Original Article

Transcatheter versus surgical aortic valve replacement in low and intermediate risk patients with severe aortic stenosis: systematic review and meta-analysis of randomized controlled trials and propensity score matching observational studies

Jintao Fu[1], Mohammad Sharif Popal[1], Yulin Li[1], Guoqi Li[1], Yue Qi[1], Fang Fang[1], Joey S. W. Kwong[2], Bin You[1], Xu Meng[1], Jie Du[1]

[1]Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [2]Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

Contributions: (I) Conception and design: J Fu, Y Li, MS Popal, J Du; (II) Administrative support: Y Li, J Du; (III) Provision of study materials or patients: J Fu, Y Li, G Li; (IV) Collection and assembly of data: Jintao Fu, Guoqi Li; (V) Data analyze and interpretation: J Fu, Y Qi, F Fang, JS Kwong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Jie Du. Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China. Email: jiedu@ccmu.edu.cn.

Background: To compare the outcome of transcatheter aortic valve replacement (TAVR) with surgical aortic valve replacement (SAVR) in low and intermediate risk patients with severe aortic stenosis (AS). Randomized controlled trials (RCT) and propensity score matching (PSM) studies compare TAVR with SAVR in patients at low and intermediate surgical risk.

Methods: Two authors searched relevant literature independently, then extracted data from the included studies, and assessed risk of bias and quality of study separately according to different study designs, besides that, the extracted data was analyzed via utilization of GRADE system to evaluate the quality of evidence separately.

Results: Overall 15 studies (5 RCTs, 10 PSM studies) with total 12,057 patients were selected. Mortality and disabling stroke during follow-up period were comparable between TAVR and SAVR (RR 1.09, 95% CI: 0.81 to 1.46; RR 0.7, 95% CI: 0.45 to 1.07, respectively), TAVR revealed to be superior to SAVR regarding acute kidney injury (AKI), and onset of new atrial fibrillation (AF) (RCT: high certainty; AKI in PSM: moderate certainty, AF in PSM: low certainty). These results of RCT and PSM studies are consistent. In RCT review, SAVR was better in the following aspects: aortic valve (AV) re-intervention (high certainty), vascular complications, pacemaker implantation (moderate certainty), but comparable in the following aspects: myocardial infarction (MI), aortic insufficient (AI) (moderate certainty), major bleeding (low certainty). In PSM review, SAVR revealed a better result in AI and vascular complications (high certainty), but in the aspects of AV re-intervention, pacemaker implantation, major bleeding and MI (low certainty), it was comparable.

Conclusions: TAVR is comparable to SAVR in terms of mortality and disabling stroke in severe AS patients at low and intermediate risk, but higher proportion of AV re-intervention observed in TAVR. Those results should encourage caution when extending the indications of TAVR into low risk patients, especially for young low risk patients.

Systematic review registration: PROSPERO CRD 42018112626.

Keywords: Transcatheter aortic valve replacement (TAVR); surgical aortic valve replacement (SAVR); low and intermediate risk; severe aortic stenosis; meta-analysis

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Introduction

Aortic stenosis (AS) remains one of the major health concerns universally, with an increased prevalence due to the global aging population (1-3). When symptoms occur, the prognosis of severe AS is dismal (4) with 5-year survival rate of 15–50% (5). Surgical aortic valve replacement (SAVR) is a conventional treatment for management of severe AS for decades. Meanwhile, transcatheter aortic valve replacement (TAVR) becomes a popular alternative strategy in recent years. TAVR has been widely demonstrated to be comparable with SAVR (6,7), even better than TAVR to some extent among prohibitive and high risk population (8), and it is not an inferior management compared to SAVR in intermediate risk patients with severe AS (6,9-11). In addition, updated version 2017 AHA/ACC guidelines primarily recommend TAVR as an optimal method for intermediate risk patients due to recent studies (12,13). Although class of recommendation of TAVR (class IIa) is lower than SAVR (class I) for intermediate patients and recommending SAVR over TAVR in low risk patients in the current guidelines (12,14), half of Europe TAVR centers performed TAVR in intermediate risk patients and many of them did TAVR in low risk patients (15). A high quality randomized meta-analysis which was conducted in 2016 compared outcomes of TAVR with SAVR in low and intermediate risk patients (6). In 2017, another large-scale RCT study was carried out, two other meta-analysis (16,17) were conducted to compare outcomes of SAVR with TAVR as well, nevertheless, they failed to assess the quality of their evidence and were limited by smaller number of included studies. Therefore, this encouraged us to perform an updated systematic review and meta-analysis of RCT and PSM to compare performance of TAVR with SAVR in low and intermediate risk patients with severe AS.

Methods

Protocol

The registered systematic review protocol is available on PROSPERO (CRD 42018112626).

Literature resources

Two authors searched relevant literature independently based on the PICOS retrieval strategy in different databases including PubMed, Cochrane CENTRAL, EmBase, and Web of Science from 2002 to 30, September, 2018. The following key words were used alone or in combination: "transcatheter aortic valve replacement", "surgical aortic valve replacement", "low risk", "intermediate risk", "randomized controlled trials", "propensity score matching", "observational study", or "aortic stenosis". Some references in relevant studies were manually searched for additional articles which could not be identified through advance search.

Study selection

Inclusion criteria were: (I) study directly compared outcomes of TAVR with SAVR; (II) patients (≥18 years) whose mean Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) ≤8% or mean European System for Cardiac Operative Risk Evaluation I (EuroSCORE I) ≤20% were selected in this review; (III) Articles reported at least one of the early and follow-up outcomes; (IV) RCT and PSM studies; (V) English studies. Exclusion criteria were: (I) patients with high and prohibitive risk; (II) non-randomized studies and other observational studies, non-PSM studies; (III) reviews, case reports; and (IV) non-English studies; the Valve Academic Research Consortium-2 (VARC-2) has been used in the selected RCT and PSM studies (18).

Data extraction process and analysis

Two authors extracted data independently from the included studies, via pre-standardized data collection forms, and any disagreements were resolved by consensus or through consulting a third author. The characteristics of all selected topics were extracted and categorized as following: number and baseline demographics of participants, year of publication, intervention details, duration of follow-up, mean STS-PROM, and EuroSCORE, early outcomes, and follow-up outcomes. A random-effect model was utilized to calculate risk ratio (RR) with corresponding 95% confidence intervals (95% CIs) for each dichotomous outcome. Data from RCT studies were analyzed separately from those of PSM studies.

Risk of bias and quality of evidence

The Cochrane Collaboration's tool for assessing risk of bias (19) was utilized to assess risk of bias of RCTs, moreover, the Newcastle-Ottawa Scale (NOS) (20) was used to assess the quality of PSM studies. Review Manager (version 5.3) and GRADE profiler 3.6 version were applied

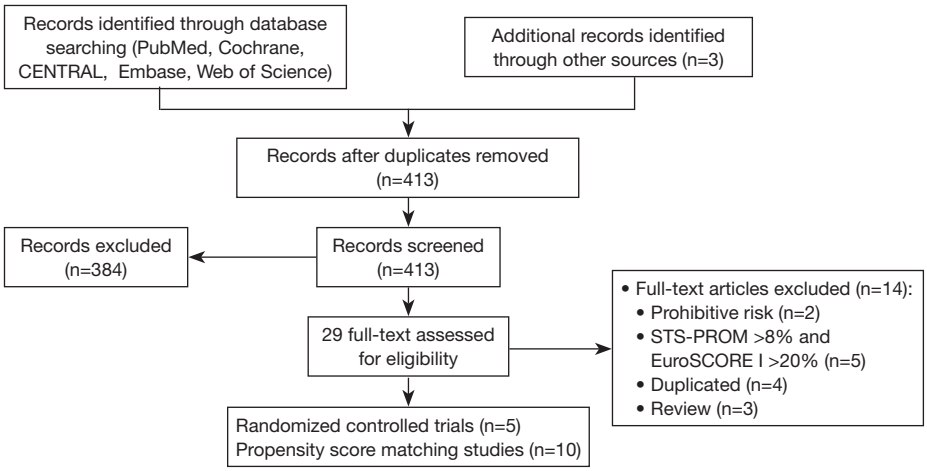

Figure 1 Flowchart of study selection.

to perform meta-analysis and evaluate the overall quality of evidence respectively (21).

Results

Baseline demographic

Our systematic literature search of electronic sources initially searched 1,427 records, and 3 additional records were identified from other sources. After de-duplication, a total of 413 titles and abstracts were assessed for eligibility. Then excluded 384 clearly irrelevant records, full-text articles of 29 records were obtained for further assessment. Eventually we included 5 RCTs (9,22-25) and 10 PSM studies (10,26-34). Flowchart of study selection is shown in *Figure 1*. Characteristics of included studies and assessments of PSM studies quality were illustrated in *Table 1*. Risk of bias in RCT studies is shown in *Figure 2*. Totally 12,057 patients were enrolled, out of that, 6,185 patients underwent TAVR procedure, and 5,872 patients for SAVR procedure. RCT studies enrolled 2,463 patients for TAVR versus 3,722 for SAVR, PSM studies included 2,460 patients for TAVR versus 3,412 patients for SAVR, respectively.

