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Authors: Guy Witberg, M.D; Uri Landes, M.D; Adi Lador, M.D; Dafna Yahav, M.D; Ran Kornowski, M.D

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Meta-Analysis of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in patients at Low Surgical Risk

Guy Witberg , MD[*a,c], Uri Landes[a,c], Adi Lador, MD[a,c], Dafna Yahav, MD[b,c], Ran Kornowski , MD[a,c].

a- Department of Cardiology, Rabin medical center, Petach-Tikva, Israel.

b- Infectious diseases unit, Rabin medical center, Petach-Tikva, Israel.

c- Sackler Faculty of Medicine, Tel-Aviv university, Tel-Aviv, Israel.

*corresponding author

contact information:

Guy Witberg, MD

Department of Cardiology, Rabin Medical Center

100 Jabutinski St, Petach Tikva, 98100

Israel

E-mail: vitberguy@gmail.com

Short title: TAVI vs. SAVR in patients at low surgical risk.

Abstract

Aims: Although transcatheter aortic valve replacement (TAVI) is officially indicated for severe aortic stenosis (AS) patients at intermediate or higher surgical risk, the procedure is increasingly being performed in patients who are at low surgical risk as well, data on the benefit of TAVI in this patient population is limited.

Methods and results: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies with propensity score matching (PSM) of TAVI vs. surgical aortic valve replacement (SAVR) in patients who are at low surgical risk (mean STS score <4% and/or logistic EuroScore <10%). The primary outcome was mortality (examined at 30 days, year and longest available follow up). The secondary outcomes included procedural complications.

Nine studies (n=6,124) were included. TAVI was associated with a numerically, but not statistically significant reduced mortality at 30 days (1.45 vs. 2.1%, p=0.05), and similar mortality at 1 year (5.1% vs. 5.0%, p=0.74),and a median of 2 years (10.8% vs. 9.8%, p=0.15). For both time points, there was significant heterogeneity between RCT/PSM studies, with the former suggesting survival advantage for TAVI and the latter for SAVR. In terms of periprocedural complications, TAVI was associated with reduced risk for stroke, bleeding and renal failure and an increase in vascular complications and Pacemaker implantation.

Conclusions: in patients who are at low surgical risk, TAVI seems to be associated with equivalent mortality up to a median follow up of 2 years compared to SAVR. More data is required before TAVI can be routinely considered as an alternative for SAVR in low risk patients.

Classifications: Aortic stenosis; TAVI; Risk stratification

Condensed abstract

We conducted a systematic review and meta-analysis of (RCTs and observational studies with PSM of TAVI vs. SAVR in patients who are at low surgical risk. Nine studies (n=6,124) were included. TAVI was associated with a numerically, but not statistically significant reduced (1.45 vs. 2.1%, p=0.05), and similar mortality at 1 year (5.1% vs. 5.0%, p=0.74),and a median of 2 years (10.8% vs. 9.8%, p=0.15). TAVI is associated with equivalent mortality up to a median of 2 years compared to SAVR. More data is required before TAVI can be routinely considered in low risk patients.

Abbreviations

TAVI=transcatheter aortic valve replacement

AS=aortic stenosis

RCT=randomized controlled trial

PSM=propensity score matching

SAVR=surgical aortic valve replacement

CVA=cerebrovascular accident

MI=myocardial infarction

AKI=acute kidney injury

PMI=pacemaker implantation

OR=odds ratio

CI=confidence intervals

Introduction

The availability of transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of patients with symptomatic aortic stenosis (AS) over the past decade.

TAVI was shown to be superior to conservative management in patients who are inoperable [1] , and at least equivalent to surgical aortic valve replacement (SAVR) among patients who are at high [2, 3] and intermediate [4,5] surgical risk.

The annual volume of TAVI procedures is growing exponentially. Real world data show a decline in average risk profile of TAVI patients [6]. The next step in the evolution of TAVI, is the expansion of its indication to include low risk patients as well. Data on the outcomes of TAVI vs. SAVR in low risk patients is limited, a meta-analysis published in 2018 found that in low risk patients TAVI was associated with increase in intermediate term mortality [7], but this was based on data from 2 small randomized controlled trials (RCT) and 4 propensity score matched (PSM) studies only. The recent publication of 2 pivotal RCTs of TAVI vs. SAVR in low risk patients [8,9] offered an opportunity to re-examine the available data on the balance between TAVI/SAVR in this patient population. A subsequent updated meta-analysis of RCTs comparing TAVI vs. SAVR in all risk groups found a survival advantage for TAVI which was consistent across all risk strata [10]. Although RCTs constitute the highest level of clinical evidence, their selection process entails an inherent bias [11] and so caution should be employed when applying their conclusions to the real world patients, who in many cases would not fulfill the inclusion criteria of RCTs. In this setting it is important to examine whether results of real world patients are consistent with those reported in RCTs.

We therefore performed an updated meta-analysis of all published RCTs and PSM studies comparing TAVI vs. SAVR in patients at low surgical risk.

Materials and methods

The registered study protocol is available on PROSPERO (CRD42017060014). We searched Medline, Embase, and Cochrane CENTRAL from April 1st , 2017 (the latest search in our previous meta-analysis), up to June 15th , 2019, for Studies comparing TAVI and SAVR Studies that met the following criteria were considered for inclusion:

-Study design was either an RCTs or observational study using PSM to create patient groups with similar baseline characteristics.

-The mean surgical risk of the TAVI and SAVR groups using the society for thoracic surgery (STS) score and/or logistic EuroScore.

- Patients were at low surgical risk for SAVR, as defined by a mean STS score <4% and/or logistic EuroScore <10% . In case the authors reported both STS and logistic EuroScore data and the results were discordant, we used the STS data for eligibility .

All titles and abstracts were screened, and those thought to possibly meet the inclusion criteria were screened for eligibility using the full text.

