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PII: S0002-9149(19)31222-6
DOI: https://doi.org/10.1016/j.amjcard.2019.10.036
Reference: AJC 24265

To appear in: *The American Journal of Cardiology*

Received date: 24 July 2019
Revised date: 28 October 2019
Accepted date: 30 October 2019

Please cite this article as: Sharath C Vipparthy MD , Venkatesh Ravi MD , Sindhu Avula MD , Soumyasri Kambhatla MD , Mobasser Mahmood MD , Ameer Kabour MD , Syed Sohail Ali MD , Marco Barzallo MD , Sudhir Mungee MD , Meta-analysis of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with Low Surgical Risk, *The American Journal of Cardiology* (2019), doi: https://doi.org/10.1016/j.amjcard.2019.10.036

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Meta-analysis of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with *Low* Surgical Risk

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No Grants were received for our study.

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Abstract

Transcatheter aortic valve implantation (TAVI) is the current standard of care for patients with severe aortic stenosis (AS) who are at high risk for surgery. However, several recent studies have demonstrated the comparable safety and efficacy of TAVI in low-risk patients as well. We sought to pool the existing data to further assert its comparability. MEDLINE, Cochrane, and Embase, databases were evaluated for relevant articles published from January 2005 to June 2019. Studies comparing outcomes of TAVI versus surgical aortic valve replacement (SAVR) in patients who are at low risk for surgery were included. Twelve studies (5 randomized controlled trials (RCTs) and 7 observational studies) totaling 27,956 patients were included. Follow-up ranged from 3 months to 5 years. Short-term all-cause mortality, short-term and 1-year cardiac mortality were significantly lower in the TAVI group. 1-Year all-cause mortality, short-term and 1-year stroke and myocardial infarction (MI) were similar in both groups. Rate of acute kidney injury (AKI) and new-onset atrial fibrillation (AF) were lower in the TAVI group, while permanent pacemaker (PPM) implantation and major vascular complications were higher in the TAVI group. Subgroup analysis of RCTs showed significantly lower 1-year all-cause mortality in the TAVI group. In conclusion, among severe AS patients at low surgical risk, TAVI when compared to SAVR, demonstrated a lower rate of short-term all-cause mortality, short-term and 1-year cardiac mortality and similar in terms of 1-year all-cause mortality. TAVI is emerging as a safe and efficacious alternative for low surgical risk patients.

Keywords: TAVI, SAVR, Low risk, severe aortic stenosis, Meta-analysis

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Introduction

Since the inception of performing TAVI for patients with prohibitive surgical risk, its scope has broadened progressively to patients at lower surgical risk. TAVI numbers have significantly grown in the United States (US), from less than 5000 in 2012 to nearly 50,000 in 2017[1]. Data from PARTNER 2A, Sapien 3 and meta-analyses of intermediate-risk studies [2,3,4,5,6] showed that TAVI was similar to SAVR in terms of mortality and stroke. SURTAVI and meta-analyses of studies comparing TAVI and SAVR in intermediate-risk patients, reinforced the available data [7,8,9,10]. TAVI is currently a class IIa indication for intermediate-risk patients but SAVR remains the choice of treatment for low risk patients in the updated ACC/AHA valve guidelines of 2017, due to lack of significant evidence of safety for TAVI in this population [11]. Meta-analyses comparing TAVI to SAVR in low surgical risk patients have so far included studies consisting of both low and intermediate-risk patients, based on risk categories determined according to the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score [4,12,13,14]. A meta-analysis published by Witberg et al., in 2018 included only patients at low surgical risk[14,15] and showed similar short-term mortality, but worse intermediate-term mortality (range 1-3 years) for TAVI compared to SAVR. Two recent meta-analyses by George Siontis et.al.[16] and Tomo Ando et.al. [14] included the results of the latest PARTNER 3 and Evolut Low-risk trials but were not exclusive to low-risk patients. In this background, we sought to develop an up-to-date meta-analysis using RCTs and observational studies, which exclusively includes low surgical risk patients, defined as STS score ≤4 or EURO score ≤10.

Methods

We performed this meta-analysis per the guidelines of the Cochrane handbook for systematic reviews of interventions [17] and the PRISMA statement guidelines[18]. We searched Medline, Embase, and

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Cochrane central from January 2005 up to June 30, 2019, using a combination of keywords and MeSH terms as follows: {'Aortic stenosis' or 'severe aortic stenosis' and 'transcatheter valve replacement' or 'TAVR' and 'Surgical aortic valve replacement' or 'SAVR'} with no restrictions on language or year of publication. We also checked references of all articles which were relevant to our study. Studies comparing TAVI and SAVR that met the following criteria were included: 1. Patients with severe AS and low surgical risk defined by a STS score of ≤4% and logistic Euroscore of ≤10%. 2.RCT or Observational study (prospective or retrospective) which adjusted the cohorts (using Propensity score matching or inverse probability weighting or weighted propensity model) to create patient groups with similar baseline characteristics. We excluded studies that did not report outcomes in low-risk populations as defined above or attempted to compare suture less SAVR with TAVI. The process of selection of studies and relevant data extraction was conducted by three reviewers (SV, SA, and MM) and a consensus was obtained upon consulting a fourth reviewer (SK). Data extracted include study design, baseline characteristics and primary outcomes of short term in-hospital or 30 day and 1-year all-cause mortality. We also extracted data for following secondary outcomes: short term(30-day or in-hospital) and 1-year stroke, cardiac mortality, new-onset or worsening AF, new PPM implantation, AKI stage II and III, MI, major/life-threatening/disabling bleeding and major vascular complications.

