Transcatheter versus surgical aortic valve replacement in intermediate risk patients: a meta-analysis

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Background: Transcatheter aortic valve replacement (TAVR) has been approved in patients with high or prohibited surgical risk for surgery for treatment of severe symptomatic aortic stenosis. Prospective studies examining the benefits of TAVR in intermediate risk patients are ongoing. Other smaller studies including lower risk patients have been conducted, but further meta-analysis of these studies is required to draw more broad comparisons.

Methods: A Medline search was conducted using standard methodology to search for clinical trials and observational studies including intermediate risk patients. We limited our meta-analysis to studies matching patient populations by propensity scores or randomization and examined clinical outcomes between TAVR and surgical aortic valve replacement (SAVR).

Results: Analysis of the TAVR and SAVR cohorts revealed no significant differences in the outcomes of 30-day [OR (95% CI): 0.85 (0.57, 1.26)] or 1-year mortality [OR (95% CI): 0.96 (0.75, 1.23)]. A trend towards benefit with TAVR was noted in terms of neurological events and myocardial infarction (MI) without statistical significance. A statistically significant decrease in risk of post-procedural acute renal failure in the TAVR group [OR (95% CI): 0.52 (0.27, 0.99)] was observed, but so was a significantly higher rate of pacemaker implantations for the TAVR group [OR (95% CI): 6.51 (3.23, 13.12)].

Conclusions: We conclude that in intermediate risk patients undergoing aortic valve replacement, the risk of mortality, neurological outcomes, and MI do not appear to be significantly different between TAVR and SAVR. However, there appears to be a significant reduction in risk of acute renal failure at the expense of an increased risk of requiring a permanent pacemaker in low and intermediate risk patients undergoing TAVR compared to SAVR.

Keywords: Transcatheter aortic valve replacement (TAVR); aortic stenosis; surgical risk; surgical aortic valve replacement (SAVR)

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Introduction

TAVR was first described in 2002 by Alain Cribier and colleagues in a 57-year-old man with a severely calcified, bicuspid aortic valve (1). Although their transvenous approach was met with limitations, Webb et al. later reported improved safety of TAVR via a transfemoral arterial approach (2). The advent of TAVR raised the hope for an alternative, less invasive treatment for aortic stenosis. Since then, the success of TAVR has been consolidated with the help of clinical trials. The Placement of Aortic Transcatheter Valve Trial (PARTNER) revealed TAVR to be non-inferior to surgical aortic valve replacement (SAVR) and superior to medical therapy for high risk and prohibitive risk surgical patients who suffered from severe, symptomatic aortic stenosis, respectively (3). The success of TAVR was further proven by the CoreValve US Pivotal Study, which indicated superiority of TAVR over SAVR in regards to mortality in patients with increased risk of death from surgery (4). This has led to the recognition of TAVR as the treatment of choice for aortic valve replacement for patients with severe, symptomatic aortic stenosis who are considered high or prohibitive risk for SAVR (5). Although SAVR currently remains the standard of care for the intermediate to low surgical risk population, several independent studies conducted predominantly in Europe have compared TAVR to SAVR in this population and demonstrated promising results for TAVR. The influx of data on outcomes from TAVR in the intermediate risk population continues to increase (6-14). For example, the ongoing SURTAVI and PARTNER II trials are investigating the safety and efficacy of TAVR compared to SAVR in an intermediate risk population. Although a number of small trials comparing outcomes between TAVR and SAVR in this population exist, only a single, small meta-analysis of these studies has been performed to date (15). A larger, more comprehensive meta-analysis is necessary to focus specifically on the population considered intermediate risk for valve replacement surgery.

Methods

Search strategy

We searched Medline, EMBASE, Google Scholar, Web of Science and Cochrane databases for studies with key words transcatheter, transact heter aortic valve implantation, percutaneous aortic valve implantation, percutaneous aortic valve replacement, transcatheter aortic valve replacement (TAVR), TAVI, TAVR, low, intermediate, moderate and propensity. All retrieved abstracts were reviewed by two authors independently and later again confirmed by a third author. The bibliographies of all articles were reviewed to look for other potential articles with eligible data for the meta-analysis. The meta-analysis has been reported according to Meta-analysis of observational studies in Epidemiology guidelines.