Studies were excluded if :

-The manuscript did not include data on overall mortality for at least short term follow up (either in hospital or 30 days).

Two reviewers (GW, UL) independently extracted the data and conflicts were resolved by a third reviewer (AL). For all outcomes, data were extracted for the largest patient population evaluated. The primary outcomes were all cause mortality (30 days, 1 year and longest available follow up). Secondary outcomes were periprocedural (in-hospital/30-day) outcomes : Cerebrovascular accident (CVA), myocardial infarction (MI), acute kidney injury (AKI), bleeding (as defined in individual studies, 5/8 studies used the VARC/VARC II criteria[12,13]), vascular complications, and the need for pacemaker implantation (PMI).

Two authors assessed the risk of bias (GW, UL). Cochrane's handbook tool [14] was used to

assess the RCTs. The Newcastle-Ottawa scale was used to assess the quality of the PSM studies [15]. The reviewers resolved conflicts through consensus.

A systematic review and meta-analysis was performed in compliance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [14] Meta-analysis was performed using the Review Manager (RevMan) software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity between the included trials was assessed using the chi-squared test for heterogeneity and the I^2 measure of inconsistency [16] , but the choice between a random/fixed effect model was not determined by the results of statistical tests for heterogeneity, but rather, as recently recommended by a scientific statement of the American heart association [18] by evaluating the functional similarity between the included studies and the goal of estimating a common effect size that will be applicable to similar populations to those included in this meta-analysis. Fixed effects, pooled estimates of odds ratio (OR) with 95% confidence intervals (CI) were calculated using the Mantel Haenszel method. For random effects, the DerSimonian and Laird random method was used. Reported values are two-tailed, and hypothesis-testing results were considered significant at $P<0.05$. Comparisons were subcategorized by the study's design (RCT/PSM).

Results

The results of the study selection process are shown in Figure 1. Our initial search yielded 1827 citations, 58 of which were judged to be potentially eligible and underwent full text review. Ten studies were found to be eligible for inclusion after full text review: 4 RCTs [8,9,18,19] and 6 PSM studies [20-25]. There were two studies from the OBSERVANT registry [20, 23], of whom only the study by Rosato et al [23] intentionaly included only low surgical risk patients, while the study by Fraccaro et al [20] was limited to patients older than

80 and intended to include also intermediate risk patients, we therefore included the study by Rosato et al and excluded the study by Fraccaro et al as a duplicate publication. From the study by Piazza et al [22], we used the mortality data on the subgroup of patients with STS<4 rather than the overall results that included intermediate risk patients as well.

The aggregated sample size was 6,124 patients (2,764 RCTs and 3,360 PSM patients).The characteristics of the trials included in this meta-analysis are shown in Table S1.

All of the PSM studies were ranked as good quality according to the Newcastle-Ottawa scale (score range 7-9). In addition, all of the RCTs were at low risk of bias in terms of the generation of randomization and concealment of allocation. Due to the invasive nature of the examined interventions, none were blinded – see the Figure S1 for the full assessment of bias.

A summary of major comorbidities, clinical and echocardiographic characteristics of the patients included in the meta-analysis is presented in Table S2.

Clnical outcomes:

Forest plots for overall mortality are shown in figure 2. Periprocedural mortality showed a numerically, but not statistically significant reduced mortality with TAVI vs. SAVR 1.4% (44/3,086) and 2.1% (64/3,038) for TAVI vs. SAVR respectively (OR 0.68 95% CI 0.46-1.00, p-0.05). One year mortality was 5.1% (109/2,125) and 5.0% 102/2,028) for TAVI and SAVR respectively (OR 1.05 95% CI 0.79-1.39, p=0.74). at longest available follow up (median 2 years) the risk of mortality was 10.8% (264/2,432) and 9.8% 229/2,333) for TAVI and SAVR respectively (OR 1.15 95% CI 0.95-1.40, p=0.15).

For both 1 year and longest available mortality, there was significant heterogeneity between the PSM/RCT subgroups (I^2=82.5% and 75.3%), with the RCT group suggesting a trend towards reduced mortality with TAVI at 1 year (OR 0.65 95% CI 0.40-1.05, p=0.08 I^2=0%), or no difference for a median of 2 years (OR 0.86 95% CI 0.62-1.22, p=0.40) and the PSM group suggesting a trend towards increased mortality with TAVI at 1 year (OR 1.35 95% CI

0.95-1.91, p=0.09 I^2=0%), and significant increase in mortality at a median of 2 years (OR 1.32 95% CI 1.05-1.67, p=0.02) – see Figure 2A,B,C.

Periprocedural complications

Periprocedural complications are summarized in Table S3 and the corresponding forest plots are shown in Figure 3. TAVI was associated with reduced risk for CVA, AKI and bleeding (Figure 3A,C,D), There was no difference in the risk for MI between TAVI/SAVR (Figure 3B) and risk for PMI and vascular complications was higher with TAVI (Figure 3E+F). Increased risk for vascular complications with TAVI was much lower in the the RCTs compared to PSM studies (OR 1.34 and OR 10.01, respectively), and in fact was not statistically different between TAVI vs. SAVR in the RCT patients only (p=0.21).

A trial sequential analysis for mortality at median follow up of 2 years suggested that a sample size of 15,463 patients will be required for a definitive meta-analysis (compared to 4,675 patients included in this meta-analysis for this outcome) and that the current Z-score did not cross either the futility or O'Brien-Flemming boundries – see Figure 4.

Discussion

We conducted a systematic review and meta-analysis of all RCTs and PSM studies evaluating TAVI vs. SAVR for patients with severe AS who are at low surgical risk.

