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An updated meta-analysis of TAVR in patients at intermediate risk for SAVR☆

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ABSTRACT

Background: Transcatheter aortic valve replacement (TAVR) has been approved for use in patients with severe aortic stenosis at intermediate, high and extreme surgical risk. This meta-analysis was performed to assess the safety and efficacy of TAVR compared to surgical aortic valve replacement (SAVR) in intermediate risk patients.
Methods: We searched PubMed, EMBASE, Web of science, and the Cochrane Central Register of Controlled Trials databases for studies comparing TAVR versus SAVR in patients at intermediate surgical risk, with a mean Society of Thoracic Surgeon score of 3–8% or a mean logistic European risk score of 10–20%. The primary endpoint was to assess the efficacy of TAVR compared to SAVR, defined as all-cause and cardiovascular mortality at 30-days, 1-year, and ≥2 years of follow-up. Secondary endpoints were the safety profile, comprising of cerebrovascular events, myocardial infarctions, permanent pacemaker placement, new onset atrial fibrillation, aortic regurgitation, vascular complications, major bleeding and acute kidney injury.
Results: This is the largest and most contemporary meta-analysis of 5647 intermediate risk patients in eleven studies published to date. There were no statistically significant differences in all-cause and cardiac mortality at 30 days, 1- year and >2-years of follow up. Acute kidney injury and atrial fibrillation occurred more frequently in patients treated with SAVR and permanent pacemaker implantation and aortic insufficiency were more frequent in patients treated with TAVR.
Conclusion: This meta-analysis suggests that for intermediate risk patients with severe aortic stenosis, TAVR has similar efficacy as SAVR but with a different adverse event profile.

1. Introduction

Recently published data have extended the indications for Transcathter Aortic Valve Replacement (TAVR) to the intermediate risk group of patients with severe aortic stenosis [1]. The outcomes have dispelled doubts and discouraging considerations on the applicability of TAVR in this group of patients. However, the claimed non-inferiority or even superiority of TAVR over Surgical Aortic Valve Replacement (SAVR) has been challenged in several aspects. Criticisms have been raised about the non-inferiority study designs- the validity of the propensity matched analysis and the inherent selection bias against the surgical arm [2]. Data on outcomes in intermediate and low risk patients are going to be vital as TAVR becomes the emerging treatment for aortic stenosis. Results so far in intermediate risk patients represent short- and medium-term findings. Long-term results up to 10 years still remains pivotal, specifically with concern to TAVR valve durability.

The ACC/AHA valvular heart disease guidelines from 2017 have modified the recommendations for TAVR. TAVR has a Class of Recommendation (COR)-I/Level of Evidence (LOE)-A, equivalent to SAVR, for symptomatic severe aortic stenosis for patients at high risk for SAVR [3]. In the intermediate surgical risk group, TAVR is also considered a reasonable alternative to SAVR with a COR-II A/LOE-B recommendation. As recently as March 2017, a second large randomized controlled trial was published comparing TAVR to SAVR in intermediate surgical risk patients [4]. The valve studied in this clinical trial is one of two commercially available valves in the United States. Unlike prior meta-analysis in intermediate risk patients which had included 7 studies and only the PARTNER 2A randomized control trial, this meta-analysis includes 11 studies and 5647 patients; the largest cohort to date. This study includes the recently published SURTAVI CoreValve pivotal trial which was not available to the authors of the prior meta-analysis.

2. Methods

2.1. Search strategy

A literature review was performed using methods specified in the PRISMA statement for reporting systematic reviews and meta-analyses [5]. Both controlled vocabulary terms (e.g., MeSH, EmTree) and keywords were utilized to search the following databases for studies that compared

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Table 1
Study characteristics of included studies in meta-analysis.

Author, year	Setting, country	Design, FU	Type of valve	STS score/Euroscore	VARC definition	Primary objective
Nielson, 2013	Two centers, Denmark	RCT 3 m	Edward SAPIEN	3.1 ± 1.5 = T 3.4 ± 1.2 = S	Yes	Composite of all-cause mortality, cerebral stroke and/or renal failure requiring hemodialysis at 30 days.
Osnabrugge, 2012	Single center Netherland	Cohort, 12 m	Core Valve	4–8 = T 4–8 = S	No	In-hospital and 1-year follow-up costs of patients undergoing
Piazza, 2013	Three centers Switzerland, Germany, Netherland	Cohort, 30d, 12 m	Core Valve	3–8 = T 3–8 = S	No	All-cause mortality at 1 year.
Weneweser, 2011	Single, Switzerland	Cohort, 30 m	Edward SAPIEN	6.4 ± 5.0 = T 4.8 ± 5.3 = S	No	All-cause mortality at 30 days and 30 months.
Macon, 2014	Single, USA	Cohort, In hospital	NR	4.24 ± 2.3 = T 4.84 ± 2.2 = S	No	Composite of in-hospital death, myocardial infarction, stroke and major vascular complications.
Latib, 2012	Single center, Italy	Case control, 30d, 12 m	Edwards- SAPIEN/ Edwards-SAPIEN XT Core Valve	4.57 ± 2.3 = T 4.60 ± 2.6 = S	Yes	All-cause mortality in both TF-TAVR and SAVR groups was at 30 days and 1 year respectively
Muneretto, 2015	Single center, Italy	Cohort, 30d, 24 m	Core Valve	6 ± 3.6 = T 4.7 ± 3.4 = S	Uc	All-cause mortality at 30 days
Castrodeza, 2016	Single Center, Spain	Cohort, 12 m, 24 m	Core Valve Edward SAPIEN XT/3	4.6 ± 2.1 = T 4.3 ± 2.4 = S	Yes	In-hospital and 1-year mortality, stroke at 1-year, and the combined endpoint of mortality and stroke at 1-year FU
Leon, 2016	Multicenter, USA, Canada	RCT 30d, 1 yr, 2 yr	Balloon expandable SAPIEN XT	5.8 ± 2.1 = T 5.8 ± 1.9 = S	Yes	Mortality from any cause or disabling stroke at 2 years.
Reardon, 2017	Multicenter, Multinational (USA, etc.)	RCT30d, 1 yr, 2 yr	Core Valve Evolut R	4.4 ± 1.5 = T 4.5 ± 1.6 = S// 11.9 ± 7.6 = T 11.6 ± 8.0 = S	Yes	Composite of death from any cause or disabling stroke at 24 months
Reardon et al., 2015	Multicenter USA	RCT 2 yr	CoreValve self-expanding	7.3 ± 3.0 = T 7.5 ± 3.3 = S	Yes	Long term mortality [2-Year]

Abbreviations: T = TAVR, S=SAVR, d = Day, m = Month, NR = Not Reported, RCT = Randomized Controlled Trials, FU = Follow-up, Yr = Year, UC=Unclear.

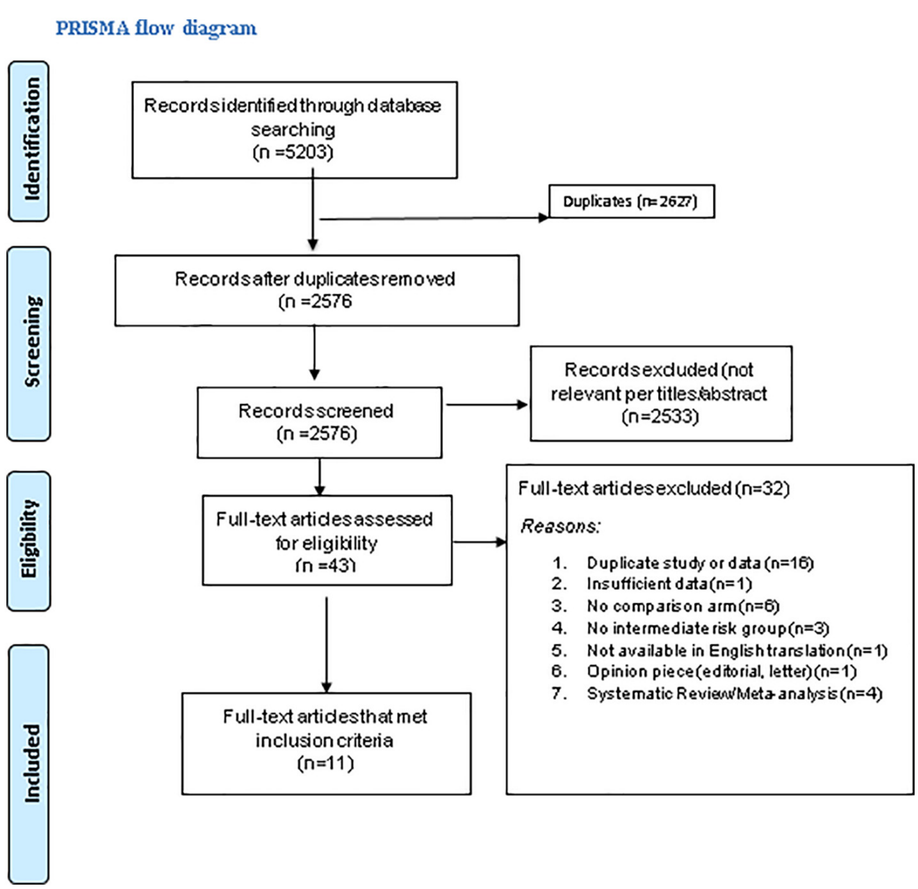


Fig. 1. PRISMA flow diagram demonstrating inclusion criteria.

