 114 111 18% 0.76 [0.32, 1.72] Total events 114 111 18% 0.76 [0.32, 1.72] Total events 114 111 18% 0.76 [0.32, 1.72] Total events 115 114 111 18% 0.76 [0.32, 1.72] Total events 100 (C) Ch <sup>2</sup> = 5.82, df = 6 (P = 0.47); P = 0% Tast for overall effect: Z = 1.75 (P = 0.08) 3.2.2 PSM Auffret.2017 10 10 71 10 71 2.1% 1.00 [0.36, 2.57] Total events 100 C) Ch <sup>2</sup> = 5.82, df = 6 (P = 0.47); P = 0% Tast for overall effect: Z = 0.01 (C) = 5.82, df = 6 (P = 0.47); P = 0% Tast for overall effect: Z = 0.01 (C) = 5.85, df = 6 (P = 0.50; P = 0%) Total events 10.00 C) Ch <sup>2</sup> = 3.85, df = 6 (P = 0.50; P = 0%) Total events 10.00 C) Ch <sup>2</sup> = 3.85, df = 6 (P = 0.50; P = 0%) Total events 10.00 C) Ch <sup>2</sup> = 3.85, df = 6 (P = 0.50; P = 0%) Total events 10.00 C) Ch <sup>2</sup> = 3.85, df = 10 (P = 0.65); P = 0% Tast for overall effect: Z = 0.01 (C) Ch <sup>2</sup> = 1.05, df = 1 (P = 0.65); P = 0% Tast for overall effect: Z = 0.01 (C) Ch <sup>2</sup> = 1.05, df = 1 (P = 0.65); P = 0% Tast for overall effect: Z = 0.01 (C) Ch <sup>2</sup> = 1.05, df = 1 (P	100 RJ
Total events $\frac{9}{10} = \frac{9}{110} \frac{79}{110} \frac{79}{110} (p^2 = 0.34); p^2 = 11\%$ Test for overall effect: $Z = 0.08$ ( $p^2 = 0.30$ ) Total ( $95\%$ cf) $5217$ $5026$ $100.0\%$ $0.90$ $[0.71, 1.14]$ Total events $159$ $173$ Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.38$ ( $p^2 = 0.41$ ); $p^2 = 0\%$ Test for overall effect: $Z = 0.38$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.58$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.58$ ( $p^2 = 0.38$ ) Test for overall effect: $Z = 0.71$ ( $10.464$ $1.061$ ) Total events $123$ 1011 124 1021 27.1% 100 [0.77, 131] Popma.2019 123 1011 124 1021 27.1% 100 [0.77, 130] Popma.2019 7 145 10 135 1.9\% 0.63 [0.23, 1.72] Total events $123$ 0.214 468 30 455 5.8\% 0.08 [0.67, 1.47] Thysegod.2017 7 145 50.2 df = 12.6\% 0.08 [0.67, 1.47] Thysegod.2017 10 71 10 71 2.1% 1.00 [0.39, 2.57] Castrodeza.2016 8 70 5 70 1.4\% 1.68 [0.52, 5.41] Auffreq.2017 10 71 10 71 2.1\% 1.00 [0.39, 2.57] Castrodeza.2016 8 70 5 70 1.4\% 1.68 [0.52, 5.41] Test for overall effect: $Z = 1.75$ ( $p^2 = 0.06$ ) 3.2.2 PSM Auffreq.2017 10 71 10 71 2.1\% 1.00 [0.79, 1.21] Total events 158 159 Test for overall effect: $Z = 1.02$ ; $df = 10.5$ , $df = 1.0p = 0.51$ ; $p = 0\%$ Test for overall effect: $Z = 1.02$ ; $df = 1.05$ , $df = 1.02$ , $df = 1.02$ , $df = 1.02$ $2.7, 1.02$ Total events 158 159 Test for overall effect: $Z = 1.02$ ; $df = 1.02$ ,	700 RJ
Heterogenetic: Tau <sup>2</sup> = 0.05; Ch <sup>2</sup> = 11.19, df = 10 (P = 0.34); P = 11% Test for overall effect: 2 = 0.80 (P = 0.50) Total (95% CI) 6217 6026 100.0% Total (95% CI) 6217 6026 100.0% Test for suboroup differences: Ch <sup>2</sup> = 0.30; df = 10 (P = 0.41); P = 4% Test for suboroup differences: Ch <sup>2</sup> = 0.03), df = 1 (P = 0.61); P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.03, df = 1 (P = 0.67), P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.02, df = 1 (P = 0.67); P = 0% Test for suboroup differences: Ch <sup>2</sup> = 0.02, df = 1 (P = 0.67); P = 0% Total events 204 a 144 Heterogenetity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.62, df = 6 (P = 0.47); P = 0% Test for overall effect: Z = 1.75 (P = 0.08) 3.22 PSM Autries 2017 10 71 10 71 2.1% 100 [0.39, 2.57] Test for overall effect: Z = 0.07 (D <sup>2</sup> = 5.62, df = 6 (P = 0.47); P = 0% Test for overall effect: Z = 0.07 (D <sup>2</sup> = 5.62, df = 6 (P = 0.47); P = 0% Test for overall effect: Z = 0.07 (D <sup>2</sup> = 5.62, df = 6 (P = 0.47); P = 0% Test for overall effect: Z = 0.01 (D <sup>2</sup> = 3.85, df = 6 (P = 0.67); P = 0% Test for overall effect: Z = 0.01 (P = 0.83), Te = 1.26 