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Health-related Quality of Life following TAVI or Cardiac Surgery in Intermediate and Low Risk Patients: A Systematic Review and Meta-analysis

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Health-related Quality of Life following Transcatheter aortic valve implantation (TAVI) or Cardiac Surgery in Intermediate and Low Risk Patients: A Systematic Review and Meta-analysis

Abstract

Recent randomized trials have shown that clinical outcomes with transcatheter aortic valve implantation (TAVI) are non-inferior to surgical aortic valve replacement (SAVR) in intermediate-to-low risk patients with symptomatic aortic stenosis. Health-related quality of life (HrQoL) outcomes in these patient groups remain uncertain. A systematic search of the literature was conducted which included nine trials and 11,295 patients. Kansas City Cardiomyopathy Questionnaire (KCCQ), a heart-failure-specific measure and EuroQol-5D (EQ-5D) (a generic health status tool) changes were the primary outcome. New York Heart Association (NYHA) classification was the secondary outcome. Improvement in KCCQ scores was greater with TAVI (MD=13.56, 95% CI (11.67, 15.46), P<0.001) at 1 month, as was the improvement of EQ-5D (MD=0.07, 95% CI (0.05, 0.08), P<0.001). There was no difference in KCCQ (MD=1.05, 95% CI (-0.11, 2.21), P=0.08) or EQ-5D (MD=-0.01, 95% CI (-0.03, 0.01), P=0.37) at 12 months. NYHA functional class 3-4 was lower in patients undergoing TAVI at 1 month (MD=0.51; 95% CI (0.34, 0.78), P=0.002) but there was no difference at 12 months (MD=1.10; 95% CI (0.87, 1.38), P=0.43). Overall, TAVI offers early benefit in HRQoL outcomes compared to SAVR, but they are equivalent at 12 months.

Keywords: Aortic stenosis; TAVI; SAVR; KCCQ; EQ5D; NYHA

Introduction

Aortic stenosis (AS) is one of the most common and prognostically significant valve diseases [1]. Its prevalence increases with age, and it is present in 2-7% of all patients over 65 years of age [1]. Symptomatic AS requires valve replacement either via Transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) and the choice has traditionally been made on surgical risk [2]. There are three categories of surgical risk (classified high-risk as above 8%, intermediate-risk as 4-8% and low-risk as less than 4%), based on a model developed to estimate the risk of death at 30 days following surgery [2]. The surgical risk score has been incorporated into the trials comparing SAVR with TAVI through the 'heart multidisciplinary team' (MDT) [2, 3].

TAVI is preferable to surgical intervention in high surgical risk patients [4] and is recommended by the current European Society of Cardiology (ESC)/ European Association for Cardio-Thoracic Surgery (EACTS) guidelines (*Figure 1*) [5]. The transfemoral (TF TAVI) 'minimalistic' approach is now the most used technique as it is associated with reduced complications and shorter hospital stay [6]. A recent meta-analysis has shown that TAVI is associated with a reduction in all-cause mortality and stroke irrespective of the baseline surgical risk or the transcatheter heart valve system used [7]. Evaluation of changes in quality of life may be a better outcome measure than survival in all patients' risk groups, and both outcomes can be combined in a cost-effectiveness analysis to measure the effect of a new intervention [8, 9]. Ando et al. evaluated health-related quality of life (HRQOL) in high-risk patients with symptomatic aortic stenosis, demonstrating superiority of TAVI at 30 days after procedure [10]. Recent Cochrane systematic reviews and meta-analyses after TAVI or SAVR in low [11] and intermediate [12] risk patients included all-cause mortality,

stroke, and hospital readmission rate, displaying non-inferiority of TAVI in terms of survival; however, it did not include functional outcomes or quality of life assessments.

Disease-specific HRQOL instruments provide critical information because of their ability to detect small but important treatment effects and are often used to guide commissioning of new treatments and as part of cost effectiveness evaluations [9]. HRQOL in patients undergoing TAVI or SAVR has been evaluated using various scoring systems including the Medical Outcomes Trust Short-Form 36-Item Health Survey (SF-36) and the Short-Form (SF-12), the Minnesota Living with Heart Failure questionnaire (MLHFQ), the EuroQoL-5D (EQ-5D), the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the MacNew tool [13, 14]. Functional outcomes have been reported principally using the New York Heart Association (NYHA) [15].

The aim of this review is to compare HRQOL and functional outcomes in intermediate-and-low risk patients treated mainly by transfemoral (TF)-TAVI as it is the most commonly used approach, or SAVR, as this area is yet uncovered as far as we know.

Methods

A systematic review and meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16], registered with PROSPERO (CRD42022330632). Ethical approval was not required. A literature search was conducted via PubMed, EMBASE, OVID and Cochrane Library to 05 June 2022. In addition, the World Health Organization International Clinical Trials Registry (http: //apps. who.int/trial search/), ClinicalTrials.gov (http://clinical- trials.gov/), and ISRCTN Register (http: //www.isrctn. com/) were searched for details of ongoing and unpublished studies. The bibliographic lists of articles of relevance were reviewed (*Supplementary figure 1).*

Eligibility criteria

All articles were screened by two authors (AG and MA) using a two-stage strategy. Initially, articles were screened based on title or abstract relying on the inclusion and exclusion criteria. Full manuscripts were then reviewed for eligibility to be included in the main analysis. Any selection disagreements between the authors were resolved through discussion between the reviewers. We included all randomized controlled trials (RCTs) that compared health-related quality of life (HRQoL) indices and functional status at 1 and 12 months between TAVI- mainly transfemoral access route and SAVR in low and intermediate (surgical) risk patients.