Our main findings are:

- Mortality for a median of 2 years was low as would be expected in low risk patients.
- TAVI was associated with lower short term mortality (32% reduction) and CVA 930% reduction), although both were statistically nonsignificant (p=0.05 for both) and higher risk for vascular complications and PMI.
- Mortality at 1 and a median of 2 years follow up was similar between TAVI and SAVR, but there was significant heterogeneity between study types with RCTs

suggesting better results for TAVI at 1 and equivalent results at 2 years, respectively, while PSM studies suggested better results for SAVR at both 1 and median of 2 years.

- Our trial sequential analysis suggests that more data is needed in order to draw definitive conclusions regarding the differences in mortality between TAVI/SAVR in low surgical risk patients.

Throughout the rapid expansion of TAVI volumes over the recent decade, the surgical risk profile of real world patients has been lower than that of those included in the randomized trials on whom the formal practice guidelines recommendations are based upon. For example, a report from a national registry in Germany recently reported that between 2012 and 2014, 85% of severe AS patients who were at intermediate surgical risk were treated by TAVI [26]. Likewise, the median STS score of patients undergoing TAVI in the US between 2012-2015 was in the intermediate risk category (6.5) [6], while the first large scale RCT of TAVI vs. SAVR in intermediate risk patients was only published in 2016 [4] and the first reference of TAVI as an alternative to SAVR in patients who are not at high surgical risk in the ESC guidelines was published during 2017 [27]. The same is true for low surgical risk patients, with registry reports on this patients' population dating back to 2015 [24] while the first large scale RCTs were only published in 2019 [8,9] and current guidelines do not consider TAVI suitable for low surgical risk patients yet. In such settings, a meta-analysis is important, as it provides physicians with the most comprehensive data regarding the balance between TAVI/SAVR and can include data from both RCTs and real world patients. The last point is significant since although RCTs are considered the best source of scientific data to guide clinical practice, they carry an inherent selection bias [11] and so it is important to see if their results are consistent with those of real world patients, and if that is not the case – consider the reasons for this discrepancy.

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The current meta-analysis represents a significant improvement in the quality of data compared to our previous publication on the same subject [7] – first, it's sample size is much larger (6,124 compared to 3,484 patients), and more importantly, the fraction of patients enrolled in RCTs is much more significant (45%).

When we compare the results regarding mortality, the periprocedural mortality is lower than previously reported (1.4% and 2.1% compared to 2.2% and 2.6% for TAVI and SAVR, respectively), with a 32% reduction in mortality with TAVI at 30 days. For 1 year mortality and beyond (up to a median of 2 years) there seems to be a discrepancy between the RCT and PSM studies. It seemed that results in the RCTs favored TAVI while those of the PSM studies favored SAVR (see figure 2B,C). The most likely explanation for these results is the difference between the PSM and RCT studies regarding the era in TAVI evolution they represent: while practically all of the patients included in the RCT group were treated during 2016-2017, the PSM studies included patients who underwent TAVI during 2008-2012. During this time gap, much progress has been made in all aspects of TAVI – first and foremost – newer generation TAVI devices have become the standard of care and replaced first generation devices, but numerous other aspects regarding TAVI have changed as well - more experience has been gained in the assessment, triage, preparation and peri procedural management of patients, as well as in performing the TAVI procedures; the use of cardiac computed tomography (CT) for preprocedural planning has become the standard of care; delivery sheath sizes have been reduced leading to a decrease in the use of non-femoral access; conscious sedation has become the standard of care rather than general anaesthesia and clinical pathways for earlier mobilization and discharge have been developed and implemented. This explanation is also supported by some of the results regarding periprocedural complications: looking at vascular complications (Fig 3F), although overall,

the risk for vascular complications is higher in TAVI compared to SAVR, this was driven solely by the PSM studies, while in the RCT (whose participants were treated using smaller sheaths and were all assessed by CT to assess the optimal access), the risk for vascular complications was not statistically significant between TAVI and SAVR. Looking at the risk for PMI (Figure 3E) although in both groups the risk was much greater with TAVI, the odds ratio was 21% lower in the RCTs compared to PSM studies, again, this is probably related to the better understanding of the pathophysiologic mechanisms of conduction abnormalities post TAVI and possible strategies to mitigate them that accumulated with more clinical and research experience in this issue [28].

If we examine the data on periprocedural outcomes, it seems that the less invasive nature and shorter admission associated with TAVI may be of great benefit for low risk patients (significant reductions in mortality, CVA, AKI and bleeding). In the current analysis these benefits did not translate into mortality benefits at longer follow ups, but it should be noted that the 1 year and beyond mortality analysis' were dominated by PSM studies, so longer follow up data from the large RCTs [8,9] is required to examine whether these short term benefit eventually translate into long term benefits as well.

These results, although only hypothesis generating, can be viewed as a telltale sign that the iterations in TAVI devices as well as more experience in the care for TAVI patients accumulated over the past decade, do result in improved outcomes for TAVI patients compared to the past, but will this improvement eventually sway the balance between TAVI/SAVR towards the transcatheter approach in patients at low surgical risk still requires more evidence.

Limitations

Our study has several limitations. First, we did not have access to individual patient data and could not present subgroup analysis according to access site or device type for the PSM

studies ,which may have different risk/benefit profiles (subgroup analysis for the RCTs have been presented by Siontis et al[10]); Second, the currently accepted risk scores for TAVI are actually based on historical SAVR patients and may not be able to accurately describe the risks involved with TAVI, causing misclassification of patient risk; Third, It should also be remembered that the latest 2 low risk RCTs [8,9] included only patients who were very good candidates for TAVI (femoral access, high coronaries, no severe valve calcifications etc) and thus the results may not appropriately reflect the balance between TAVI/SAVR in real world low surgical risk patients; Fourth, the follow up period in the studies included in this meta-analysis (median 2 years) is insufficient to assess long term differences between TAVI and SAVR, especially in low risk patients whose life expectancy post TAVI/SAVR is expected to be longer than the average TAVI patient in current clinical practice; Fifth, 3 of the studies did not use the VARC/VARC II definitions for the secondary outcomes . Finally, some additional issues that are beyond the scope of this meta-analysis need to be taken into account when choosing between TAVI/SAVR: long term prosthetic valve durability, an issue on which data is still limited [29], is of vital importance for low risk patients, and the cost effectiveness of TAVI as opposed to SAVR will also need to undergo extensive scrutiny before expanding TAVI indications to include low risk patients – a change that will have wide scale economic implications in countries with predominantly public healthcare systems.