We defined all-cause mortality at 30 days, 1-, 2-, 3-year and disabling stroke at 30 days, 1-year as primary endpoints. Secondary outcomes were as followings: vascular complication, aortic valve (AV) re-intervention, aortic insufficiency (AI), major bleeding, permanent pacemaker implantation, myocardial infarction (MI), new-onset of atrial fibrillation (AF), acute kidney injury (AKI).

Primary endpoints

Mortality

Pooled analysis of included studies illustrated that there was no significant statistical difference between all-cause mortality of TAVR and that of SAVR at 30 days, 1 year, 2, or 3 years.

(I) 30 days' comparison of 15 studies (RR 0.81, 95% CI: 0.60 to 1.08, Heterogeneity P=0.07, I^2 =37%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.96, 95% CI: 0.70 to 1.31, Heterogeneity P=0.58, I^2 =0%; PSM: RR 0.73, 95% CI: 0.47 to 1.13, Heterogeneity P=0.04, I^2 =50%, *Figure 3*).

(II) 1-year comparison of 12 studies (RR 0.94, 95% CI: 0.78 to 1.12, Heterogeneity P=0.02, I^2 =50%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.91, 95% CI: 0.77 to 1.08, Heterogeneity P=0.41, I^2 =0%; PSM: RR 1.01, 95% CI: 0.75 to 1.36, Heterogeneity P=0.007, I^2 =64% , *Figure 4*).

(III) 2-year comparison of 7 studies (RR 0.99, 95% CI: 0.84 to 1.18, Heterogeneity P=0.13, I^2 =39%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.90, 95% CI: 0.79 to 1.03, Heterogeneity P=0.53, I^2 =0%; PSM: RR 1.29, 95% CI: 0.97 to 1.73, Heterogeneity P=0.32, I^2 =12%, *Figure 5*).

(IV) 3-year comparison of 3 studies (1 RCT study) (RR 1.09, 95% CI: 0.81 to 1.46, Heterogeneity P=0.05,

Table 1 Characteristics of included studies

Study ID	Period	Design	Follow-up (month)	Country	Sample size	Female (n)	Mean age	STS or EuroSCORE	Diabetes	NYHA III or IV	Chronic lung disease	Study quality (NOS)
Hans 2015	2009–2013	RCT	24	Northern Europe	TAVR 145	67	79.2±4.9	S 2.9±1.6	26	70	17	–
					SAVR 135	64	79.0±4.7	S 3.1±1.7	28	61	16	
Martins 2016	2011–2013	RCT	24	North America	TAVR 1011	463	81.5±6.7	S 5.8±2.1	381	782	321	–
					SAVR 1021	461	81.7±6.7	S 5.8±1.9	349	776	306	
Reardon 2017	2012–2016	RCT	24	North America Europe	TAVR 879	371	79.9±6.2	S 4.4±1.5	302	520	NA	–
					SAVR 867	383	79.8±6.0	S 4.5±1.6	290	463	NA	
David 2014	2011–2012	RCT	36	USA	TAVR 394	183	83.2±7.1	S 7.3±3.0	136	338	NA	–
					SAVR 401	189	83.5±6.3	S 7.5±3.2	172	348	NA	
Nielsen 2012	2008–2011	RCT	3	Northern Europe	TAVR 34	25	80±3.6	S 3.1±1.5	1	18	1	–
					SAVR 36	24	82±4.4	S 3.4±1.2	3	16	1	
Vinod 2016	2011–2014	PSM	12	North America	TAVR 1,077	412	81.9±6.6	S 5.2	NA	781	376	9
					SAVR 944	425	81.6±6.8	S 5.4	NA	718	311	
Corrado 2015	2010–2012	PSM	12	Italy	TAVR 650	383	80.5±6.2	E 9.5±7.1	161	385	154	9
					SAVR 650	387	80.3±5.1	E 10.2±9.2	165	388	141	
Gerhard 2015	2007–2012	PSM	36	Germany	TAVR 216	116	78.3±5.2	E 8.7±2.7	NA	NA	20	7
					SAVR 216	105	78.2±4.6	E 8.8±2.8	NA	NA	19	
Javier 2016	2009–2014	PSM	24	Spain	TAVR 70	34	79±7.7	S 4.6±2.1	26	37	21	7
					SAVR 70	36	78±5.6	S 4.3±2.4	18	40	11	
Nicolo 2013	2006–2010	PSM	12	Europe	TAVR 255	156	80.6±5.7	E 17.3±9.1	79	196	52	8
					SAVR 255	151	79.7±4.9	E 17.6±11.7	60	190	57	
Christian 2017	2014	PSM	In-hospital	Germany	TAVR 805	486	77.5±4.4	E 6.8±1.7	190	614	14	8
					SAVR 805	486	77.5±4.4	E 4.2±1.4	190	614	14	
Nobuyuki 2018	2009–2017	PSM	36	Germany	TAVR 354	177	79.5	S 3.5	101	203	35	7
					SAVR 177	94	78	S 3.2	53	107	22	
Azeem 2012	2007–2011	PSM	12	Italy	TAVR 111	49	80.5±6.9	S 4.6±2.3	21	75	29	7
					SAVR 111	49	79.4±3.0	S 4.6±5.6	24	77	25	
Ruben 2012	2006–2010	PSM	12	Netherlands	TAVR 42	21	78.8±6.6	E 12.9±6.8	11	NA	10	7
					SAVR 42	20	79.3±5.5	E 12.5±6.4	8	NA	8	
Alberto 2016	2010–2014	PSM	1	Europe	TAVR 142	54	76.4±7.2	S 6.7±3.2	43	67	16	8
					SAVR 142	57	76.2±7.6	S 7.2±2.9	41	69	17	

STS, Society of Thoracic Surgeons predicted risk of mortality; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; NOS, Newcastle-Ottawa tool; RCT, randomized controlled trials; PSM, propensity score matching; NA, not available; S, STS score; E, EuroSCORE; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

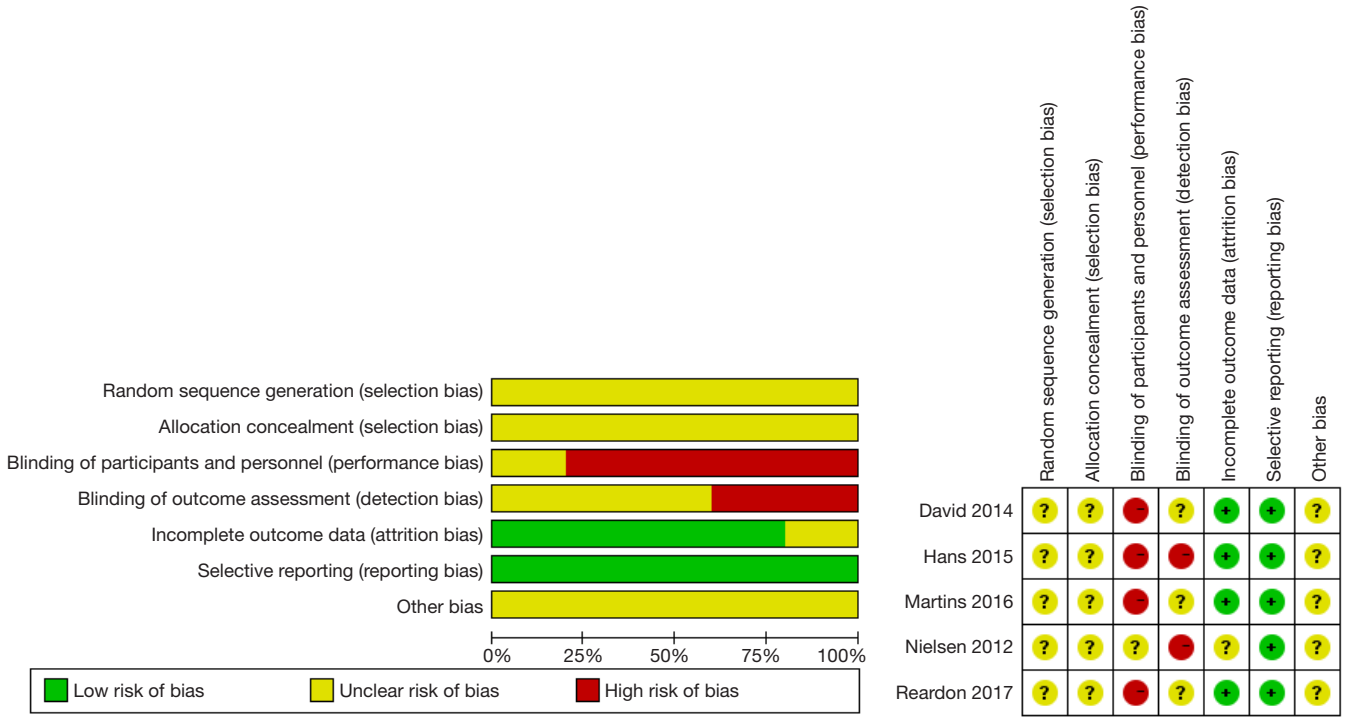

Figure 2 Risk of bias summary in RCT studies. RCT, randomized controlled trials.