outcomes after transcatheter aortic valve replacement/implantation (TAVR/TAVI) with surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis who were considered to have an intermediate surgical risk profile: Ovid/MEDLINE (1946–2017); PubMed/MEDLINE (1946–2017; Elsevier/Embase (1947–2017); Elsevier/Scopus (1823–2017); Wiley/Cochrane Library (1898–2017); Thomson-Reuters/Web of Science Core Collection (1900–2017); and ClinicalTrials.gov (1997–2017). Literature searches were completed on April 6, 2017. The complete Ovid/MEDLINE search strategy, upon which the other database searches were modeled, is available in Appendix 1.

2.2. Study selection, data extraction and quality assessment

The inclusion criteria were studies comparing TAVR with SAVR in intermediate surgical risk patients defined by a mean Society of Thoracic Surgeon (STS) score of 3–8% or a mean logistic European score of 10 to 20% [6–7]. The studies needed to have binary and continuous outcome data on TAVR patients. No publication date or language limits were applied. Both observational and randomized clinical interventional studies were included. The PRISMA checklist for Randomized Control Trials (RCTs) and MOOSE criteria for observational studies were implemented in this manuscript. Additionally, published abstracts, articles, conference proceedings, and completed clinical trials with results were included.

Two independent reviewers initially screened all the titles and abstracts for relevance. Disagreements were resolved by consensus. The same procedure was followed for full-text screening. Two reviewers read each article and resolved discordant choices by consensus. Letters, case studies, and systematic reviews/meta-analyses were excluded.

Initially, 5203 studies were screened and 11 studies were included in the meta-analysis. Of the 11 clinical studies, 4 were randomized controlled trials [4,8–10] while the other 7 were observational studies [11–17]. Seven of the clinical studies were conducted outside the US. All RCTs included in the meta-analysis were conducted in the United States. Most studies were conducted with the primary objective to assess for equivalence between TAVR and SAVR except one study which was a cost analysis study [18]. Five studies [4,9,11–12,15] predominantly used the Core valve for TAVR. Several studies were excluded due to: lack of SAVR arm as a comparison, TAVR arm with mean STS score <3% or mean Log Euroscore <10, studies using Partner 2A trial surgical arm for comparison, and studies with >70% low surgical risk aortic stenosis patients.

Information obtained from each article includes: author information, year of publication, sample size, types of valves used, study location, study design, number of centers involved, STS score, Logistic Euroscore, primary objective of each study, demographic information (age, gender), follow up period, cardiac variables (prior myocardial infraction, prior percutaneous intervention, coronary artery disease, coronary artery bypass graft, heart failure (per NYHA classification), stroke, peripheral arterial disease, COPD, tobacco use, atrial fibrillation, permanent pacemaker, diabetes mellitus, and hypertension for the descriptive analysis. All-cause mortality, cardiovascular mortality, stroke, myocardial infarction, aortic regurgitation, bleeding (major or life threatening), vascular access complications, permanent pacemaker placement, acute kidney injury, and

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short term mortality (30 days)						
Castrodeza, 2016	4	70	2	70	0.3%	2.00 [0.38, 10.57]
Latib, 2012	2	111	2	111	0.3%	1.00 [0.14, 6.97]
Leon, 2016	39	1011	41	1021	5.1%	0.96 [0.63, 1.48]
Macon, 2014	1	35	2	37	0.2%	0.53 [0.05, 5.57]
Muneretto, 2014	1	55	0	55	0.1%	3.00 [0.12, 72.08]
Nielsen, 2012	2	34	0	36	0.1%	5.29 [0.26, 106.27]
Osnabrugge, 2012	2	42	3	42	0.3%	0.67 [0.12, 3.79]
Piazza, 2013	20	255	18	255	2.5%	1.11 [0.60, 2.05]
Reardon, 2017	17	864	14	796	1.9%	1.12 [0.56, 2.25]
Wenaweser, 2011	17	257	7	107	1.3%	1.01 [0.43, 2.37]
Subtotal (95% CI)		**2734**		**2530**	**12.2%**	**1.05 [0.79, 1.39]**
Total events	105		89			
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 9 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.1.2 Medium term mortality (1 year)						
Castrodeza, 2016	8	70	5	70	0.8%	1.60 [0.55, 4.65]
Latib, 2012	7	111	9	111	1.0%	0.78 [0.30, 2.02]
Leon, 2016	123	1011	124	1021	17.4%	1.00 [0.79, 1.27]
Nielsen, 2012	4	34	0	36	0.1%	9.51 [0.53, 170.33]
Osnabrugge, 2012	7	42	5	42	0.8%	1.40 [0.48, 4.06]
Piazza, 2013	42	255	43	255	6.3%	0.98 [0.66, 1.44]
Reardon, 2017	58	864	54	796	7.4%	0.99 [0.69, 1.42]
Wenaweser, 2011	44	257	20	107	4.2%	0.92 [0.57, 1.48]
Subtotal (95% CI)		**2644**		**2438**	**38.1%**	**1.00 [0.86, 1.17]**
Total events	293		260			
Heterogeneity: Tau² = 0.00; Chi² = 3.90, df = 7 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
1.1.3 Long term mortality (=>2 year)						
Leon, 2016	166	1011	170	1021	24.9%	0.99 [0.81, 1.20]
Muneretto, 2014	6	55	3	55	0.5%	2.00 [0.53, 7.60]
Reardon, 2015	30	202	45	181	5.5%	0.60 [0.39, 0.91]
Reardon, 2017	99	864	92	796	13.3%	0.99 [0.76, 1.29]
Wenaweser, 2011	58	257	24	107	5.4%	1.01 [0.66, 1.53]
Subtotal (95% CI)		**2389**		**2160**	**49.7%**	**0.93 [0.76, 1.13]**
Total events	359		334			
Heterogeneity: Tau² = 0.02; Chi² = 6.27, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 0.75 (P = 0.45)						
Total (95% CI)		**7767**		**7128**	**100.0%**	**0.98 [0.89, 1.08]**
Total events	757		683			
Heterogeneity: Tau² = 0.00; Chi² = 13.71, df = 22 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Chi² = 0.60, df = 2 (P = 0.74), I² = 0%						

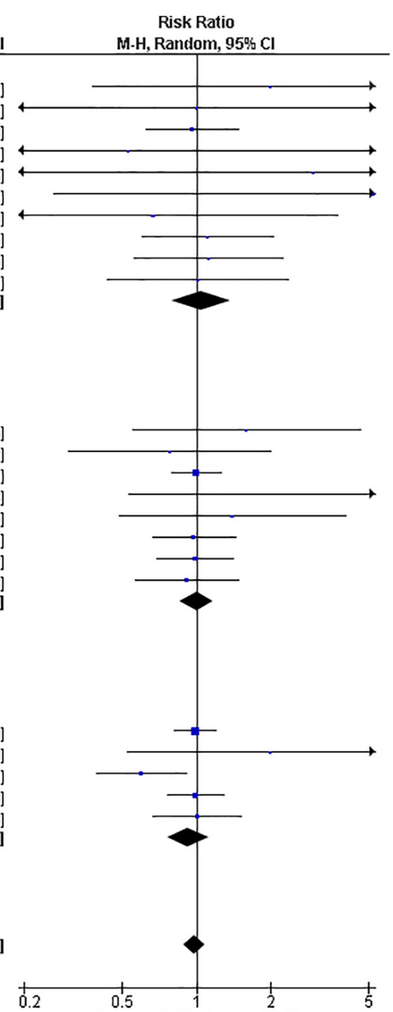


Fig. 2. Risk ratios and Forest plot of mortality outcomes.

