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The Risk Factors of Myocardial Infraction after Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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Abstract

Background: Myocardial infarction (MI) is a frequent perioperative complication of transcatheter aortic valve replacement (TAVR) associated with significant morbidity and mortality in comparison to surgical aortic valve replacement (SAVR).

Objectives: This meta-analysis aims to assess the periprocedural incidence of MI, along with its risk factors in adult patients undergoing TAVR and SAVR due to severe aortic stenosis.

Methods: A systematic literature review of the major electronic databases was performed to identify relevant articles published from January 2007 to September 2017. A meta-analysis was performed to quantify the incidence and prognostic factors for periprocedural MI following TAVR via "Review Manager (REVMAN) 5.3 Copenhagen".

Results: A total of 32 studies with a combined cohort of 15961 patients undergoing TAVR were included in this meta-analysis. Using a fixed-effects model, it was found that the TAVR procedure may lead to significantly low risk of myocardial infarction as compared to the SAVR (0.5% *vs*. 1.1%; RR, 0.44; 95% CI, 0.25-0.75; P=0.003; I^2 =0%) The incidence and extent of periprocedural MI further to TAVR have been found associated with both short- and long-term mortality (p=0.002 and p=0.003, respectively).

Conclusions: Incidence of MI was associated with lower risk of TAVR compared to SAVR. However, further studies are warranted to assess the role of CK-MB and troponin, as a prognostic factor to predict the clinical outcome. This study provides an evidence-based analysis on risk factors that could help predict the incidence of perioperative myocardial infarction in patients with severe aortic stenosis undergoing TAVR in comparison with SAVR.

Keywords: Transcatheter aortic valve replacement; Myocardial infarction; Risk factors; Prognosis; Myocardial infarction; Transcatheter aortic valve replacement; Creatine kinase-MB; Valve academic research consortium; Leave-one-out; Coronary heart disease

Background

Transcatheter aortic valve replacement (TAVR) has become a valuable surgical intervention in high-risk and inoperable patients with severe aortic stenosis [1]. Ten years after the first surgery performed by Cribier et al., more than 50,000 patients have been treated via TAVR worldwide [2]. The TAVR surgical procedure is less invasive than the conventional surgical aortic valve replacement surgery (SAVR), as it does not involve aortic cross-clamping and cardioplegia. However, TAVR is still associated with several peri- and post-operative complications.

Myocardial injury is a frequent perioperative complication during cardiac surgery and its incidence is related to history of prior cardiovascular pathologies. Several valid hypotheses have been formulated on the underlying etiologies of myocardial injury, such as myocardial ischemia due to severe hypotension, direct trauma during balloon inflation or prosthetic valve placement, and coronary embolization due to aortic valve debris [3]. Although myocardial infarction is associated with complications occurring during either conventional cardiac surgery or percutaneous coronary intervention, there are no objective biomarkers for quantifying risk of MI in patients undergoing TAVR in standardized clinical practice [4,5]. Moreover, the incidence of myocardial infarction related to TVAR is still debated, as the definition of periprocedural myocardial infarction is still arbitrary, i.e., MI is considered to occur when the level of expression of the creatine kinase-MB (CK-MB) is 2-10 times higher than physiological values [6-8]. The Valve Academic Research Consortium (VARC) and the most up-to-date VARC-2 include internationally recognized definitions of endpoints for patients undergoing TAVR reflecting device, procedure and subject-related effectiveness and safety, which have been devised in an attempt of providing standardized criteria for clinical endpoints for TAVR clinical trials.

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Previous meta-analyses [9] did showed association of TF-TAVR with lower risk of MI compared to SAVR but the review did not account specifically to MI and their risk factors. This systematic review and meta-analysis aims to estimate the pooled incidence of myocardial infarction (MI), as defined via the VARC or VARC-2 criteria, identify its incidence and risk factors of MI in patients with severe aortic stenosis undergoing TAVR in comparison with SAVR.

Methods

Sources of data and guidelines for the systematic review

This systematic review and meta-analysis was performed in accordance with the "Preferred Reporting Items for Systematic reviews and Meta-Analysis" (PRISMA) [10] and the criteria set out in the "Meta-analysis of Observational Studies in Epidemiology" statements for systematic reviews and meta-analyses [11]. A systematic literature review of the major electronic databases of scientific and medical articles, i.e., PubMed, Embase, ScienceDirect, Web of Science, SciELO, BIOSIS and China National Knowledge Infrastructure (CNKI), was performed. Studies were included if published from January 2007 to March 10, 2018. The keywords used for retrieving relevant studies were: "aortic valve replacement", "transcatheter aortic valve replacement", "transcatheter aortic valve implantation", "surgical aortic valve implantation" "myocardial injury" and "myocardial infarction". To supplement such a review of the above-mentioned electronic databases, the bibliographies of all selected articles were carefully reviewed to verify whether further articles were eligible for inclusion in this systematic review and meta-analysis. The corresponding authors and/or first authors of the publications were contacted if any further information was required, whether results were unclear, or any potential data of interest were not reported.

Eligibility

Studies were considered eligible for inclusion in this systematic review ad meta-analysis, if they fulfilled the following criteria:

- The clinical data were included in an original, peer-reviewed study rather than review articles or conference abstracts, expert opinion, case reports, studies without full-text studies
- The patients reported in the study underwent TAVR and directly compared the prognostic results of SAVR due to severe aortic stenosis;
- The outcomes reported included incidence of myocardial infarction and/or any prognostic factors associated with it.

The study achieved high rating (i.e., six stars or above) as per the Newcastle-Ottawa Quality Assessment Scale (NOS) [12].

Data extraction and quality assessment

Two reviewers carefully analyzed the eligible studies for inclusion in this systematic review and meta-analysis, extracted clinical data of interest and assessed their methodological quality, independently. Data were extracted from each article via a custom-written Microsoft Excel spreadsheet that includes:

- The first author, publication year, study design (prospective/retrospective), country, sample size, diagnostic criteria, age duration of the study, number of patients involved in each of the TAVR and SAVR cohorts, mean follow-up time, and scientific/medical rigour of the studies.
- Characteristics of the patient population, including gender, age, NYHA functional class, comorbidity (hypertension, CAD, porcelain aorta, prior PCI, prior CABG, PAD, heart failure, prior MI, kidney disorders, early TAVR surgery);
- Risk factors includes prosthesis type, and procedural variables that includes success rate, approach applied such as transfemoral, transapical, transaortic, subclavian; prosthesis size (mm), time of procedure, 30-day outcome that include major vascular complications, major or life-threatening bleeding, pacemaker, stroke, death and 30-day mortality.

The "Critical Appraisal of the Health Research Literature" was deployed to assess the quality of selected studies reporting either the prevalence or incidence of a health-related condition [13]. The quality of the studies was rated on a scale from 1 (very poor) to 8 (high). Any disagreements were resolved by consensus.

Study endpoints

The primary endpoint in this study was incidence of MI, whilst the secondary endpoints included risk factors for MI, prognostic role of MI on clinical outcome (mortality) after TAVR. The Valve Academic Research Consortium (VARC) and the most up-to-date VARC-2 were adopted as definitions of endpoints.