Two authors (SV, VR) assessed the risk of bias and used Cochrane's handbook tool [19] to assess the RCTs. The Newcastle-Ottawa tool was used to assess the quality of the observational studies [20]. The reviewers resolved conflicts through consensus. A funnel plot was used to assess publication bias. The principal summary effects measures were the odds ratio (OR) and corresponding 95% confidence intervals (CI) estimated by using Mantel-Haenszel random-effects model [21]. Two-sided p-value ≤ 0.05 was considered statistically significant. We conservatively used a priori, the Mantel-Haenszel Random-effects model assuming substantial variability in the treatment effect size across studies [22]. The presence of statistical heterogeneity was evaluated by Cochran's Q test I2 statistic: with I^2 values > 50%, we planned to explore individual study characteristics. Publication bias was assessed by using Funnel plots [23]. Sensitivity analysis was done with the sequential exclusion of individual trials to evaluate the robustness of the results. We also planned a priori subgroup analysis to explore potential effects on outcome measures data from RCTs only. Statistical analysis was performed using Review Manager (RevMan), Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

We retrieved a total of 2676 studies for the title and abstract analysis of which 65 studies were screened for inclusion criteria. 13 studies met inclusion criteria of which 1 (Schymik et.al, 2015) was excluded [24] as it was considered a duplicate of another study (Schymik et.al, 2018). The above 2 studies [24,25] were derived from the TAVIK registry with overlapping periods and the former study sought to include both low and intermediate-risk patients, where-as the latter only included patients at low risk. We, therefore, chose the latter study for inclusion. 12 studies, 5 RCTs[26-30] and 7 observational studies [25, 31-36] were ultimately included in our analysis as outlined in figure 1. From these 12 studies, a total of 27,956 patients were included in our analysis. Among them, 9,577 patients were in the TAVI group and 18,379 patients were in the SAVR group. The baseline characteristics are shown in the Table.1A, B. 8 of the 12 studies specifically included patients at low surgical risk [25-27,32-36]. 4 of the other studies intended to include patients at low to intermediate surgical risk 28-31. Among these, 2 of the studies separately listed outcomes for low surgical risk subgroup [28,31] and the other 2 studies [29,30] had a mean STS score in the low-risk range (3.1+/-1.5 and 2.9+/-1.6 respectively). We estimate less than 0.8% of the total patients included in this study to have an STS or euro score value above the low surgical risk cut off.

The primary all study pooled analysis demonstrated that the short-term all-cause mortality was significantly lower in the TAVI group (OR 0.66, 95% CI 0.55-0.80, P<0.0001). There was no significant difference between the 2 groups in the outcomes of 1-year all-cause mortality (OR 0.96, 95% CI 0.73 –

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1.28, P = 0.80). The TAVI cohort did significantly better in terms of 1-year cardiac mortality (OR 0.54, 95% CI 0.32-0.90, P=0.02). There was no significant difference between the groups for short-term stroke (OR 0.71, 95% CI 0.49-1.01, P= 0.06) and 1-year stroke (OR 0.68, 95% CI 0.44-1.07, P= 0.10), MI, short term cardiac mortality and 1-year major vascular complications (see Forest plots in figure 2, 3, 4.). The TAVI cohort demonstrated a lower rate of short and 1-year AF, AKI, major/life-threatening or disabling bleeding. The SAVR group did significantly better in terms of short and 1-year PPM implantation and short term major vascular complications. See Figures 2, 3, 4. for Forest plots of the primary pooled analysis.

Further sensitivity analysis demonstrated that the difference in the outcome of short-term all-cause mortality dissipated when GARY registry data were removed from the analysis. (OR 0.73, 95%CI 0.48 – 1.11, p = 0.14). The difference in 1-year cardiovascular mortality dissipated when the results of Mack et al (PARTNER 3) were removed from the analysis (OR 0.58, 95% CI 0.33- 1.02, p = 0.06).