Exclusion criteria included papers that evaluated non-transfemoral TAVI, non-English, non-comparative, and duplicate studies. Patients undergoing surgery using alternative access routes such as transapical, transventricular or transaortic were also excluded. Other exclusions were studies that only evaluated all-cause mortality, echocardiographic findings, and procedural

complications. Trials that evaluated cost-effectiveness (Quality-adjusted life year) were excluded from the main analysis.

Primary outcome

Valve Academic Research Consortium-2 recommends that a comprehensive assessment of HRQOL for patients undergoing TAVI incorporate both a heart failure-specific measure as well as one or more generic measures [17]. The primary outcome in this meta-analysis was Kansas City Cardiomyopathy Questionnaire (KCCQ) as an instrument for heart failure-specific measurement and EQ-5D for generic health status measurement. Other outcomes including SF-12, SF-36 and MLHFQ were included in our extraction, however, they were excluded at a later stage due to the lack of homogeneity of data reporting at 1 and 12 months in some studies, as well as the lack of data reporting in other trials.

KCCQ overall score is a 23-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference, and quality of life. KCCQ has been recommended as a heart failure-specific performance measure for quantifying the HRQoL [18]. The KCCQ can sensitively estimate the effect of heart failure on the patients and is strongly associated with the clinical events over time, hence, can improve the patient-centeredness care [18]. Scores for KCCQ summary and its subscales range from 0 to 100 with the higher scores indicating better health status [19]. KCCQ overall scores were evaluated in 6 studies, at baseline, 1 and 12 months.

EQ-5D is a generic (rather than heart-failure specific) self-administered questionnaire composed of health state description and evaluation. Health state description is assessed by five dimensions:

mobility, self-care, usual activities, anxiety/depression, and pain/discomfort. Similar to KCCQ, EQ-5D allows patient-centeredness when assessing treatment effects in patients [20]. In the evaluation section, patients use a visual analogue scale to evaluate their overall health status scale of 0 to 100, with a higher score corresponding to better health status [20]. EQ5D utility scores was evaluated in 2 studies, at baseline, 1 and 12 months.

Secondary outcome

NYHA functional classification scores were evaluated at baseline, 1 and 12 months in 6 studies [21]. NYHA category is reported either as a proportion in each category or in categories 1-2 and 3-4.

Data synthesis

All analysis was performed using R v4.1.2 [22], incorporating the meta, dmetar, and altmeta packages [23-25], to meta-analyse the extracted data. Publication bias is assessed for the primary and co-primary outcomes by inspection of funnel plots and by Lin's hybrid test [26]. Different outcomes (including KCCQ, EQ-5D and NYHA) were analysed and their methods are highlighted in the *supplementary appendix*.

Assessment of heterogeneity

Heterogeneity among the studies was assessed using the Cochran Q test ($\chi 2$). Inconsistency was quantified by calculating I^2 and interpreted using the following guide: 0%-25% may represent low heterogeneity, 25%-75% may represent moderate heterogeneity, and 75%-100% may represent substantial heterogeneity [27].

Methodological quality and risk of bias assessment

Studies eligible for inclusion were assessed for quality and risk of bias by two authors independently. Cochrane's tool was used to evaluate the risk of bias. Agency for healthcare research and quality (AHRQ) standard was used to provide an overall rating of good, fair or poor quality [28].

Results

KCCQ overall

Improvement of KCCQ scores from baseline was higher with TAVI compared to SAVR ($p<0.001$) at 1 month *(figure 2)*. Heterogeneity was assessed by inspection of the I^2 statistic and its confidence interval; then an influence study was undertaken as the 95% confidence interval of effect of one study (Popma 2019) lies outside the 95% confidence interval of the pooled size effect. *Supplementary figure 2* displays the influence analysis for KCCQ change scores at 1 month, Baujat plot comparing influence on pooled effect with contribution to heterogeneity and the effect on heterogeneity I^2 statistic of removing one study (Popma 2019). There was a significant improvement in KCCQ scores at 1 month after removing Popma 2019 ($p<0.001$; *Supplementary figure 2*). There was no significant difference in the improvement of KCCQ scores from baseline between TAVI and SAVR at 12 months ($p=0.08$; *figure 2*). Publication bias was assessed at 1 and 12 months, using funnel plots. *Supplementary figure 3* displays the funnel plots for at 1 month and 12 months.

EQ-5D utility scores

Change from baseline EQ-5D utility indices is shown in supplementary table 2, with analyses involving three studies and for only the two Baron studies. Heterogeneity is substantial when all three studies are included (85%, CI 61%-95%), and the UKTAVI study [35] is classed as an outlier, as its 95% confidence interval of effect lies outside the 95% confidence interval of the pooled effect size. UK TAVI is not included in the main analysis but is reported quantitatively. Forrest plots for the two-study comparisons are shown in *Figure 3*. There was a significant difference between TAVI and SAVR at 1 month (MD=0.07, 95% CI (0.05, 0.08), P<0.001). EQ-5D difference at 12 month was reported in 2 studies. There was no significant difference between TAVI and SAVR at 12 months (MD=-0.01, 95% CI (-0.03, 0.01), P=0.37). Assessment of influence or publication bias is non-informative as there are only two included studies.

NYHA

The proportion of NYHA class 3-4 patients is less at 1 month *(Figures 4 and 5)* following TAVI compared to SAVR. Results from *Figure 5* displays a larger reduction for TAVI, relative to SAVR both at 1 and 12 months, however with a reduction in the difference after 12 months (0.435 reduction in TAVI and 0.382 reduction in SAVR at 1 month and 0.432 reduction in TAVI and 0.423 reduction in SAVR at 12 months respectively). These findings were consistent with the results displayed by *Figure 6*, where there was no significant difference at baseline (MD=1.01; 95% CI (0.93, 1.10), P=0.80). At 1 month, there was a higher proportion of SAVR patients NYHA classes 3 and 4 in the SAVR cohort compared to TAVI (MD=0.51; 95% CI (0.34, 0.78), P=0.002). At 12 months, there was no significant difference in the risk of NYHA class 3-4 (MD=1.10; 95% CI (0.87, 1.38), P=0.43) *(Figure 6)*.