Statistical analysis

Heterogeneity in the findings reported in selected studies was assessed via the Cochran's Q statistic, with $p<0.10$ indicating heterogeneity, and its extent quantified via the I^2 statistic, defined as low, moderate, and high for values of 25%, 50%, and 75% respectively. The pooled incidence of MI was computed, along with corresponding odds and hazards ratios. In case of significant heterogeneity between studies, the DerSimonian-Laird random-effects model was deployed; otherwise, the fixed-effects model was applied. Reported values are two-tailed and results were considered statistically significant if $p<0.05$, i.e., within 95% confidence intervals (C.I.). In presence of a high heterogeneity, a leave-one-out (LOO) type of sensitivity analysis approach was applied, thus discarding one study at a time to assess their relative influence on the pooled results. All statistical tests were performed via the software "Review Manager (REVMAN) 5.3 Copenhagen" (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Literature search

The flowchart in Figure 1 illustrates the selection procedure adopted to identify relevant published studies for inclusion in this systematic review and meta-analysis. A total of 322 potentially relevant articles were identified via both electronic and manual literature reviews. Further to the first screening by titles and abstracts evaluated against the above-mentioned inclusion and exclusion criteria, fifty-five articles remained for further investigation. Amongst the 267 articles excluded, 119 were duplicates, 145 were irrelevant, 2 were reviews and 1 study involved animal subjects instead of humans. Further assessment of the remaining 55 articles by full-texts led to 23 articles being excluded, 15 studies were irrelevant, and 8 studies did not report any diagnostic criteria in patients undergoing TAVR. Eventually, 32 articles were included in this systematic review and meta-analysis. The initial agreement on the eligibility of selected studies between reviewers was 93%, thus supporting a high level of agreement between the two reviewers.

Baseline characteristics of the TAVR *vs.* SAVR studies are reported in Table 1. The 32 included studies were carried out in fifteen countries

(USA, Canada, Italy, Germany, the Netherlands, UK, Poland, Japan, France, Switzerland, Sweden, New York, England, California and Israel) and involved 3890 patients while amongst 3778 patients belongs to TAVR while 3778 patients with SAVR. All selected studies were published from 2010 to 2017. Patients in 16 studies were diagnosed via the VARC II criteria, while in the other 19 studies via the VARC criteria. A total of 12,109 (61.6%) of the patients were males and the average patient age was above 80 years in all included studies except for 3 [14-16]. Patient information on prior history of coronary heart disease (CHD), surgical approach adopted, and valve types are presented in Table 1.

Primary outcome

Incidence of myocardial infarction: *TAVR vs. SAVR:* Nine (n=9) studies reported the history of myocardial infarction in pre- and post-surgery. Using a fixed-effects model, it was found that the TAVR procedure was associated with significantly lower risk of 30-day myocardial infarction as compared to SAVR (0.5% *vs.* 1.1%; RR, 0.44; 95% CI, 0.25-0.75; p=0.003; I^2 =0%) Figure 2. Visual assessment of the Egger's funnel plot did not indicate any publication bias (Supplementary Figure S1)

Sub-group analyses: To assess whether the incidence of MI varies between TAVR and SAVR, sub-group analyses was carried out.

- **Only in TAVR Cohort:** In the subgroup analysis, considering TAVR *vs.* SAVR studies, in which only TAVR studies. Ten (n=10) studies reported incidence of myocardial infarction before and after the surgery. As illustrated in Figure 3, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.0001), and the I^2 value (82%). Using a fixed-effects model, it was found that the Pre MI-procedure was significantly low risk of myocardial infarction as compared to the post MI (16.1% *vs.* 0.4%; RDIFF, 0.16; 95% CI, 0.15-0.17; P=0.0001; I2 =82%).
- **Only in SAVR Cohort:** Ten (n=10) studies reported incidence of myocardial infarction before and after the surgery. As illustrated in Figure 4, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.0001), and the I^2 value (90%). Using a fixed-effects model, it was found that the Pre MI-procedure may lead to significantly low risk of myocardial infarction as compared to the post MI (15.5% *vs.* 1.0%; RDIFF, 0.14; 95% CI, 0.13-0.16; P=0.0001; I^2 =90%).

Secondary outcomes: risk factors

Balloon expanded valve: Three (n=3) studies reported the balloon expanded valve. As illustrated in Figure 5, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.57), and the I^2 value (70%). Using a fixed-effects model, it was found that degree of Myocardial injury according to baseline and procedural characteristics for the TAVR and SAVR was not was not significantly associated to balloon expanded valve (8.3% *vs.* 7.7%; RR, 1.08; 95% CI, 0.83-1.42; P=0.57; I^2 =70%).

NYHA functional class

- **I-II:** Five (n=5) studies reported the NYHA I-II functional class. As illustrated in Figure 6, there was no significant evidence of

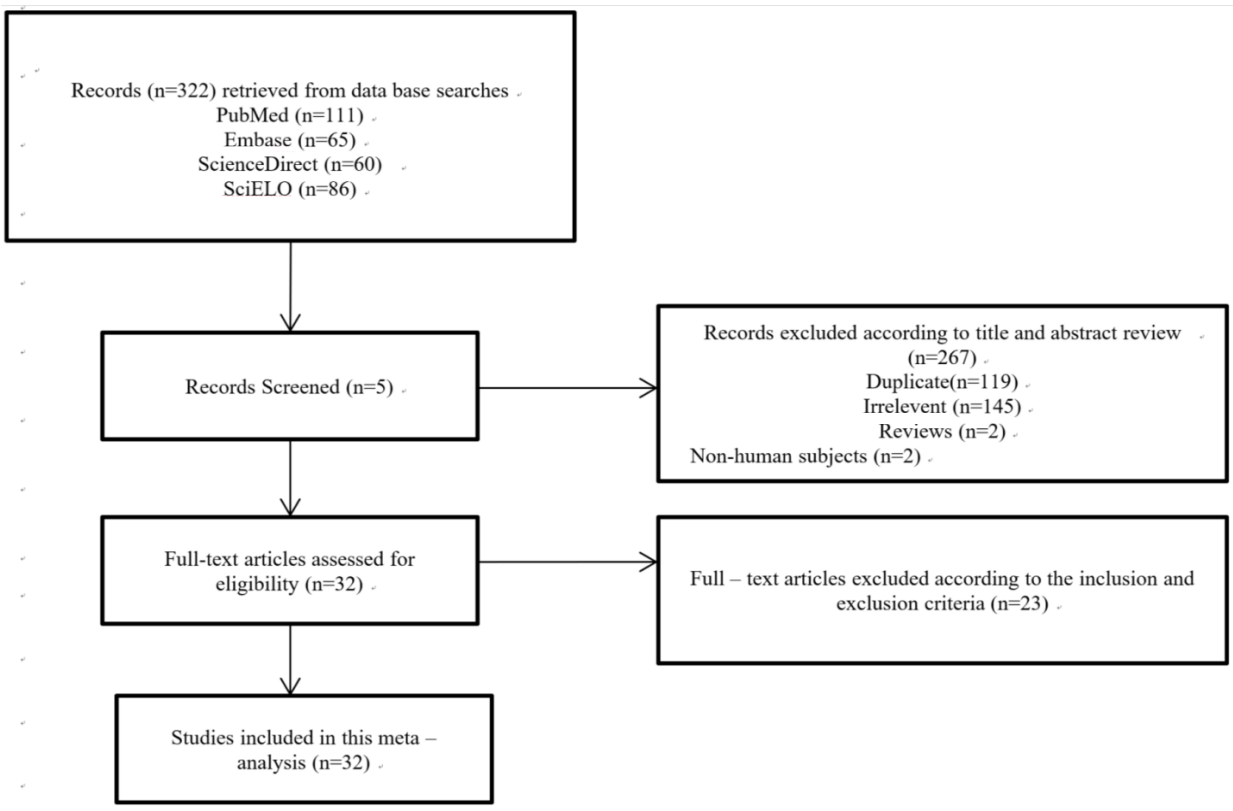

Figure 1: Study selection flow chart.