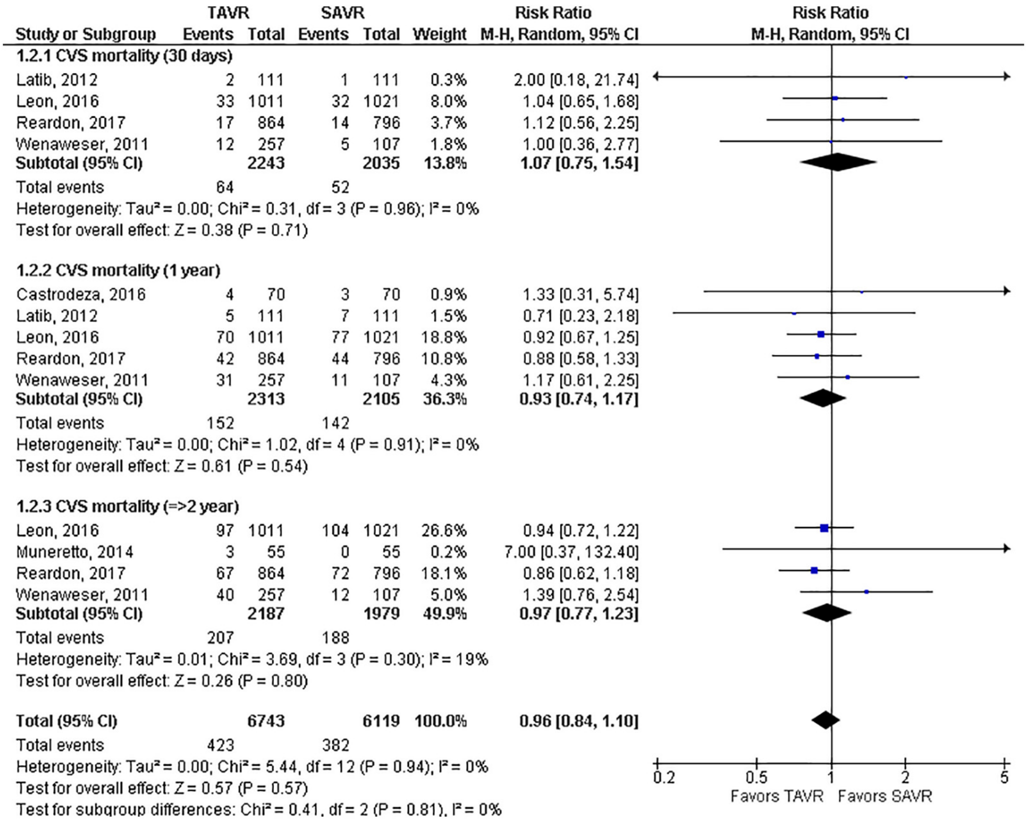


Fig. 3. Risk ratios and Forest plot of cardiovascular mortality.

atrial fibrillation variables were collected for statistical analysis. We evaluated the clinical studies for completeness of follow up.

Quality assessment of the RCTs were judged on allocation concealment, randomization, blinding, completion of follow-up, inclusion/exclusion criteria, and intention-to-treat analysis per PRISMA guidelines and Cochrane handbook [5,19]. Quality assessment of cohort studies was performed using New Castle Ottawa score system (NOS score) [20] details of which are attached in Appendix 2.

2.3. Endpoints

The primary endpoint was to assess the efficacy of TAVR compared to SAVR, defined as all-cause and cardiovascular mortality at 30-days, 1-year, and ≥2 years of follow-up. Secondary endpoints were the safety profile, comprising of cerebrovascular events, myocardial infarctions, permanent pacemaker placement, new onset atrial fibrillation, aortic regurgitation, vascular complications, major bleeding and acute kidney injury.

2.4. Statistical analysis

Statistical analyses were performed using Review Manager V.5.3 software (available from The Cochrane Collaboration) and STATA IC-13 (Stata Corp LP, Texas, US). A study or trial level pooled analysis of the included RCT's/Observational studies was performed to evaluate the efficacy of TAVR for intermediate risk patients and to assess the safety profile. The Mantel Haenszel risk ratio (MH RR) with 95% CI was calculated to measure the effect. The $\chi 2$ statistic was calculated and a formal test of heterogeneity was conducted. The I^2 index was used to summarize the proportion of the total variability in the estimates due to between-study variation [21]. I^2 of <25%, 25–50% and >50% was used to classify heterogeneity as low, moderate, and high. The random-effects model was used to assess the overall estimate [22]. Potential publication bias was assessed by using funnel plots of Standard Error (SE) of Relative Risk (RR) versus RR [23]. Sensitivity analysis was performed by removing studies with sample size <100. Subgroup analysis of the overall mortality was conducted based on study design. All tests were two tailed and a *p*-value ≤0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

There were 5203 studies initially screened. Table 1 summarizes all the studies included. The PRISMA diagram outlines the search strategy (Fig. 1). Eleven clinical studies with a total of 5647 patients: 2936

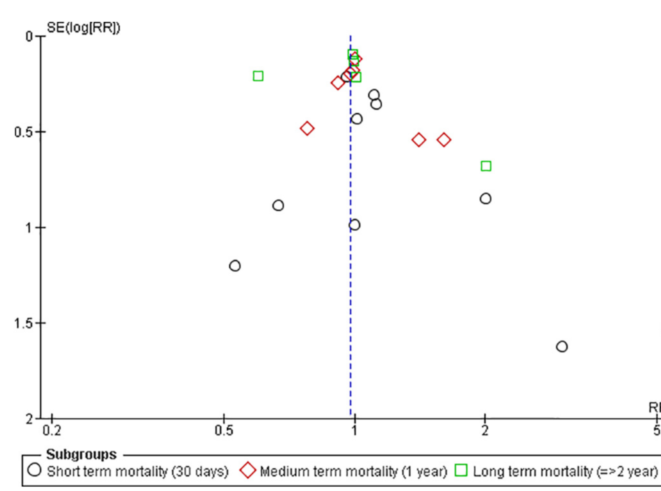


Fig. 4. Funnel plot for all-cause mortality.

patients assigned to the TAVR group and 2530 patients to the SAVR group were used in the meta-analysis.

3.2. Patient characteristics and interventions

In this meta-analysis, 51.9% of the patients were assigned to TAVR arm and 48.1% to the SAVR arm. The mean age in the TAVR and SAVR groups are 80.2 ± 1.7 and 80.3 ± 1.6 years respectively. There were more diabetics (18.1% vs. 16.7%), hypertensives (30.7% vs. 26.7%), and patients with prior Myocardial Infarction (MI) (8.5% vs. 7.3%), prior percutaneous coronary intervention (11.8% vs. 10.8%), and New York Heart Association Class (NYHA) III-IV (39.5% vs. 34.4%) in the TAVR arm as compared to the SAVR arm.

3.3. Outcomes

There were no statistically significant differences in all-cause mortality at 30-days (3.9% vs. 3.5%; MH-RR = 1.05, 95%, CI 0.79–1.39, $p = 0.74$), 1-year (11.1% vs. 10.6%; MH-RR = 1.00, 95%, CI 0.86–1.17, $p = 0.97$) and ≥2 year follow up (15% vs 15.4%; MH-RR = 0.93, 95%, CI 0.76–1.13, $p = 0.45$) between the 2 groups (Fig. 2).

There were no statistically significant differences in cardiovascular mortality in TAVR compared to SAVR at 30-days (2.8% vs. 2.6%; MH-RR = 1.07, 95% CI 0.75–1.54, $p = 0.71$), 1-year (6.6% vs. 6.8%; MH-RR = 0.93, 95% CI 0.74–1.17, $p = 0.54$) and ≥2 year follow up (9.5% vs. 9.5% MH-RR = 0.97, 95% CI: 0.77–1.23, $p = 0.57$) (Fig. 3).

There was no heterogeneity among the studies using random effect models in the combined efficacy endpoint for all-cause mortality and cardiovascular mortality. Funnel plots for all-cause mortality appeared symmetrical around the summary effect size or the line of no difference thus demonstrating minimal publication bias (Fig. 4).