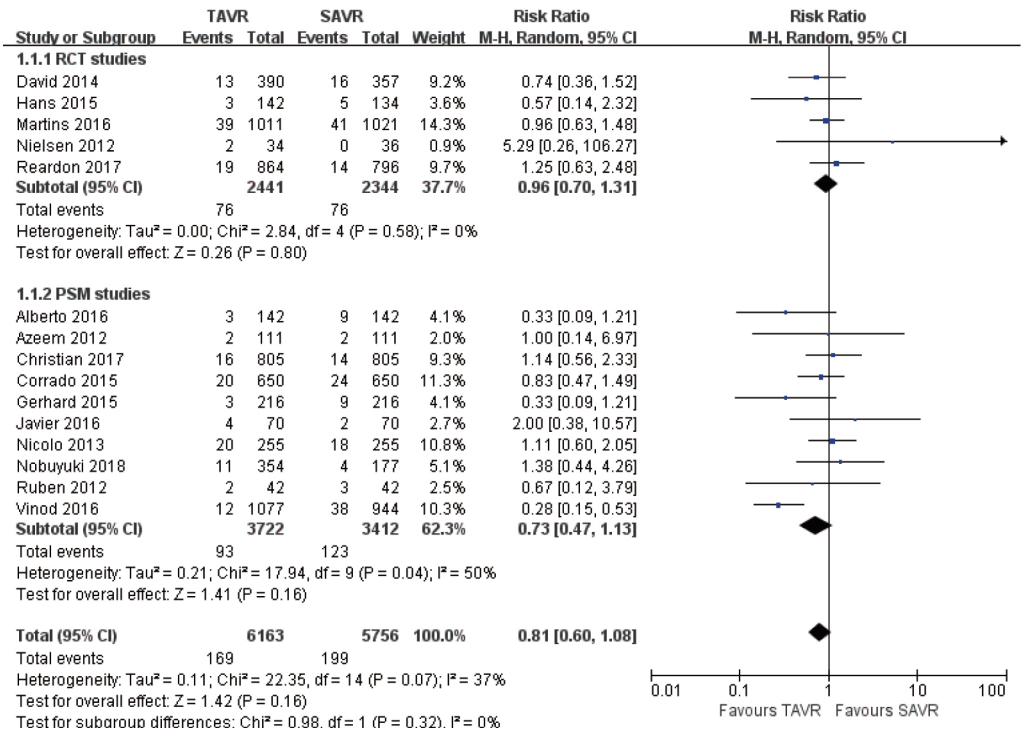

Figure 3 Thirty days all-cause mortality.

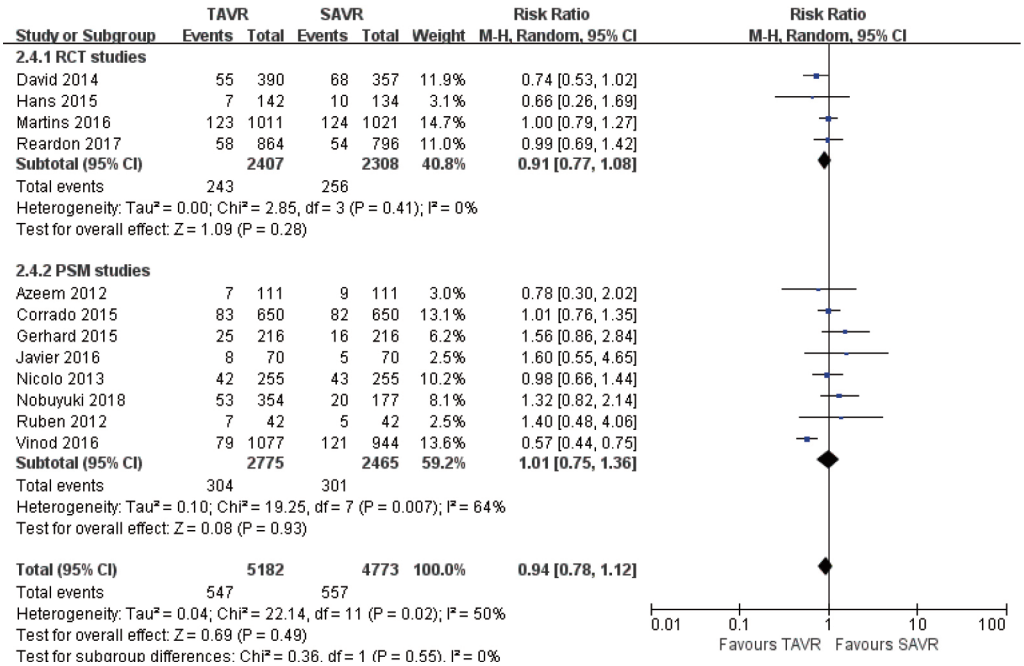

Figure 4 One-year all-cause mortality.

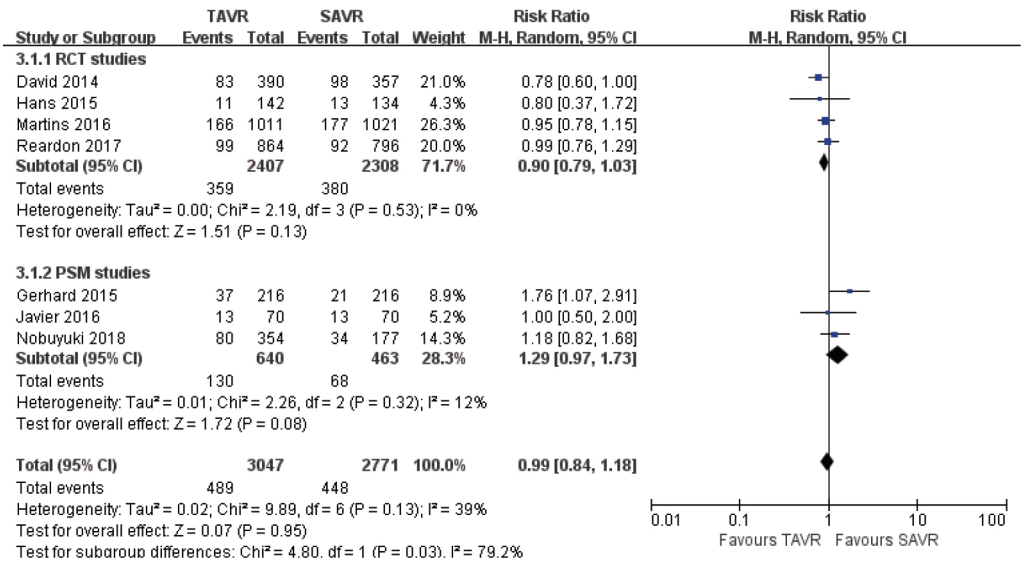

Figure 5 Two-year all-cause mortality.

I^2 =66%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.87, 95% CI: 0.71 to 1.06; PSM: RR 1.26, 95% CI: 0.99 to 1.61, Heterogeneity P=0.59, I^2 =0%, *Figure 6*).

Disabling stroke

Pooled analysis of the included studies revealed that, disabling stroke rate for TAVR was lower than that of SAVR at 30 days, however, there was no significant statistical difference between TAVR and SAVR at 1 year.

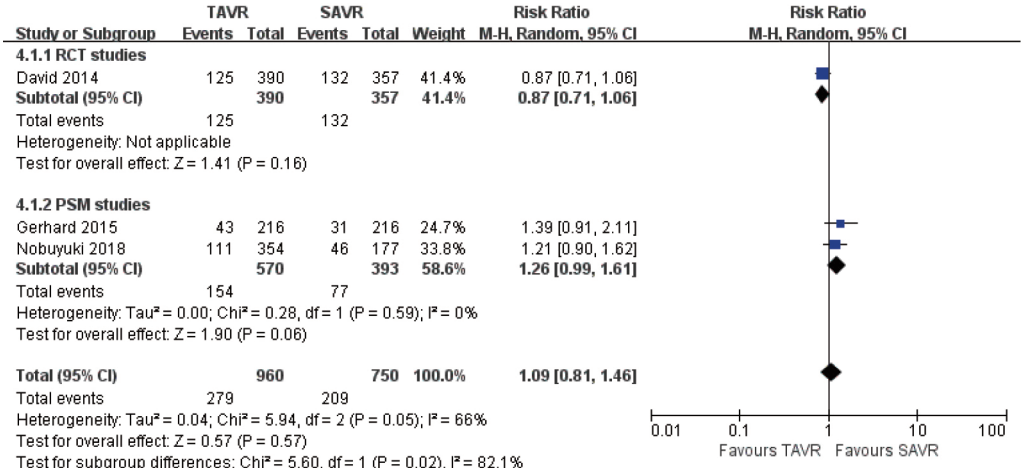

Figure 6 Three-year all-cause mortality.