SS. No	Study	Year	Country	Study Design	Patients (N) (TAVR, SAVR)	Male (%) (TAVR, SAVR)	Age Years, (TAVR, SAVR)	History of CAD (%) (TAVR, SAVR)	TAVR VS SAVR				TA Approach (%) (TAVR, SAVR)	Self-expanding	Study Quality
									Pre MI		Post MI				
									TAVR	SAVR	TAVR	SAVR			
1	Latib et al. [29]	2012	Italy	Prospensity score matched case-control	111,111		80.5 ± 6.9, 79.4 ± 3.0		16	16	0	2			
2	Appel et al. [30]	2012	Sweden	Prospective	45,45	22(48.8), 22(48.8)	81 ± 8, 77 ± 5		13	4	1	1	16		
3	D Errigo et al. [31]	2012	Italy	Observational prospective	133,133	83,80	79.4 ± 7.4, 78.8 ± 6.9		16	17	1	1	123 (92.5)		
4	Tamburino et al. [32]	2012	Italy	Observational study	218,400	101 (46.3), 195 (48.75)	80.9 ± 5.2, 70.3 ± 9.9		42	32	0	1			
5	Smith et al. [33]	2011	New York		348, 351	201 (57.8), 198 (56.4)	83.6 ± 6.8, 84.5 ± 6.4		92	103	0	2	104, 103		
6	Wenaweser et al. [34]	2011	Switzerland	Prospective	257,107	113 (43.9), 54 (50.5)	82.1 ± 6.2, 79.7 ± 5.5	49,17	47	9	1	0	55		
7	Tamburino et al. [35]	2015	Italy	Observational study	650,650	267 (41.1), 263 (40.1)	80.5 ± 6.2, 80.3 ± 5.1		72	75	3	5	259		
8	Thourani et al. [36]	2016	USA	Observational study	1077, 944	665 (61.7), 519 (54.9)	81.9 ± 6.6, 81.6 ± 6.76	750 (70.0), 628 (67.0)	172	167	3	18			
9	Leon et al. [8]	2010	New York	PARTNER Trial multicenter	179, 179	82 (45.8), 84 (46.9)	83.1 ± 8.6, 83.2 ± 8.3	121, 133	33	47	0	0			
10	Reardon et al. [37]	2017	England	SURTAVI Trial randomized	879, 867	508 (57.8), 484 (55.8)	79.9 ± 6.2, 79.8 ± 6.0	549, 556	125	116	8	9			

P: Prospective, R: Retrospective, MI: Myocardial Infarction, VARC: Valve Academic Research Consortium, CHD: Coronary Heart Disease, TA: Transapical

Table 1: Basic characteristics of included studies (TAVR vs. SAVR).

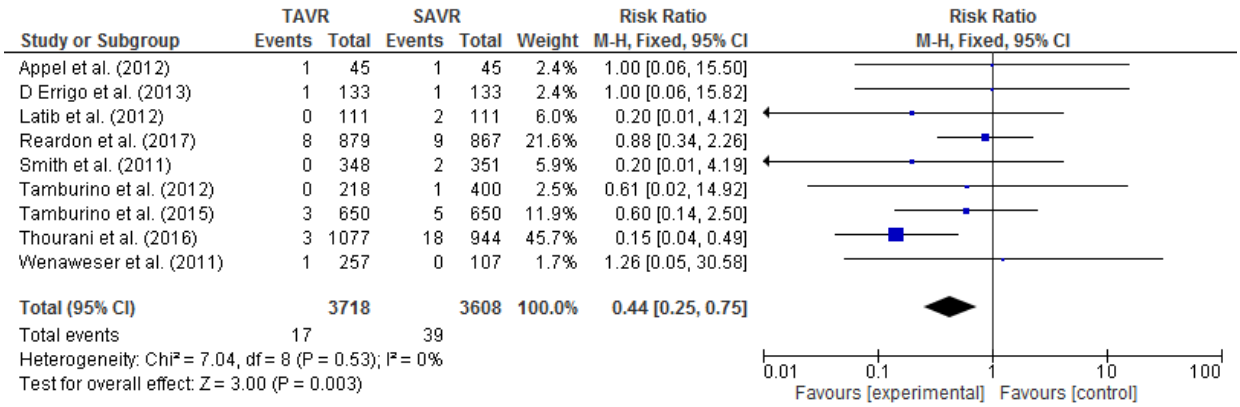

Figure 2: Comparison of incidence of myocardial infarction after the surgery between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

heterogeneity amongst trials as assessed by the Cochran's Q (p=0.12), and the I^2 value (33%). Using a fixed-effects model, it was found that the MI injury was lower in TAVR with I-II functional class as compared to the SAVR but the association was insignificant (53.9% *vs.* 51.7%; RR, 0.92; 95% CI, 0.84-1.02; P=0.12; I^2 =33%).

- **III-IV:** Nine (n=9) studies reported the NYHA III-IV functional class. As illustrated in Figure 7, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.13), and the I^2 value (81%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of III-IV functional class as compared to the SAVR (67.8% *vs.* 65.6%; RR, 1.02; 95% CI, 0.99-1.06; P=0.13; I^2 =81%).

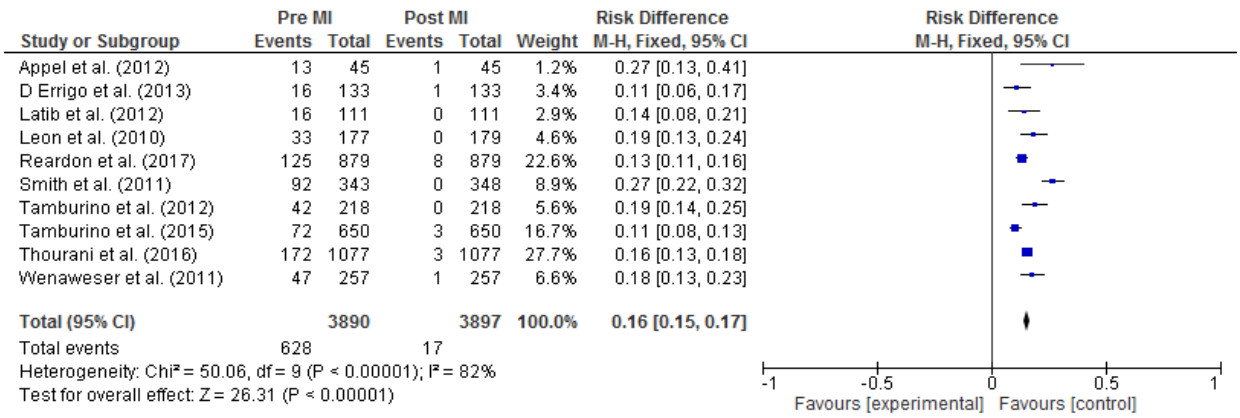

Figure 3: Comparison of incidence of myocardial infarction before and after the surgery between patients undergoing Transcatheter Aortic Valve Replacement (TAVR).