Sensitivity analysis measured the effect of individual studies on the summary effect size. It showed that the summary effect after removing studies by Nielsen et al., Osnabruggae et al., and Macon et al. [9,12,14], showed no statistical difference at 30 days ($p = 0.78$), one year ($p = 0.89$), and longer follow up ($p = 0.99$) for primary efficacy endpoint.

Safety endpoints of MI and stroke were compared between the TAVR and SAVR groups at 30 days, 1 year at ≥2 years respectively (Figs. 5 and 6). There was no significant difference in MI between the TAVR and SAVR groups at 30-days (MH-RR = 0.70, 95% CI: 0.41–1.20, $p = 0.19$) 1-year (MH-RR = 0.95, 95% CI: 0.63–1.45, $p = 0.81$), and ≥2 years (MH-RR = 1.05, 95% CI: 0.73–1.50, p = 0.81). Similarly, no significant difference was found in stroke between TAVR compared with SAVR at 30 days (MH-RR = 0.81, 95% CI: 0.62–1.05, $p = 0.11$), 1-year (MH-RR = 0.90, 95% CI: 0.72–1.13, $p = 0.36$) and ≥2 years follow up (MH-RR = 1.02, 95% CI 0.83–1.27, $p = 0.84$).

There was a higher incidence of acute kidney injury (AKI) (Fig. 7A) and atrial fibrillation (AF) (Fig. 7B) with SAVR compared to TAVR (AKI: MH-RR = 0.41, 95% CI: 0.28–0.58, $p < 0.001$; AF: MH-RR = 0.31, 95% CI: 0.27–0.36, p < 0.001).

Vascular access complications (Fig. 8A) (MH-RR = 4.43, 95% CI: 1.61–12.14, $p = 0.004$), and permanent pacemaker placement (Fig. 8B) (MH-RR = 2.81, 95% CI: 1.43–5.52, $p = 0.003$) occurred at higher rates in the TAVR group compared to the SAVR group. There was no significant difference between the TAVR and SAVR groups in major/life threatening bleeding (MH-RR = 0.78 with 95% CI: 0.31–1.98, $p = 0.60$).

Post-procedure Aortic Regurgitation (AR) or Paravalvular Leak (PVL) was assessed at 30-days, 1-year, and ≥2 years based on its severity. At 30-days TAVR had significantly higher rate of PVL irrespective of severity (MH-RR: 5.05, 95% CI: 3.06–8.31, $p < 0.001$) (Fig. 9A). This difference persisted at both 1-year (MH-RR: 4.98, 95% CI: 2.94–8.46, p < 0.001) (Fig. 9B) and ≥2 years follow (MH-RR: 5.72, 95% CI: 3.21–10.18, p <

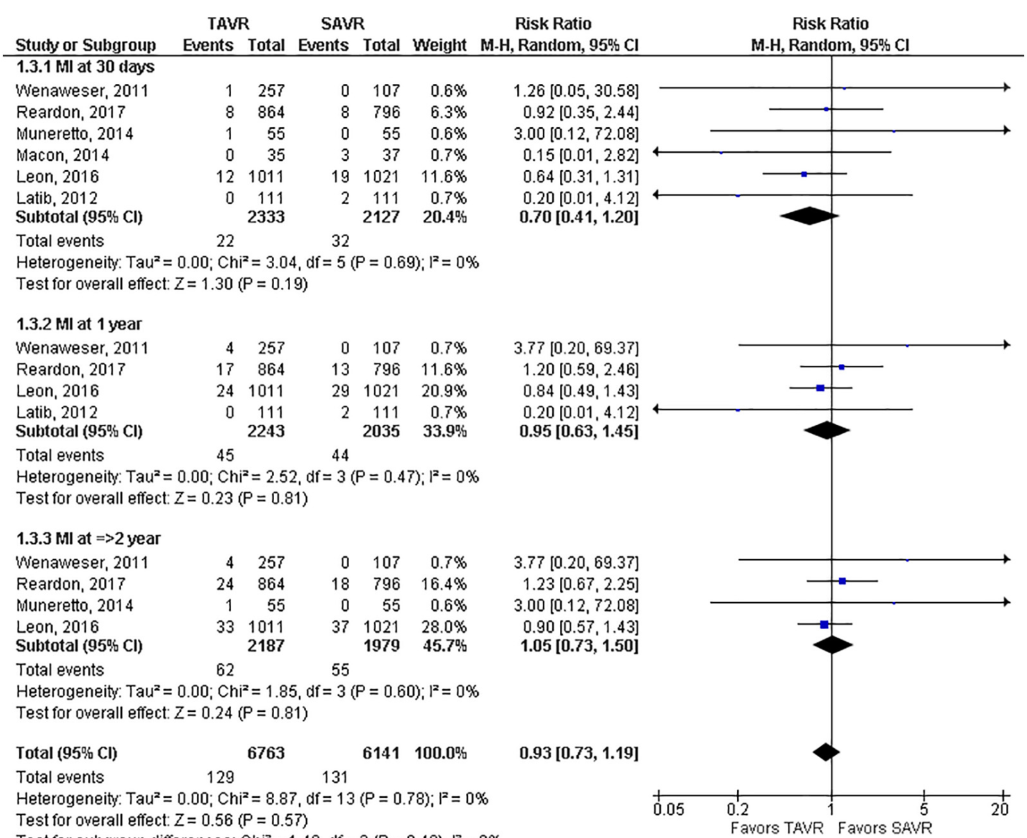


Fig. 5. Risk ratios and Forest plot of myocardial infarction.

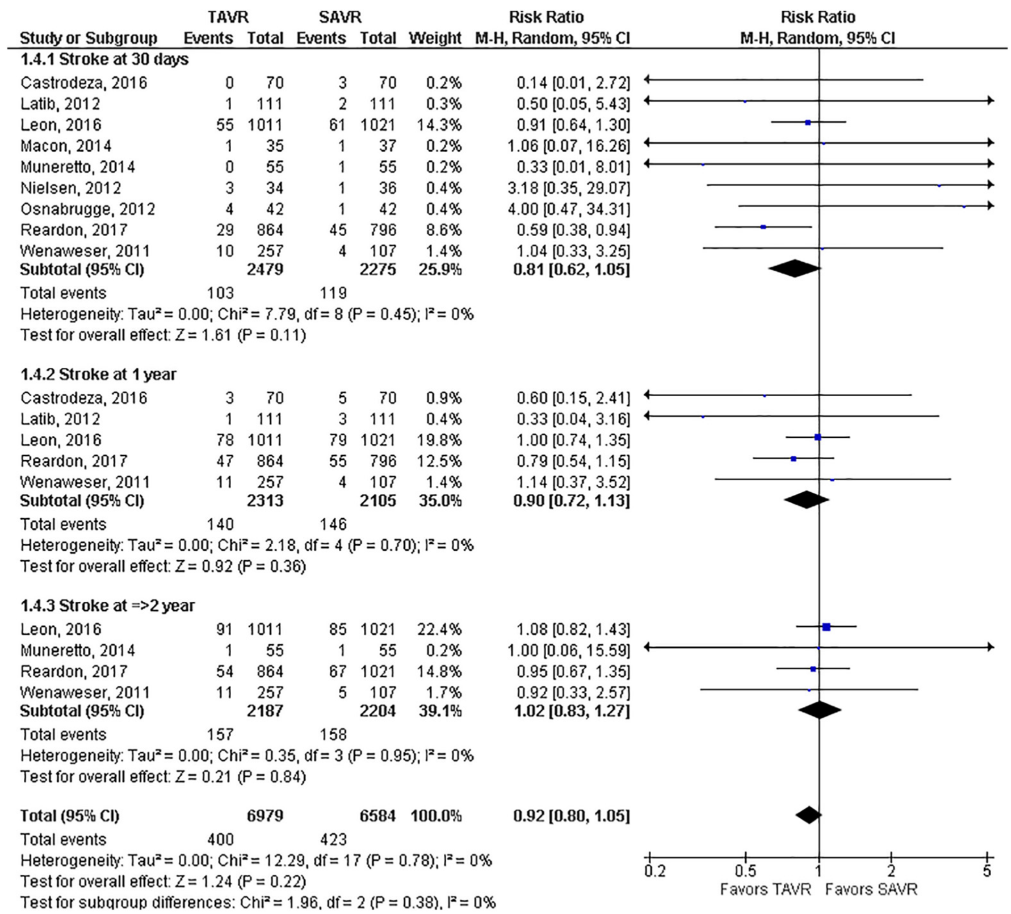


Fig. 6. Risk ratios and Forest plot of stroke.