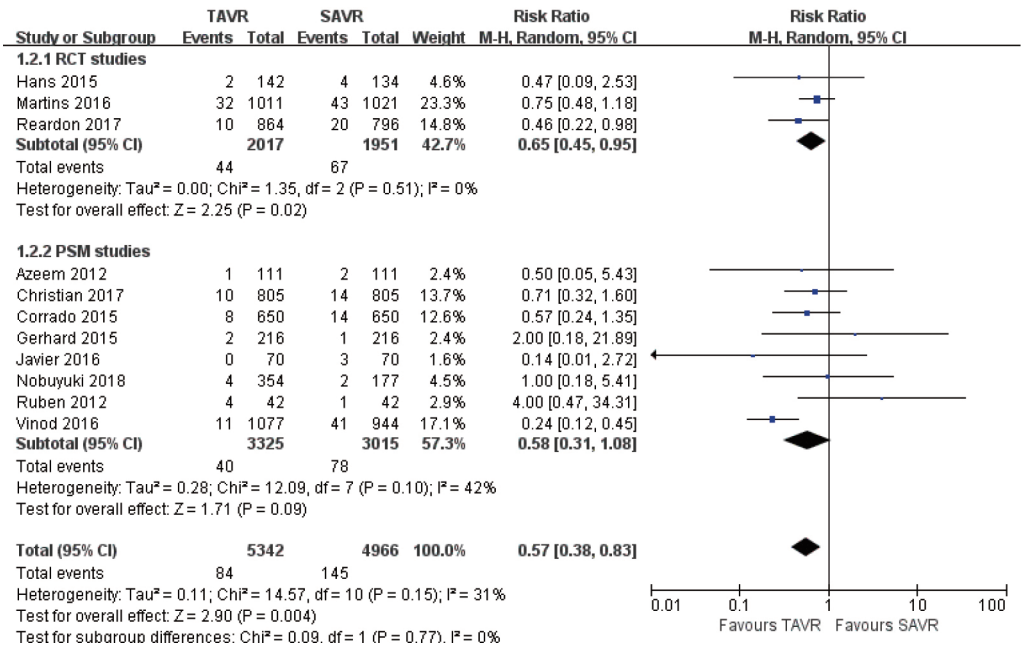

Figure 7 Thirty days disabling stroke.

(I) 30 days comparison of 11 studies (RR 0.57, 95% CI: 0.38 to 0.83, Heterogeneity P=0.15, I^2 =31%), this pooled result is in accordance with RCT studies (RCT: RR 0.65, 95% CI: 0.45 to 0.95, Heterogeneity P=0.51, I^2 =0%), and PSM studies showed that, there was no significant difference between TAVR and SAVR (PSM: RR 0.58, 95% CI: 0.31 to 1.08, Heterogeneity P=0.10, I^2 =42%, *Figure 7*).

(II) 1-year comparison of 6 studies (RR 0.70, 95% CI: 0.45 to 1.07, Heterogeneity P=0.01, I^2 =65%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.78, 95% CI: 0.55 to 1.11, Heterogeneity P=0.27, I^2 =17%; PSM: RR 0.63, 95% CI: 0.27 to 1.46, Heterogeneity P=0.006, I^2 =76%, *Figure 8*).

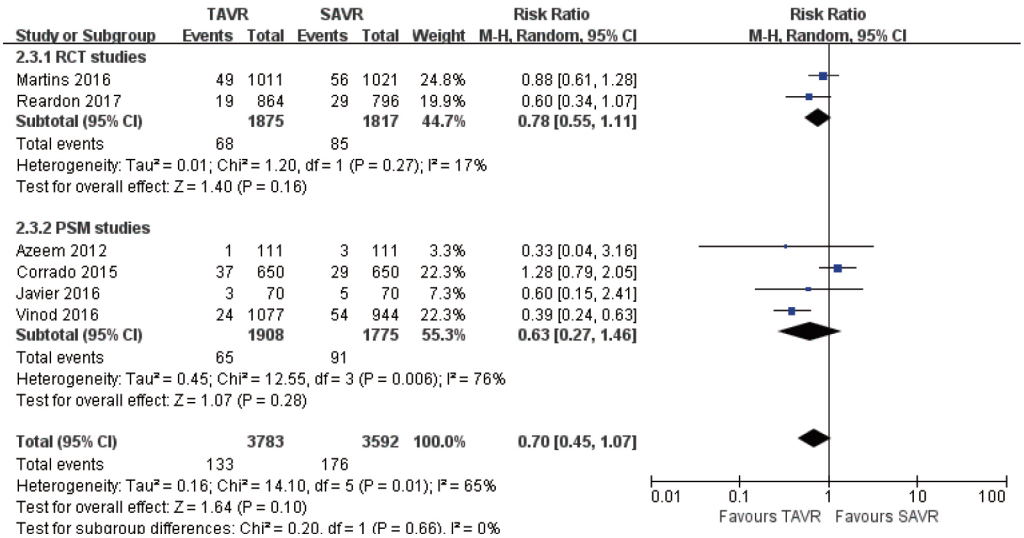

Figure 8 One-year disabling stroke.

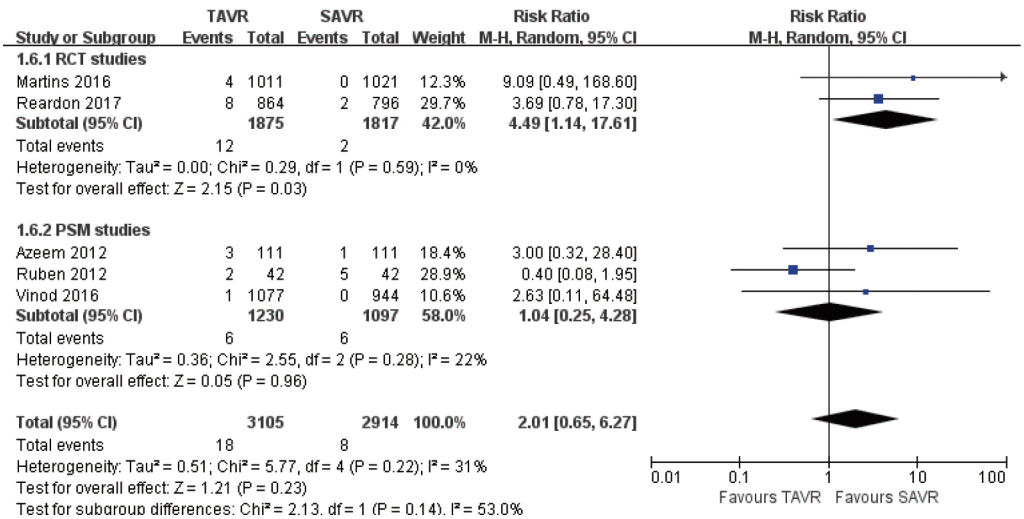

Figure 9 Thirty days AV re-intervention. AV, aortic valve.

Secondary endpoints

AV re-intervention

Although pooled analysis of included studies demonstrated that, there was no statistical difference between aortic valve re-intervention of TAVR and SAVR at 30 days, yet the aortic valve re-intervention rate for TAVR was significantly higher than SAVR at 1-, 2-year during follow-up period.

(I) 30 days comparison of 5 studies (RR 2.01, 95% CI: 0.65 to 6.27, Heterogeneity P=0.22, I^2 =33%), this pooled result is in accordance with PSM studies (PSM: RR 1.04, 95% CI: 0.25 to 4.28, Heterogeneity P=0.28, I^2 =22%), the rate of AV re-intervention for TAVR in RCT studies was significantly higher than that of SAVR (RCT: RR 4.49, 95% CI: 1.14 to 17.61, Heterogeneity P=0.59, I^2 =0%, *Figure 9*).

(II) 1-year comparison of 3 studies (1 PSM study) (RR 2.63, 95% CI: 1.35 to 5.11, Heterogeneity P=0.39, I^2 =0%), this pooled result is in accordance with RCT studies (RCT: RR 3.43, 95% CI: 1.57 to 7.52, Heterogeneity P=0.62, I^2 =0%), and there was no

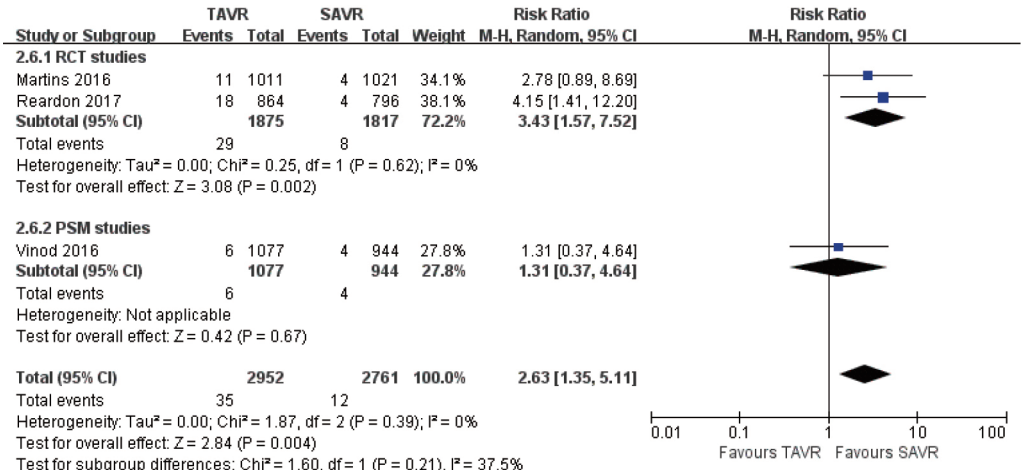

Figure 10 One-year AV re-intervention. AV, aortic valve.