Coronary artery disease (CAD): Three (n=3) studies reported the clinical history. As illustrated in Figure 8, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.34), and the I^2 value (0%). Using a fixed-effects model, it was found that the SAVR may lead to insignificantly low risk of CAD as compared to the TAVR (61.2% *vs*. 54.7%; RR, 0.97; 95% CI, 0.91-1.03; P=0.34; I^2 =0%).

Prior Percutaneous coronary intervention (PCI): Nine (n=9) studies reported the prior percutaneous coronary intervention. As illustrated in Figure 9, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.0001), and the I^2 value (86%). Using a fixed-effects model, it was found that the TAVR may lead to significantly high risk of prior percutaneous coronary intervention as compared to the SAVR (25.1% *vs*. 19.9%; RR, 1.24; 95% CI, 1.14-1.34; P=0.0001; I^2 =86%).

Prior CABG: Seven (n=7) studies reported the prior coronary artery bypass graft. As illustrated in Figure 10, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.05), and the I^2 value (86%). Using a fixed-effects model, it was found that the TAVR may lead to significantly high risk of prior coronary artery bypass graft as compared to the SAVR (24.7% *vs*. 21.7%; RR, 1.10; 95% CI, 1.00-1.20; P=0.05; I^2 =86%).

Prior heart failure: Two (n=2) studies reported the prior heart failure. As illustrated in Figure 11, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.001), and the I^2 value (0%). Using a fixed-effects model, it was found that the TAVR may lead to significantly high risk of prior heart failure as compared to the SAVR (38.4% *vs*. 16.2%; RR, 2.40; 95% CI, 1.85-3.12; P=0.001; I^2 =0%).

Prior MI: Nine (n=9) studies reported the prior myocardial infarction. As illustrated in Figure 12, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.80), and the I^2 value (70%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of prior myocardial infarction as compared to the SAVR (16.0% *vs*. 15.6%; RR, 1.01; 95% CI, 0.91-1.12; P=0.80; I^2 =70%).

Chronic obstructive pulmonary disease (COPD): Six (n=6) studies reported the chronic obstructive pulmonary disease. As illustrated in Figure 13, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.33), and the I^2 value (76%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of prior myocardial infarction as compared to the SAVR (30.7% *vs*. 29.1%; RR, 1.04; 95% CI, 0.96-1.13; P=0.33; I^2 =76%).

STS-PROM (%): Five (n=5) studies reported the STS-PROM (%). As illustrated in Figure 14, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.31), and the I^2 value (60%). Using a fixed-effects model, it was found that the (MDIFF: -0.07, 95% CI, -0.20-0.07; P=0.31; I^2 =60%).

30 Days-outcomes

Major vascular complication: Eight (n=8) studies reported the major vascular complication. As illustrated in Figure 15, there was a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.001), and the I^2 value (90%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of prior myocardial infarction as compared to the SAVR (8.0% *vs*. 3.7%; RR, 2.36; 95% CI, 1.92-2.91; P=0.001; I^2 =90%).

Major or life-threatening bleeding: Five (n=5) studies reported the major or life-threatening bleeding. As illustrated in Figure 16, there is a significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.001), and the I^2 value (99%). Using a fixed-effects model, it was found that the TAVR may lead to significantly low risk of major or life-threatening bleeding as compared to the SAVR (10.0% *vs*. 30.24%; RR, 0.30; 95% CI, 0.26-0.33; P=0.001; I^2 =99%).

30 Days mortality

Four (n=4) studies reported the 30 days mortality. As illustrated in Figure 17, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.32), and the I^2 value (49%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of prior myocardial infarction as compared to the SAVR (4.9% *vs*. 3.5%; RR, 1.26; 95% CI, 0.80-1.99; P=0.32; I^2 =49%).

Subgroup analysis

Age: Ten (n=10) studies reported age of the patients. As illustrated in Figure 18, there was a significant evidence of heterogeneity amongst

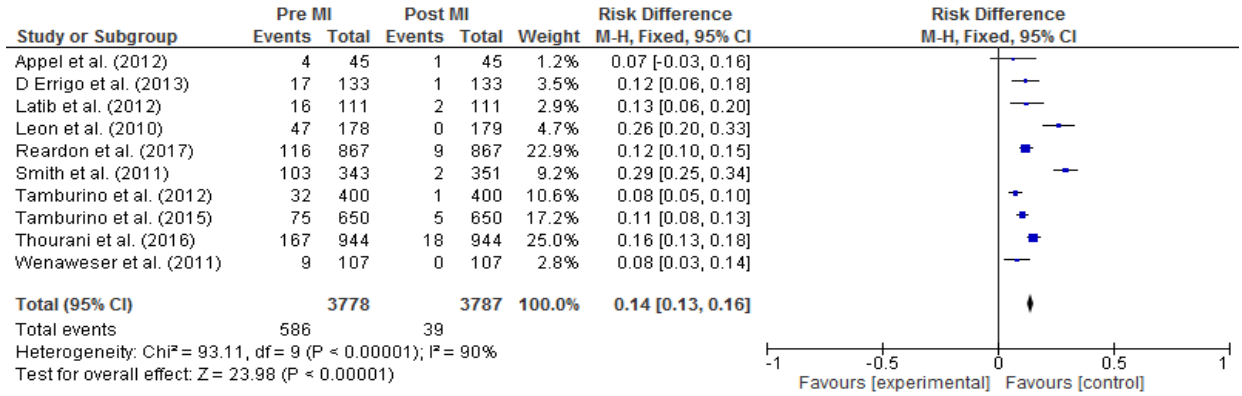

Figure 4: Comparison of incidence of myocardial infarction before and after the surgery between patients undergoing Surgical Aortic Valve Replacement (SAVR).

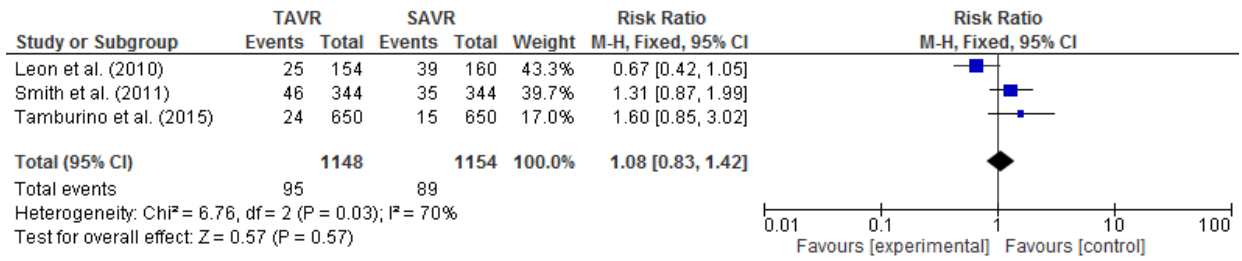

Figure 5: Comparison of balloon expanded valve between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