0.05 (D <sup>2</sup> = 1.27) Total events 10 15 122 0 1 4.43 5.10 1.00 [0.79, 1.01] Total events 10 15 122 0 1 4.43 5.10 1.00 [0.79, 1.04] Total events 10 15 122 0 1 4.24 1.34 1.48 (D <sup>3</sup> = 1.06, D <sup>3</sup> = 1.26 (P = 0.65); P = 0% Test for overall effect: Z = 0.01 (P = 0.83), df = 1 (P = 0.65); P = 0% Test for overall effect: Z = 0.01 (P = 0.82, df = 1 20 P = 0.65); P = 0% Test for overall effect: Z = 0.01 (P = 0.82, df = 1 20 P = 0.65); P = 0% Test for overall effect: Z = 0.01 (P = 0.82, df = 1 0, P = 0.65); P = 0% Test for overall effect: Z = 0.01 (P = 0.82, df = 1 0, P = 0.65);	100 RJ
$\frac{12}{10} = \frac{12}{10} = 12$	R] 100
Total events 159 173 Heterogeneily: Tau" = 0.01; Ch <sup>µ</sup> = 18,78, df = 18 (P = 0.41); l <sup>µ</sup> = 4% Test for subcroup differences: Ch <sup>µ</sup> = 0.33, df = 1 (P = 0.87), l <sup>µ</sup> = 0% 1-year 1-	100 <sup>1</sup> RJ
Test for overall effect: $Z = 0.88 \ (P = 0.39)$ Test for subcroup differences: $Ch^{\mu} = 0.03$ , $df = 1 \ (P = 0.87)$ , $\mu = 0\%$	RJ 100
$\frac{1 - year}{32.1 \text{ RCT}} \xrightarrow{\text{TAVR}} \text{TAVR} \xrightarrow{\text{SAVR}} Odds Ratio Ratio Ra$	
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Subtotal (95% Cl) 4089 3896 66.2% 0.86 $[0.72, 1.02]$ Total events 284 314 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.62, df = 6 (P = 0.47); I <sup>2</sup> = 0% Test for overall effect: Z = 1.75 (P = 0.08) 3.22 PSM Auffret,2017 10 71 10 71 2.1% 1.00 [0.39, 2.57] Castrodeza,2016 8 70 5 70 1.4% 1.68 $[0.52, 5.41]$ Husari,2012 1 30 5 30 0.4% 0.17 $[0.02, 1.56]$ Latib,2012 7 111 9 111 1.8% 0.76 $[0.27, 2.13]$ Genabrugge,2012 7 42 5 42 1.3% 1.48 $[0.43, 5.10]$ Plazza, 2013 42 255 4.3 255 8.8% 0.97 $[0.61, 1.55]$ Tamburinc,2015 83 650 82 650 18.0% 1.00 $[0.79, 1.27]$ Total events 158 159 Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.85, df = 6 (P = 0.70); I <sup>2</sup> = 0% Test for overall effect: Z = 0.142 (P = 0.16) Test for overall effect: Z = 0.00; Chi <sup>2</sup> = 1.05, df = 1 (P = 0.65); I <sup>2</sup> = 0% Test for overall effect: Z = 1.42 (P = 0.16) Test for suboroup differences: Chi <sup>2</sup> = 1.05, df = 1 (P = 0.31), I <sup>2</sup> = 4.4% 2-year TAVR SAVR Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl 3.3.1 RCT Gleason,2018 85 390 99 357 19.9% 0.73 $[0.52, 1.01]$	
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Test for overall effect: $Z = 1.75$ (P = 0.08)         3.2.2 PSM         Auffret.2017         10       71       10       71       2.1%       1.00 [0.39, 2.57]         Castrodeza, 2016       8       70       5       70       1.4%       1.68 [0.52, 5.41]         Fusari, 2012       1       30       5       30       0.4%       0.17 [0.02, 1.58]         Castrodeza, 2013       42       255       43       255       8.8%       0.97 [0.61, 1.55]         Tamburino, 2015       83       650       82       650       18.0%       1.01 [0.79, 1.41]         Subtotal (95% Cl)       1229       1229       33.8%       1.00 [0.79, 1.04]         Total events       158       159         Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 3.65, df = 6 (P = 0.70); l <sup>2</sup> = 0%         Total (95% Cl)       5318       5125       100.0%       0.90 [0.79, 1.04]         Total events       442       473         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52, df = 1 (P = 0.65); l <sup>2</sup> = 0%         Test for overall effect: Z = 1.42 (P = 0.16)         TAVR       Odds Ratio	
Auffret,2017       10       71       71       71       10       71       71 <td></td>	