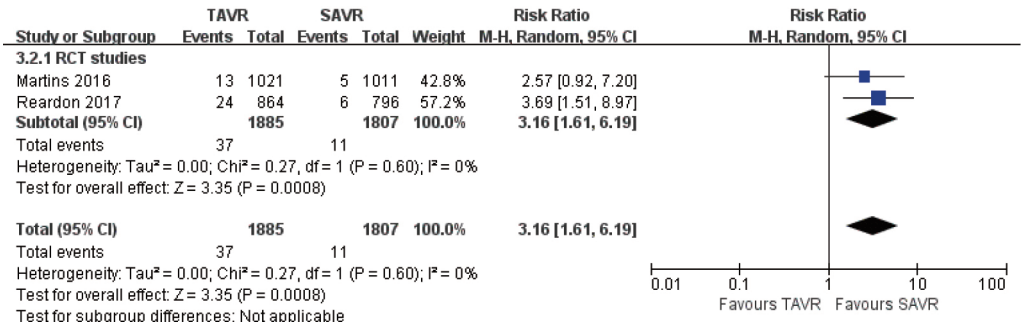

Figure 11 Two-year AV re-intervention. AV, aortic valve.

statistically difference in PSM studies (PSM: RR 1.31, 95% CI: 0.37 to 4.64, *Figure 10*).

(III) 2-year comparison of 2 studies (2 RCT studies) (RR 3.16, 95% CI: 1.61 to 6.19, Heterogeneity P=0.60, I^2 =0%, *Figure 11*).

30 days AI ≥ moderate (including paravalvular leakage PVL)

30 days comparison of 3 studies (1 RCT study) (RR 6.55, 95% CI: 2.78 to 15.45, Heterogeneity P=0.41, I^2 =0%), this pooled result is in accordance with PSM studies (PSM: RR 10.09, 95% CI: 3.68 to 27.65, Heterogeneity P=0.91, I^2 =0%), there was no statistically difference in RCT studies (RCT: RR 2.12, 95% CI: 0.41 to 10.82, *Figure 12*).

30 days vascular complications

Pooled analysis of 11 studies exposed that vascular complications rate for TAVR is significantly higher than that of SAVR at 30 days (RR 6.46 , 95% CI: 3.02 to 13.81, Heterogeneity P<0.001, I^2 =88%) , this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 3.86, 95% CI: 1.50 to 9.92, Heterogeneity P<0.001, I^2 =85%; PSM: RR 11.87, 95% CI: 2.53 to 55.79, Heterogeneity P<0.001, I^2 =91%, *Figure 13*).

30 days AKI

Pooled analysis of 7 studies disclosed that acute kidney injury rate for TAVR is significantly lower than SAVR at 30 days (RR 0.36, 95% CI: 0.27 to 0.47, Heterogeneity P=0.37, I^2 =8%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.39, 95% CI: 0.28 to 0.53, Heterogeneity P=0.65, I^2 =0%; PSM: RR 0.29, 95% CI: 0.16 to 0.55, Heterogeneity P=0.11, I^2 =54%, *Figure 14*).

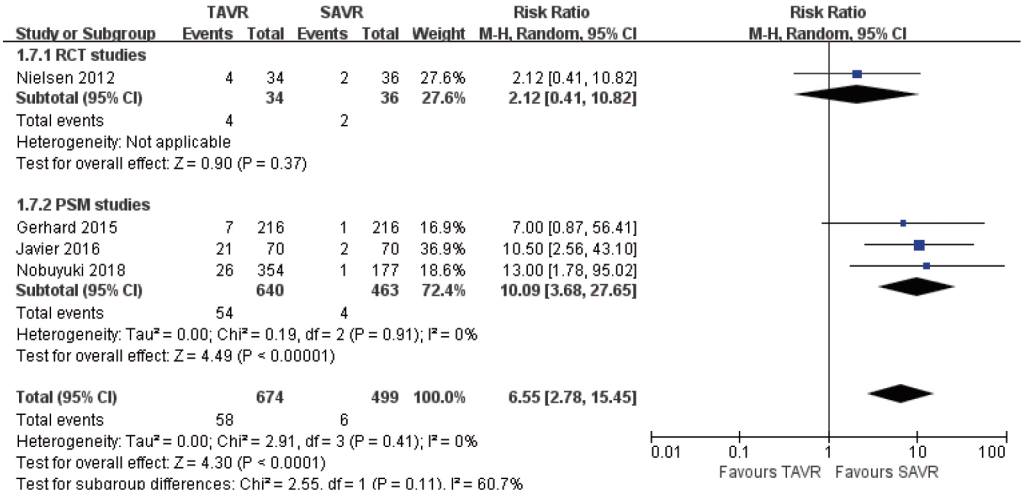

Figure 12 Thirty days AI (moderate or more). AI, aortic insufficient.

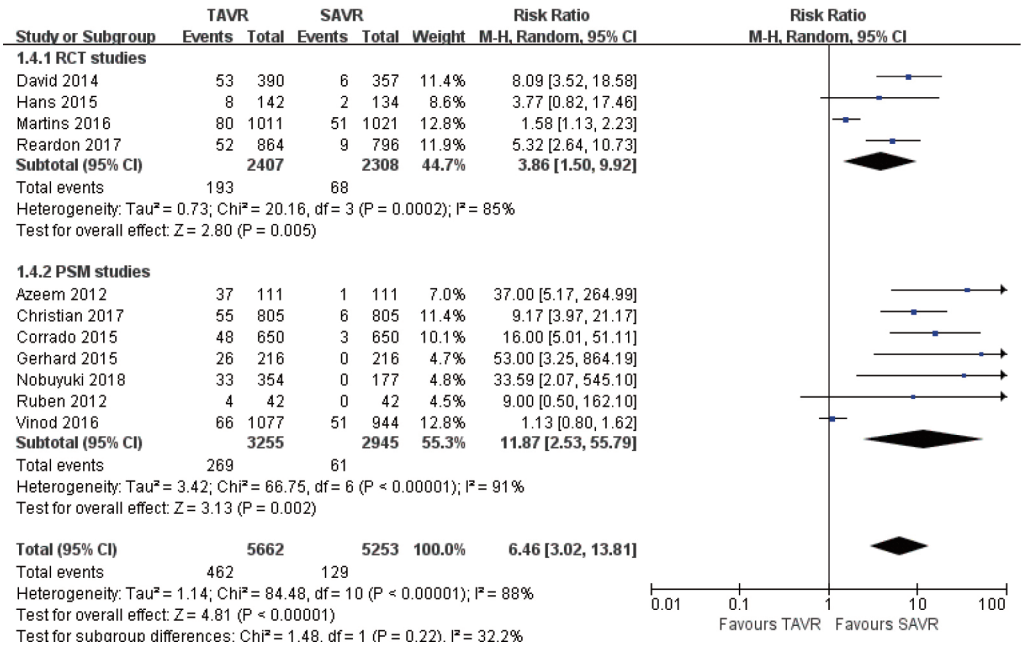

Figure 13 Thirty days vascular complications.

30 days major bleeding

Pooled analysis of 11 studies revealed that there was no significant statistical difference between major bleeding of TAVR and SAVR at 30 days (RR 0.55, 95% CI: 0.30 to 1.00, Heterogeneity P<0.001, I^2 =96%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.5, 95% CI: 0.22 to 1.15, Heterogeneity P<0.001, I^2 =97%; PSM: RR 0.62, 95% CI: 0.21 to 1.78, Heterogeneity P<0.001, I^2 =96%, *Figure 15*).

1-year new onset AF

Pooled analysis of 4 studies (1 PSM study) illustrated that new onset of atrial fibrillation rate in TAVR is significantly lower than SAVR at 1-year (RR 0.31, 95% CI: 0.23 to 0.42, Heterogeneity P=0.002, I^2 =80%), this pooled result is in accordance with RCT studies and PSM studies separately

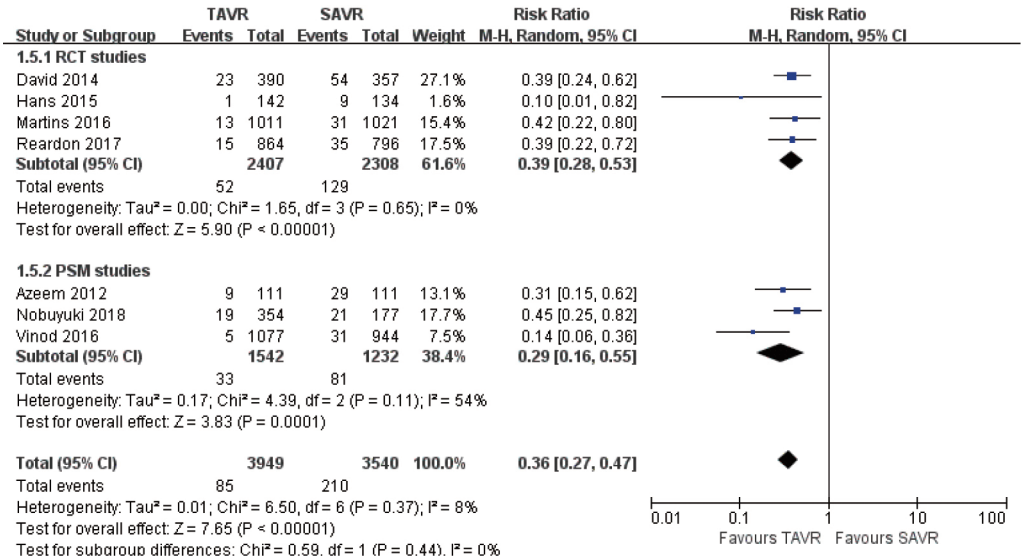

Figure 14 Thirty days AKI. AKI, acute kidney injury.