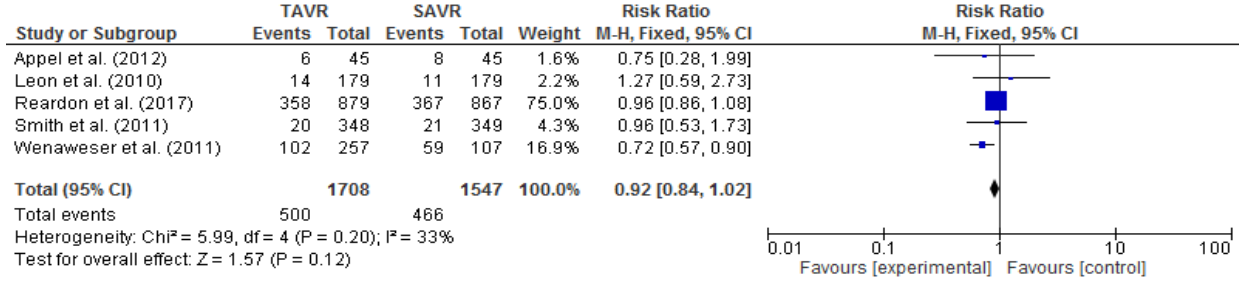

Figure 6: Comparison of NYHA functional class I-II between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

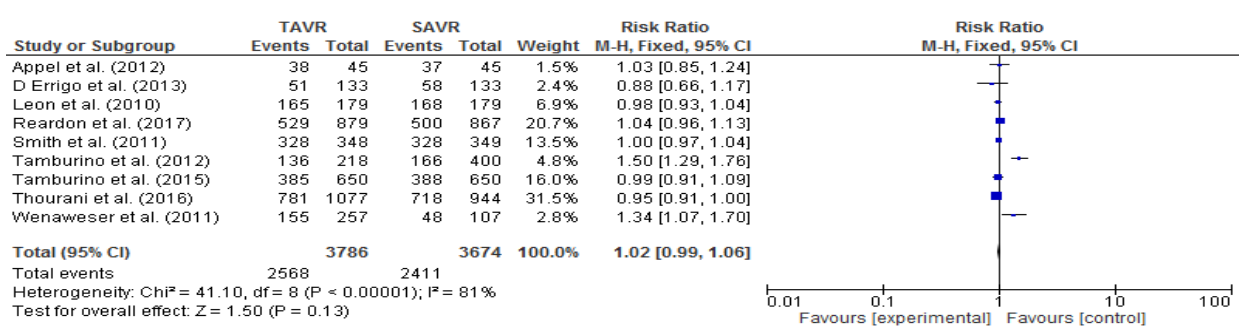

Figure 7: Comparison of NYHA functional class III-IV between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

trials as assessed by the Cochran's Q (p=0.0001), and the I^2 value (97%). Using a fixed-effects model, it was found that the significantly MDIFF (0.89; 95% CI, 0.61-1.18; P=0.0001; I^2=97%).

Gender: Male: Nine (n=9) studies reported the gender of the patients. As illustrated in Figure 19, there was no significant evidence of heterogeneity amongst trials as assessed by the Cochran's Q (p=0.07), and the I^2 value (0%). Using a fixed-effects model, it was found that the TAVR may lead to insignificantly high risk of myocardial infarction as compared to the SAVR (53.9% *vs.* 51.7%; RR, 1.04; 95% CI, 1.00-1.09; P=0.07; I^2 =0%).

Discussion

TAVR is a novel surgical intervention for patients who are not willing to undergo the conventional surgical valve replacement or who are at a high risk of perioperative and/or postoperative morbidity and mortality [17]. TAVR has been routinely applied following relatively recent improvements in transcatheter heart valves that make such a surgical intervention easier and safer to perform it [18]. A widespread adoption of this innovative method warrants a concise and systematic analysis of the results attained from studies to date, leading the VARC to publish standardized definitions of relevant endpoints to improve the consistency, and the scientific and medical rigours of the data

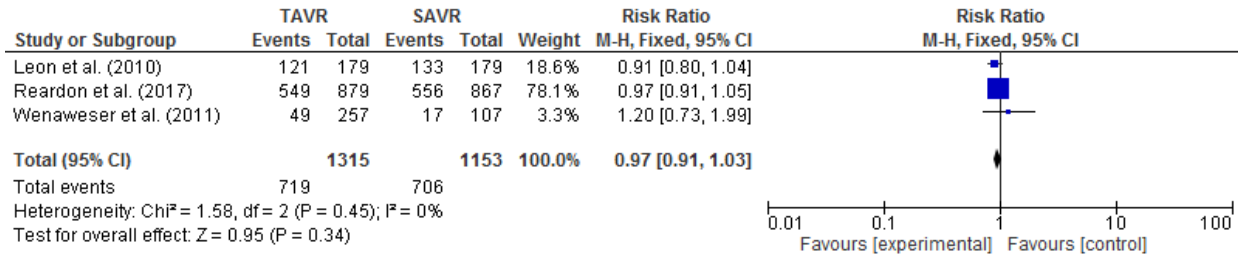

Figure 8: Comparison of Coronary artery disease (CAD) between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

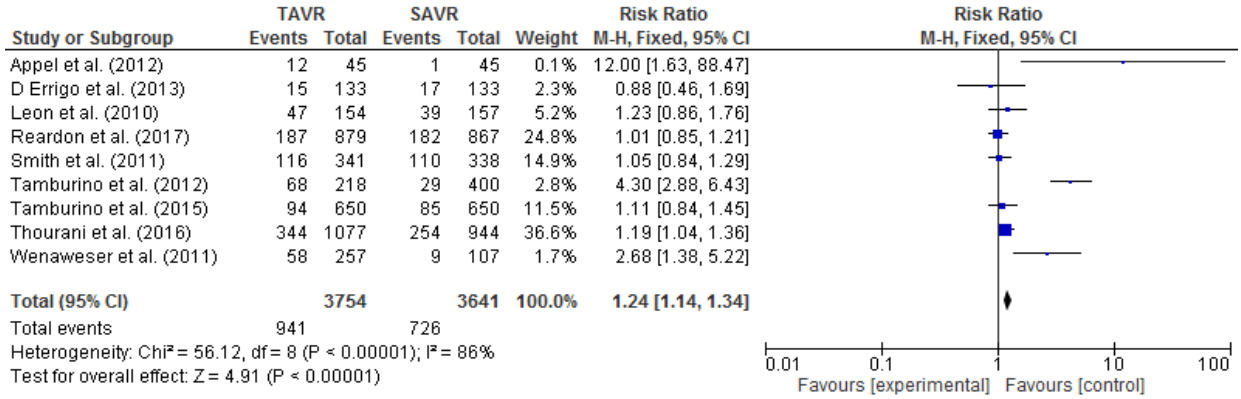

Figure 9: Comparison of Prior Percutaneous Coronary Intervention (PCI) between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