When subgroup analyses for all short-term and 1-year outcomes were performed using RCTs alone, the 1-year all-cause mortality was significantly lower in the TAVI group (RR 0.61, 95% CI 0.38-0.96, P=0.03). Short term all-cause mortality and major vascular complication rates were similar in both groups. The rest of the outcomes of the RCT-only cohort were similar to the overall cohort (See forest plots of RCT only studies in Supplemental figure1, 2, 3). We also performed subgroup analysis to compare the incidence of PPM by valve type, Self-Expanding(SEV) versus Balloon-Expandable (BEV) among low risk patients and the trend was similar to those in high and intermediate risk patients with SEV causing higher short-term and 1-year PPM implantation rates than BEV, when compared to SAVR (short-term : OR 9.17, 95% CI 0.93-90.76 P = 0.06 for SEV, OR 1.67, 95% CI 0.92-3.02 for BEV P= 0.09, and 1-year: OR 7.71, 95% CI 2.45-24.25 P<0.001 for SEV, OR 1.4 95% CI 0.82-2.39, P =0.21 for BEV, see forest plots of short-term and 1-year PPM by valve type in supplemental figure 5).

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All the RCTs were at low risk of bias in terms of generation of randomization, concealment of allocation, selective reporting and all except STACCATO trial was at low risk for attrition bias (supplemental figure 6). All the Observational studies were ranked as good quality according to the Newcastle-Ottawa tool score range (7-8) (Supplemental figure 7). The funnel plots are shown in supplemental figure 4.

Discussion

Our study showed a significantly lower short-term and similar 1-year all-cause mortality among the TAVI cohort when compared to SAVR cohort. Additionally, 1-year cardiac mortality was lower in the TAVI group. When we conducted an RCT-only analysis the TAVI group fared better than the SAVR group in terms of 1-year all-cause mortality. Importantly risk of short-term and 1-year stroke was similar in both groups. The overall risk of short-term and 1-year MI, short-term cardiac mortality outcomes were similar in both groups. The outcomes of AKI, Major bleeding, AF were lower in the TAVI group, where-as the PPM requirement and short term major vascular complications (in the entire cohort) were higher in the TAVI group. Additionally, incidence of PPM implantation in BEV seemed to be similar to that of SAVR group, but more long-term data is necessary in this regard.

Although a previous meta-analysis by Witberg et.al [15] included 5 of the 12 studies we included, their primary outcomes were significantly different from ours. In their study, there was no significant difference between the groups in short term mortality and there was increased mortality in the TAVI group in the intermediate term which was defined as a median of 2 years follow up. In our 1-year outcomes, TAVI was non-inferior or superior (RCT-only analysis showed 39% reduction). We consider our results to be more accurate since our sample size was larger and we included more RCTs. Furthermore, the heterogeneity for their late mortality outcomes was high (I^2 =51%). Their results of short term CVA, MI, major bleeding, AKI, PPM implantation, vascular complications were similar to ours.

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They did not separately perform analysis for outcomes of cardiac mortality and AF, and 1-year outcomes of CVA, MI, AKI, PPM, bleeding and vascular complications. There was a 41% reduction in the outcome of short-term cardiac mortality and a 46% reduction in the 1-year cardiac mortality in our study. Also, we chose Schymik et.al., 2018 observational study over Schymik et.al, 2015 (which was included in their meta-analysis) which included low-risk patients exclusively and Witberg et.al included more intermediate-risk patients both numerically and proportionately.

Two recently published meta-analyses by George Siontis et.al.[16] and Tomo Ando et.al. [14] included the results of PARTNER 3 and Evolut Low-risk trials. However, these studies were significantly different from ours. Firstly, both studies were Meta-analyses that included RCTs only, but Siontis et.al. included patients of all surgical risks and Tomo Ando et.al., included Low to intermediate-risk population. Secondly, both studies had a significantly lower sample size (8020 and 7143) compared to our sample size (27956). Thirdly, Siontis et.al., did not perform a comprehensive analysis of short-term mortality and complications. Fourthly, although Tomo Ando et.al., did perform subgroup analysis of patients with STS<4 for composite 1-year all-cause mortality or disabling stroke, they included only 2 studies and did not perform separate analysis for all-cause mortality and disabling stroke. They did not perform subgroup analysis of other short and 1-year outcomes either for STS<4 cohorts. Their overall results of lower composite outcome in the TAVI group in STS <4 is similar to lower 1-year all-cause mortality in our RCT-only analysis.

There was no significant heterogeneity (I^2 <50) for most outcomes, except for PPM implantation, major bleeding, short-term vascular complications, and short-term AF. This high heterogeneity did not improve during sensitivity analysis and possible reasons behind the high heterogeneity for outcomes of PPM implantation and vascular complications could be improving techniques, valve types(for PPM), evolving safer prostheses and improving operator experience. We noted that the removal of GARY registry data

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during sensitivity analysis dissipated the difference in short-term all-cause mortality. We propose that this may be due to a large sample size that had a result in favor of TAVI in the GARY registry study.