$\begin{array}{c ccccc} Castrodeza,2016 & 8 & 70 & 5 & 70 & 1.4\% & 1.68 [0.52, 5.41] \\ Fusar;2012 & 1 & 30 & 5 & 30 & 0.4\% & 0.67 [0.02, 1.58] \\ Latib,2012 & 7 & 111 & 9 & 111 & 1.8\% & 0.76 [0.27, 2.13] \\ Oenabrugge,2012 & 7 & 42 & 5 & 42 & 1.3\% & 1.48 [0.43, 5.10] \\ Piazza. 2013 & 42 & 255 & 43 & 255 & 8.8\% & 0.97 [0.61, 1.55] \\ Tamburio,2015 & 83 & 650 & 82 & 656 & 18.0\% & 1.01 [0.73, 1.41] \\ Subtotal (95\% Cl) & 1229 & 1229 & 33.8\% & 1.00 [0.79, 1.04] \\ Total events & 158 & 159 \\ Heterogeneity: Tau2 = 0.00; Chi2 = 3.85, df = 6 (P = 0.70); l2 = 0\% \\ Test for overall effect: Z = 0.01 (P = 0.99) \\ Total events & 442 & 473 \\ Heterogeneity: Tau2 = 0.00; Chi2 = 10.52, df = 13 (P = 0.65); l2 = 0\% \\ Test for overall effect: Z = 1.42 (P = 0.16) \\ Test for suboroub differences: Chi2 = 1.05, df = 1 (P = 0.31), l2 = 4.4\% \\ \hline \begin{array}{c} 2-year \\ Tave \\ 2-year \\ 3.3.1 RCT \\ Gleason,2018 & 85 & 390 & 99 & 357 & 19.9\% & 0.73 [0.52, 1.01] \end{array}$	
Fusari.2012       1       30       5       30       0.4%       0.17 [0.02, 1.58]         Latib.2012       7       111       9       111       1.8%       0.76 [0.27, 2.13]         Osnabrugge.2012       7       412       5       42       1.3%       1.48 [0.43, 5.10]         Piazza.       2013       42       255       8.8%       0.97 [0.61, 1.55]         Tamburino.2015       83       650       82       650       18.0%       1.01 [0.73, 1.41]         Subtotal (95% Cl)       1229       1229       33.8%       1.00 [0.79, 1.27]         Total events       158       159         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.85, df = 6 (P = 0.70); l <sup>2</sup> = 0%       0.90 [0.79, 1.04]         Total events       442       473         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52, df = 13 (P = 0.65); l <sup>2</sup> = 0%       0.90 [0.79, 1.04]         Test for overall effect: Z = 0.10; Chi <sup>2</sup> = 1.05, df = 1 (P = 0.31). l <sup>2</sup> = 4.4%       0.01       0.1       1         Q-year       TAVR       SAVR       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total Events Total Weight M-H, Random, 95% Cl       M-H, Random, 95% Cl         Study or Subgroup       Events Total Events Total Weight M-H, Random, 95% Cl       M-H, Random,	
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
Subtotal (95% Cl)       1229       1229       33.8%       1.00 [0.79, 1.27]         Total events       158       159         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.85, df = 6 (P = 0.70); I <sup>2</sup> = 0%         Test for overall effect: Z = 0.01 (P = 0.99)         Total events       442       473         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52; df = 13 (P = 0.65); I <sup>2</sup> = 0%       0.90 [0.79, 1.04]         Test for overall effect: Z = 1.42 (P = 0.16)       Test for subaroup differences: Chi <sup>2</sup> = 1.05, df = 1 (P = 0.31), I <sup>2</sup> = 4.4%         2-year       TAVR       SAVR       Odds Ratio         Study or Subgroup       Events       Total Events       0.03 (Dds Ratio         Study or Subgroup       Events       Total Events       Total Weight       M-H, Random, 95% Cl         3.3.1 RCT       Gleason,2018       85 390       99 357       19.9%       0.73 [0.52, 1.01]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.85, df = 6 (P = 0.70); P = 0%         Test for overall effect: Z = 0.01 (P = 0.99)         Total (95% Cl)       5318       5125       100.0%       0.90 [0.79, 1.04]         Total events       442       473         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52; df = 13 (P = 0.65); P = 0%       0.01       0.1       1         Test for overall effect: Z = 1.42 (P = 0.16)       Test for suboroup differences: Chi <sup>2</sup> = 1.05. df = 1 (P = 0.31). I <sup>2</sup> = 4.4%       Favours [TAVR] Favours [SAVR]         2-year       TAVR       SAVR       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total Events Total Weight       M-H, Random, 95% Cl       M-H, Random, 95% Cl         3.3.1 RCT       Gleason,2018       85 390       99 357       19.9%       0.73 [0.52, 1.01]	