Conclusions

The current available data suggests that for low risk patients , TAVI is associated with a trend towards improved periprocedural mortality and CVA compared to SAVR, and is equivalent to SAVR in terms of mortality for up to a median follow up of 2 years. The current evidence base is still insufficient to derive definitive conclusions and longer follow up data from the published low risk TAVI RCTs and data from those still underway (the

NOTION 2 trial - NCT02825134) is required before TAVI can be routinely considered an alternative for SAVR in low risk severe AS patients.

Impact on daily practice

Our results suggest that TAVI should not be a priori denied from patients who are at low surgical risk for SAVR and this should be reflected by the major cardiology practice guidelines. Until more definitive data on the balance between TAVI/SAVR in this patient population is available, Heart Team discussions concerning the optimal management of low risk patients with severe AS must consider the remaining limitations of TAVI and make judicious, evidence-based decisions for individual patients.

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Conflict of interests

The authors have no conflict of interest to disclose

Figure Legends

Figure 1. Study selection process for inclusion in the meta-analysis.

LV=left ventricle PSM=propensity score matching SAVR=surgical aortic valve replacement STS=society of thoracic surgeons

Figure 2. mortality.

Forrest plots of the odds ratio for 30 days (A) and 1 year (B) and longest available (median 2 years) mortality for TAVI vs. SAVR.

SAVR=surgical aortic valve replacement TAVI=transcatheter aortic valve implantation

Figure 3. Periprocedural complications .

Forest plots of the odds ratio for periprocedural CVA (A) , MI (B) Major bleeding (C) , AKI (D) PMI (E), and vascular complications (F) after TAVI vs. SAVR in low risk patients.

AKI=acute kidney injury CVA=cerebrovascular accident MI=myocardial infarction PMI=pacemaker implantation SAVR=surgical aortic valve replacement TAVI=transcatheter aortic valve implantation

Figure 4. Trial sequential analysis for longest available (median 2 years) mortality .

Trial sequential analysis for longest available (median 2 years) mortality.