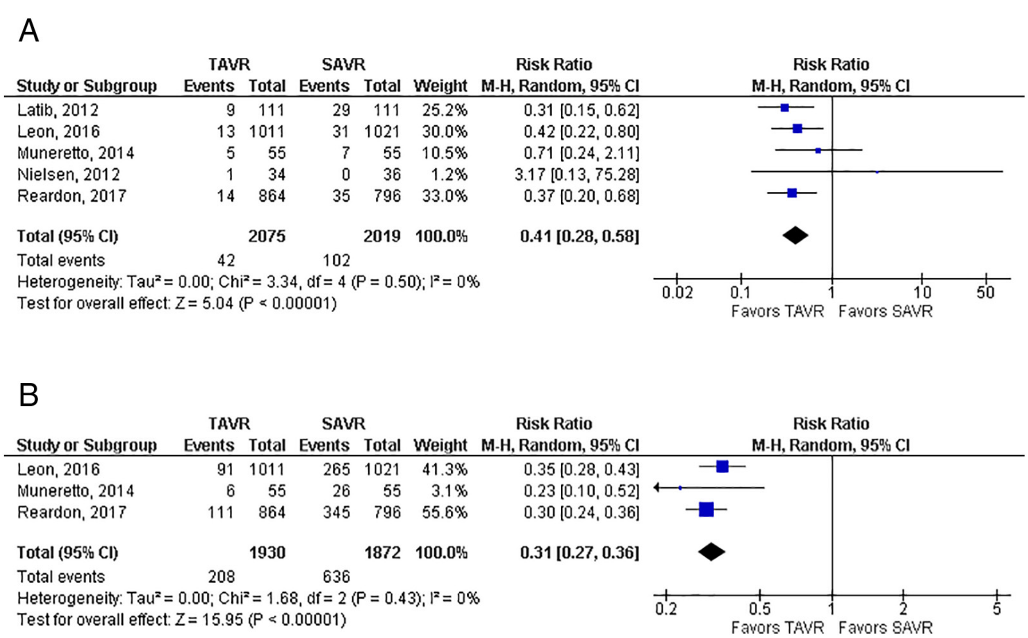


Fig. 7. Risk ratios and Forest plots of acute kidney injury (A) and atrial fibrillation (B).

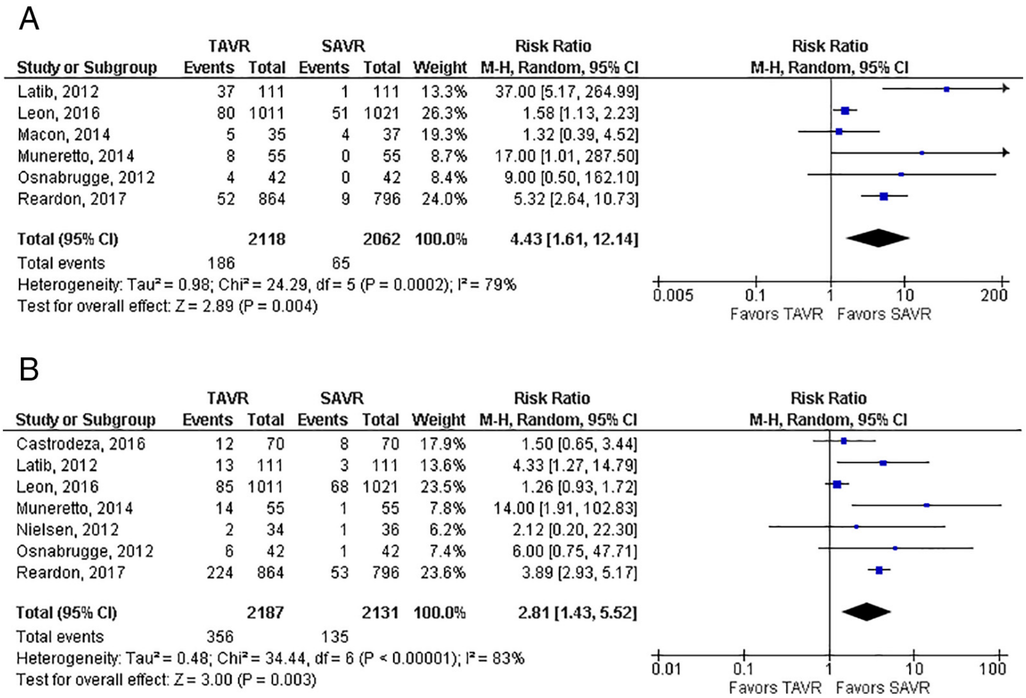


Fig. 8. Risk ratios and Forest plots of vascular complications (A) and pacemaker implantation (B).

0.001) (Fig. 9C). These trends were also true for more clinically relevant PVL with respect to moderate and severe PVL, although not statistically significant in these subgroups (MH-RR 2.81, 95% CI: 0.68–11.58, $p = 0.15$) and (MH-RR 2.22, 95% CI: 0.56–8.73, $p = 0.25$) respectively.

3.3.1. Subgroup analysis

Due to the clinical and methodological diversity in these studies within this meta-analysis, subgroup analysis as pre-specified in the methods section was performed.

Out of 11 studies, 4 studies were RCTs while others were observational cohort studies. There was no statistical difference noted in all-cause mortality at 30-days, 1-year, and ≥2 years follow up in the TAVR arm compared to SAVR arm based on the design of the studies (30 days: MH-RR = 1.05, 95% CI: 0.79–1.39, $p = 0.74$; 1-year: MH-RR = 1.00, 95% CI: 0.86–1.17, $p = 0.97$ and ≥2 years: MH-RR = 1.06, 95% CI: 0.74–1.51, $p = 0.76$) (Appendix 3).

4. Discussion

In the midst of a revolutionary paradigm shift as to how aortic stenosis is treated, conventional full sternotomy aortic valve replacement has been challenged by TAVR- in the prohibitive or extreme risk patient and now in the high and intermediate risk patients.

This contemporary meta-analysis of 11 studies including 5647 patients compares outcomes in intermediate risk patients with severe aortic stenosis.

Previously published randomized control trials have found no statistically significant differences in composite endpoints of death and stroke between TAVR and SAVR in the intermediate risk patient. The design of the Sapien-3 registry and claims of inherent selection bias favoring TAVR have been raised as criticism of these studies. The surgical arm in the PARTNER-2 study had patients with a lower ejection fraction; higher number of patients with moderate to severe mitral insufficiency and inclusion of a significant number of patients with untreated coronary artery disease [1,10]. Furthermore, the PARTNER 2 and SURTAVI trials had a minority of patients in the surgical arm that underwent minimally invasive aortic valve replacement and also the use of newer generation surgical valves such as sutureless valves was infrequent.

A meta-analysis such as this, provides confidence that in spite of criticisms of the individual studies, there is no statistical difference in all-cause mortality; cardiac mortality; stroke; myocardial infarction and major bleeding between SAVR and TAVR in the intermediate risk patient with severe AS.

The interplay of acute kidney injury (AKI) after aortic valve replacement is complex. Hypothermia, non-pulsatile blood flow during cardiopulmonary bypass, euvolemic hemodilution during open heart surgery, cholesterol emboli during aortic cannulation are all considered risk factors of AKI after SAVR [24]. The presumed mechanism of AKI after TAVR relates to contrast volume; cholesterol emboli from catheter manipulation and acute tubular necrosis from hypotension during pacing required for valve deployment. In this meta-analysis, the incidence of AKI was 59% significantly lower with TAVR than with SAVR.

In the randomized control trials, rates of Atrial Fibrillation (AF) have been higher after SAVR than after TAVR (31% vs. 11.7% in the Corevalve US Pivotal Trial and 16.0% vs. 8.6% in the PARTNER-2 trial) [9–10]. It is established that post-operative AF after SAVR is associated with higher mortality and the same appears to hold true for TAVR [25]. In this meta-analysis, the relative risk of developing AF was 69% significantly lower with TAVR than after SAVR. This is due to the less invasive nature of TAVR without leaving behind a surgical scar which contributes to atrial fibrillation in the SAVR population, predisposing the patient to AF. Reduction in rates of atrial fibrillation have significant clinical implications including theoretical long term reduction in morbidity. This is by consequence of potentially reduced rates of heart failure and stroke, which are known entities of long standing atrial fibrillation.