Test for overall effect: Z = 0.01 (P = 0.99)         Total (95% Cl)       5318       5125       100.0%       0.90 [0.79, 1.04]         Total events       442       473         Heterogeneity: Tau² = 0.00; Chi² = 10.52, df = 13 (P = 0.65); l² = 0%       0.01       0.1       1         Test for overall effect: Z = 1.42 (P = 0.16)       0.50 df = 1 (P = 0.31), l² = 4.4%       Favours [TAVR] Favours [SAVR]         2-year       TAVR       SAVR       Odds Ratio         Study or Subgroup       Events Total Events Total Weight       M-H, Random, 95% Cl       M-H, Random, 95% Cl         3.3.1 RCT       Gleason,2018       85       390       99       357       19.9%       0.73 [0.52, 1.01]	
Total events     442     473       Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52; dF = 13 (P = 0.65); I <sup>2</sup> = 0%     0.01     0.1       Test for overall effect: Z = 1.42 (P = 0.16)     Test for subaroup differences: Chi <sup>2</sup> = 1.05. df = 1 (P = 0.31). I <sup>2</sup> = 4.4%     0.01     0.1       2-year     TAVR     SAVR     Odds Ratio       Study or Subgroup     Events     Total Events     Total Weight       M-H, Random, 95% CI     M-H, Random, 95% CI       3.3.1 RCT     Gleason,2018     85     390       Gleason,2018     85     390     99     357	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.52, df = 13 (P = 0.65); l <sup>2</sup> = 0% Test for overall effect: Z = 1.42 (P = 0.16) Test for suboroup differences: Chi <sup>2</sup> = 1.05. df = 1 (P = 0.31). l <sup>2</sup> = 4.4% <b>1 0</b> .01 <b>1 1 0</b> .01 <b>1 1 0</b> .01 <b>1 1 1 0</b> .01 <b>1 1</b>	
2-year       TAVR       SAVR       Odds Ratio       Odds Ratio         2-year       TAVR       SAVR       Odds Ratio       Odds Ratio         3.3.1 RCT       Gleason,2018       85       390       99       357       19.9%       0.73 [0.52, 1.01]	100
2-year         TAVR         SAVR         Odds Ratio           Study or Subgroup         Events         Total         Weight         M-H. Random. 95% Cl         M-H. Random. 95% Cl           3.3.1 RCT         Gleason,2018         85         390         99         357         19.9%         0.73 [0.52, 1.01]	
Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           3.3.1 RCT         Gleason,2018         85         390         99         357         19.9%         0.73 [0.52, 1.01]	
IAVR         SAVR         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Random, 95% Cl         M-H, Random, 95% Cl           3.3.1 RCT         Gleason,2018         85         390         99         357         19.9%         0.73 [0.52, 1.01]	
3.3.1 RCT Gleason,2018 85 390 99 357 19.9% 0.73 [0.52, 1.01]	
Gleason,2018 85 390 99 357 19.9% 0.73 [0.52, 1.01]	
Mack,2019 12 496 14 454 3.6% 0.78 [0.36, 1.70]	
Makkar,2020 166 1011 170 1021 40.4% 0.98 [0.78,1.24]	
Popma,2019 33 725 31 678 8.8% 1.00 [0.60, 1.64]	
Reardon,2017 98 864 92 796 24.2% 0.98 [0.72, 1.32]	
Thyregod,2019 11 145 13 135 3.1% 0.77 [0.33, 1.78]	
Total events 405 419	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.82, df = 5 (P = 0.73); l <sup>2</sup> = 0%	
Test for overall effect: Z = 1.23 (P = 0.22)	
3.3.2 PSM	
Subtotal (95% CI) 0 0 Not estimable	
Total events 0 0	
Heterogeneity: Not applicable	
Test for overall effect: Not applicable	
Total (95% CI) 3631 3441 100.0% 0.91 [0.79, 1.06]	
Total events 405 419	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.82, df = 5 (P = 0.73); l <sup>2</sup> = 0% Test for overall effect: Z = 1.23 (P = 0.22)	
Test for suboroup differences: Not applicable Favours [TAVR] Favours [SAVR]	100