Our study has several limitations. We have only analysed 1-year outcomes and 5-10 year outcomes are definitely desirable prior to contemplating TAVI for younger, low-risk patients. We may have included ≤0.8% of intermediate-risk patients, which could have affected the results. We included several studies that have used 1st generation devices which may have adversely affected the outcomes in the TAVI group. Subgroup analysis according to the access site or device type was not feasible as we did not have access to outcomes by device type or access site. We did not include trials with sutureless surgical aortic valves since we intended not to compare multiple newer modalities of treatment. Seven of our studies were observational with potential for bias, which may have been minimized by propensity matching, inverse probability weighting, and weighted propensity score model use. Three of the studies [30,34,35] included did not use VARC (Valve academic research consortium) II criteria to define their complications.

In conclusion, among severe AS patients with low surgical risk, TAVI is superior to SAVR in terms of short-term all-cause mortality and 1-year cardiac mortality, and similar in terms of 1-year all-cause mortality, short and 1-year stroke, MI and short term cardiac mortality, with a higher risk of PPM implantation and vascular complications. When only RCTs were analyzed TAVI was also superior to SAVR in terms of 1-year all-cause mortality. Additionally, TAVI derives its appeal from its less invasive nature and overall lower peri-procedural morbidity and hospitalization. We conclude that TAVI is superior to SAVR, in terms of mortality up-to 1 year and is a safe and efficacious alternative for select low-risk patients especially among the elderly. However, concerns of higher cost, long-term durability of TAVI valve, subclinical leaflet thrombosis, aortic regurgitation in low-risk cohorts, needs to be further evaluated and improved upon. The risk of PPM implantation in TAVI group could be of major impact, especially in younger patient population. This seems to be significantly lesser with BEV than SEV, but

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additional long-term data is desirable. The efficacy and safety of TAVI in the low-risk cohort over 5-10 years, durability of valves, data for repeat procedures and costs over lifetime need to be evaluated if TAVI needs to be considered for younger patients with low risk.

Conflicts of interest: Dr. Sudhir Mungee holds a consultant position with speakers-bureau of Edwards Lifesciences.

Acknowledgments: Our study was not funded by any association. I, Sharath Vipparthy, the corresponding author that I have listed everyone who contributed significantly to the work.

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Figure Legends

Table 1.A Baseline characteristics

Study	Intervention	DM, n (%)	CVA, n (%)	CAD, n (%)	CKD, n (%)	PAD, n (%)	Pulmonary Disease, n (%)	EF %	AVA Cm²	NYHA III-
PARTNER3- RCT- 2019	TAVI	155 (31.2 %)	17(3.4 %)	137 (27.7 %)	1 (0.2 %)	34 (6.9 %)	25 (5.1 %)	65.7+/-9.0	0.8+/-0.2	155 (3
	SAVR	137 (30.2 %)	23(5.1 %)	127 (28.0 %)	1 (0.2 %)	33 (7.3 %)	28 (6.2 %)	66.2+/-8.6	0.8+/-0.2	108 (2
EVOLUT RCT-2019	TAVI	228 (31.4 %)	74(10.2 %)	121 (16.6 %)	3 (0.4 %)	54 (7.5 %)	104 (15.0 %)	61.7+/-7.9	0.8+/-0.2	182 (2
	SAVR	207 (30.5 %)	80(11.8 %)	101(14.8 %)	1 (0.1 %)	56 (8.3 %)	117 (18.0 %)	61.9+/-7.7	0.8+/-0.2	193 (2
SURTAVI-STS<3-2018	TAVI	30 (22.9 %)	21(16.1 %)	63 (48.1 %)	0 (0.0)	25 (19.1 %)	9 (6.9 %)	NA	NA	53 (4(
	SAVR	21 (17.1 %)	14(11.4 %)	63 (51.2 %)	1 (0.8 %)	18 (14.6 %)	4 (3.3 %)	NA	NA	60 (48
NOTION-Thyregod et.al. RCT -2015	TAVI	26 (17.9 %)	24(16.6 %)	8 (5.5 %)	2 (1.4 %)	6 (4.1 %)	17(11.7 %)	NA	NA	61 (45
	SAVR	28 (20.7 %)	22(16.3 %)	6 (4.4 %)	1 (0.7 %)	9 (6.7 %)	16 (11.9 %)	NA	NA	57 (4
STACCATO- Nielsen RCT-2012	TAVI	1(2.9 %)	1(2.9 %)	NA	1 (2.9 %)	2 (5.9 %)	1 (2.9 %)	56.5 +/-9.7	0.66+/-0.17	N
	SAVR	3 (8.3 %)	1(2.8 %)	NA	0 (0.0)	3 (8.3 %)	1 (2.8 %)	56.3+/-10	0.71+/-0.17	N
Virtanen (obs) 2019	TAVI	68 (22.4 %)	46 (15.2 %)	57 (18.8 %)	NA	39 (12.8 %)	54 (17.8 %)	NA	NA	5 (1.
	SAVR	68 (22.4 %)	43 (14.2 %)	57 (18.8 %)	NA	42 (13.8 %)	59 (19.4 %)	NA	NA	8 (2.
LRT-Waksman obs - 2018	TAVI	61 (30.5 %)	19 (9.5 %)	42 (21.0 %)	12 (6 %)	4 (2 %)	16 (8 %)	63.5+/-7.5	NA	35 (17
	SAVR	186 (25.9 %)	51(7.1 %)	67 (9.3 %)	52 (7.3 %)	46 (6.4 %)	125 (17.4 %)	58.7+/-8.7	NA	145 (2
Bekeredjian (obs) -2018	TAVI	1296 (21.4 %)	817 (13.5 %)	1648 (27.2 %)	NA	NA	531 (8.8 %)	54.59 (0.155)	0.74 + (0.007)	4720 (
	SAVR	3152.5 (21.8 %)	1014.9 (7%)	3469 (23.9 %)	NA	NA	1268 (8.8 %)	55.916 (0.128)	0.803 (0.005)	112791