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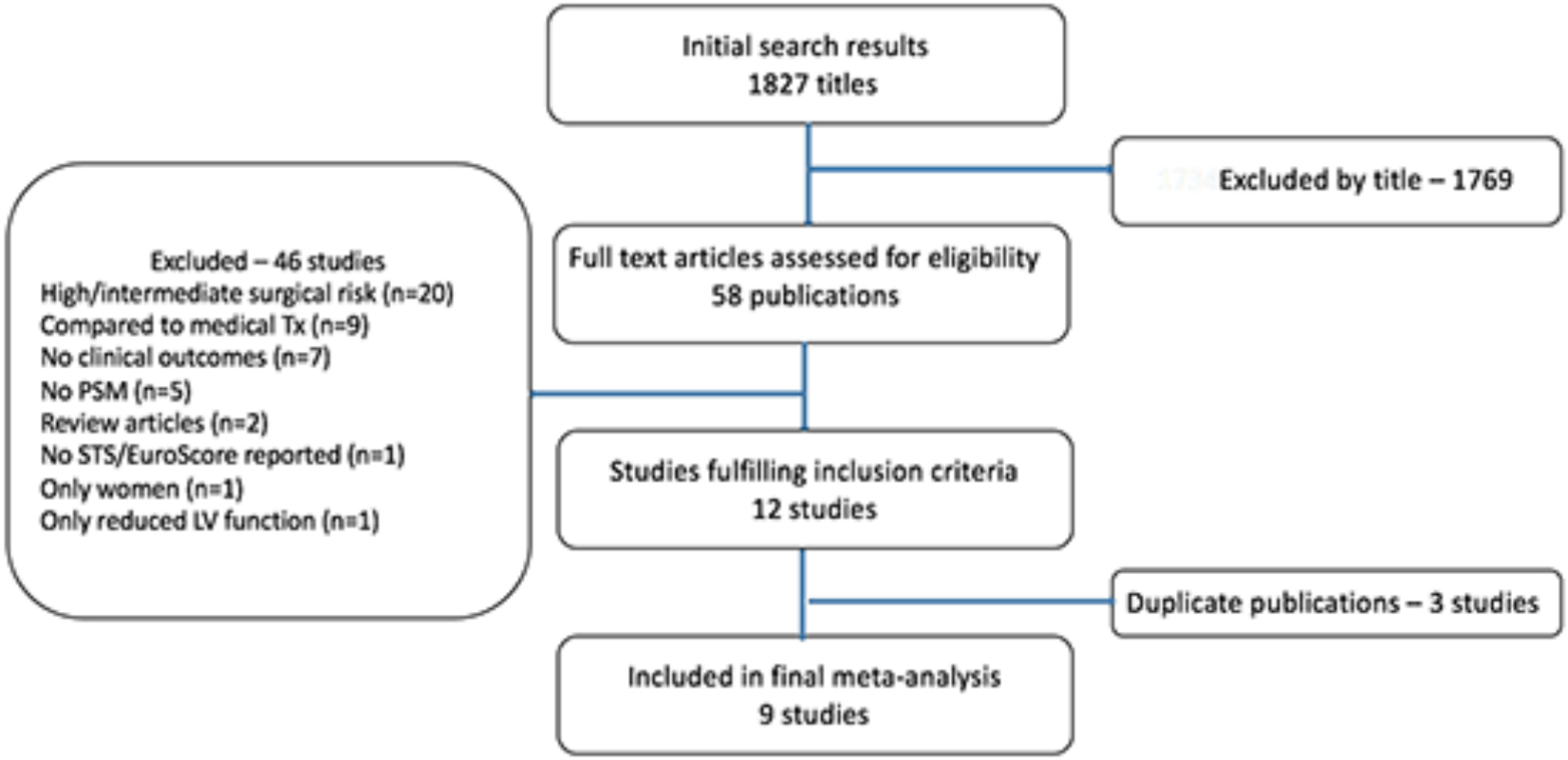
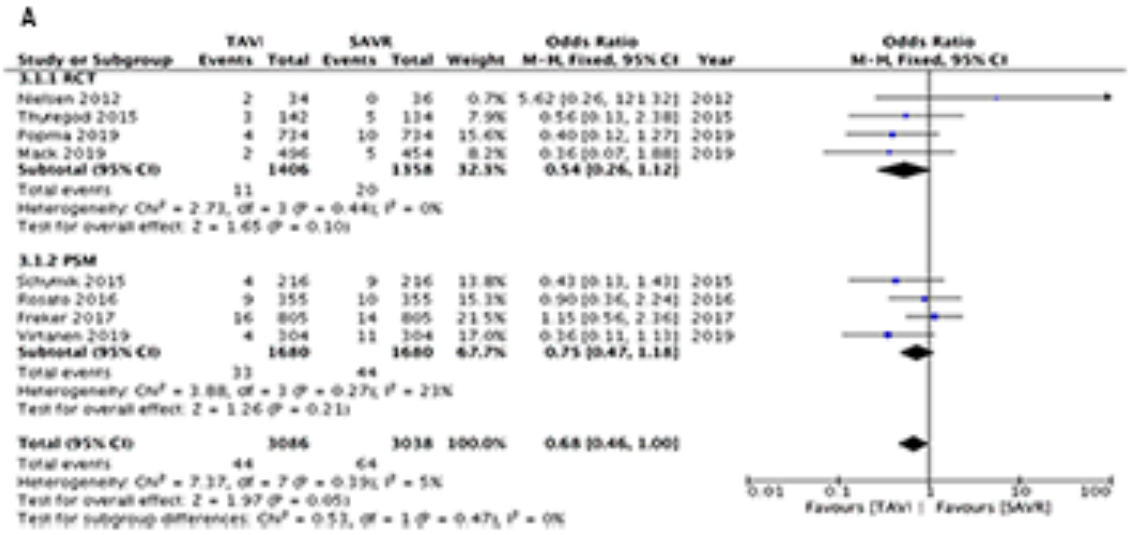