long-term durability of SAVR needs to be evaluated during at least 10 years of follow-up (36). The longest follow-up period for TAVR in low-risk patients was just 6 years (24), and the result of this 6-year follow-up indicated that TAVR is associated with a higher all-cause mortality rate. Only one RCT reported the 5-year outcome of TAVR vs. SAVR in low-surgical-risk patients (13); this RCT found that TAVR is as safe as SAVR but only had a small sample size of 145 in the TAVR group and 135 in the SAVR group. Although the present meta-analysis included six studies with 7,072 patients, it was still not powerful enough to demonstrate the safety and efficacy of TAVR vs. SAVR. Furthermore, the relatively short length of the follow-up in the included studies meant that the long-term efficacy of TAVR could not be evaluated. Thus, further studies are required to investigate the long-term efficacy of TAVR in low-to-intermediate-surgical-risk patients.

TAVR has evolved since its inception. Procedural safety and bioprosthetic valve performance have improved with the implementation of new-generation TAVR devices, advanced imaging planning, growing operator experience, and new delivery systems. TAVR valve systems have undergone major innovations since the first TAVR procedure was performed

in 2002 (37). For example, the newest SAPIEN valve system (SAPIEN 3 Ultra, Edwards Lifesciences) is the third generation of SAPIEN valve system, following the SAPIEN, SAPIEN XT, and SAPIEN 3 (38). SAPIEN 3 Ultra has an improved delivery system compared with SAPIEN 3. The improvements in TAVR devices and delivery systems have contributed to the current success of TAVR. The procedural outcomes of TAVR are also influenced by factors such as the learning curve and advanced imaging planning. CT is currently used to assess vascular access and plays a primary role in TAVR planning (39). Furthermore, CT can be used to accurately assess the aortic root and provide a reliable measurement of the aortic annulus. These factors contribute to a lower procedural failure rate in TAVR. Part of the success of the recent PARTNER 3 study is due to the support of preprocedural CT imaging (14). These improvements may have caused TAVR to gain better clinical outcomes. More clinical trials are needed to evaluate the safety and efficacy of TAVR.