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Gerhard schymik (obs)-2018	TAVI	NA	9 (6.8 %)	NA	NA	NA	NA	64.8 +/-N6.6	0.66 +/-0.15	N
	SAVR	NA	3 (3.2 %)	NA	NA	NA	NA	64.5+/-6.6	0.64 +/-0.20	N
Frerker (obs)-2017	TAVI	190 (23.6 %)	33 (4.1 %)	164 (20.4 %)	85 (10.6 %)	5 (0.6 %)	14 (1.7 %)	NA	NA	614 (7
	SAVR	190 (23.6 %)	33 (4.1 %)	164 (20.4 %)	85 (10.6 %)	5 (0.6 %)	14 (1.7 %)	NA	NA	614 (7
Rosato (obs)-2016	TAVI	53 (14.9 %)	15 (4.2%)	56 (15.8 %)	NA	36 (10.1 %)	65 (18.3 %)	NA	0.67 +/- 0.26	180 (5
	SAVR	57(16.1 %)	15 (4.2 %)	45 (12.7 %)	NA	31 (8.7 %)	70 (19.7 %)	NA	0.71 +/- 0.25	182 (5
Piazza (obs) - 2013	TAVI	NA	NA	NA	NA	NA	NA	NA	NA	N
	SAVR	NA	NA	NA	NA	NA	NA	NA	NA	N

EVOLUT = Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement. LRT: Transcatheter Aortic valve replacement in Low-Risk Patients with Symptomatic Severe Aortic stenosis. NA, Not available;NOTION = Nordic Aortic Valve Intervention; PARTNER = Placement of Aortic Transcatheter Valve trial; RCT, Randomized controlled trial; STACCATO = Transapical Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation.

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Table1.B Baseline characteristics

Study	Publication year	Design	Follow up	Sample size	STS score (mean)	Logistic Euro score (mean)	Age in years (mean)	Male (per
PARTNER3	2019	RCT	1 year	TAVI 496	1.9+/-0.7	NA	73.3+/-5.8	335
				SAVR 494	1.9+/-0.6	NA	73.6+/-6.1	323
EVOLUT	2019	RCT	2 years	TAVI 725	1.9+/-0.7	NA	74.1+/-5.8	46
				SAVR 678	1.9+/-0.7	NA	73.6+/-5.9	449
SURTAVI-STS<3	2018	RCT	1 year	TAVI 131	2.3+/-0.5	NA	75.1+/-6.5	89
				SAVR 123	2.3+/-0.5	NA	75.4+/-5.5	84
NOTION	2015	RCT	5 Years	TAVI 145	2.9+/-1.6	II -1.9+/-1.2 (I- 8.4+/-4.0)	79.2+/-4.9	78
				SAVR 135	3.1+/-1.7	II - 2.0 +/-1.3 (I-8.9+/-5.5)	79.0+/-4.7	71
STACCATO	2012	RCT	3 months	TAVI 34	3.1+/-1.5	9.4+/-3.9	80+/-3.6	9(
				SAVR 36	3.4+/-1.2	10.3+/-5.8	82+/-4.4	12
Virtanen	2019	Observational Study	3 years	TAVI 304	2.1 (0.9)	II - 2.6 (1.4)	77.9	14
				SAVR 304	2.1 (0.5)	II - 2.5 (1.3)	78.1	151
LRT-Waksman	2018	Observational Study	30 days	TAVI 200	1.8+/-0.5	NA	73.6+/-6.1	123
				SAVR 719	1.6+/-0.6	NA	70+/-8.3	438
Bekeredjian	2018	Observational study	1 year	TAVI 6062	2.862 (0.010)	I- 112.879 (0.077)	78.869 (0.123)	3689
				SAVR 14487	2.743 (0.007)	I - 11.410 (0.079)	78.372 (0.058)	8866