The heterogeneity statistic, I^2, is moderately high at one month and influence analysis shows that it is Leon 2016 that contributes greatly to the pooled effect size and to this heterogeneity. Testing of the effect of one-at-a-time removal of each study shows that removal of Leon 2016 would reduce I^2 to 25% (*Supplementary figure 4*). However, the new pooled effect size still lies within the confidence interval of the 4-study analysis (*Figure 6*). *Supplementary figure 4* also displays the influence analysis for NYHA change scores at 1-month post-operative, Baujat plot comparing influence on pooled effect with contribution to heterogeneity and the effect on heterogeneity I^2 statistic of removing one study (Leon 2016). There was still a significant difference at 1 month after removing Leon 2016 ($P<0.001$) (*Supplementary figure 4*). Publication bias was assessed for at 1 and 12 months, using funnel plots. *Supplementary figure 5* displays the funnel plots for NYHA class 3-4 at 1 month and 12 months.

Figure 4 displays a reduction in the patients in class 3 and 4 from baseline to after 1 and 12 months, and an increase in the number of patients in classes 1 and 2. Visualization of NYHA class in both TAVI and SAVR at different time points suggests that there is a legitimate decrease in the proportion of patients at NYHA class 3-4 at 1 and 12 months; the decrease in the number of class 3-4 far outweighs the loss-to-follow-up, giving evidence that the decrease is real and not an artefact of patient drop-out. There is a larger reduction in the pooled number of patients in NYHA class 3-4 undergoing TAVI, relative to SAVR, both at 1 and 12 months (*figure 5*).

Methodological Quality and Risk of Bias Assessment

Selection bias, performance bias, detection bias, attrition bias, reporting bias were all assessed and were categorized into low, some concern and high risk of bias. The findings are summarised in Figure 7.

Discussion

SAVR still remains the gold standard treatment of choice for intermediate-to-low surgical risk patients with severe aortic stenosis, and current guidelines recommend TAVI for patients who have a high-risk of surgery [5]. Recent trials such as NOTION [29], PARTNER 3 [33], and EVOLUT [36] have shown that TAVI has superior HRQoL outcomes at 1 month compared to SAVR and is non-inferior at 12 months in low-risk patients. In this meta-analysis, KCCQ and EQ-5D HRQoL scores show superiority for TAVI at 1 month but no significant difference compared to SAVR at 12 months. This was also the case for the improvement of NYHA classification. Assessment of HRQOL is influenced by factors that are uniquely perceived by each individual and are influenced by physical limitations (such as pain/discomfort) as well as emotional and social factors including self-care. These outcomes are important in promoting a patient-centered approach, which helps to facilitate shared decision-making and ensure that patient preferences are used to guide management [38, 39, 40]. HRQOL measures also provide a framework for clinical monitoring, where reduced HRQOL outcomes have been shown to be independent predictors of both further hospitalization and mortality [41, 42]. TAVI results in better mobility and performance of usual activities earlier than after SAVR [19, 20, 38]. Moreover, the incidence of anxiety and depression can be high early after cardiac surgery and can be associated with longer-term health outcomes of the patients [43, 44]. This could explain why KCCQ scores are lower in the surgical cohort as this includes social interference measures [19]. Anxiety and depression are assessed by EQ-5D as one of the five dimensions [20], and the significant improvement in EQ-5D scores at 1 month following TAVI could reflect a reduced incidence of post-operative mental health problems compared to cardiac surgery.

NYHA class 3-4 was significantly less with TAVI compared to SAVR at 1 month and likely reflects earlier mobilization and a reduction in length of hospital stay (average of 8 days for SAVR compared to 3 days for TAVI as shown by the trials included in this analysis) [10, 21, 45, 46]. This improvement in functional status is consistent with the findings reported by Gavina et al [47], who have shown a greater improvement in functional class at 6 months after TAVI compared to cardiac surgery [47]. This functional improvement was attributed to higher effective prosthetic orifice area index (EAOI) following TAVI, potentially improving left ventricular remodeling [47]. Furthermore, TAVI resulted in an immediate hemodynamic response displayed as an immediate reduction in left ventricular ejection time (LVET) (suggesting rapid unloading of the ventricle) and a subsequent increase in HRQoL which was evaluated by EQ-5D-5L 12-weeks after the intervention [48]. Some of the trials included in this analysis also have shown that echocardiographic parameters remain superior following TAVI including a larger mean valve area, effective orifice area and mean valve gradient [29, 30, 32, 49] at 12 months. This again could potentially explain the earlier improvement in the NYHA class [49].

Potential explanations for higher HRQoL scores in TF-TAVI compared to SAVR at 1 month include early mobilisation, less coronary care unit stay, less pain/discomfort, and less sedative use in TF-TAVI [10]. This may potentially be due to both EQ-5D and KCCQ including physical limitations and mobility domains, meaning TAVI holds the advantage early on due to being less invasive. Better health outcomes can be attributed to a significantly lower incidence of acute kidney injury (AKI), new onset or worsening atrial fibrillation, major bleeding events and cardiogenic shock at 30 days after TAVI [29, 30, 32, 44, 49-51]. This reduces the risk of post-

procedural mortality and the risk of hospitalisation that can worsen the patients' outcomes and hence result in poor health outcomes. Patients with severe aortic stenosis are characteristically older and have many comorbidities including a high prevalence of chronic renal insufficiency [49], which could be precipitated by acute injury secondary to major bleeding events or cardiogenic shock, which are significantly higher in SAVR at 30 days [28, 29, 31, 46, 49, 50]. Another likely contributor is that the mean in-hospital time or time spent in the intensive care unit (ICU) is shorter in patients that underwent TF-TAVI [45].