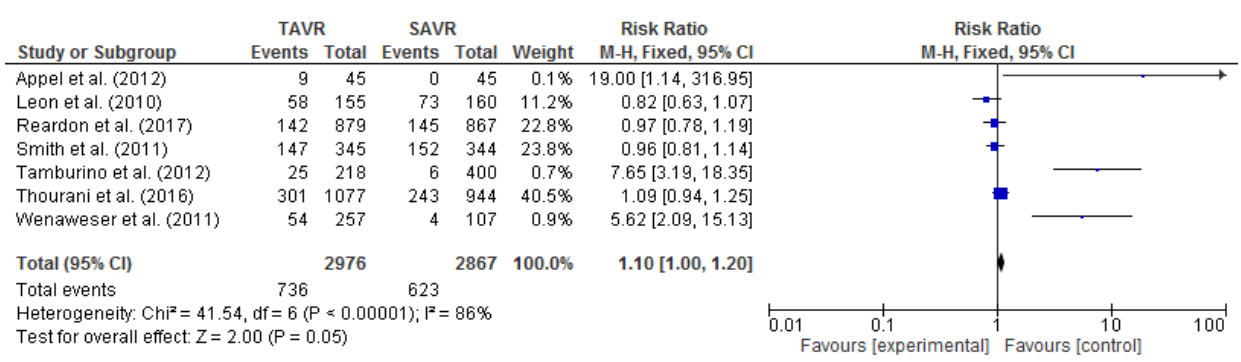

Figure 10: Comparison of Prior Coronary bypass graft (CABG) between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

collected, as well as ensure that reports on such results derived from clinical trials are easy to comprehend, compare, and, therefore, adopt [19]. Myocardial infarction is diagnosed in the original VARC criteria as "a peak value exceeding 10 × the 99th percentile upper reference limit (URL) for CK-MB, or a peak value exceeding 5 × the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads". The updated VARC-2 recommended a relatively looser definition of "a peak value exceeding 15 × the URL for troponin or 5 × for CK-MB", which may partly explain the higher rate of myocardial infarction observed in patients diagnosed via the VARC II/revised criteria, as compared with those diagnosed via the initial VARC criteria in this meta-analysis.

The incidence of myocardial infarction after TAVR was 11.67% for the overall patient population analyzed. It is worth noting that the incidence of myocardial infarction was extremely high (59.0%) in one included study [20], which might be due to the considerably higher number of patients treated via the TA approach and self-expanding valves, as well as the higher prevalence of CHD (Table 1). Ribeiro et al. [21] and Rodés-Cabau et al. [22] found that the TA approach was the main procedural factor associated with a significant increase in the level of expression of cardiac biomarkers, as well as a higher degree of severity of myocardial infarction (MI) post-TAVR, which requires the use of large catheters passing through the ventricular apex for treatment. Transcatheter heart valve type and the use of prosthetic heart valves also are amongst the most important biomarkers for predicting incidence of MI further to TAVR, as also supported by findings from this meta-analysis on the significance of prosthesis depth. Sinning et al. found that self-expanding valves with a higher degree of oversizing may lead

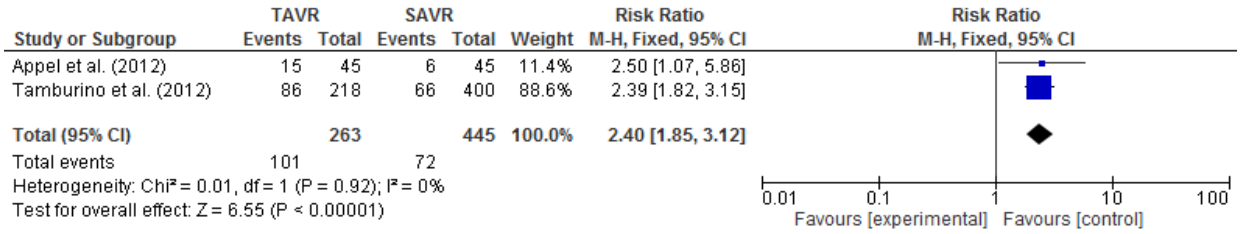

Figure 11: Comparison of Prior heart failure between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

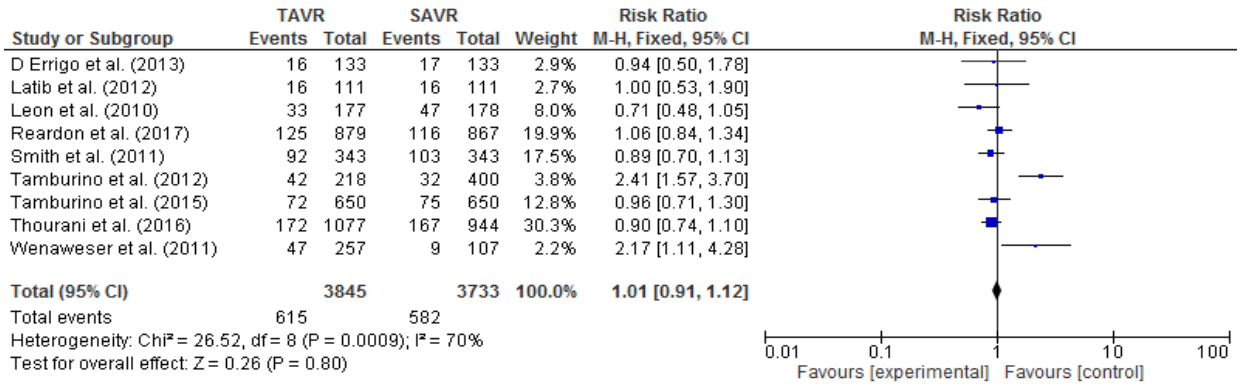

Figure 12: Comparison of Prior myocardial infarction between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

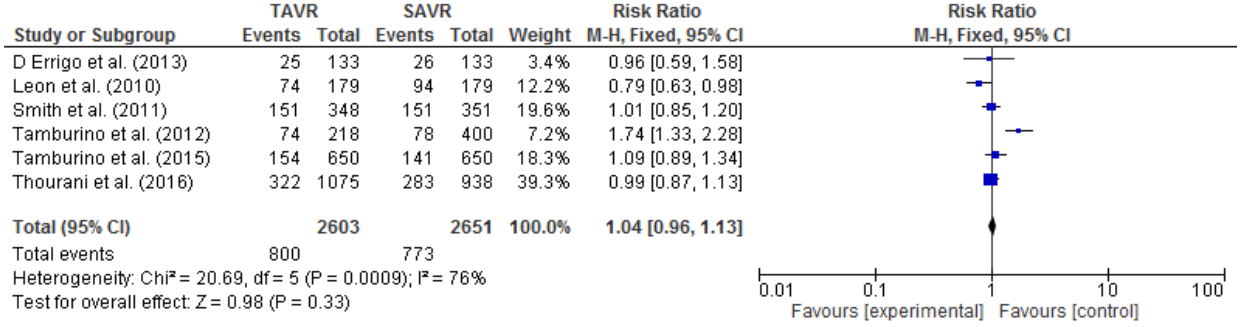

Figure 13: Comparison of Chronic obstructive pulmonary disease (COPD) between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

to a higher compression of the myocardial tissue and a higher degree of trauma with respect to balloon-expandable valves [23]. Patients with CHD or peripheral arterial disease may be more prone to incur MI, as they undergo a more complex TAVR surgical procedure, leading to a longer procedural duration and a higher myocardial oxygen demand-supply mismatch. Since patients with low ventricular ejection fraction (LVEF) tendentially have infarcted, scared, or inactive myocardium, which may release low levels of expression of CK-MB or troponin via a TAVR-related myocardial tissue compression, the baseline LVEF was found to be highly associated with the incidence of MI [23,24]. Barbash et al. [25] and Yong et al. [26] confirmed that patients with baseline renal insufficiency and those without preprocedural β (beta) blockers are associated with a high incidence of MI and of a higher extent. Major periprocedural complications, such as major/life-threatening bleeding, valve embolization/need for a second valve and conversion to open-heart surgery were also found to be associated with a higher increase in the level of expression of the cardiac biomarker "CK-MB". In agreement with previous studies [21-23,26], renal dysfunction, beta-blocker use, early TAVR experience, prosthesis depth, procedural duration, TA approach and perioperative complications were found to be significant predictive factors for MI in patients after TAVR (Table 2, $p << 0.05$) for short- and long-term follow-ups (Table 3).

