Aortic and Mitral Valve Replacement Versus Transcatheter Aortic Valve Replacement in Propensity-Matched Patients

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Background. Recent studies have suggested that transcatheter aortic valve replacement (TAVR) may have superior outcomes compared with aortic valve replacement (AVR) for high-risk patients with significant mitral regurgitation (MR). Considering significant MR is frequently addressed with a mitral valve repair or replacement (MVR) at the time of open aortic valve replacement, this study compares TAVR and AVR/MVR in propensity-matched pairs of patients with significant MR.

Methods. We evaluated all patients presenting with moderate or greater MR undergoing either TAVR or AVR/MVR at a single institution from 2002 to 2012. Patients who underwent other cardiac operations or had preoperative endocarditis were excluded. Of 306 patients in the AVR/MVR group and 147 patients in the TAVR group, propensity analysis matched 40 pairs of patients. Standard univariate, logistic regression, and propensity matching techniques were used.

Results. There was no significant difference between TAVR patients and AVR/MVR patients, respectively, in preoperative average age (76 ± 7.4 versus 78 ± 6.9 years, p = 0.68), ejection fraction (53 ± 15 versus 51 ± 17, p = 0.68), The Society of Thoracic Surgeons score (9.9 ± 3.1 versus 9.3 ± 3.4, p = 0.61), or 30-day mortality (7.5% versus 2.5%, p = 0.6). Postoperative MR was significantly improved for both TAVR and AVR/MVR, but AVR/MVR showed significantly greater improvement (L2.33 ± 1.23 versus L0.88 ± 0.79, p < 0.001). Among 30-day survivors, midterm survival was significantly better in the AVR/MVR group compared with the TAVR group (log rank p = 0.04).

Conclusions. In a propensity-matched analysis of patients with significant MR, AVR/MVR and TAVR had equivalent perioperative outcomes, but AVR/MVR had more reduction in MR and may have superior midterm survival when compared with TAVR among 30-day survivors.


Mitral regurgitation (MR) is a frequent coexisting condition in patients with aortic stenosis. Published series of aortic valve replacement (AVR) or transcatheter
aortic valve replacement (TAVR) report rates as high as 48% to 90% of patients presenting with some degree of MR [1, 2]. Increasing severity of MR in patients undergoing AVR or TAVR has been associated with increased perioperative risk and decreased long-term survival [3–8]. As a result, some studies have recommended that patients undergoing AVR with moderate or greater MR be considered for simultaneous mitral valve replacement/repair (MVR) [6, 9]. Although cases of simultaneous TAVR and transcatheter mitral intervention have been reported, this dual valve therapy remains clinically rare, and TAVR remains almost exclusively an isolated aortic valve therapy [10].

A recent analysis of the randomized Placement of Aortic Transcatheter Valve (PARTNER) trial examined the impact of MR on outcomes of patients with severe aortic stenosis undergoing TAVR or isolated AVR. At 2 years, patients with significant MR undergoing AVR had poorer survival when compared with AVR patients not having significant MR. In contrast, this impact was not seen in patients undergoing TAVR. Although this finding suggested TAVR may be a superior therapeutic option for high-risk patients with severe aortic stenosis and significant MR, overall 2-year mortality remained sobering at 37%, particularly with 42% of patients having residual moderate/severe MR [11, 12]. The question remains whether AVR/MVR may offer incremental benefit for this patient population, albeit with potentially increased perioperative surgical risk. We sought to compare simultaneous AVR/MVR with TAVR in a propensity-matched group of patients with significant MR.

Patients and Methods

Between January 1, 2002, and December 31, 2012, 1,209 open AVR and, starting November 15, 2007, 337 Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) TAVR procedures were performed at a single institution. The initial study population was limited to patients undergoing open AVR with concomitant MVR (n = 306) and patients undergoing TAVR who presented with moderate or greater mitral regurgitation (n = 147). Patients with active endocarditis and concomitant cardiac procedures other than MVR including bypass grafting were excluded. The Institutional Review Board at the University of Pennsylvania approved the study and waived the need for patient consent. Data were retrieved from the University of Pennsylvania’s prospective The Society of Thoracic Surgeons (STS) registry and partially extracted from each patient’s electronic medical record. Midterm survival was determined using the Social Security Death Index if adequate internal documentation was unavailable.