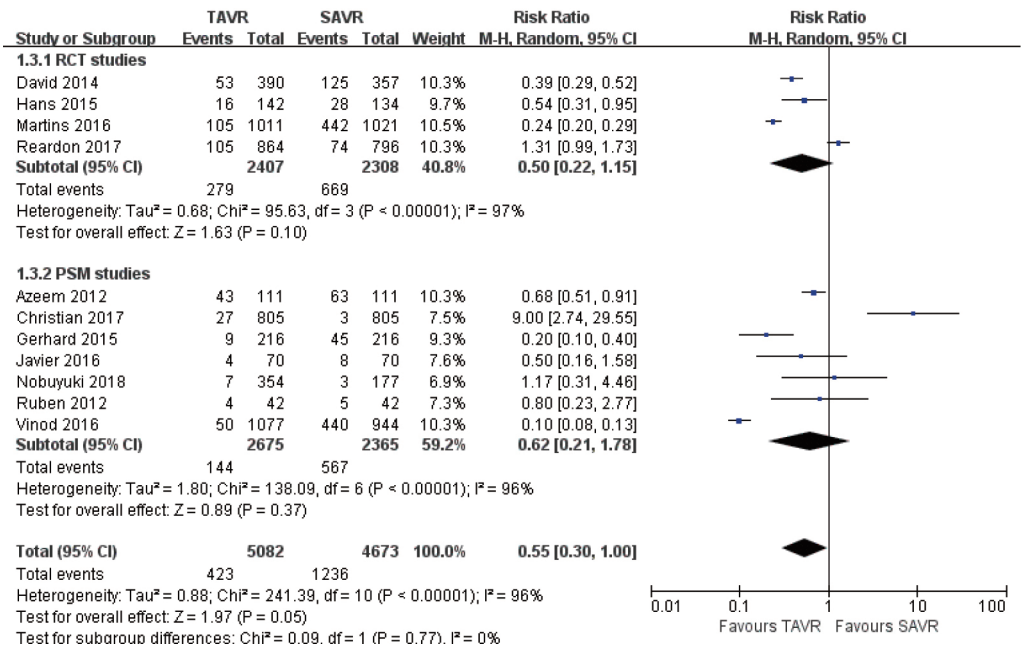

Figure 15 Thirty days major bleeding.

(RCT: RR 0.36, 95% CI: 0.31 to 0.42 , Heterogeneity P=0.96, I^2 =0%; *Figure 16*).

1-year permanent pacemaker implantation

Pooled analysis of 5 studies showed that permanent pacemaker implantation rate for TAVR is higher than SAVR at 1-year (RR 2.13, 95% CI: 1.34 to 3.40, Heterogeneity P<0.001, I^2 =88%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 2.71, 95% CI: 1.11 to 6.64, Heterogeneity P<0.001, I^2 =92%; PSM: RR 1.88, 95% CI: 0.98 to 3.62, Heterogeneity P=0.002, I^2 =90%, *Figure 17*).

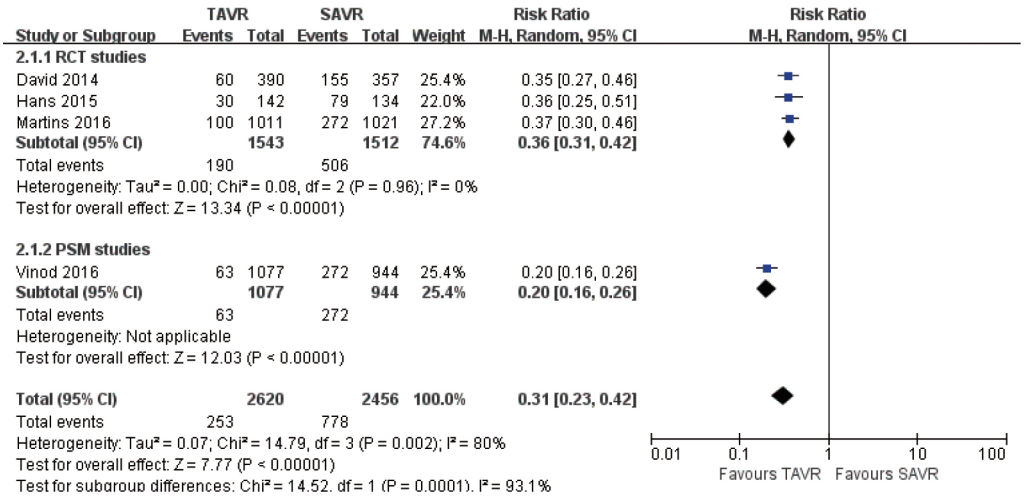

Figure 16 One-year new onset AF. AF, atrial fibrillation.

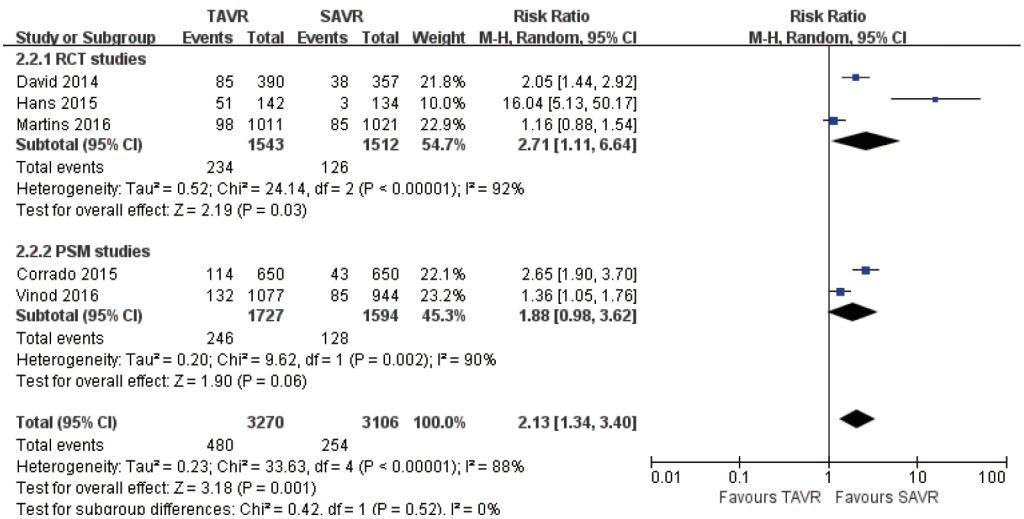

Figure 17 One-year permanent pacemaker implantation.

1-year MI

Pooled analysis of 6 studies exposed that there was no significant statistical difference between myocardial infarction of TAVR and SAVR at 1 year (RR 0.56, 95% CI: 0.31 to 1.02, Heterogeneity P=0.02, I^2 =63%), this pooled result is in accordance with RCT studies and PSM studies separately (RCT: RR 0.81, 95% CI: 0.55 to 1.19, Heterogeneity P=0.83, I^2 =0%; PSM: RR 0.28, 95% CI: 0.05 to 1.67, Heterogeneity P=0.004, I^2 =82%, *Figure 18*).

Low surgical risk patients' results

Mortality

Furthermore, low risk patients were stratified for comparison between TAVR and SAVR, 3 of the included studies provided enough data to calculate pooled 30 days all-cause mortality. Pooled analysis showed that there was no significant statistical difference between TAVR and SAVR in aspect of 30 days mortality in low risk patients (RR 1.1, 95% CI: 0.64 to 1.90, Heterogeneity P=0.53, I^2 =0%).

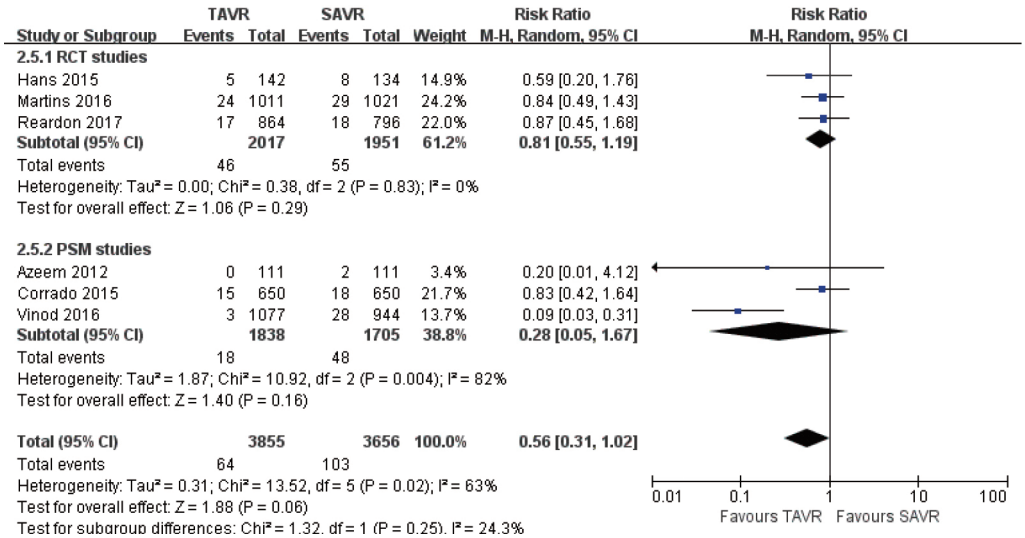

Figure 18 One-year MI. MI, myocardial infarction.