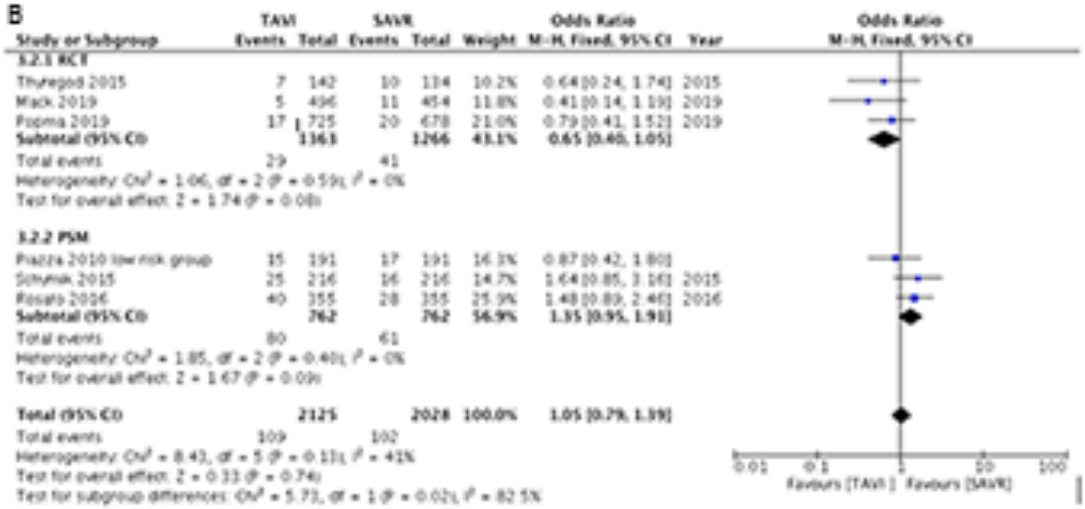
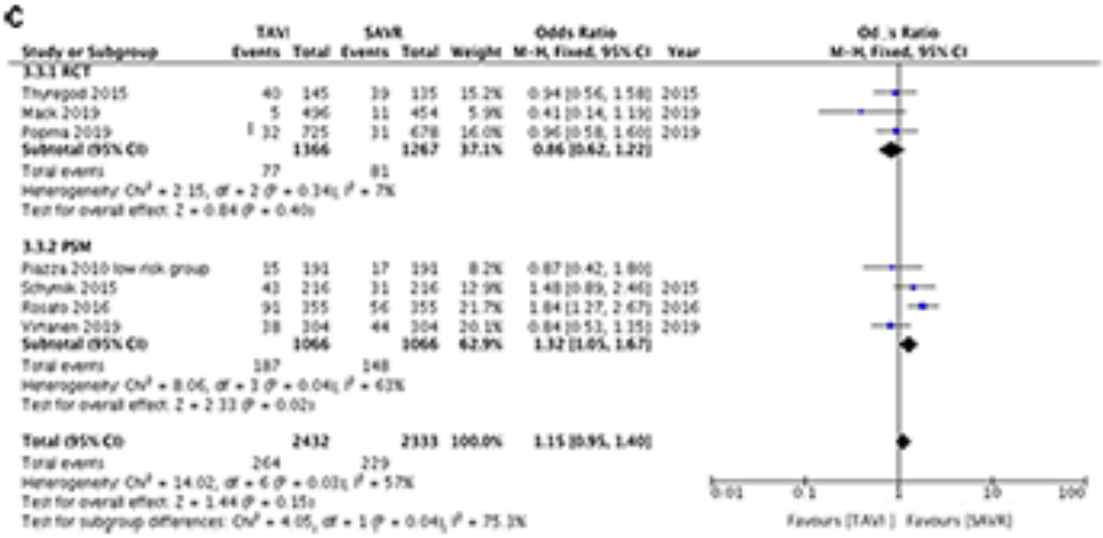
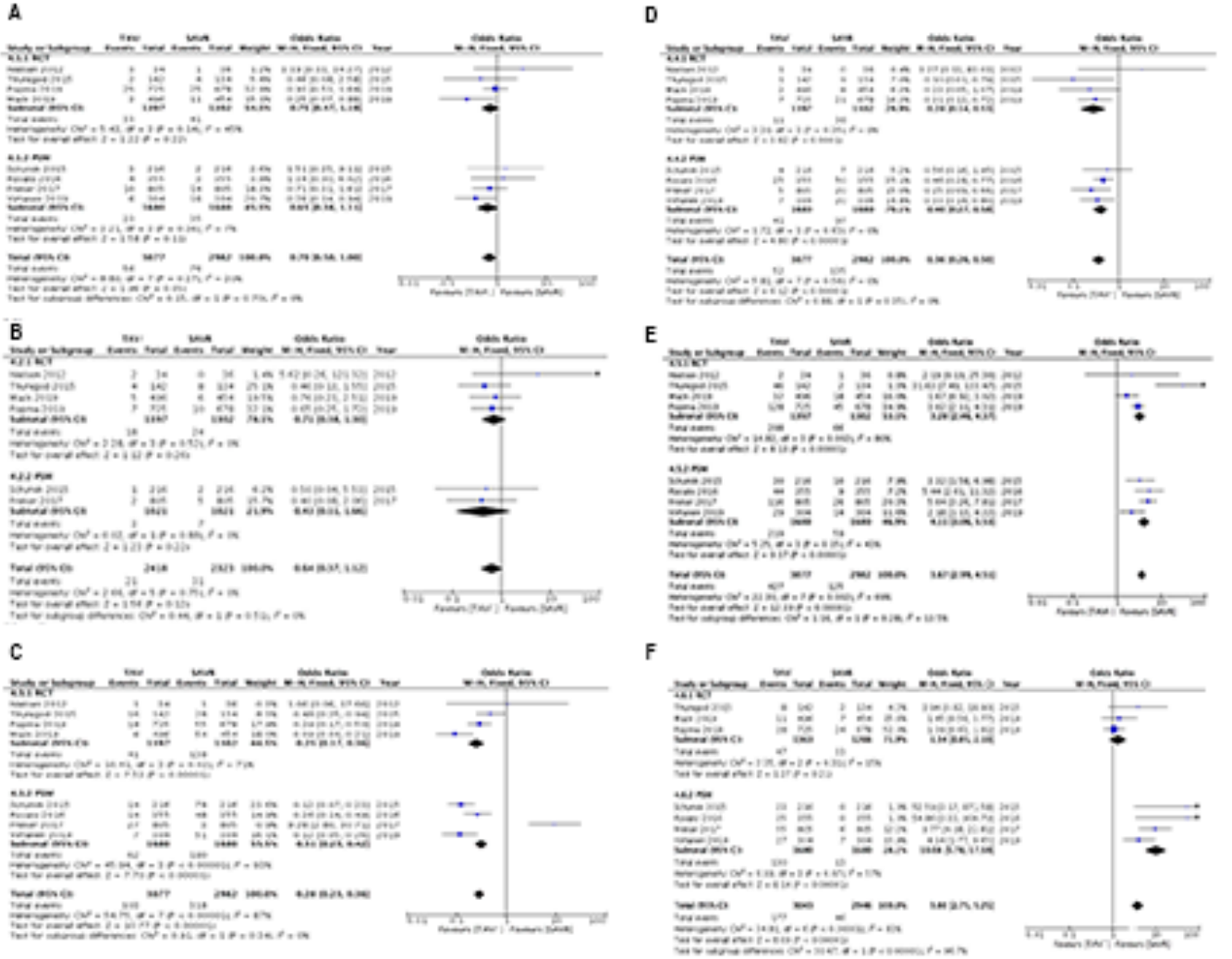
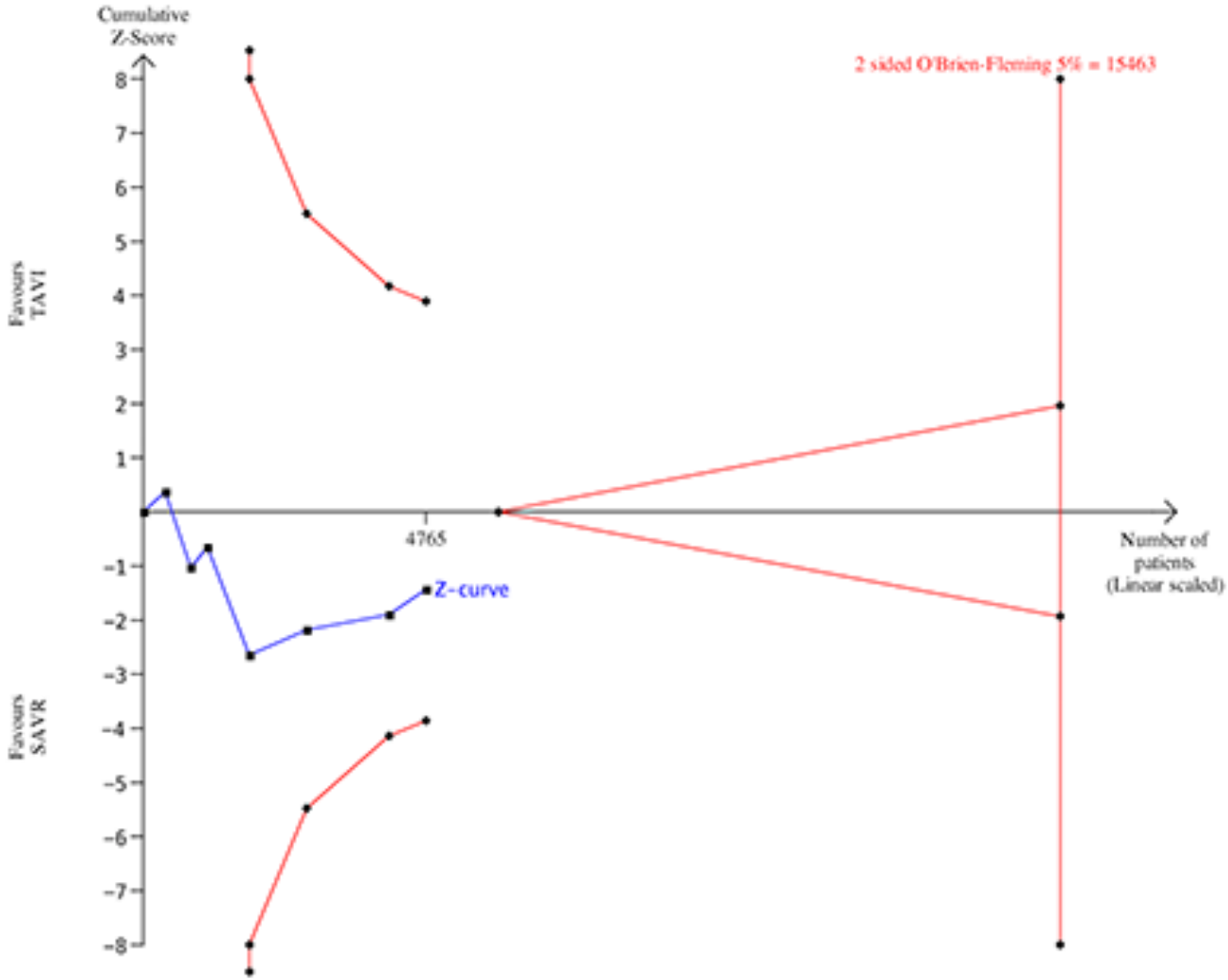