Study characteristics

All randomized control trials (RCTs) and studies using propensity score matching based on clinical characteristics and surgical risk scores, i.e., the Society of Thoracic Surgeons (STS) Score or Euroscore, and categorizing patients into intermediate risk groups were included in the study. We gave priority to the STS score if both scores were available as it has been demonstrated to be superior to Euroscore in predicting outcomes (16,17). STS predicted risk of mortality (PROM) (mean <8%) was used as a benchmark for inclusion on the basis of the SURTAVI definition of the intermediate risk categories. Euroscore (mean <20%) was used only if the STS score was not available. Inclusion was restricted to comparison studies only and studies with isolated data from only one of the two interventions were not included (13,14,18,19). We included all studies irrespective of the type of TAVR valve and the route of vascular access. The study characteristics and the distribution of patients between the two study groups are demonstrated in Table 1.

Outcome measures

The Valve Academic Research Consortium (VARC) in its most recent update has defined clinical endpoints to help future clinical trials standardize outcomes when using TAVR as intervention (20). Even though some of our studies were conducted before the most recent updates from VARC, they still primarily used VARC endpoints to quantify outcomes. We pooled data from individual studies to determine 30-day mortality, 1-year mortality, stroke and all neurological events at 30 days, MI at 30 days, acute renal failure at 30 days, and pacemaker implantation at 30 days.

Meta-analysis

Random effects meta-analyses were carried out using RevMan 5.2 (Cochrane, Oxford, UK). The presence and
<table>
<thead>
<tr>
<th>Name of the study</th>
<th>Type of study</th>
<th>Matched number of patients included for meta-analysis</th>
<th>Outcomes measured</th>
<th>Risk Stratification qualifying factor</th>
<th>Type of valve</th>
<th>Route of access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyregod et al. 2015</td>
<td>Multicenter, randomized, nonblinded, superiority trial</td>
<td>TAVR=139 SAVR=135</td>
<td>Mortality, neurological events, stroke, TIA, MI, renal failure, need for PPM, vascular compromise</td>
<td>STS (SAVR) 3.1±1.7</td>
<td>CoreValve (100%) in sizes 23, 26, 29, 31 mm</td>
<td>TF preferred approach. Left axillary second choice</td>
</tr>
<tr>
<td>Latib et al. 2012</td>
<td>Propensity score matched case control study</td>
<td>TAVR=111 SAVR=111</td>
<td>Mortality, neurological events, stroke, TIA, MI, renal failure, need for PPM</td>
<td>STS (TAVR) 4.57±2.28</td>
<td>Edwards-Sapien XT (58.3%) and CoreValve (41.7%)</td>
<td>TF (100%) non-TF patients excluded</td>
</tr>
<tr>
<td>Piazza et al. 2013</td>
<td>Prospective 3-center cohort study</td>
<td>TAVR=255 SAVR=255</td>
<td>Mortality and neurological events</td>
<td>STS (TAVR &amp;SAVR) 3–8%</td>
<td>Edwards-Sapien and CoreValve</td>
<td>TF preferred approach followed by axillary, TA and direct aortic</td>
</tr>
<tr>
<td>Tamburino et al. 2015</td>
<td>Observational prospective multicenter cohort study</td>
<td>TAVR=650 SAVR=650</td>
<td>Mortality, neurological outcomes, myocardial infarction (MI), renal failure, cardiac tamponade, need for PPM, vascular complications, infection, need for PCI, need for CABG, MACCE, hospitalizations, bleeding</td>
<td>Euroscore (TAVR) 9.5±7.1%</td>
<td>CoreValve (60.4%) and Edwards-Sapien XT (39.4%)</td>
<td>TF (81.8%), TA (13.6%), Subclavian (3.8%), Direct aortic (0.8%)</td>
</tr>
<tr>
<td>Schymik et al. 2015</td>
<td>Propensity score matched cohort study</td>
<td>TAVR=216 SAVR=216</td>
<td>Mortality, stroke, MI, renal failure, bleeding vascular complications, need for PPM</td>
<td>Euroscore (TAVR) 5.7±3.2</td>
<td>Edwards SAPIEN and SAPIEN XT THV (TF and Transapical), CoreValve (TF), Symetic ACURATE (TA)</td>
<td>TF and TA</td>
</tr>
<tr>
<td>Muneretto et al. 2014</td>
<td>Prospective cohort study</td>
<td>TAVR=55 SAVR=55</td>
<td>Mortality, neurological complications, postoperative MI, bleeding, renal failure, bleeding and peripheral vascular complications</td>
<td>Euroscore (TAVR) 6±3.6</td>
<td>CoreValve (100%)</td>
<td>TF (100%)</td>
</tr>
</tbody>
</table>
degree of between-study heterogeneity was assessed using Cochran’s Q statistic (P<0.10) and $I^2$ values. Due to inherent differences in study populations and clinical sites, random effects meta-analyses were conducted for all outcomes. Odds ratios of 30-day mortality, 1-year mortality, and 30-day adverse events were meta-analyzed, with summaries representing the mean of the random effects distributions. Because the majority of studies reported adverse events by the number of occurrences, 30-day odds ratios were analyzed without consideration of competing risks. Publication bias was assessed using Harbord’s modified test for small-study effects, with 30-day mortality considered the primary outcome.