All patients underwent preoperative and postoperative echocardiograms. To provide consistent loading conditions and comparable measurements without the effects of general anesthesia, transthoracic echocardiograms were preferentially selected over transesophageal echocardiograms. Preoperative echocardiograms from a 3-month window preceding the date of surgery, postoperative echocardiograms from any time after the procedure until the date of discharge, and follow-up echocardiograms from after 3 months from the date of surgery were analyzed. Median echocardiogram follow-up time was 1.1 years. The MR grade was extracted from echocardiogram reports with a grade scheme of mild, 1+; moderate, 2+; moderate-severe, 3+; and severe, 4+. Significant MR was defined as moderate or more, or 2+.

Because there were clinically relevant differences in preoperative risk profiles between the open AVR/MVR patients and TAVR patients, propensity score matching based on STS risk score was used to reduce bias due to confounding variables. The STS score was calculated assuming that patients were having only AVR, as the calculator cannot give a risk score for AVR/MVR. Propensity scores for treatment group membership were calculated for each patient using a nonparsimonious logistic regression model. Matching was completed by a greedy 5 to 1 digit match algorithm using a nearest available pair matching method [13]. With a one-to-one match, this technique achieved 40 matched pairs. A second covariate-based propensity-matched model designed to validate the STS-based propensity model was performed using the patient variables of age, sex, urgent cardiac surgery, New York Heart Association (NYHA) functional class, hypertension, renal failure, peripheral vascular disease, diabetes mellitus, and redo status that generated 50 matched pairs.

Of the 40 patients undergoing simultaneous AVR/MVR included in the STS-based propensity-matched analysis, 15 patients underwent mitral replacement with a biologic prosthesis, 1 patient received a mechanical mitral prosthesis, and 24 patients underwent mitral repair. Thirty-nine patients in the AVR/MVR group underwent aortic replacement with a biologic prosthesis, and 1 patient in the AVR/MVR group received a mechanical prosthesis. Three patients received 19mm prostheses, 11 received 21mm, 17 received 23mm, 7 received 25mm, 1 patient received 27mm, and 1 received 29mm. For the 40 patients in the TAVR group, there were 24 transfemoral, 15 transapical, and 1 transaortic access. Twenty-five patients received 23mm SAPIEN prostheses and 15 received 26mm SAPIEN prostheses. The prosthesis for the TAVR patients was from Edwards Lifesciences, and that report has been previously published [12].

Continuous variables were analyzed by two-sample t test for normally distributed data and by Wilcoxon-Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed by Fisher’s exact test. For repeated measures, paired t tests were used for within-subject analysis of continuous variables. Kaplan-Meier survival analysis was used for analysis of time-dependent outcomes. All propensity score matching and statistical analysis was performed with SAS software, version 9.3 (SAS Institute, Cary, NC). The primary outcomes for the study were improvement in MR and midterm mortality.

Results

The preoperative characteristics of the patients undergoing TAVR or AVR/MVR are presented in Table 1.
Using a model that matched on STS score, there was no difference in age (78.15 ± 1.1 years, 76.63 ± 1.2 years, \( p = 0.345 \)) or STS score (9.9 ± 3.1, 9.3 ± 3.4, \( p = 0.61 \)), respectively. There was a significantly higher percentage of NYHA class III/IV, redo operations, peripheral arterial disease, and hypertension and significantly fewer emergent/urgent operations in the TAVR patients compared with the AVR/MVR patients. There were no other differences in preoperative characteristics including sex, ejection fraction, diabetes, or renal failure. A second propensity model based on patient covariates was also used that had no difference in age, NYHA, redo operations, peripheral arterial disease, renal failure, hypertension or urgent/emergent status.

The postoperative outcomes were similar between the TAVR and AVR/MVR patients. The 30-day mortality rate for TAVR was 2.5% (n = 1), with 1 death from cardiogenic shock. Among AVR/MVR patients, the 30-day mortality rate was 7.5% (n = 3), with all 3 patients having sepsis and multisystem organ failure (\( p = 0.61 \)). There was no difference in the stroke rate between TAVR and AVR/MVR. There was also no difference in the intensive care unit stay, prolonged ventilation, or renal failure. Please see Table 2 for complete outcomes.