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Schymick	2018	Observational Study	2 years	TAVI 132	2.16 +/- 0.65	I - 8.16 +/-2.15	80.7 +/- 3.1	36
				SAVR 93	1.72 +/- 0.56	I - 6.43 +/- 2.15	77.4 +/- 2.5	40
Frerker	2017	Observational Study	Index hospitalization only	TAVI 805	NA	I - 6.8+/-1.7	77.5 +/- 4.4	319
				SAVR 805	NA	I- 4.2 +/- 1.4	77.5 +/- 4.4	319
Rosato	2016	Observational study	3 years	TAVI 355	NA	II -2.6+/-0.8 (I -6.3+/-2.7)	80.1+/-6.4	20
				SAVR 355	NA	II- 2.5+/-0.8 (I - 6.3+/- 3.0)	80.0+/-5.1	209
Piazza	2012	Observational Study	1 year	TAVI 15	All < 4	NA	NA	
				SAVR 17	All < 4	NA	NA	

AVA, Aortic valve area; CVA, cerebrovascular accident; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; EF, Ejection fraction; ICD, Implantable cardioverter-defibrillator.;NA, Not available; NYHA, New York heart association; PAD, Peripheral arterial disease.

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Figure 1. PRISMA flow chart

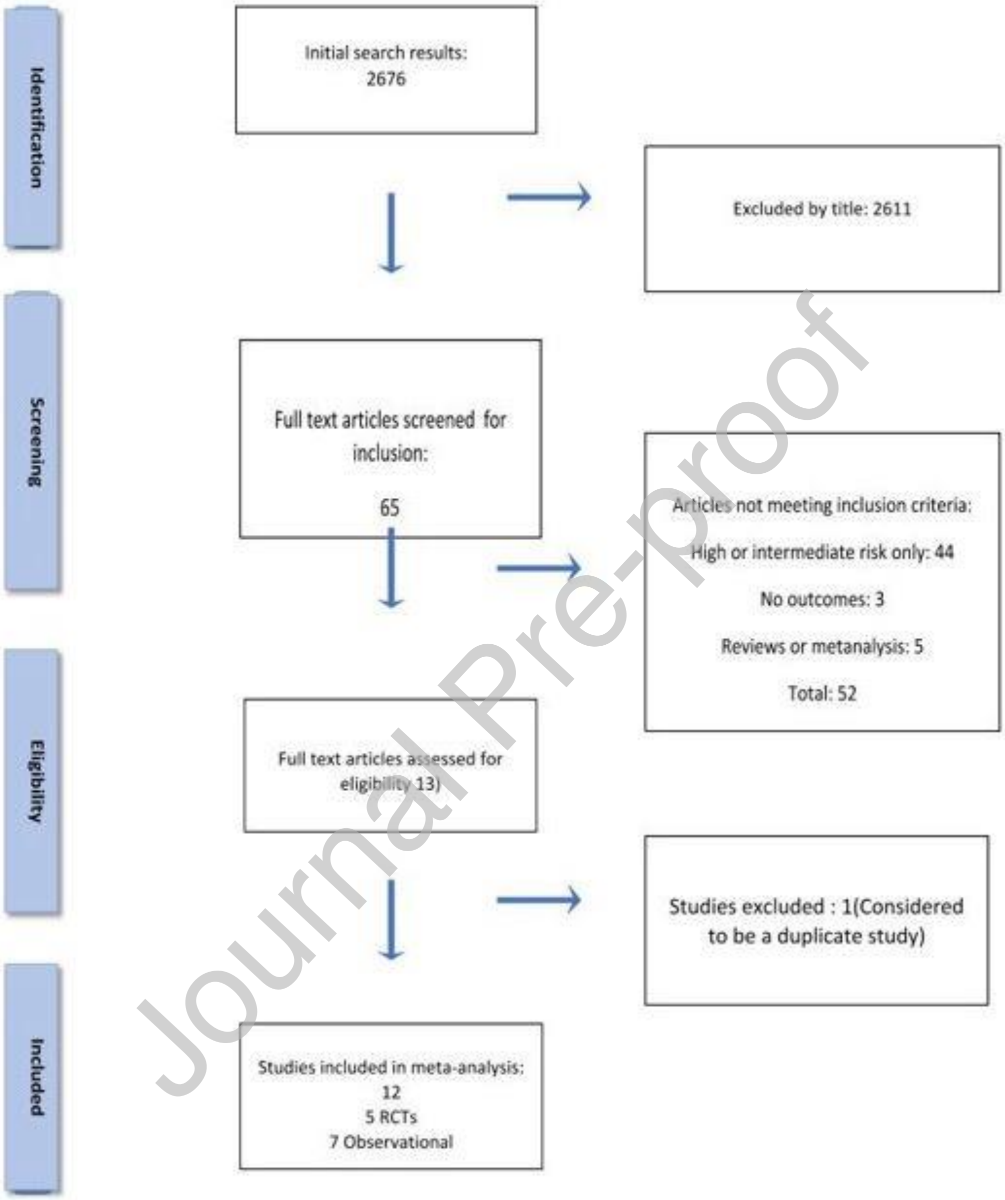

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Figure:2

Forest plots of all-study analysis A)Short term all-cause mortality B)1-year all-cause mortality C)short term stroke D)1-year stroke E)Short term cardiac mortality F)1-year cardiac mortality. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.