TAVI was however found to be inferior to SAVR in the rates of cardiac tamponade, permanent pacemaker (PPM) implantation, major vascular damage and paravalvular regurgitation [49, 52]. The incidence of requiring a PPM was also higher in the TAVI cohort, however, the mortality rate at 24 months did not increase in the population requiring a PPM in these studies [29, 32, 52]. There was also an increased risk of major vascular events including femoral/radial artery dissection and thrombosis in the TF-TAVI cohort described in several studies [29, 30, 52]. These are likely due to the access route taken during the procedure, however, TAVI still resulted in lower all-cause mortality 1 year post procedure [53] and is at least non-inferior at 2 years post procedure regardless of the pre-intervention surgical risk [7, 54]. Complications associated with SAVR are usually more severe and lead to greater morbidity than the complications associated with TAVI, which potentially explains the significance of improvement of HRQoL displayed by TAVI at 1 month.

In terms of cost-effectiveness, TAVI was shown to be superior in low-to-intermediate surgical risk patients compared to SAVR [55-57]. Cost per quality-adjusted life years (QALY) was shown to be lower in patients who underwent TF TAVI as displayed by the trials, yielding a higher incremental cost-effectiveness ratio per QALY saved. This can potentially be due to the more

significant improvement in HRQoL early on after the intervention as shown by our analysis of the trials [29-37]. This can be also due to the shorter hospital stays as discussed above, as well as improved cardiac clinical outcomes [29, 30, 32, 46] and HRQOL measures [29-37] leading to reduced lifetime costs of TAVI vs SAVR. More research is needed into why the early HRQoL benefit from TAVI is lost. HRQoL outcomes to 5 years utilizing multiple measures such as SF-36, SF-12, MLHFQ and EQ5D is now required.

According to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease, new information from randomized studies comparing TAVI to SAVR in intermediate-to-low-risk patients has led to a need to clarify if TAVI should be used in lower-risk patients [5]. At 12 months, TAVI shows non-inferiority in clinical outcomes including re-intervention and re- hospitalization [52]. Additionally, studies found that there was no increase in the overall 5-year mortality and all-cause mortality in the TF-TAVI cohorts, thereby displaying non-inferiority of TAVI [29, 30]. Our analysis has shown that TAVI has better HRQoL for medium and lower-risk patients in the short term, but similar to SAVR at 12 months; hence TAVI could potentially be considered as an alternative gold standard for aortic stenosis in the absence of coronary artery disease requiring surgical revascularization, severe primary mitral or tricuspid valve disease, significant dilatation/aneurysm of the aortic root and/or ascending aorta, or other anatomical/procedural factors that would indicate the need for SAVR [5]. The presence of more robust evidence in the future on longer HRQOL benefit and data on cost-effectiveness of TAVI could make this possible.

Limitations

Limitations of our meta-analysis include the lack of homogenous HRQoL data, which resulted in the exclusion of some studies from some meta-analyses. This led to us only being able to use data that was used in consensus in most of the studies. Differing times of follow up only allowed comparisons across a few consistent time-points (1 and 12 months). Additionally, HRQoL measures are subjectively reported and are not standardised which can result in less accurate results. Moreover, the inconsistent reporting of data and lack of homogenous data at different time intervals does not allow the inclusion of other HRQoL measures such as the subcategories of KCCQ, SF-12, SF-36 and MLHFQ. Furthermore, other functional outcomes such as the 6-minute walking test was not reported by the trials. The recent 'low-risk' studies principally assessed the KCCQ overall summary and not KCCQ categorical breakdowns, making analysis of the specific reasons for KCCQ being superior at 1 month but not 12 months difficult. Moreover, some baseline characteristics that affect quality of life (such as frailty, heart failure and other comorbidities) were not reported by some studies. Our meta-analysis is a study-level and not patient-level analysis and may therefore be subject to biases. Nonetheless, the selected studies featured low levels of bias across all the Cochrane domains (Figure 7). It also does not address the patients who have been excluded from the selected randomized trials.

Conclusion

In conclusion, TAVI offers early benefit in HRQoL outcomes in intermediate-to-low risk patients compared to SAVR, however, further robust trials are required to better analyse its benefit on patients on the long term. Implementation of TAVI as a gold standard therapy for lower risk patients could have a better impact on the patients' recovery and hence quality of life as it is less invasive, potentially supporting the superiority of TAVI in terms of cost-effectiveness.

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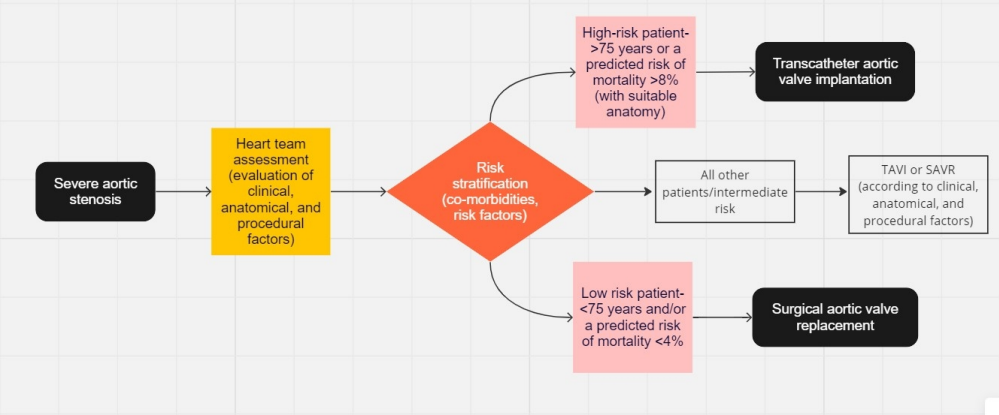