Results

Study population

A total of 1,733 abstracts were identified with a literature search, of which 29 full articles were retrieved and reviewed in depth. A total of 6 publications (1 RCT and 5 propensity score matched observational studies) were identified for inclusion (Figure 1) (6-8,10-12). Outcomes were abstracted and meta-analyzed if reported by a minimum of 4 studies. Consistent with the current Food and Drug Administration (FDA) restrictions for TAVR in low to intermediate risk patients in the United States, all studies originated from Europe (3 in Italy, 2 in Germany, and 1 in Denmark). A total of 2,848 patients were propensity score matched in the included studies and were included in the meta-analysis. Duplicate data was not accepted. There was no evidence of publication bias detected (P=0.8). Study population demographics were similar, with average ages ranging from 78–81 years and percentage of women ranging from 47% to 59%. Of the studies reporting baseline comorbidities, diabetes prevalence ranged from 20% to 25%, COPD prevalence was 12% to 37%, prevalence of peripheral vascular disease was 5% to 30%, and the prevalence of prior myocardial infarction (MI) ranged from 5% to 14% (Table 2). Full patient demographics and characteristics are listed in Table 2.

Outcomes

All studies reported 30-day mortality; however, 1-year mortality was limited to 4 publications. The overall 30-day mortality ranged from 0.9–7.5%, increasing to 6.1–17.0% after a year. Mortality odds ratios comparing TAVR to SAVR were close to null (1.0) for all abstracted 30-day and 1-year mortality outcomes (Figures 2,3). Thirty day adverse events were reported by 5 studies. Because the 30-day mortality rate among these studies was low (0.9–3.4%), competing risk bias was considered minimal and outcomes were analyzed using odds ratios.