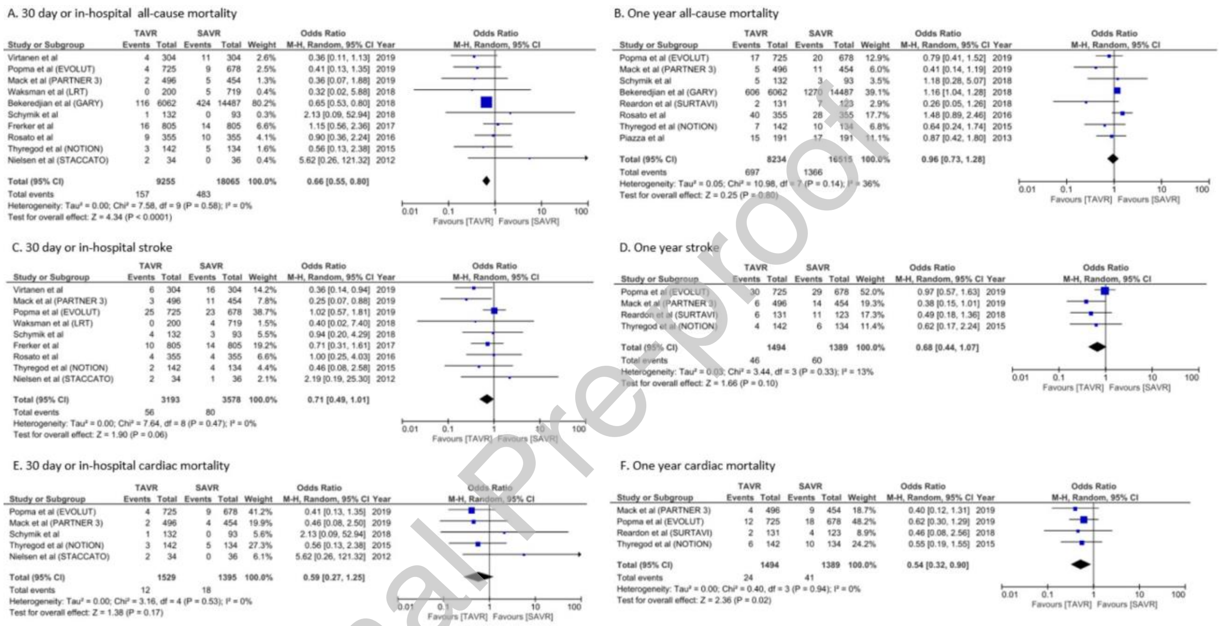

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Figure:3

Forest plots of all-study analysis G)Short term new onset or worsening AF H) 1-year AF I)Short term new PPM implantation J) 1-year PPM implantation K)Short term AKI stage II and III L) 1-year AKI stage II and III. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.