Figure 1: [Current treatment approach for patients with severe aortic stenosis] [5]

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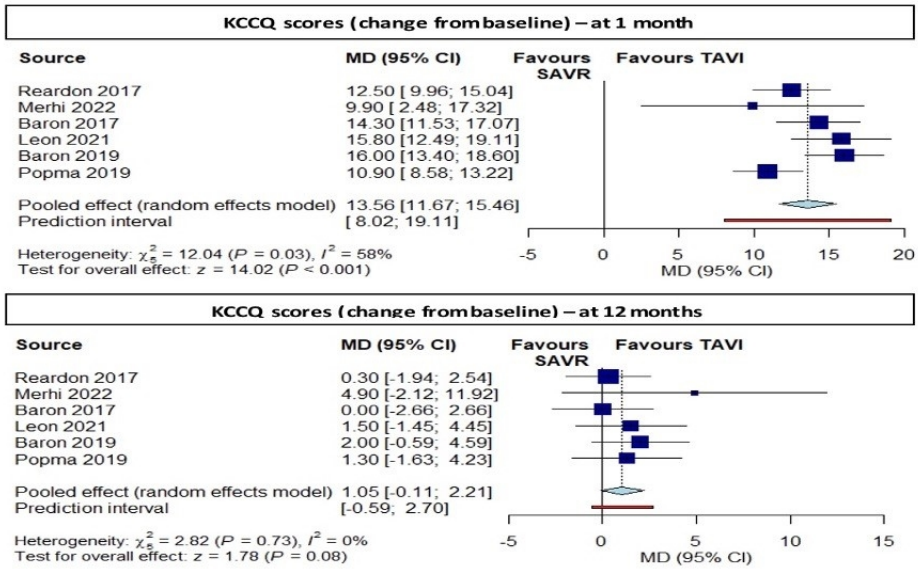

Figure 2: [Difference in KCCQ overall scores after 1 and 12 months reported in 6 studies]

165x102mm (144 x 144 DPI)

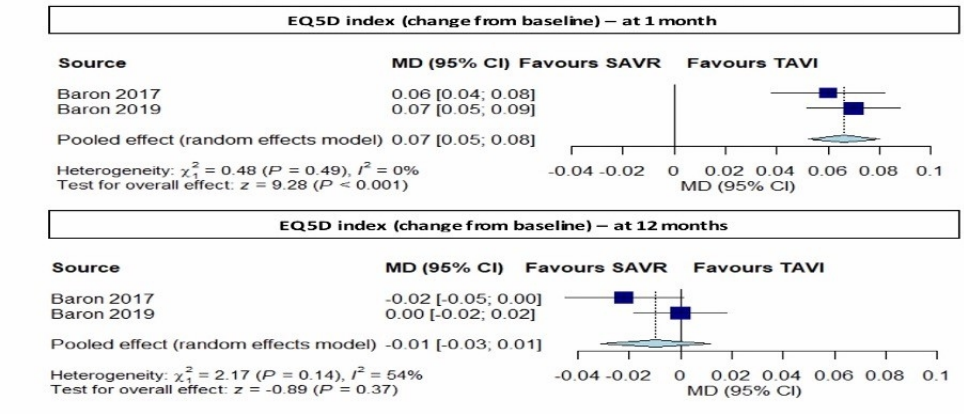

Figure 3: [Difference in EQ5D utility scores after 1 and 12 months reported in 2 studies]

165x70mm (144 x 144 DPI)

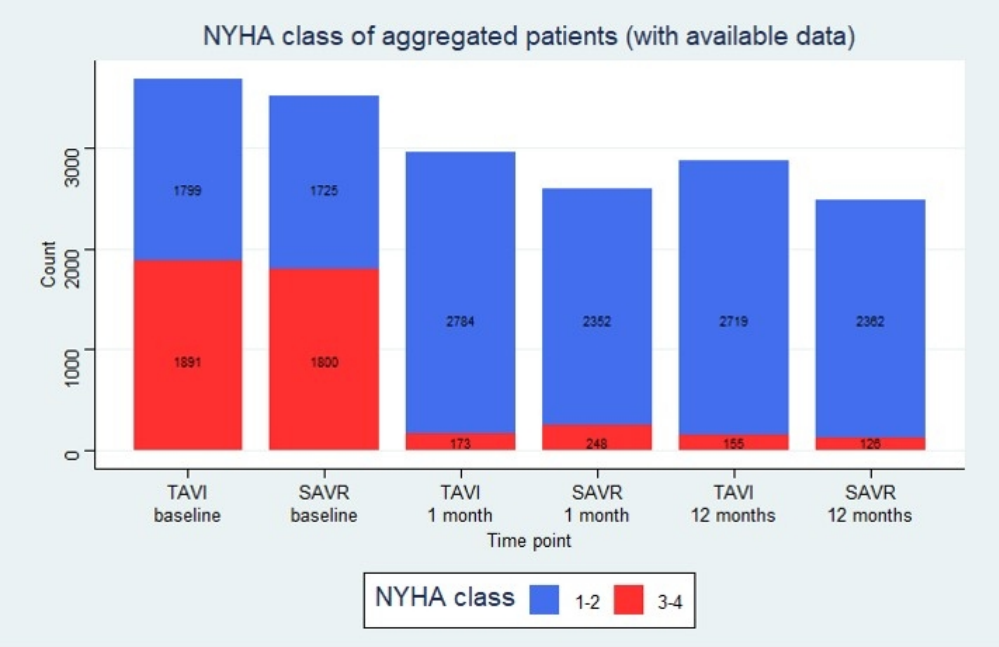

Figure 4: NYHA class of patients aggregated across all studies at each time point (6 studies at baseline and 12 months, 4 studies at 1 month)

125x81mm (144 x 144 DPI)