The preoperative, postoperative, and follow-up MR outcomes are displayed in Figure 1. Of the 40 TAVR patients, 36 had moderate preoperative MR, 3 had moderate to severe MR, and 1 patient had severe MR. Of the 40 AVR/MVR patients, 24 had moderate preoperative MR, 2 had moderate to severe MR, and 14 had severe MR. Postoperative MR was significantly improved in both groups, with a decrease in average MR in TAVR patients from 2.13 ± 0.4 to 1.25 ± 0.78 (\( p < 0.001 \)), and a decrease in AVR/MVR patients from 2.75 ± 0.95 to 0.43 ± 0.78 (\( p < 0.001 \)). Between the two groups, the AVR/MVR group showed

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**Table 1. Preoperative Characteristics STS Propensity-Matched Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TAVR (n = 40)</th>
<th>All AVR/MVR (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, years</td>
<td>78.15 ± 1.1</td>
<td>76.63 ± 1.2</td>
<td>0.345</td>
</tr>
<tr>
<td>STS score</td>
<td>9.9 ± 3.1</td>
<td>9.3 ± 3.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Male</td>
<td>50 (20)</td>
<td>52.5 (21)</td>
<td>0.5</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>51.85 ± 2.7</td>
<td>53.35 ± 2.4</td>
<td>0.682</td>
</tr>
<tr>
<td>NYHA class I/II</td>
<td>5 (2)</td>
<td>30 (12)</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>95 (38)</td>
<td>70 (28)</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>55 (22)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40 (16)</td>
<td>22.5 (9)</td>
<td>0.074</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10 (4)</td>
<td>5 (2)</td>
<td>0.338</td>
</tr>
<tr>
<td>COPD</td>
<td>47 (19)</td>
<td>8 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>95 (38)</td>
<td>70 (28)</td>
<td>0.003</td>
</tr>
<tr>
<td>Emergent/urgent/urgent</td>
<td>12.5 (5)</td>
<td>35 (14)</td>
<td>0.017</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>50 (20)</td>
<td>7.5 (3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percent (n).

AVR/MVR = aortic valve replacement/mitral valve replacement or repair; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS = The Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

**Table 2. Postoperative Characteristics of Propensity-Matched Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TAVR (n = 40)</th>
<th>AVR/MVR (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>2.5 (1)</td>
<td>2.5 (1)</td>
<td>0.753</td>
</tr>
<tr>
<td>Total stay ICU, hours</td>
<td>84.4 ± 14.1</td>
<td>99.13 ± 31.1</td>
<td>0.668</td>
</tr>
<tr>
<td>Permanent stroke</td>
<td>0 (0)</td>
<td>2.5 (1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>25 (10)</td>
<td>17.5 (7)</td>
<td>0.293</td>
</tr>
<tr>
<td>Heart block</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td>0.247</td>
</tr>
<tr>
<td>Sternal infection</td>
<td>0.0 (0)</td>
<td>2.5 (1)</td>
<td>0.5</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2.5 (1)</td>
<td>7.5 (3)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percent (n).

AVR/MVR = aortic valve replacement/mitral valve replacement or repair; ICU = intensive care unit; TAVR = transcatheter aortic valve replacement.
significantly greater improvement, with an average change of $-2.33 \pm 1.23$ compared with $-0.88 \pm 0.79$ in the TAVR group ($p < 0.001$; Fig 2). In the AVR/MVR group, 100% of patients showed postoperative improvement in MR compared with 65% of the TAVR patients ($p = 0.003$); MR remained stable in 35% of the TAVR patients and in none of the AVR/MVR patients ($p = 0.001$; Fig 3).

Kaplan-Meier analysis of the midterm survival comparing STS propensity-matched TAVR and AVR/MVR patients showed no significant difference between the groups (log rank $p = 0.51$; Fig 4). Landmark analysis of 30-day survivors is depicted in Figure 5, which shows that midterm survival was significantly greater for AVR/MVR patients compared with TAVR patients (log rank $p = 0.02$). Similar results for overall survival and landmark analysis were found in the covariate-based propensity-matched group of 50 pairs of patients (Figs 6, 7, respectively). There was no difference in midterm survival (log rank $p = 0.03$), but landmark analysis of 30-day survivors demonstrated superior survival for the AVR/MVR group (log rank $p = 0.04$). Among these 50 matched pairs of patients, there was a significantly higher STS score for TAVR patients ($9.78 \pm 3.69$) compared with AVR/MVR patients ($4.29 \pm 3.47$, $p < 0.001$).