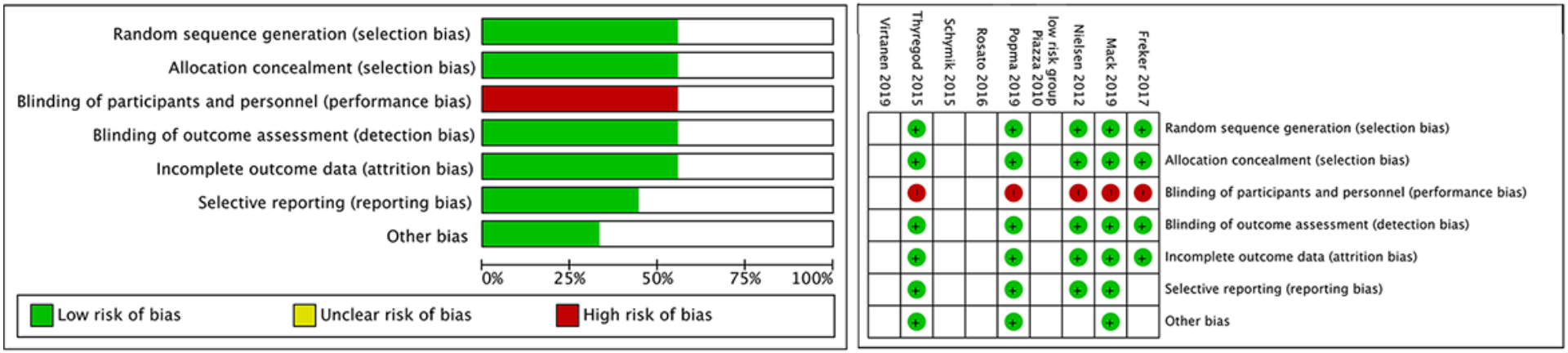




Supplementary material

Figure S1: Risk of bias assessment for the studies included in the meta-analysis

A- Randomized studies



B- Propensity score matched studies (Newcastle-Ottawa scale)

	Selection				Comparability	Outcome			Overall
	representativeness of exposed cohort	selection of non exposed cohort	ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Schymick	1	1	1	1	2	1	1	1	9
Rosato	1	1	1	1	2	1	1	1	9
Freker	1	0	1	1	2	1	0	1	7
Piazza	1	1	1	1	2	1	1	1	9
Virtanan	1	1	1	1	2	1	1	1	9

Table S1: characteristics of studies included in the meta-analysis

Study	Publication year	Design	Sample size	Follow up	STS (mean)	EuroScore (mean)
Nielsen et al[18]	2012	RCT	TAVI-34	3 months	3.1	9.4
			SAVR-36		3.4	10.3
Thyregod et al[19]	2015	RCT	TAVI-142	5 years	2.9	8.4
			SAVR-134		3.1	8.9
Mack et al[8]	2019	RCT	TAVI-496	1 year	1.9	
			SAVR-454			
Popma et al[9]	2019	RCT	TAVI-725	2 year	1.9	
			SAVR-678			
Piazza et al[22]	2013	PSM	TAVI-191	1 year	<4*	
			SAVR-191		<4*	
Schymik et al[24]	2015	PSM	TAVI-216	3 years	-	8.7
			SAVR-216			8.8
Rosato et al[23]	2016	PSM	TAVI-355	3 years	-	6.3
			SAVR-355			6.3
Freker et al[21]	2017	PSM	TAVI-805	In hospital	-	6.8
			SAVR-805			4.2
Virtanen et al[25]	2019	PSM	TAVI-304	3 years	2.1	2.6
			SAVR-304		2.1	2.5