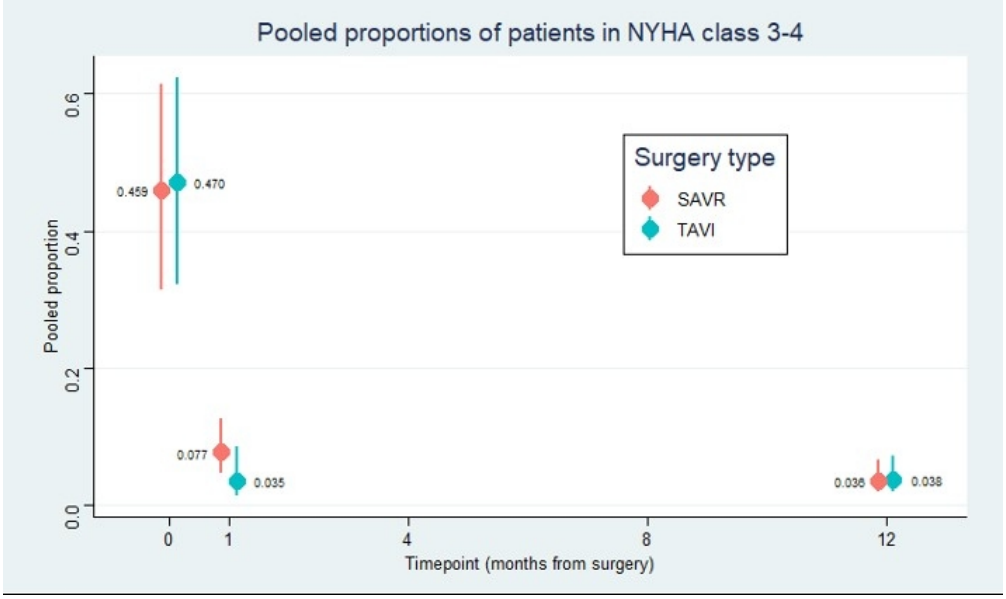

Figure 5: [Pooled proportions of classes 3 and 4]

125x74mm (144 x 144 DPI)

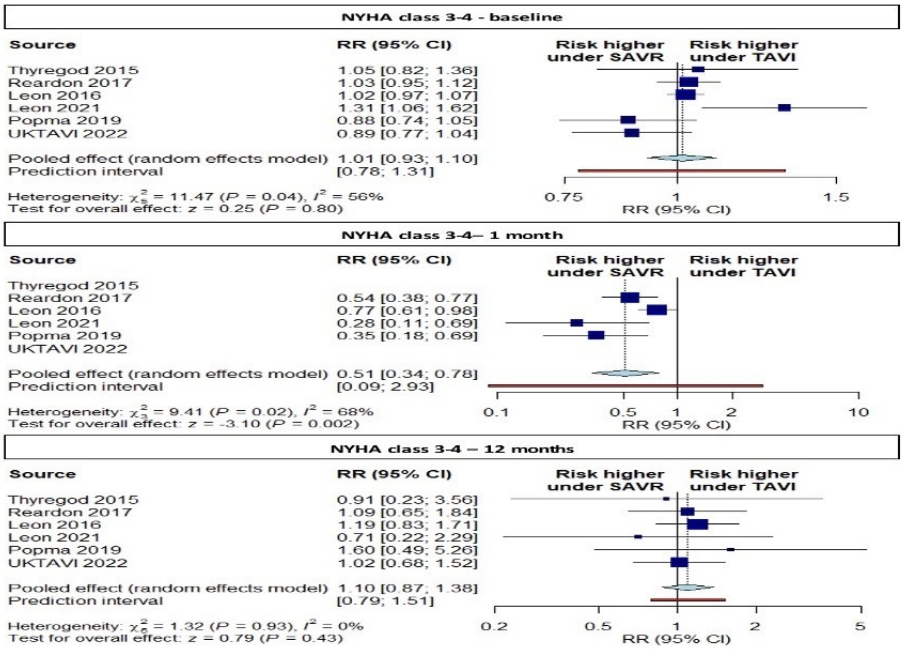

Figure 6: [Risk of NYHA class 3-4 at baseline, 1 and 12 months]

165x109mm (144 x 144 DPI)