Despite newer generation TAVR devices with smaller profiles, vascular complications occur in 4.2–5.6% of procedures [26]. In this meta-analysis, vascular complications occurred at a significantly higher frequency with TAVR than with SAVR. In the earlier iterations of the device, aortic injury and iliac avulsions occurred more often due to the large size of the first generation sheaths. Current complications are usually at the access site with dissections, hematomas and thrombosis being the most frequent. These can most often be managed with endovascular techniques.

Permanent pacemaker rates after TAVR valves have been higher than after SAVR in most of the previously published studies with the exception of the PARTNER-2A study (8.5% vs 6.9% p-ns) [10]. Different platforms have different pacemaker rates and the rates are modifiable by implant techniques and impacted by the underlying degree of conduction system disease. In this meta-analysis, the rate of pacemaker implantation was 2.8 fold significantly higher in the TAVR arm. However, this finding is not confined to a specific TAVR valve type as this study did not differentiate outcomes between the two commercially available valves in the United States.

Similar to permanent pacemaker rates, the incidence of paravalvular leak (PVL) has been consistently higher following TAVR in all previous

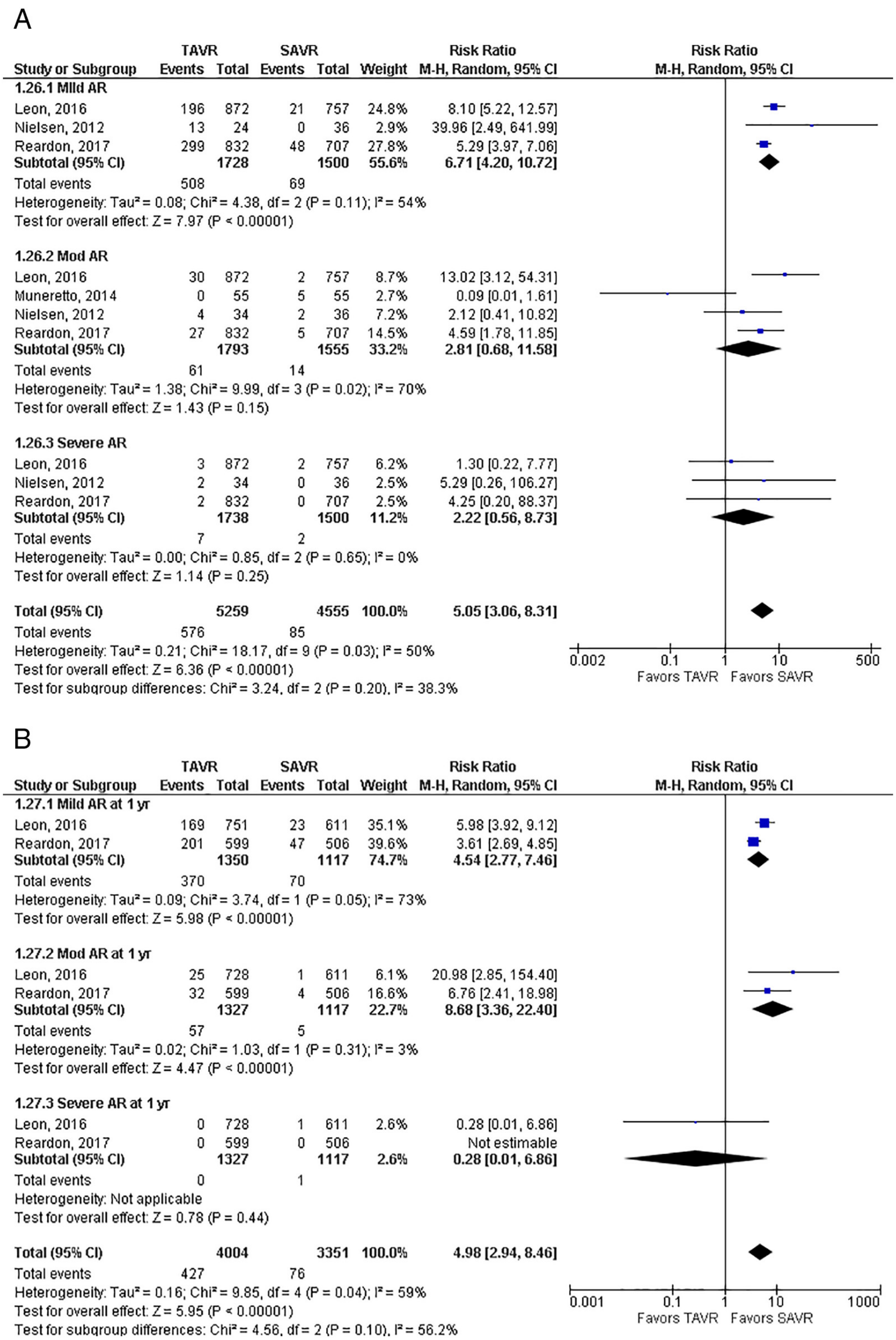


Fig. 9. Risk ratios and Forest plots of aortic insufficiency at 30 days (A), 1-year (B) and 2-years (C).

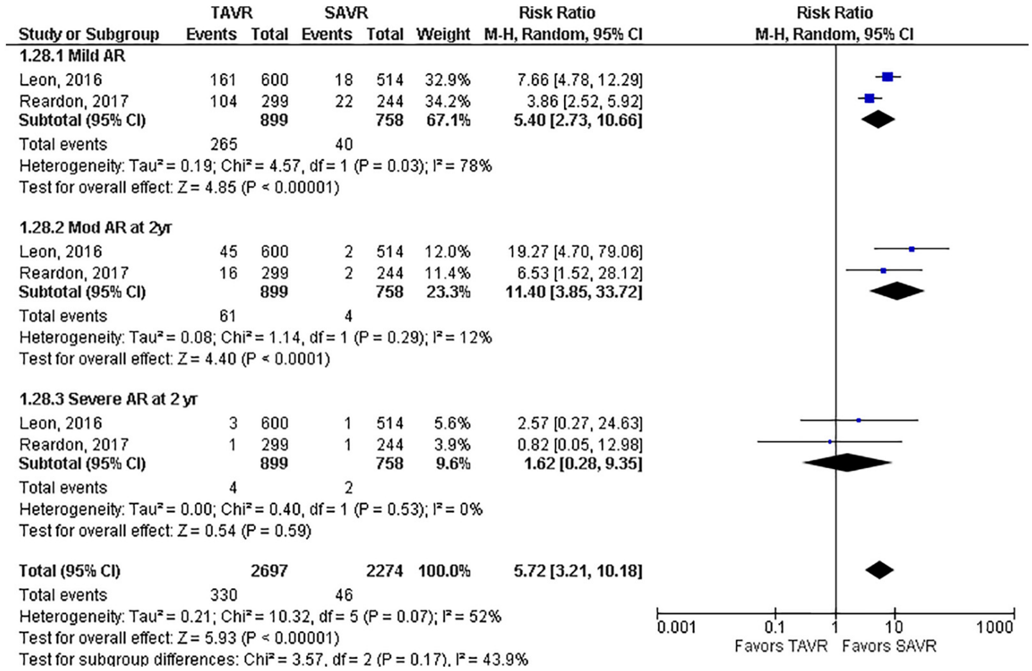


Fig. 9 (*continued*).

studies. In this meta-analysis, the post procedure total PVL - up to 2 years - was significantly higher in the TAVR group. Furthermore, PVL rates were significantly higher in the TAVR arm, attributed to significant higher rates of mild PVL. Moderate and severe PVL have been associated with increased mortality after TAVR. Although not statistically significant in this study, there was a trend for higher moderate and severe PVL rates in the TAVR arm. With the current generation of TAVR valves, the incidence of moderate/severe PVL has been reduced to as low as 2% in the S3i study [1].