No significant difference was detected between TAVR vs. SAVR at 30 days in regards to MI [OR (95% CI): 0.48 (0.21, 1.11)], stroke [OR (95% CI): 0.61 (0.31, 1.20)], or adverse neurological events [OR (95% CI): 0.63 (0.35, 1.14)], but a trend towards fewer events in the TAVR group was observed with a 40–50% lower odds of developing these complications (Figures 4-6). There was also a 40–50% lower odds of acute renal failure in the TAVR group as compared to the SAVR group at 30 days, which reached statistical
Table 2 Baseline characteristics of 6 matched studies comparing transcatheter aortic valve replacement (TAVR) to surgical aortic valve replacement (SAVR)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (N=1,426) average (range)</th>
<th>SAVR (N=1,422) average (range)</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>80 [78–81]</td>
<td>79 [79–80]</td>
<td>(6-8,10-12)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>54% (46–59%)</td>
<td>53% (47–60%)</td>
<td>(6-8,10-12)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>23% (18–27%)</td>
<td>22% (16–26%)</td>
<td>(6-8,10-12)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>44% (30–57%)</td>
<td>42% (15–58%)</td>
<td>(6,7,11,12)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73% (66–86%)</td>
<td>77% (69–82%)</td>
<td>(6-8,12)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.2 (1.1–1.2)</td>
<td>1.1 (1.1–1.2)</td>
<td>(6,7,10)</td>
</tr>
<tr>
<td>Previous myocardial infarction (MI) (%)</td>
<td>7% (2–14%)</td>
<td>9% (3–14%)</td>
<td>(6,8,10-12)</td>
</tr>
<tr>
<td>Previous Stroke/TIA (%)</td>
<td>10% (3–17%)</td>
<td>10% (4–18%)</td>
<td>(6-8,10,11)</td>
</tr>
<tr>
<td>Chronic lung disease (%)</td>
<td>22% (9–47%)</td>
<td>18% (9–27%)</td>
<td>(6-8,10-12)</td>
</tr>
<tr>
<td>Peripheral arteriopathy (%)</td>
<td>14% (4–26%)</td>
<td>17% (7–34%)</td>
<td>(6-8,10-12)</td>
</tr>
<tr>
<td>NYHA III-IV (%)</td>
<td>61% (48–75%)</td>
<td>64% (45–75%)</td>
<td>(6-8,10,12)</td>
</tr>
</tbody>
</table>

Figure 2 Thirty day mortality. Displayed is 30 days mortality of TAVR vs. SAVR in this intermediate risk population. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

Figure 3 One year mortality. Displayed is one year mortality of TAVR vs. SAVR in this intermediate risk population. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

Discussion

The SURTAVI trial is an ongoing multicenter trial comparing the clinical outcomes for transcatheter and surgical valve replacement in intermediate risk patients defined by a STS risk score of 3–8%. As we await the
results of this study, we designed a meta-analysis of trials comparing the two interventions in intermediate surgical risk patients in order to draw broader conclusions. This study design differed from that of the only previous, smaller meta-analysis in that we took into consideration the standard deviation for the risk scores (15). This was the reason for CoreValve US Pivotal Study not meeting the inclusion criteria (4). The results of the STACCATO trial were also not included in our meta-analysis as the early termination of the study was felt to have a high likelihood of skewing the results. Our meta-analysis is also broader, including several studies that were not randomized, controlled clinical trials but that still yielded comparable data on lower risk patients (11-12). This resulted in a larger
patient population and subsequently a meta-analysis with greater statistical power.

Although mortality, neurological outcomes, and MI were not significantly different between interventions, we did notice a trend favoring TAVR for 30-day MI and neurological outcomes. We did, however, find a significant decrease in acute renal failure and an increase in rates of pacemaker implantations post-TAVR across the different studies [OR (95% CI): 6.51 (3.23, 13.12)]. Another recent meta-analysis comparing self-expanding valves to balloon-expandable valves also demonstrated a higher incidence of acute renal failure and an increase in rates of pacemaker implantations post-TAVR (25), our analysis demonstrates an overwhelming increase in the rates of pacemaker implantations post-TAVR across the different studies [OR (95% CI): 6.51 (3.23, 13.12)]. Another recent meta-analysis comparing self-expanding valves to balloon-expandable valves also demonstrated a higher incidence of rates of pacemaker implantation in patients with self-

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<table>
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<tr>
<th>Study or subgroup</th>
<th>Events</th>
<th>Total</th>
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<th>Total</th>
<th>Weight</th>
<th>M-H, random, 95% CI</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td>Schymik 2015</td>
<td>30</td>
<td>216</td>
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<td>216</td>
<td>26.9%</td>
<td>3.32 [1.58, 6.98]</td>
<td>3.32</td>
<td>1.32 [1.72, 17.26]</td>
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<tr>
<td>Latib 2012</td>
<td>13</td>
<td>111</td>
<td>3</td>
<td>111</td>
<td>16.8%</td>
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<td>4.78</td>
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<td>Tamburino 2015</td>
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<td>23</td>
<td>650</td>
<td>32.8%</td>
<td>4.84 [3.03, 7.73]</td>
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<td>Muneretto 2015</td>
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<td>55</td>
<td>1</td>
<td>55</td>
<td>8.8%</td>
<td>18.44 [2.33, 145.98]</td>
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<td>2</td>
<td>135</td>
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<td>32.89 [7.79, 138.87]</td>
<td>32.89</td>
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**Total (95% CI)**
- **Events**: 1171
- **Total**: 1167