Almost all included studies found that TAVR increases the risk of PPI; thus, the current meta-analysis found that the incidence of PPI was 14.7% in the TAVR group vs. 5.6% in the SAVR group. The predictors of the need for PPI are old age, a thick interventricular septum, and a high logistic EuroSCORE (40). Patients must be assessed for the presence of these risk factors to enable the selection of the best AVR treatment strategy. The 2-year incidences of other complications, such as MI, stroke, reintervention, major vascular complication, paravalvular leak, and AKI, were <10%. However, the rates of bleeding and AF were extremely high in the SAVR group. The incidence of bleeding was 17.0% in the TAVR group vs. 44.3% in the SAVR group, which is consistent with the findings of the PARTNER-I study (41). Another common complication after AVR is AF, with an incidence of 18.3% in the TAVR group vs. 39.0% in the SAVR group. A previous study reported AF rates of about 35 and 60% in the TAVR and SAVR groups, respectively (42). This discrepancy regarding the AF rates in the present meta-analysis vs. the previous study may be attributed to advances in the TAVR device, as the TAVR device has progressed to the third generation. In summary, TAVR was not associated with a higher complication rate than SAVR.

# LIMITATIONS

The present meta-analysis has several limitations besides those inherent in the original studies. First, the meta-analysis included both RCTs and observational studies, which may have resulted in bias; however, the subgroup analysis found that the results were robust, regardless of study type. Second, the meta-analysis was based on a study level instead of a patient level, as the raw data were not available; this prevented further subgroup analyses based on baseline characteristics. Third, some studies had a sample size of <100, which may cause bias. Fourth, a number of eligible patients may have had a higher STS score than the mean STS score used in the meta-analysis, which might have resulted in an underestimation of the real effect of TAVR. Fifth, some included studies did not provide echocardiographic baseline characteristics and outcomes, and so the data could not be analyzed. Finally, owing to the absence of data, the safety of TAVR during a longer follow-up period could not be investigated, although a longer follow-up may be of great significance.

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# CONCLUSIONS

For patients with a low-to-intermediate surgical risk, TAVR has at least an equivalent clinical effect to SAVR for up to 2 years after the procedure.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

# **AUTHOR CONTRIBUTIONS**

WL and XN came up the idea and supported the work. YLo and YG write the manuscript. YLo and YY independently screened eligible studies and evaluated the quality of studies. ZX and KS independently extracted the baseline and outcome data. Disagreement was resolved by YZ and YLi. All authors contributed to the article and approved the submitted version.

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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. 2020.590975/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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