Comment

This study compares propensity-matched groups of patients with significant MR undergoing isolated TAVR or AVR/MVR. For this high-risk patient cohort with concomitant aortic and mitral valve disease, this study demonstrated excellent perioperative outcomes for both groups. The 30-day mortality was 2.5% ($n = 1$) for TAVR patients and 7.5% ($n = 3$) for AVR/MVR patients, with a stroke rate of 0% in the TAVR group and 2.5% ($n = 1$) in the AVR/MVR group. These rates are similar to the outcomes reported in the Placement of Aortic Transcatheter Valve (PARTNER) A trial patients, with mortality at 30 days, 1 year, and 2 years for TAVR patients of 3.4%, 24.2%, 33.9%, respectively, and for AVR patients, 6.5%, 26.8%, and 35%, respectively [14]. The 1-year and 2-year mortality of patients in this study is lower than that of the PARTNER A trial patients, with 15% 1-year mortality and 25% 2-year mortality among TAVR patients and 17% 1-year and 22% 2-year mortality among AVR/MVR patients. The lower mortality is remarkable because all patients in this study had the additional risk factor of significant MR at presentation. Beyond 2 years, the survival curves for AVR/MVR and TAVR diverge in this study, in both the STS and covariate-based models, with a significant midterm survival advantage for patients undergoing AVR/MVR. To address sampling bias and any bias inherent in the STS score, a second propensity model based on other patient variables and comorbidities was analyzed. The similar survival curves and statistical analysis of the two models further corroborates the possibility that there is a midterm survival advantage to AVR/MVR over TAVR for patients with significant MR who survive the postoperative period.
The risks and benefits of isolated AVR compared with open AVR and MVR are still actively debated [4–6, 15–19]. For patients with moderate MR, double valve operations have been shown to have superior MR outcomes but have yet to consistently demonstrate a clear survival benefit [4–6, 15]. Mitral regurgitation has also been shown to modestly improve in the setting of isolated AVR [5, 15, 20–22]. The studies of isolated aortic valve intervention, however, have not arrived at a reproducible set of similar preoperative factors that can be reliably used to predict whose MR will improve without mitral valve intervention, and often have contradictory results [1, 2, 5, 6, 20, 21, 23, 24]. The introduction of TAVR as a possible isolated aortic valve replacement adds another significant interventional arm to the decision tree in terms of the most beneficial intervention for high-risk patients requiring AVR [25]. A certain percentage of patients undergoing TAVR have also been shown to have improved MR, but similar to the AVR, there is still no single factor or group of validated patient factors that can be used to reliably predict improvement in MR after TAVR [2, 8].

In this study, all patients had significant MR, which was defined as moderate or greater MR. The TAVR group had more patients with moderate MR (90%) because severe MR was an exclusion criterion for the PARTNER trial, and the open AVR/MVR patients had more severe MR (35%), which would be expected in a cohort of patients receiving a double valve operation. The grouping of moderate or greater MR has been used in a number of other studies in recognition that severity grading can vary between echocardiographic readers, and patients can have several preoperative studies reporting different MR severities [11]. The use of significant MR in this study is consistent with these prior studies and is meant to be inclusive of all patients who would be considered for a surgical mitral valve intervention at the time of open AVR. Previous studies have also demonstrated that MR is frequently the result of left ventricular dysfunction and is associated with patients with more comorbidities, biasing, if anything, the AVR/MVR patients toward having worse outcomes [26].

Using PARTNER A and B study data, a recently published study has suggested that TAVR may be associated with lower mortality when compared with isolated AVR in the setting of significant MR. Barbanti and colleagues [11] showed that moderate or greater MR led to a significant survival difference in AVR patients compared with AVR patients with mild or no MR. The degree of MR did not affect TAVR mortality, but the 2-year AVR mortality was 49% and there was no report of any significant difference in survival between AVR and TAVR. Internal review of open AVR/MVR operations in a similar patient cohort at our institution revealed 30-day, 1-year, and 2-year mortality rates of 5.8%, 14%, and 18% (unpublished data, 2013). Our outcomes demonstrated lower mortality rates compared with PARTNER A trial outcomes for patients with and patients without significant MR. Since the PARTNER

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**Fig 5.** Long-term landmark survivor analysis of patients with significant mitral regurgitation, comparing aortic valve replacement/mitral valve replacement (AVR/MVR [blue line]) versus transcatheter aortic valve replacement (TAVR [red line]).