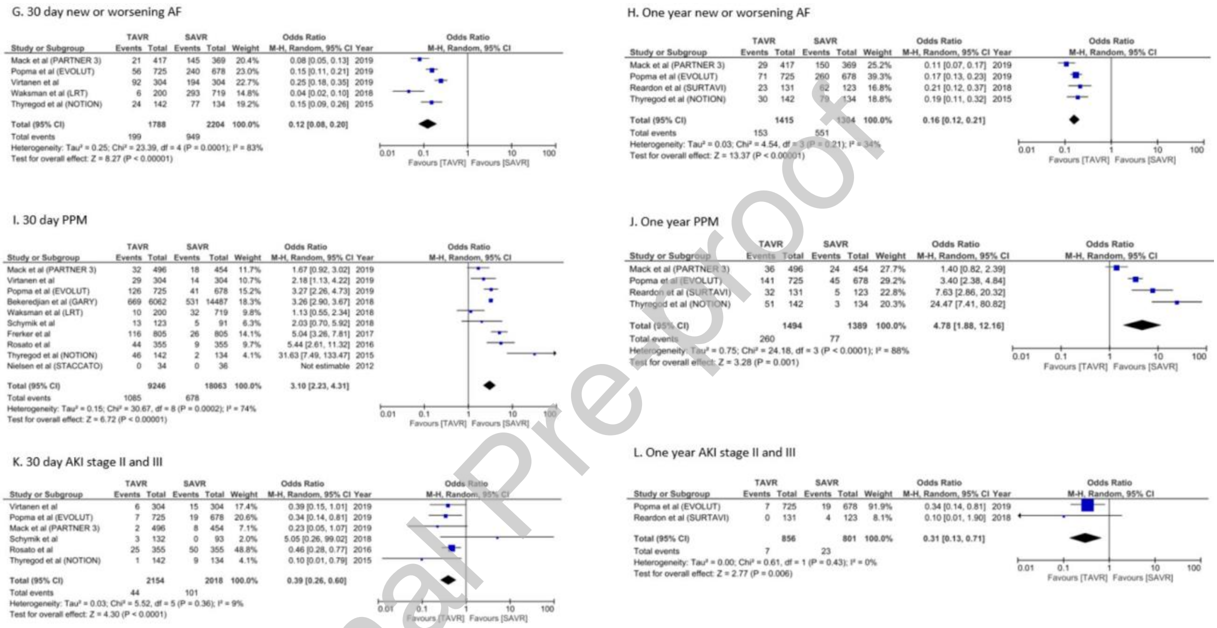

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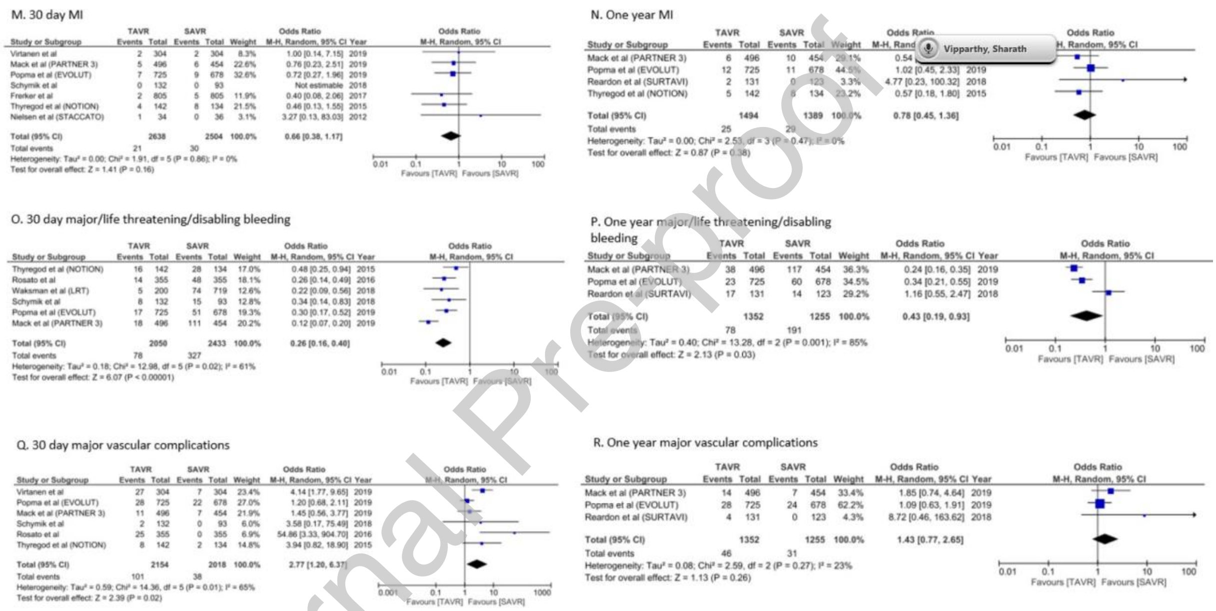
Figure:4

Forest plots of all-study analysis M) Short term MI N) 1-year MI O)Short term major/life-threatening/disabling bleeding P) 1-year major/life-threatening/disabling bleeding Q)Short term major vascular complications R) 1-year major vascular complications. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.



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Supplemental Figure 1:

Forest plots of RCT only analyses A)Short term all-cause mortality, B) 1-year all-cause mortality, C)short term stroke, D) 1-year stroke, E)Short term cardiac mortality, F) 1-year cardiac mortality. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.

Supplemental Figure 2:

Forest plots of RCT-only analyses G) Short term new onset or worsening AF, H) 1-year AF, I)Short term new PPM implantation, J) 1-year PPM implantation, K)Short term AKI stage II and III, L) 1-year AKI stage II and III. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.

Supplemental Figure 3:

Forest plots of RCT only analyses M)Short term MI, N) 1-year MI, O)Short term major/life-threatening/disabling bleeding, P) 1-year major/life-threatening/disabling bleeding, Q)Short term major vascular complications, R) 1-year major vascular complications. Data are events in each group and weighted odds ratios. The horizontal line is 95% CI. The diamond shape is the pooled mean difference of all studies.

Supplemental Figure 4:

Funnel plots:A) Short term all-cause mortality, B) 1-year all-cause mortality, C) Short term stroke, D) Short term cardiac mortality, E) Short term new PPM implantation, F) Short term MI, G) Short term major/life-threatening/disabling bleeding.

Supplemental Figure 5:

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Forest plots of PPM by valve type, A) short-term PPM by valve type B) 1-year PPM by valve type.

Supplemental Figure 6: Quality assessment of RCT: Risk of Bias summary

EVOLUT = Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement;NOTION = Nordic Aortic Valve Intervention; PARTNER = Placement of Aortic Transcatheter Valve trial; STACCATO = Transapical Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation.

Supplemental Figure 7: Quality assessment of observational studies

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