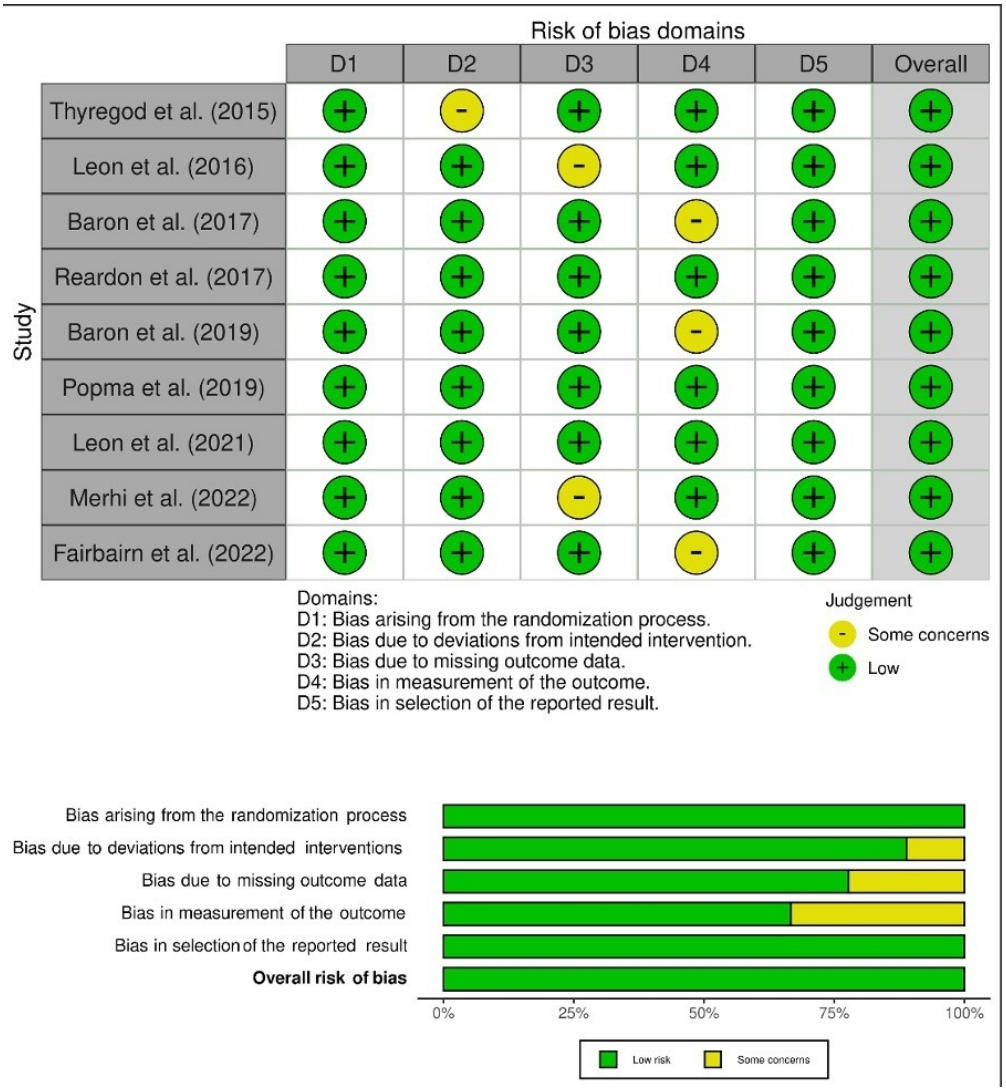

Figure 7: [Risk of Bias Assessment utilising Cochrane RoB 2.0]

159x172mm (144 x 144 DPI)

Study	Thyregod et al. (2015) [29]	Leon et al. (2016) [30]	Baron et al. (2017) [31]	Reardon et al. (2017) [32]	Baron et al. (2019) [33]	Popma et al. (2019) [34]	Leon et al. (2021) [35]	Merhi et al. (2022) [36]	Fairbairn et al. (2022) [37]
Year	2015	2016	2017	2017	2019	2019	2021	2022	2022
Type	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial	Multi-Centre Randomized-Controlled trial
Outcomes	NYHA follow-up for 12 months	NYHA follow-up for 24 months	KCCQ and EQ-5D for 24 months	KCCQ and NYHA for 24 months	KCCQ and EQ-5D for 12 months	KCCQ for 24 months	KCCQ and NYHA for 24 months	KCCQ for 12 months	EQ-5D and NYHA for 12 months
Total (TAVI), n=	145	1011	950	864	494	734	496	76	458
Total (SAVR), n=	135	1020	883	796	449	734	454	62	455
Age years (TAVI), mean	79.2 ± 4.9	81.5 ± 6.7	81.6 ± 6.7	79.9±6.2	73.3 ±5.8	74.0±5.9	73.3 ± 5.8	75.0 ± 5.0	81
Age years (SAVR), mean	79.0 ±4.7	81.7 ± 6.7	81.8 ± 6.8	79.7±6.1	73.6 ±6.1 (p=0.467)	73.8±6.0	73.6 ± 6.1	73.3 ± 6.5 (p= 0.08)	81
Male (TAVI),%	53.8	54.2	55	57.6	67.4	63.8	67.5	68	53.9
Male (SAVR), %	52.6	54.8	56.6	55	71.3 (p=0.204)	66.5	71.1	79 (p=0.16)	53.2
BMI (TAVI),n	N/A	28.6 ± 6.2	N/A	2.3 <21 kg/m2	N/A	N/A	30.7 ± 5.5	N/A	27.1
BMI (SAVR), n	N/A	28.3 ± 6.2	N/A	2.6 <21 kg/m2	N/A	N/A	30.3 ± 5.1	N/A	27.7
STS Risk (TAVI), mean	2.9 ± 1.6	5.8 ± 2.1	5.8 ± 2.1	4.4±1.5	1.9 ±0.7	1.9±0.7	1.9 ± 0.7	1.8 +- 0.6	2.6
STS Risk (SAVR), mean	3.1 ±1.7	5.8 ± 1.9	5.6 ± 1.7	4.5±1.6	1.9 ±0.6 (p=0.225)	1.9±0.7	1.9 ± 0.6	1.6 +- 0.6 (p= 0.10)	2.7
NYHA Class (TAVI), %	baseline class1: 4.9 ,class 2: 46.5, class 3: 46.5, class 4: 2.1	Class 3 or 4= 77.3%	class 3 (correlates to KCCQ 53.3 ± 21.9)	baseline class 2: 39.8, class 3: 54.6, class 4: 5.6	N/A	baseline class1: 10.5 ,class 2: 64.9, class 3: 24.5, class 4: 0.1	class 3 or 4 = 31.3 %	N/A	class 3 or 4 = 40.3 %
NYHA Class (SAVR), %	baseline class1: 2.2 ,class 2: 52.2, class 3: 42.5, class 4: 3.0	Class 3 or 4= 76.1%	class 3 (correlates to KCCQ 53.1 ± 21.1)	baseline class 2: 41.8, class 3: 51.6, class 4: 6.5	N/A	baseline class1: 9.9 ,class 2: 62.1, class 3: 27.5, class 4: 0.4	class 3 or 4 = 23.8	N/A	class 3 or 4 = 45.2 %
Coronary artery disease (TAVI),%	N/A	69.2	N/A	62.6	27.6	N/A	27.7	N/A	30