PSM=propensity score matching RCT=randomized controlled trial SAVR=surgical aortic valve replacement STS=society of thoracic surgeons

TAVI=transcatheter aortic valve implantation

Table S2: baseline characteristics of patients included in the meta-analysis

Study		Age	Pulmonary disease^	DM	CVA	PVD	CKD[$]	NYHA III-IV	EF (%)	AVA (cm^2)	AVG (mmHg)
Nielsen et al[18]	TAVR	80.0±3.6	2.9%^	8.3%	2.9%	5.9%	2.9%	NA	56.5±9.7	0.66±0.17	81±26 (peak)
	SAVR	82.0±4.4	2.8%^	2.9%	2.8%	8.3%	0.0%	NA	56.3±10	0.71±0.17	66±23 (peak)
Thyregod et al[19]	TAVR	79.2±4.9	11.7%	17.9%	16.6%	4.1%	1.4%	48.7%	NA	NA	NA
	SAVR	79.0±4.7	11.9%	20.7%	16.3%	6.7%	0.7%	45.5%	NA	NA	NA
Mack et al[8]	TAVR	73.3±5.8	5.1%	31.2%	3.4%	6.9%	NA	31.2%	65.7±9	0.80±0.20	49±12 (mean)
	SAVR	73.6±6.1	6.2%	30.2%	5.1%	7.3%	NA	23.8%	66.2±8.6	0.80±0.20	48±12 (mean)
Popma et al[9]	TAVR	74.0±5.9	15.1%	31.1%	10.1%	7.6%	NA	24.6%	61.7±7.9	0.80±0.20	47±12 (mean)
	SAVR	73.8±6.0	17.2%	30.5%	11.4%	8.5%	NA	27.9%	61.9±7.7	0.80±0.20	47±12 (mean)
Piazza et al[22]	TAVR	79.9±6.0	17.8%	27.4%	9.9%	8.2%	NA	87.1%	NA	NA	NA
	SAVR	79.4±4.8	15.8%	25.7%	7.4%	10.1%	NA	86.8%	NA	NA	NA
Schymik et al[24]	TAVR	78.3±5.2	9.3%	NA	2.8%	5.1%	3.2%	NA	62.2±11.3	NA	NA
	SAVR	78.2±4.6	8.8%	NA	3.7%	6.9%	3.2%	NA	62.0±10.5	NA	NA
Freker et al[23]	TAVR	77.5±4.4	1.7%	23.6%	4.1%	0.6%	10.6%	76.4%	NA	NA	NA
	SAVR	77.5±4.4	1.7%	23.6%	4.1%	0.6%	10.6%	76.4%	NA	NA	NA
Rosato et al[21]	TAVR	80.1±6.4	18.3%	14.9%	4.2%	10.1%	NA	50.7%	NA	0.67±0.26	53±15 (mean)
	SAVR	80.0±5.1	19.7%	16.1%	4.2%	8.7%	NA	51.3%	NA	0.71±0.25	53±15 (mean)
Virtanen et al[25]	TAVR	77.9±6.0	17.8%	22.4%	8.6%	NA	5.1%	1.6%(IV)	NA	NA	NA
	SAVR	78.1±4.8	19.4%	22.4%	7.9%	NA	5.0%	2.6%(IV)	NA	NA	NA

AVA= aortic valve area AVG=aortic valve gradient CKD=chronic kidney disease CVA=cerebrovascular disease DM=diabetes mellitus EF=ejection fraction NA=not available NYHA=New York heart association PVD=peripheral vascular disease

*the patient characteristics are reported for a PSM cohort of 405 matched pairs, the mortality data included in this meta-analysis is derived from 191 matched pairs of patients with STS <4%
$ definitions of CKD in each study:
[8] Creatinine>2mg/dL [9] Creatinine>2mg/dL [18]Creatinine>200 mmol/L [19] Creatinine>2mg/dL [23] Creatinine>1.2mg/dL [24]Creatinine>200 mmol/L [25] eGFR<30 mL/min/1.73m^2

^ definitions of pulmonary disease in each study:
[8] COPD [9] COPD [18] COPD [19] chronic lung disease [21] pulmonary disease [22] COPD [23] COPD requiring medication [24] pulmonary disease [25] pulmonary disease

Table S3 – summary of periprocedural complications

	TAVI	SAVR	OR(95% CI)
CVA			
Summary	56/3077(1.8%)	76/2982(2.5%)	0.70(0.50-1.00)
MI			
Summary	21/2418(0.9%)	31/2323(1.30%%)	0.64(0.37-1.12)
Bleeding			
Summary	103/3077(3.3%)	318/2982(10.6%)	0.28(0.23-0.36)
AKI			
Summary	52/3077(1.7%)	135/2982(4.5%)	0.36(0.26-0.50)
PMI			
Summary	427/3077(13.8%)	125/2982(4.2%)	3.67(2.99-4.51)
Vascular complications			
Summary	177/3043(5.8%)	46/2946(1.6%)	3.80(2.75-5.25)

AKI-acute kidney injury CVA=cerebrovascular accident MI=myocardial infarction OR=odds ratio PMI=pacemaker implantation SAVR=surgical aortic valve replacement TAVI=transcatheter aortic valve implantation