Disabling stroke

Three of the included studies provided enough data to calculate pooled 30 days disabling stroke. Pooled analysis showed there was no significant statistical difference between TAVR and SAVR in low risk patients for 30 days disabling stroke (RR 0.84, 95% CI: 0.43 to 1.64, Heterogeneity P=0.57, I^2 =0%).

However, only one study reported 1, 2, 3 years follow-up results in low risk patients that SAVR is superior to TAVR for mortality and disabling stroke, these are needed to verify by developing further studies.

Heterogeneity analysis

Sensitivity analysis was conducted for the heterogeneity of outcome in which P<0.1 and I^2>50%. In the aspects of 1-year disabling stroke, mortality, MI, 30 days vascular complication, the heterogeneity of these outcomes significantly decreased when we deleted one study (10) (P=0.81, I^2 =0%, P=0.71, I^2 =0%, P=0.36, I^2 =0%, P=0.6, I^2 =0%, respectively), this study is considered to be the source of the heterogeneity, but we can't delete it when considering the large sample size of this study. 30 days major bleeding, the heterogeneity didn't change significantly when we deleted any one study, the result trend to be stable. 30 days vascular complication, the heterogeneity reduced remarkably (P=0.62, I^2 =0%) when we deleted one RCT study (9), the surgical approach of 775 patients (75.9%) who underwent SAVR is trans-femoral, compared with other studies, this unconventional approach may be the reason for higher vascular complication which would result in high heterogeneity. And we also conducted subgroup analysis based on different study design.

Quality of evidence (GRADE)

In this process, we defined primary endpoints as "critical outcome" and secondary endpoints as "important outcome", and GRADE system was utilized to evaluate the quality of evidence from RCT studies (*Figure S1*) and PSM studies (*Figure S2*) separately according to GRADE handbook. Afterwards, we tried to combine GRADE findings with pooled results which were derived from forest plots to make comments for each outcome (shown in *Table 2*). The strategies were as follows: (I) if pooled results identified with both RCT results and PSM results, we regarded RCT GRADE finding as pooled results' certainty; (II) if pooled results only identified with RCT while were not in accordance with PSM studies, we downgraded 1 level of RCT GRADE findings as pooled results' certainty; (III) if pooled results only identified with PSM but not in accordance with RCT studies, we support to conduct further studies (CFS).

Discussion

First TAVR in human was performed by Alain Cribier in 2002 in France (35), during those years, TAVR became an important and popular alternative treatment for

Table 2 Summary of GRADE findings and analysis results

Outcome	Time	Design	Superiority/similar (FP)	Quality of the evidence (grade)	Pooled result	Comment
Mortality	30 days	RCT	Similar	Moderate	Similar	Moderate certainty
		PSM		Low		
	1 year	RCT		Moderate		
		PSM		Low		
	2 years	RCT		Moderate		
		PSM		Low		
	3 years	RCT		Moderate		
		PSM		Low		
Disabling stroke	30 days	RCT	TAVR	High	TAVR	Moderate certainty
		PSM	Similar	Low		
	1 year	RCT	Similar	Moderate	Similar	Moderate certainty
		PSM		Low		
AV re-intervention	30 days	RCT	SAVR	High	Similar	CFS
		PSM	Similar	Low		
	1 year	RCT	SAVR	High	SAVR	Moderate certainty
		PSM	Similar	Low		
	2 year	RCT	SAVR	High	SAVR	High certainty
AI	30 days	RCT	Similar	Moderate	SAVR	CFS
		PSM	SAVR	High		
Vascular complications	30 days	RCT	SAVR	Moderate	SAVR	Moderate certainty
		PSM		High		
AKI	30 days	RCT	TAVR	High	TAVR	High certainty
		PSM		Moderate		
Major bleeding	30 days	RCT	Similar	Low	Similar	Low certainty
		PSM		Low		
New onset AF	1 year	RCT	TAVR	High	TAVR	High certainty
		PSM		Low		
Pacemaker implantation	1 year	RCT	SAVR	Moderate	SAVR	Low certainty
		PSM	Similar	Low		
MI	1 year	RCT	Similar	Moderate	Similar	Moderate certainty
		PSM		Low		

FP, forest plot; AV, aortic valve; AI, aortic insufficient; PVL, paravalvular leakage; AKI, acute kidney injury; AF, atrial fibrillation; MI, myocardial infarction; RCT, randomized controlled trial; PSM, propensity score matching. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; CFS, conduct further studies.

symptomatic severe AS patients, who were at prohibitive and high surgical risk (7,36-38). Updated version 2017 AHA/ACC guideline (12) has extended TAVR from high risk patients to intermediate risk patients compared to 2014 AHA/ACC guideline (13), however, 2017 ESC/EACTS guideline (14) conservatively recommends intermediate risk patients should be comprehensively evaluated by the heart team according to the individual patient characteristics when making decision between TAVR and SAVR. Therefore, we performed this updated systematic review to synthetically evaluate the performance of TAVR when compared with SAVR in low and intermediate risk population.

This review shows that mortality and disabling stroke during follow-up period are comparable between TAVR and SAVR (RCT: moderate certainty, PSM: low certainty), TAVR is superior to SAVR in aspects of AKI and new onset of AF (both RCT: high certainty, AKI in PSM: moderate certainty, AF in PSM: low certainty), meanwhile, SAVR is superior to TAVR in aspects of AV re-intervention, AI (including PVL), vascular complications, permanent pacemaker implantation according to RCT review. AV re-intervention and AI (moderate or more) are important indicators of evaluating durability of valve, at the same time, durability of TAVR valve is an important concern after TAVR, Matthew (39) has reported early failure cases of transcatheter aortic valves which including cusp rupture, valve thrombosis and accelerated calcification. The latest US Pivotal study (40) has reported 5-year freedom from severe structural valve deterioration of self-expand TAVR CoreValve is comparable with SAVR in high risk population, 5-year freedom from AV re-intervention is lower than SAVR, but both adverse events are uncommon in high risk patients. In spite of several available data reported excellent durability of TAVR valve, these are not enough to reduce concern about the durability because of insufficient follow-up time and restricted population, careful follow-up of all patients with TAVR valve and long-term valve deterioration assessment in low and intermediate risk patients, standardized definitions are warranted and will provide more information on both understanding and management of various forms of valve failure (41). From economic perspective, cost-utility of treatment may play a crucial role for patients who are from developing and low income countries. Although recent study (42) reported TAVR is cost-effective for the treatment of in severe AS patients at intermediate surgical risk, they remained moderate-to-high uncertainty surrounding the base-case incremental cost-effectiveness ratio. What's more, many studies (29,43-45) have reported that cost associated with TAVR in operable population was significantly higher than SAVR regardless of intermediate or high risk patients, the difference was predominantly caused by higher transcatheter valve cost, SAVR may be an economically and clinically attractive treatment when taking the similar primary outcomes(mortality and disabling stroke) compared TAVR with SAVR and different costs into account for patients at low and intermediate risk who cannot afford to pay for costs. Patients, especially those who have absolute contraindication for SAVR or place a lower value on the risk of long-term valve failure, are more likely to obtain benefits from TAVR.

Strength and limitation

The strength of the review is that we included both RCT studies and PSM studies together. RCT is golden standard for evaluating intervention's effectiveness and safety, however, PSM is an effective method for reducing confounding factors in observational study as well, this review analyzed a real-world data from PSM studies and avoided the possible selection bias of clinical trials. Other strengths of this review including a comprehensive search for relevant studies, independently extract data, assess eligibility, risk of bias, the quality of PSM studies and evidence separately based on the different study design and the credibility of subgroup analysis (RCT subgroup and PSM subgroup).

The limitation of this review included the followings: different generation transcatheter valve which may influence outcome of TAVR, such as AI, AV re-intervention. With the development of valve technology, more durable valve appears to reduce valve deterioration and AV re-intervention. Previous review (6) reported that transfemoral TAVR is superior to transapical TAVR versus SAVR in low and intermediate risk population, to a certain extent, TAVR approach is an important factor which can affect the outcome, we failed to grouping patients according to different intervention access due to the limited information in PSM studies, other limitation included publication bias, heterogeneity, heart team's experience and skills.