The incidence of MI during TAVR (perioperatively) has been found to be associated with higher 30-day, 6-month, and 1-year overall mortality, as well as long-term overall (at a follow-up higher than 1-year post-op) and cardiac mortality. These endpoints are associated with peak levels of cardiac troponins and CK-MB leading to poor clinical outcomes, secondary to percutaneous coronary intervention, coronary bypass and heart valve surgery [27,28]. Furthermore, there is

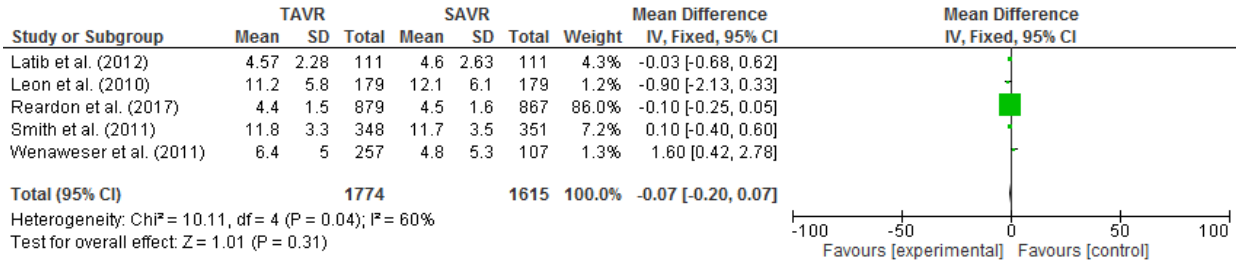

Figure 14: Comparison of STS-PROM (%) between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

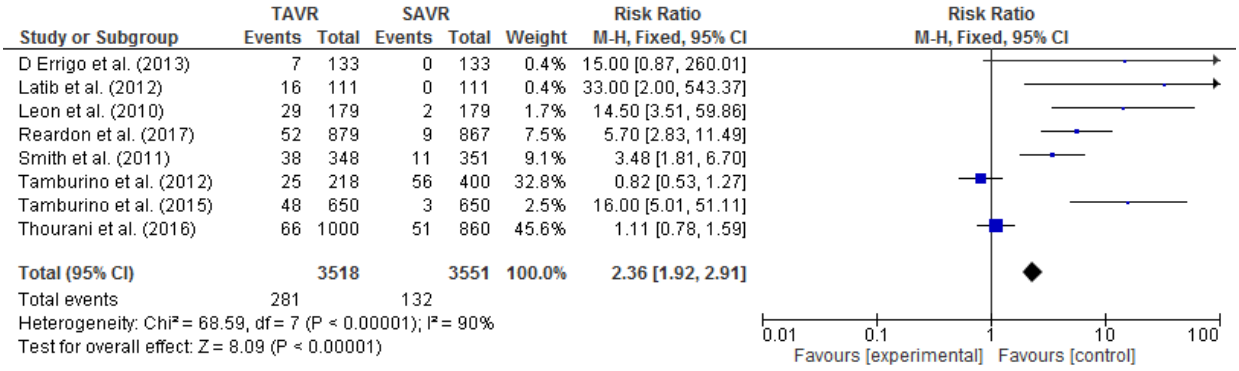

Figure 15: Comparison of Major vascular complication between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

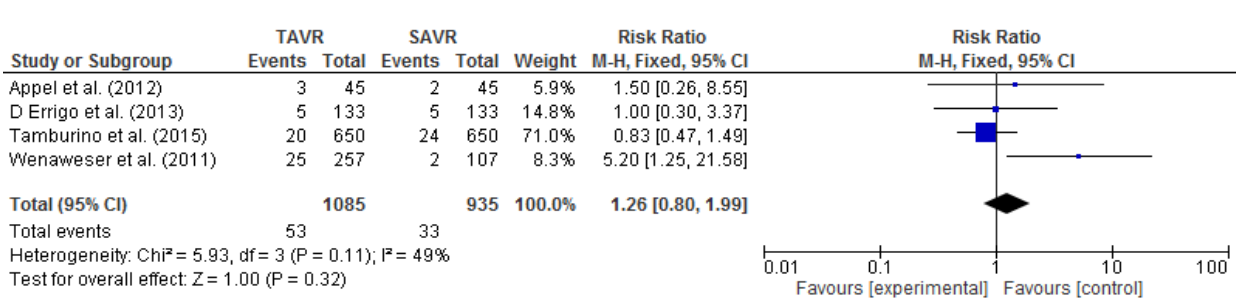

Figure 16: Comparison of Major life-threatening bleeding between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

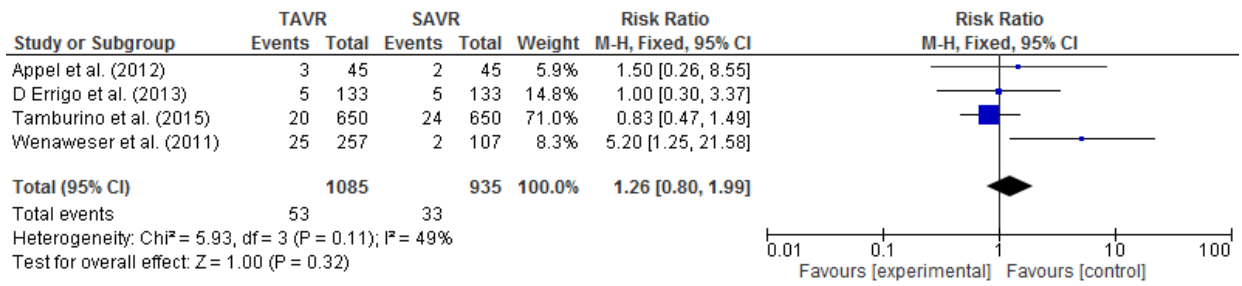

Figure 17: Comparison of 30 days mortality between patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

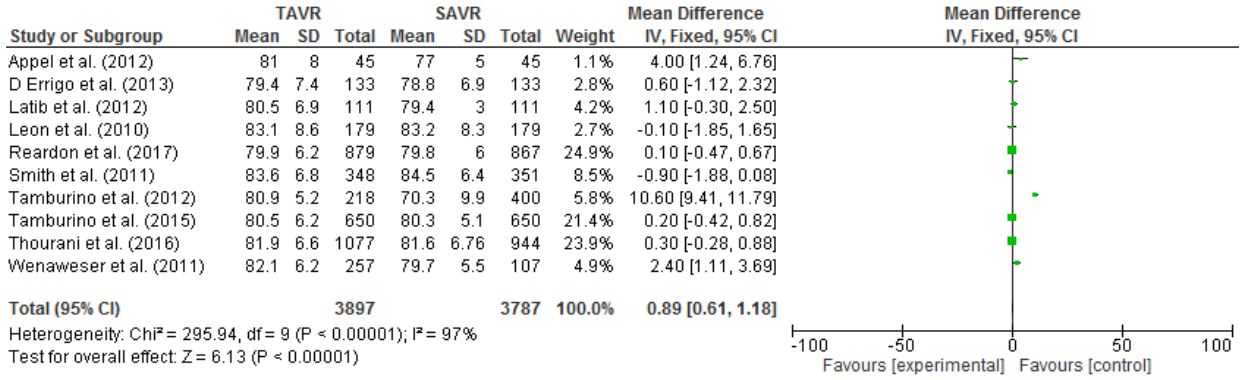

Figure 18: Comparison of mean age of the patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic Valve Replacement (SAVR).