Coronary artery disease (SAVR),%	N/A	66.5	N/A	64.2	27.6 (p=0.999)	N/A	28	N/A	33.3
Previous myocardial infarction (TAVI), %	5.5	18.3	17.4	14.5	5.7	6.7	N/A	5	N/A
Previous myocardial infarction (SAVR),%	4.4	17.5	16.4 (p = 0.62)	13.9	5.8 (p=0.999)	5.3	N/A	5 (p >0.99)	N/A
Previous CABG (TAVI),%	N/A	23.6	23.1	16	N/A	2.5	3	N/A	N/A
Previous CABG (SAVR),%	N/A	25.6	22.4 (p = 0.75)	17.2	N/A	2.3	1.8	N/A	N/A
Previous PCI (TAVI), %	7.6	27.1	25.7	21.3	N/A	13.9	N/A	9	N/A
Previous PCI (SAVR),%	8.9	27.6	24.8 (p = 0.68)	21.2	N/A	12.7	N/A	10 (p=0.93)	N/A
Peripheral vascular disease (TAVI),%	4.1	27.9	22	30.8	6.9	7.6	6.9	5	N/A
Peripheral vascular disease (SAVR),%	6.7	32.9	25.7 (p = 0.11)	29.9	7.4 (p=0.801)	8.5	7.3	2 p 0.38	N/A
Diabetes mellitus (TAVI), %	17.9	37.7	36.8	34.1	31.4	31.1	31.3	25	N/A
Diabetes mellitus (SAVR), %	20.7	34.2	33.9 (p =0.26)	34.8	30.1 (p=0.724)	30.5	30.2	27 (p=0.75)	N/A
COPD any (TAVI), %	11.7	31.8	2.8	none:64.6 mild: 22.0 moderate: 10.3 severe: 3.0	5.1	15.1	5.1	chronic lung disease 16	N/A
COPD any (SAVR), %	11.9	30.0	2.2 (p = 0.53)	none:66.5 mild: 20.2 moderate: 9.7 severe: 3.6	6 (p=0.569)	17.2	6.2	3 (P=0.02)	N/A
Atrial fibrillation (TAVI),%	27.8	31.0	32	28.1	15.6	15.5	15.7	9	N/A
Atrial fibrillation (SAVR),%	25.6	35.2	36.3 (p = 0.09)	26.5	18.8 (p=0.225)	14.9	18.8	7 (p=0.75)	N/A
Permanent pacemaker (TAVI),%	3.4	11.7	N/A	9.7	N/A	3.4	2.4	N/A	N/A
Permanent pacemaker (SAVR),%	4.4	12.0	N/A	9	N/A	3.8	2.9	N/A	N/A

Frailty (TAVI), %	N/A	5-meter walk test time>7 sec-44.4, serum albumin<3.5g/dl-15.2	45.5	Falls in past 6 months: 11.8, Five meter gait speed > 6 seconds: 51.8, six minute walk (meters): 254.1 ± 115.8	N/A	N/A	0	N/A	CSHA Clinical Frailty Scale score >=5: 12.8%
Frailty (SAVR), %	N/A	5-meter walk test time>7 sec-46.4, serum albumin<3.5g/dl-14.7	46.4 (p = 0.76)	Falls in past 6 months: 12.7, Five meter gait speed > 6 seconds: 52.9, six minute walk (meters): 260.9 ± 117.9	N/A	N/A	0	N/A	CSHA Clinical Frailty Scale score >=5: 13.4%
Aortic-valve Area (TAVI), cm2	N/A	0.7± 0.2	0.7 ± 0.2	N/A	0.8 ± 0.2	0.8±0.2	N/A	N/A	0.7
Aortic-valve Area (SAVR), cm2	N/A	0.7± 0.2	0.7 ± 0.2 (p = 0.32)	N/A	0.8 ± 0.2 (p= 0.780)	0.8±0.2	N/A	N/A	0.7
Aortic-valve Gradient (TAVI), mmHg	N/A	44.9± 13.4	44.8 ± 13.8	N/A	49.4 ± 12.7	47.2±12.3	N/A	N/A	73
Aortic-valve Gradient (SAVR), mmHg	N/A	44.6± 12.5	44.8 ± 12.4 (p value = 0.93)	N/A	48.4 ± 11.8 (p=0.203)	46.7±12.2	N/A	N/A	74
Left ventricular ejection fraction (TAVI), %	N/A	56.2± 10.8	56.5 ± 10.4	N/A	65.7 ± 9.0	61.7±7.9	N/A	N/A	57
Left ventricular ejection fraction (SAVR), %	N/A	55.3± 11.9	55.3 ± 11.9 (p = 0.11)	N/A	66.2± 8.6 (p=0.431)	61.9±7.7	N/A	N/A	57
Mitral regurgitation (TAVI), %	N/A	16.8	16.6	N/A	N/A	N/A	N/A	N/A	10.7
Mitral regurgitation (SAVR), %	N/A	19.1	19.4 (p = 0.19)	N/A	N/A	N/A	N/A	N/A	13.3

Serum creatinine> 2mg/dl (TAVI), %	1.4	5.0	5.1	1.6	0.2	0.4	N/A	N/A	N/A
Serum creatinine (SAVR), %	0.7	5.2	4.9 (p = 0.87)	2.1	0.2 (p=0.999)	0.1	N/A	-	N/A
History of hypertension (TAVI), %	71	N/A	N/A	92.7	N/A	84.9	N/A	79	N/A
History of hypertension (SAVR), %	76.3	N/A	N/A	90.3	N/A	82.9	N/A	77 (p=0.83)	N/A
Stroke (TAVI), %	16.6	32.1	8.9	6.6	3.4	N/A	3.4	N/A	N/A
Stroke (SAVR), %	16.3	31.0	9.3 (p = 0.79)	7.2	5.1 (p=0.257)	N/A	5.1	N/A	N/A