Conclusions

TAVR is comparable to SAVR in terms of mortality and disabling stroke for severe AS patients at low and intermediate risk, but higher proportion of AV re-

intervention was observed in TAVR. Those results should encourage caution when extending the indications of TAVR into low risk patients, especially for these young low risk patients, because of insufficient follow-up time to report the durability of TAVR valve.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

GRADE summary of findings for outcomes in RCT review of TAVR vs SAVR for severe AS in low and intermediate risk patients

Patient or population: patients with severe AS
Settings: RCT studies
Intervention: TAVR
Comparison: SAVR

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk SAVR	Corresponding risk TAVR	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
30 days All cause mortality	Study population		RR 0.96 (0.7 to 1.31)	4785 (5 studies)	⊕⊕⊕⊖ moderate[1]	
	32 per 1000	31 per 1000 (23 to 42)				
	Moderate					
	37 per 1000	36 per 1000 (26 to 48)				
30 days Disabling stroke	Study population		RR 0.65 (0.45 to 0.95)	3968 (3 studies)	⊕⊕⊕⊕ high	
	34 per 1000	22 per 1000 (15 to 33)				
	Moderate					
	30 per 1000	19 per 1000 (13 to 28)				
30 days Major bleeding	Study population		RR 0.5 (0.22 to 1.15)	4715 (4 studies)	⊕⊕⊖⊖ low[2,3]	
	290 per 1000	145 per 1000 (64 to 333)				
	Moderate					
	280 per 1000	140 per 1000 (62 to 322)				
30 days Vascular complication	Study population		RR 3.86 (1.5 to 9.92)	4715 (4 studies)	⊕⊕⊕⊖ moderate[4]	
	29 per 1000	114 per 1000 (44 to 292)				
	Moderate					
	16 per 1000	62 per 1000 (24 to 159)				
30 days AKI	Study population		RR 0.39 (0.28 to 0.53)	4715 (4 studies)	⊕⊕⊕⊕ high	
	56 per 1000	22 per 1000 (16 to 30)				
	Moderate					
	56 per 1000	22 per 1000 (16 to 30)				
30 days AV re-intervention	Study population		RR 4.49 (1.14 to 17.61)	3692 (2 studies)	⊕⊕⊕⊕ high	
	1 per 1000	5 per 1000 (1 to 19)				
	Moderate					
	1 per 1000	4 per 1000 (1 to 18)				
30 days AI (moderate or more)	Study population		RR 2.12 (0.41 to 10.82)	70 (1 study)	⊕⊕⊕⊖ moderate[5]	
	56 per 1000	118 per 1000 (23 to 601)				
	Moderate					
	56 per 1000	119 per 1000 (23 to 606)				
1-year All cause mortality	Study population		RR 0.91 (0.77 to 1.08)	4715 (4 studies)	⊕⊕⊕⊖ moderate[6]	
	111 per 1000	101 per 1000 (85 to 120)				
	Moderate					
	98 per 1000	89 per 1000 (75 to 106)				
1-year Disabling stroke	Study population		RR 0.78 (0.55 to 1.11)	3692 (2 studies)	⊕⊕⊕⊖ moderate[7]	
	47 per 1000	36 per 1000 (26 to 52)				
	Moderate					
	46 per 1000	36 per 1000 (25 to 51)				
1-year Permanent pacemaker implantation	Study population		RR 2.71 (1.11 to 6.64)	3055 (3 studies)	⊕⊕⊕⊖ moderate[8]	
	83 per 1000	226 per 1000 (92 to 553)				
	Moderate					
	83 per 1000	225 per 1000 (92 to 551)				
1-year New onset AF	Study population		RR 0.36 (0.31 to 0.42)	3055 (3 studies)	⊕⊕⊕⊕ high	
	335 per 1000	120 per 1000 (104 to 141)				
	Moderate					
	434 per 1000	156 per 1000 (135 to 182)				
1-year Myocardial infarction	Study population		RR 0.81 (0.55 to 1.19)	3968 (3 studies)	⊕⊕⊕⊖ moderate[9]	
	28 per 1000	23 per 1000 (16 to 34)				
	Moderate					
	28 per 1000	23 per 1000 (15 to 33)				
1-year AV reintervention	Study population		RR 3.43 (1.57 to 7.52)	3692 (2 studies)	⊕⊕⊕⊕ high	
	4 per 1000	15 per 1000 (7 to 33)				
	Moderate					
	5 per 1000	17 per 1000 (8 to 38)				
2-year All cause mortality	Study population		RR 0.9 (0.79 to 1.03)	4715 (4 studies)	⊕⊕⊕⊖ moderate[10]	
	165 per 1000	148 per 1000 (130 to 170)				
	Moderate					
	145 per 1000	130 per 1000 (115 to 149)				
2-year AV reintervention	Study population		RR 3.16 (1.61 to 6.19)	3692 (2 studies)	⊕⊕⊕⊕ high	
	6 per 1000	19 per 1000 (10 to 38)				
	Moderate					
	6 per 1000	19 per 1000 (10 to 37)				
3-year All cause mortality	Study population		RR 0.87 (0.71 to 1.06)	747 (1 study)	⊕⊕⊕⊖ moderate[11]	
	370 per 1000	322 per 1000 (263 to 392)				
	Moderate					
	370 per 1000	322 per 1000 (263 to 392)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Serious imprecision
[2] Serious imprecision and inconsistency
[3] Serious inconsistency
[4] Serious imprecision
[5] No explanation was provided
[6] Serious imprecision
[7] Serious inconsistency
[8] Serious imprecision
[9] Serious imprecision
[10] Serious imprecision
[11] Serious imprecision

Figure S1 GRADE assessment of quality of evidence (RCT review).

GRADE summary of findings for outcomes in PSM review of TAVR vs SAVR for severe AS in low and intermediate risk patients

Patient or population: patients with severe AS
Settings: PSM studies
Intervention: TAVR
Comparison: SAVR

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk SAVR	Corresponding risk TAVR	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
30 days All cause mortality	Study population		RR 0.73 (0.47 to 1.13)	7134 (10 studies)	⊕⊕⊖⊖ low	
	36 per 1000	26 per 1000 (17 to 41)				
	Moderate					
	39 per 1000	28 per 1000 (18 to 44)				
30 days Disabling stroke	Study population		RR 0.58 (0.31 to 1.08)	6340 (8 studies)	⊕⊕⊖⊖ low	
	26 per 1000	15 per 1000 (8 to 28)				
	Moderate					
	20 per 1000	12 per 1000 (6 to 22)				
30 days Major bleeding	Study population		RR 0.62 (0.21 to 1.78)	5040 (7 studies)	⊕⊕⊖⊖ low	
	240 per 1000	149 per 1000 (50 to 427)				
	Moderate					
	119 per 1000	74 per 1000 (25 to 212)				
30 days Vascular complication	Study population		RR 11.87 (2.53 to 55.79)	6200 (7 studies)	⊕⊕⊕⊕ high[1]	
	21 per 1000	246 per 1000 (52 to 1000)				
	Moderate					
	5 per 1000	59 per 1000 (13 to 279)				
30 days AKI	Study population		RR 0.29 (0.16 to 0.55)	2774 (3 studies)	⊕⊕⊕⊖ moderate[2]	
	66 per 1000	19 per 1000 (11 to 36)				
	Moderate					
	119 per 1000	35 per 1000 (19 to 65)				
30 days AV re-intervention	Study population		RR 1.04 (0.25 to 4.28)	2327 (3 studies)	⊕⊕⊖⊖ low	
	5 per 1000	6 per 1000 (1 to 23)				
	Moderate					
	9 per 1000	9 per 1000 (2 to 39)				
30 days AI (moderate or more)	Study population		RR 10.09 (3.68 to 27.65)	1103 (3 studies)	⊕⊕⊕⊕ high[3]	
	9 per 1000	87 per 1000 (32 to 239)				
	Moderate					
	6 per 1000	61 per 1000 (22 to 166)				
1-year All cause mortality	Study population		RR 1.01 (0.75 to 1.36)	5240 (8 studies)	⊕⊕⊖⊖ low	
	122 per 1000	123 per 1000 (92 to 166)				
	Moderate					
	116 per 1000	117 per 1000 (87 to 158)				
1-year Disabling stroke	Study population		RR 0.63 (0.27 to 1.46)	3683 (4 studies)	⊕⊕⊖⊖ low	
	51 per 1000	32 per 1000 (14 to 75)				
	Moderate					
	51 per 1000	32 per 1000 (14 to 74)				
1-year New onset AF	Study population		RR 0.2 (0.16 to 0.26)	2021 (1 study)	⊕⊕⊖⊖ low	
	288 per 1000	58 per 1000 (46 to 75)				
	Moderate					
	288 per 1000	58 per 1000 (46 to 75)				
1-year Permanent pacemaker implantation	Study population		RR 1.88 (0.98 to 3.62)	3321 (2 studies)	⊕⊕⊖⊖ low	
	80 per 1000	151 per 1000 (79 to 291)				
	Moderate					
	78 per 1000	147 per 1000 (76 to 282)				
1-year Myocardial infarction	Study population		RR 0.28 (0.05 to 1.67)	3543 (3 studies)	⊕⊕⊖⊖ low	
	28 per 1000	8 per 1000 (1 to 47)				
	Moderate					
	28 per 1000	8 per 1000 (1 to 47)				
1-year AV reintervention	Study population		RR 1.31 (0.37 to 4.64)	2021 (1 study)	⊕⊕⊖⊖ low	
	4 per 1000	6 per 1000 (2 to 20)				
	Moderate					
	4 per 1000	5 per 1000 (1 to 19)				
2-year All cause mortality	Study population		RR 1.29 (0.97 to 1.73)	1103 (3 studies)	⊕⊕⊖⊖ low	
	147 per 1000	189 per 1000 (142 to 254)				
	Moderate					
	186 per 1000	240 per 1000 (180 to 322)				
3-year All cause mortality	Study population		RR 1.26 (0.99 to 1.61)	963 (2 studies)	⊕⊕⊖⊖ low	
	196 per 1000	247 per 1000 (194 to 315)				
	Moderate					
	202 per 1000	255 per 1000 (200 to 325)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Very large effect
[2] Large effect
[3] Very large effect

Figure S2 GRADE assessment of quality of evidence (PSM review).