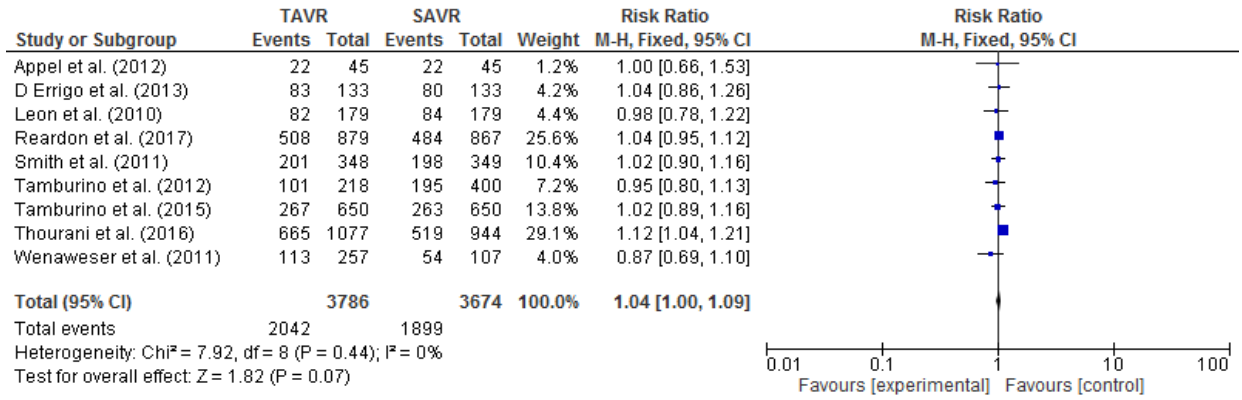

Figure 19: Comparison of male patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic Valve Replacement (SAVR).

a drastic stepwise increase in long-term mortality according to various degrees of expression of CK-MB after TAVR [21]. Patients at a high risk of MI could benefit from a closer clinical follow-up, as well as more patient-specific medications (e.g. beta-blockers, angiotensin-receptor blockers, or angiotensin-converting enzyme inhibitors) for preventing left ventricular remodeling [21].

This systematic review and meta-analysis has several limitations. First, due to a considerable variability in the patient selection criteria (demographics and clinical history), procedural methods, study design, population and follow-up duration for patients undergoing TAVR across institutions, there was a significant level of heterogeneity in the studies when assessing the extent of statistical significance of the perioperative incidence of myocardial infarction and any prognostic factors associated with it [29-32]. Considering that the baseline characteristics and procedural parameters of patients from the selected studies could not be entirely retrieved, it was not possible to accurately assess the effects of gender, age, clinical history, heart valve type and surgical approach on the outcome measures [33-36]. Because it was

S. No	Author, year	Prior PCI		Prior CABG		Prior heart failure		Prior myocardial infarction		COPD		STS-PROM, %		CK-MB Levels	
		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
1.	Latib et al. [29]	-	-	-	-	-	-	16	16	-	-	4.57 ± 2.28	4.60 ± 2.63	-	-
2.	Appel et al. [30]	12	1	9	0	15	6	-	-	-	-	-	-	20.54 ± 17.99	25.89 ± 20.08
3.	D Errigo et al. [31]	15	17	-	-	-	-	16	17	25	26	-	-	-	-
4.	Tamburino et al. [32]	68	29	25	6	86	66	42	32	74	78	-	-	-	-
5.	Smith et al. [33]	116	110	147	152	-	-	92	103	151	151	11.8 ± 3.3	11.7 ± 3.5	-	-
6.	Wenaweser et al. [34]	58	9	54	4	-	-	47	9	-	-	6.4 ± 5.0	4.8 ± 5.3	-	-
7.	Tamburino et al. [35]	94	85	-	-	-	-	72	75	154	141	-	-	-	-
8.	Thourani et al. [36]	344	254	301	243	-	-	172	167	322	283	5.2	5.4	-	-
9.	Leon et al. [8]	47	39	58	73	-	-	33	47	74	94	11.2 ± 5.8	12.1 ± 6.1	10	17
10.	Reardon et al. [37]	187	182	142	145	-	-	125	116	-	-	4.4 ± 1.5	4.5 ± 1.6	-	-

Table 2: Clinical outcomes of the patients undergoing Transcatheter Aortic Valve Replacement (TAVR) or Surgical Aortic-valve replacement (SAVR).

S. No	Author, year	Prior percutaneous coronary intervention		Major vascular complications		Major or Life threatening bleeding		Pacemaker		Stroke		Death		LVEF, %	
		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
1.	Latib et al. [29]	-		16	-	43	63	13	3	1	2	2	2	53.5 ± 12.5	53.6 ± 10.7
2.	Appel et al. [30]	12	1	-	-	-	-	-	-	1	1	-	-	3	3
3.	D Errigo et al. [31]	15	17	7	0	-	-	12	0.8	-	2	-	-	54.2 ± 11.4	54.3 ± 11.3
4.	Tamburino et al. [32]	68	29	25	56	12	36	45	9	5	12	15	19	51.1 ± 10.6	55.4 ± 8.9
5.	Smith et al. [33]	116	110	38	11	-	-	13	12	13	7	12	22	52.5 ± 13.5	53.3 ± 12.8
6.	Wenaweser et al. [34]	-	-	-	-	-	-	60	4	10	4	17	7	51 ± 14	57 ± 12
7.	Tamburino et al. [35]	94	85	48	3	-		98	23	8	14	-	-	53.6 ± 11.4	54.2 ± 11.2
8.	Thourani et al. [36]	344	254	66	51	50	440	109	68	29	57	12	38	58.5	55.4
9.	Leon et al. [8]	-	-	29	2	30	7	6	9	9	2	9	5	53.9 ± 13.1	51.1 ± 14.3
10.	Reardon et al. [37]	187	182	105	9	-	74	224	53	57	57	19	14	-	-

Table 3: TAVR *vs.* SAVR.

not completely clear how some studies had applied the definitions for clinical outcomes according to either the VARC or the VARC-II criteria for assessing primary endpoints, publication bias may exist despite the best efforts of the authors of this systematic review and meta-analysis to conduct a comprehensive, unbiased literature survey [37].

Conclusion

In conclusion, this study provides a comprehensive, evidence-based informed quantification of MI in patients with severe aortic stenosis further to TAVR. Periprocedural MI remains a relatively common complication of TAVR. The prognostic factors for MI include patient history, procedural method and perioperative complications, which were associated with both short- and long-term mortality. These results provide invaluable insights for improving treatment for patients with severe aortic stenosis undergoing TAVR but at a high risk of MI.

Declarations

Ethics approval and consent to participate- Not applicable.

Consent for publication- Not applicable.

Availability of data and material- All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests- The authors declare that they have no competing interests

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Authors' Contributions

JL, WCH conducted conception and design, while LG, MO analyzed and interpreted the patient data. WCH, MO jointly wrote the manuscript, while provision of materials, patients, or resources were undertaken by PLC, CDK. BMH, CDK provided Statistical expertise. WCH, BMH were tasked with the Literature search.

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