Test for overall effect: Z = 1.99 (P = 0.05); I² = 73%

**Heterogeneity**:
- Tau² = 0.38; Chi² = 14.98, df = 4 (P = 0.005); I² = 73%

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**Figure 7** Acute Renal Failure at 30 days. Displayed is acute renal failure at 30 days of TAVR vs. SAVR in this intermediate risk population. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

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<td>32.89</td>
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</tr>
</tbody>
</table>

**Total (95% CI)**
- **Events**: 201
- **Total**: 39

Test for overall effect: Z = 1.99 (P = 0.05); I² = 59%

**Heterogeneity**:
- Tau² = 0.33; Chi² = 9.73, df = 4 (P = 0.05); I² = 59%

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**Figure 8** Pacemaker implantation at 30 days. Displayed is pacemaker implantation at 30 days of TAVR vs. SAVR in this intermediate risk population. TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

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outcomes of early first- and second-generation valves. Newer valve designs that allow smaller diameter access and the ability to fully recapture and reposition the valve are becoming standard of care, so operators can likely expect lower rates of related complications in the future. This is likely to lower the overall mortality and complication rates of the procedure in the future. Despite the fact that this data included older first- and second-generation valves, there was still a trend towards lower MI rates and neurological event rates. It is likely that as novel trials include newer valve designs that these outcomes favoring TAVR can be expected to improve significantly.

Although the PARTNER A trial failed to show a statistical difference in the incidence of pacemaker implantation between TAVR or SAVR (25), our analysis demonstrates an overwhelming increase in the rates of pacemaker implantations post-TAVR across the different studies [OR (95% CI): 6.51 (3.23, 13.12)]. Another recent meta-analysis comparing self-expanding valves to balloon-expanding valves also demonstrated a higher incidence of rates of pacemaker implantation in patients with self-
expanding prosthesis, as has a small meta-analysis of all types of valves (15,26). Significantly higher rates of pacemaker implantation were also noted in the CoreValve US Pivotal trial (4). Unlike the PARTNER A trial, our meta-analysis included patients receiving both balloon-expandable and self-expanding valves. Coupled with the results of the other meta-analyses and the CoreValve trial, the fact that the PARTNER A trial, which included exclusively balloon-expandable valves, did not reveal an increase pacemaker rate may indicate the risk is attributable to self-expanding valves. This inference must be placed in context, however, considering that newer generation balloon-expandable valves are also accepted to have a higher pacemaker implantation rate than SAVR (27).

Although it is a fairly comprehensive data set, this meta-analysis has several limitations. All of the trials included studied the use of earlier generation valves that are not currently the standard of practice. Although the newer valves may indeed have lower complication rates as compared to the first generation valves, this is not an absolute certainty, and definitive conclusions about the TAVR valves most commonly used today cannot be definitively drawn from this data. We assessed for publication bias, and although our results indicate publication bias is unlikely, it cannot be completely ruled out. Our meta-analysis also relied heavily on the Euroscore and STS score for risk stratification. Although these tools are the gold standard for surgical risk stratification for valve replacement, they have their own limitations. Specifically, they do not fully account for overall frailty and cognitive impairment, both of which contribute significantly to surgical risk. Subsequently, patients with low scores may have higher operative risk than the score itself may indicate, so our patient population could be somewhat higher risk than the scores would suggest. Despite these limitations, the data presented remain strong and yield more insight into the lower risk TAVR population, which has not been rigorously studied in the United States.

Conclusions

As we eagerly await the results of the SURTAVI and PARTNER II trials, we compared outcomes for patients who underwent TAVR as compared to SAVR in patients who are considered intermediate risk for surgery. Risk of mortality, neurological outcomes, and MI do not appear to be significantly different between the two groups, but there appears to be a significant reduction in risk of acute renal failure and an increased risk of requiring a permanent pacemaker in patients undergoing TAVR rather than SAVR.

Acknowledgements

None.

Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

References