**Fig 6.** Kaplan-Meier survival analysis for 50 matched pairs using comorbidity model (Blue line = aortic valve replacement/mitral valve replacement [AVR/MVR]; red line = transcatheter aortic valve replacement [TAVR].)

**Fig 7.** Landmark survival analysis for 50 matched pairs using comorbidity model. (Blue line = aortic valve replacement/mitral valve replacement [AVR/MVR]; red line = transcatheter aortic valve replacement [TAVR].)
trials excluded patients from receiving a mitral valve intervention, the hypothesis of the present analysis was that using AVR/MVR patients instead of isolated AVR patients may be equivalent or superior to TAVR for patients with aortic and mitral valve disease. In the PARTNER study, excluding patients receiving open AVR from also receiving possible surgical intervention for their mitral valve disease potentially biased the surgical comparison group by exposing patients to the risk of cardiopulmonary bypass and an open operation without offering the maximal potential surgical benefit of an open operation, including a possible AVR/MVR.

In previous studies comparing isolated AVR or aortic root replacement to combined AVR/MVR in the setting of MR, AVR/MVR has consistently shown equivalent perioperative and superior MR outcomes but has failed to show a survival benefit outside certain subgroups of patients [9, 15]. The MR outcomes of this study are consistent with previous studies that show MR can improve with isolated aortic valve intervention, but surgically addressing MR leads to better postoperative and long-term MR outcomes [9, 15, 27]. The indications for double valve operations are not well defined, and large studies have shown an increased operative mortality with double valve operations compared with isolated AVR [4–6, 15, 18, 19, 28]. This study is remarkable because it demonstrates, in contrast to previous studies, that there is potentially a survival benefit from surgically addressing significant concomitant MR at the time of an aortic valve operation with a double valve operation.

In this study, there were numerically, although not statistically significant, more operative deaths in the AVR/MVR cohort compared with the TAVR patients. To a degree, this is to be expected owing to the more invasive nature and risks associated with a complicated double valve operation. Overall midterm survival was not significantly different between the two groups, though, and landmark analysis of 30-day survivors showed a significant mortality benefit for AVR/MVR compared with TAVR. The surgical patients were at exceedingly high risk in this study, and the STS score was calculated assuming the patients were having only AVR as the calculator cannot give a risk score for AVR/MVR. On the whole, that would bias the surgical AVR/MVR group by underestimating their risk when compared with patients with the same STS score only undergoing TAVR. The rationale for the landmark analysis of operative survivors was used to consider the long-term implications of these two strategies (TAVR versus AVR/MVR) without being overly biased by early perioperative risk. That allows for inference to potential benefits of the AVR/MVR strategy among lower risk patients, in whom TAVR may be approved in the near future, and the addition of a simple mitral ring may not add significant perioperative risk.

There are a number of limitations to this study, including retrospective analysis, the use of echocardiography reports instead of a central core imaging laboratory, and the lack of randomization. Although we used modern statistical techniques, including propensity matching, we cannot rule out influence of unmeasured confounders on our analysis. The two models of propensity-matched patients for this study included 40 and 50 patients, respectively, which compare favorably with outcomes reported by Barbanti and colleagues for the PARTNER A patients, including 65 and 59 patients with significant MR. Further investigation, ideally involving larger cohorts and randomization among AVR/MVR, TAVR, and AVR would help determine the most beneficial operation for this high-risk patient cohort. It is also possible that continued progress in the development of transcatheter mitral valve therapies will lead to a less invasive transcatheter double valve comparator to the open AVR/MVR intervention.

In conclusion, the management of significant MR at the time of aortic valve intervention remains challenging. Although TAVR had excellent perioperative outcomes in this high-risk patient cohort with significant improvement in MR, combined AVR and MVR showed superior reduction in MR and a survival advantage among 30-day survivors. This study suggests that in the care of an expert, multidisciplinary heart team, a double valve operation may provide outcomes superior to those of isolated TAVR for selected patients.

References