Long-term data on durability of TAVR valves will be very valuable in the future as the clinical implications of bioprosthetic valve degeneration has not yet been determined in this setting. These results are eagerly awaited from the randomized control trials in the intermediate risk population over the next half decade. This will allow comparison with established data from surgical valve literature. A published meta-analysis of pooled observational studies found that surgical valve patients have a 94% freedom from structural degeneration at 10 years, which rapidly deteriorate thereafter [27]. Long standing durability, higher rates of PVL and pacemaker implantation in the TAVR arm should all be considered when weighing the risks and benefits of the optimal AVR approach for the individual patient.

There are limitations in this meta-analysis worth discussing. Comparison of SAVR with TAVR valves of different generations is a major limitation of this study. Since the intent was to limit the conclusion to intermediate risk patients, studies where the TAVR arm had <70% intermediate risk AS patients were excluded from this analysis which may underestimate the effect size. An inherent limitation of this meta-analysis is the inclusion of study-level data and not individual-level data that includes a minority of patients with low or high risk surgical despite the mean STS score of the entire study population is in the intermediate risk range. Moreover, all outcomes were not reported in every study and therefore variability exists in the total size of the subgroup cohorts, although these values are well defined in the representative forest plots. Also, consistent definitions of intermediate risk for surgical aortic valve replacement are variable among different studies. Furthermore, the impact of non-femoral access for TAVR cannot be ascertained in this study.

This meta-analysis provides evidence to support the routine use of TAVR in intermediate risk severe AS patients. There are 3 caveats when considering routine use of TAVR in this group of patients: (1) the long-term durability of TAVR valves is unknown, (2) the higher incidence of permanent pacemaker implantation may be an important consideration in these lower risk patients and (3) TAVR valves have not been compared to minimally invasive aortic valve replacement and with sutureless surgical valves. Further randomized studies with long-term outcomes would be ideal to address these issues. Specifically with regards to sutureless valves, they particularly confer an advantage in patients where controlling cardiopulmonary bypass comorbidity is imperative, in calcified roots, porcelain aortas, and patients with prior implantation of aortic homografts [28]. Although it is unlikely there will be a randomized control trial comparing TAVR valves and sutureless surgical valves, especially as the conclusion of the current low risk TAVR trials are approaching, there is a published meta-analysis comparing the two groups [29]. Similar to the message of this current meta-analysis, it supports the notion that patient selection is imperative when determining not only what type of procedure is performed but also what type of valve is used.

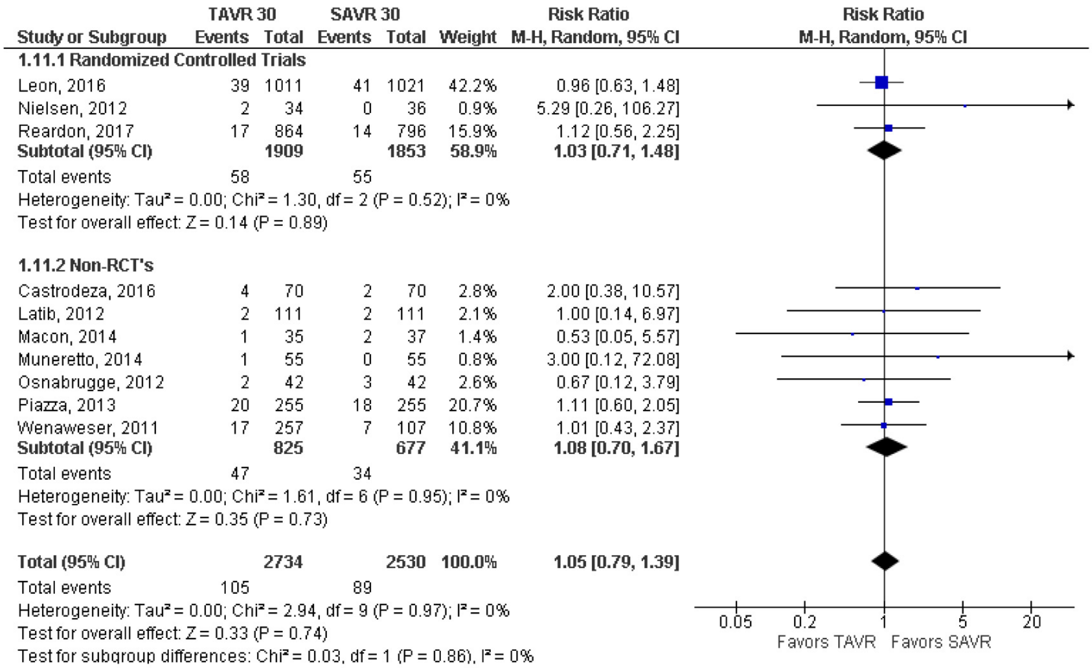
With the positive results in intermediate-risk patients, trials enrolling low risk patients have begun. One trial (PARTNER III) will evaluate all-cause mortality, stroke, and re-hospitalization at 1-year between TAVR using the SAPIEN-3 valve and SAVR in low surgical risk patients with severe AS, and the second study will utilize the CoreValve Evolut-R and examine all-cause mortality and disabling stroke at 2 years [30–31].

5. Conclusion

In conclusion, TAVR is as effective as SAVR, with comparable safety and efficacy in patients with severe aortic stenosis at intermediate surgical risk. This effect is independent of type of study design or sample size of the study. Future research should explore durability, cost effectiveness and quality of life in intermediate risk patients and compare them to minimally invasive SAVR with sutureless valves.

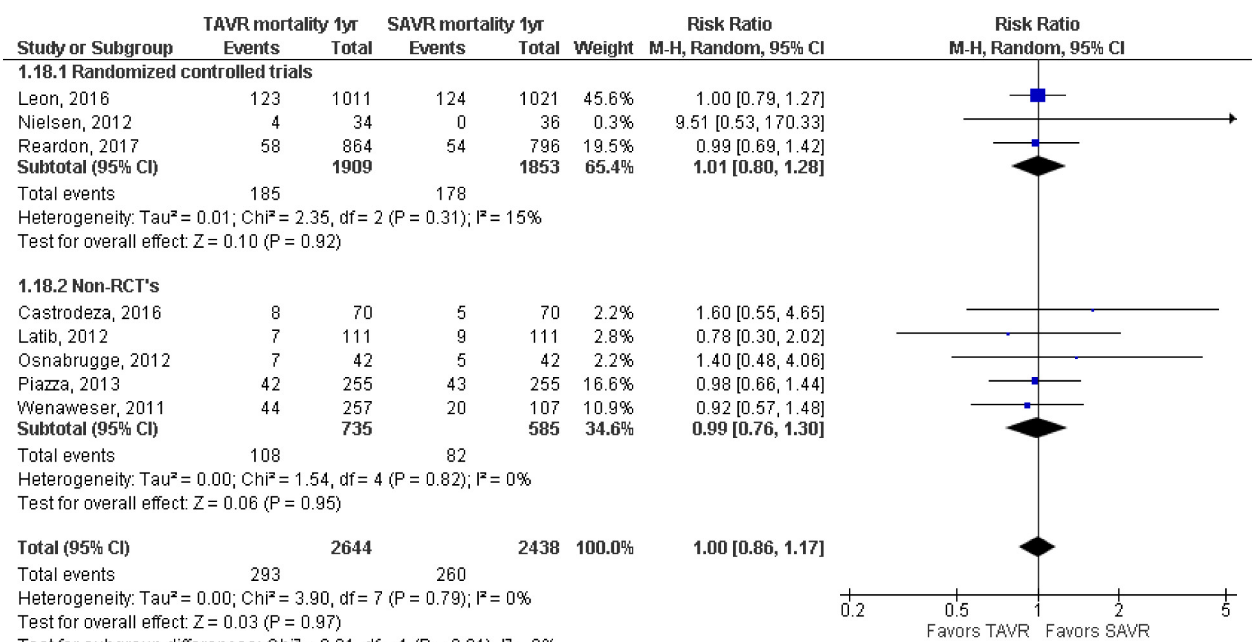
Appendix 1. Sub-group analysis at 30 days, 1-year, and 2-years

Sub-group analysis at 30 days



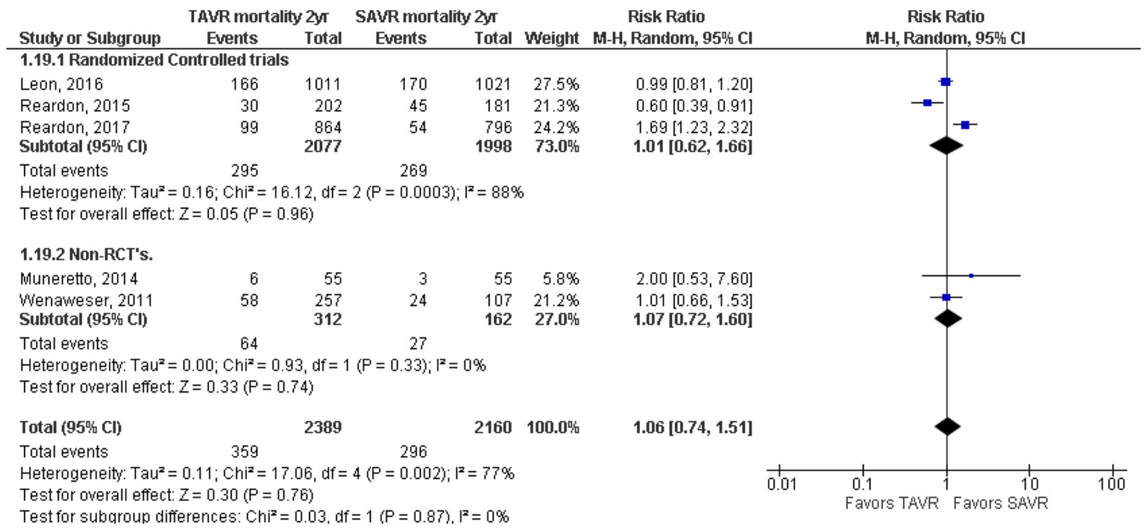
Study or Subgroup	TAVR 30 Events	TAVR 30 Total	SAVR 30 Events	SAVR 30 Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Randomized Controlled Trials						
Leon, 2016	39	1011	41	1021	42.2%	0.96 [0.63, 1.48]
Nielsen, 2012	2	34	0	36	0.9%	5.29 [0.26, 106.27]
Reardon, 2017	17	864	14	796	15.9%	1.12 [0.56, 2.25]
Subtotal (95% CI)		**1909**		**1853**	**58.9%**	**1.03 [0.71, 1.48]**
Total events	58		55			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.11.2 Non-RCT's						
Castrodeza, 2016	4	70	2	70	2.8%	2.00 [0.38, 10.57]
Latib, 2012	2	111	2	111	2.1%	1.00 [0.14, 6.97]
Macon, 2014	1	35	2	37	1.4%	0.53 [0.05, 5.57]
Muneretto, 2014	1	55	0	55	0.8%	3.00 [0.12, 72.08]
Osnabrugge, 2012	2	42	3	42	2.6%	0.67 [0.12, 3.79]
Piazza, 2013	20	255	18	255	20.7%	1.11 [0.60, 2.05]
Wenaweser, 2011	17	257	7	107	10.8%	1.01 [0.43, 2.37]
Subtotal (95% CI)		**825**		**677**	**41.1%**	**1.08 [0.70, 1.67]**
Total events	47		34			
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 6 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**2734**		**2530**	**100.0%**	**1.05 [0.79, 1.39]**
Total events	105		89			
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 9 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						

Sub-group analysis at 1-year



Study or Subgroup	TAVR mortality 1yr Events	TAVR mortality 1yr Total	SAVR mortality 1yr Events	SAVR mortality 1yr Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Randomized controlled trials						
Leon, 2016	123	1011	124	1021	45.6%	1.00 [0.79, 1.27]
Nielsen, 2012	4	34	0	36	0.3%	9.51 [0.53, 170.33]
Reardon, 2017	58	864	54	796	19.5%	0.99 [0.69, 1.42]
Subtotal (95% CI)		**1909**		**1853**	**65.4%**	**1.01 [0.80, 1.28]**
Total events	185		178			
Heterogeneity: Tau² = 0.01; Chi² = 2.35, df = 2 (P = 0.31); I² = 15%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.18.2 Non-RCT's						
Castrodeza, 2016	8	70	5	70	2.2%	1.60 [0.55, 4.65]
Latib, 2012	7	111	9	111	2.8%	0.78 [0.30, 2.02]
Osnabrugge, 2012	7	42	5	42	2.2%	1.40 [0.48, 4.06]
Piazza, 2013	42	255	43	255	16.6%	0.98 [0.66, 1.44]
Wenaweser, 2011	44	257	20	107	10.9%	0.92 [0.57, 1.48]
Subtotal (95% CI)		**735**		**585**	**34.6%**	**0.99 [0.76, 1.30]**
Total events	108		82			
Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 4 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**2644**		**2438**	**100.0%**	**1.00 [0.86, 1.17]**
Total events	293		260			
Heterogeneity: Tau² = 0.00; Chi² = 3.90, df = 7 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

Sub-group analysis at 2 years



2. Quality assessment of observational studies

Studies/authors	Selection				Compare control	Outcome		
Cohort	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts on basis of design or analysis	Assessment of outcome	FU long enough	Adequate FU
Osnabrugge, 2012	Yes	Yes	Yes	Yes	Yes	Yes	No	1 yr
Weneweser, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Macon, 2014	Uc	Uc	Uc	Uc	Uc	Uc	No	No
Muneretto, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Castrodeza, 2016	Yes	Yes	Yes	Yes	yes	Yes	No	No
Piazza, 2013	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Case-control	Selection				Compare cases and controls	Exposure		
	Case definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls based on design or analysis	Ascertainment of exposure	Same method of ascertain cases and control	Non-response rate
Latib, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC

NB: UC = Unclear, FU = Follow-Up.

3. Ovid MEDLINE search strategy

	Ovid MEDLINE search strategy
1	exp Aorta/
2	aorta.ab,kw,ti.
3	aortic.ab,kw,ti.
4	1 or 2 or 3
5	exp "Prostheses and Implants"/
6	exp Aortic Valve/
7	prosthes?s.ab,kw,ti.
8	(valve or valves or valvular).ab,kw,ti.
9	"xerotransplant*".ab,kw,ti.
10	"implant*".ab,kw,ti.
11	"replacement*".ab,kw,ti.

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(*continued*)

	Ovid MEDLINE search strategy
12	exp Heart Valve Prosthesis Implantation/
13	5 or 7 or 8 or 9 or 10 or 11 or 12
14	4 and 13
15	6 or 14
16	percutaneous.ab,kw,ti.
17	transapical.ab,kw,ti.
18	trans-apical.ab,kw,ti.
19	17 or 18
20	transarterial.ab,kw,ti.
21	trans-arterial.ab,kw,ti.
22	20 or 21
23	transaxillary.ab,kw,ti.
24	trans-axillary.ab,kw,ti.
25	23 or 24
26	transcarotid.ab,kw,ti.
27	trans-carotid.ab,kw,ti.
28	26 or 27
29	transcatheter.ab,kw,ti.
30	trans-catheter.ab,kw,ti.
31	29 or 30
32	transcutaneous.ab,kw,ti.
33	trans-cutaneous.ab,kw,ti.
34	32 or 33
35	transfemoral.ab,kw,ti.
36	trans-femoral.ab,kw,ti.
37	35 or 36
38	transiliac.ab,kw,ti.
39	trans-iliac.ab,kw,ti.
40	38 or 39
41	transluminal.ab,kw,ti.
42	trans-luminal.ab,kw,ti.
43	41 or 42
44	(transubclavian or transsubclavian).ab,kw,ti.
45	trans-subclavian.ab,kw,ti.
46	44 or 45
47	transvascular.ab,kw,ti.
48	trans-vascular.ab,kw,ti.
49	47 or 48
50	16 or 19 or 22 or 25 or 28 or 31 or 34 or 37 or 40 or 43 or 46 or 49
51	15 and 50
52	exp Transcatheter Aortic Valve Replacement/
53	TAVI.ab,kw,ti.
54	TAVR.ab,kw,ti.
55	52 or 53 or 54
56	51 or 55
57	exp Thoracic Surgery/or exp. Thoracic Surgical Procedures/
58	(surgery or surgeries or surgical).ab,kw,ti.
59	57 or 58
60	15 and 59
61	SAVR.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
62	60 or 61
63	56 and 62
64	“risk*”.ab,kw,ti.
65	intermediate.ab,kw,ti.
66	moderate.ab,kw,ti.
67	medium.ab,kw,ti.
68	low.ab,kw,ti.
69	65 or 66 or 67 or 68
70	64 and 69
71	63 and 70

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