Patient-centered benefit-risk analysis of transcatheter aortic valve replacement [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Aortic stenosis (AS) treatments include surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). Choosing between SAVR and TAVR requires patients to trade-off several benefits and risks. The objective of this research was to determine which outcomes associated with TAVR and SAVR patients consider most important, collect quantitative data about how patients weigh these benefits and risks, and evaluate patients’ preferences for SAVR or TAVR.

Methods: Patients with aortic stenosis were recruited from advocacy organization databases. An online adapted swing weighting (ASW) method was used to elicit attribute tradeoffs from 93 patients. The ASW exercise consisted of a series of pairwise comparisons of attributes. Survey data were used to estimate the weight that patients put on the AS treatment attributes, which were incorporated into a quantitative benefit-risk analysis (BRA) to evaluate patients’ preferences for TAVR and SAVR.

Results: On average, patients put greater value on attributes that favored TAVR than SAVR. The value patients placed on the lower short-term mortality rate, reduced procedural invasiveness, and quicker time to return to normal quality of life associated with TAVR, offset the value they placed on the time over which SAVR has been proven to work. There was substantial heterogeneity in patients’ preferences. This was partly explained by age, with differences in preference observed between patients <60 years to those ≥60 years. A Monte Carlo Simulation found that 75.1% of patients prefer TAVR.

Conclusions: Most AS patients are willing to tolerate sizable increases in clinical risk in exchange for the benefits of TAVR, resulting in a large proportion of patients preferring TAVR to SAVR. Further work should be undertaken to characterize the heterogeneity in preferences for AS treatment attributes. Shared decision-making tools based on attributes important to patients can support patients’ selection of the procedure that best meets their needs.

Keywords

TAVR, aortic valve, transcatheter, patient preference, benefit-risk analysis
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Introduction
Aortic stenosis (AS) is a progressive cardiovascular condition resulting from narrowing (or stenosis) of the aortic valve. This narrowing prevents the valve from fully opening, decreasing blood flow out of the heart and forcing it to work harder to maintain sufficient blood flow. If left untreated, AS can lead to severe cardiovascular complications and death. As of 2015, 12.4% of the United States population over age 75 (nearly 2.5 million people) were reportedly diagnosed with AS. More than one in eight people (13.3%) over the age of 75 in the US have moderate-to-severe AS. Patients with AS may be asymptomatic for many years until the valve is narrowed severely enough to cause symptoms. Symptoms of AS include chest pain and angina, syncope, dyspnea, fatigue, and palpitations, all of which are exacerbated by physical activity. Under-treatment of AS patients is common, with more than half of patients referred to cardiologists failing to receive surgical treatment. Once symptoms appear, often between the ages of 70 and 80 years old, the prognosis of untreated patients is poor. Among untreated patients, average survival is 50% at two years and 20% at five years after the onset of AS symptoms.

The traditionally recommended treatment for AS is surgical aortic valve replacement (SAVR). Such invasive surgery, involving a large incision in the chest, may not be suitable for all patients, especially those with comorbidities. The alternative, transcatheter aortic valve replacement (TAVR), is a minimally invasive, catheter-based procedure to replace the aortic valve in patients with AS. TAVR is the first-line therapy for inoperable patients with severe AS and an alternative to SAVR in operable high-risk patients. Among patients who are at intermediate surgical risk, both TAVR and SAVR are associated with improvements in disease-specific and generic health status. However, TAVR is associated with a reduced rate of complications and a quicker recovery time, with patients returning to a normal quality of life more quickly. When first available, the benefits of TAVR were offset by reportedly increased risks of stroke and the need for a pacemaker. Recent clinical data reveal similar, if not improved rates of stroke and need for pacemaker among TAVR patients. Furthermore, at a median two-year follow-up, all-cause mortality for patients undergoing TAVR was 20.2% compared with 21.9% for patients undergoing SAVR.

The choice of TAVR or SAVR involves patients making trade-offs between multiple treatment attributes, including invasiveness, speed of recovery, mortality rates, and risks of complications. Given the challenging nature of this decision, tools have been developed to support patient decision-making. However, little is known about the weights that patients assign to which attributes, how they make trade-offs between these attributes, and whether and how these preferences vary between patients. The objective of this research was to determine which outcomes associated with TAVR and SAVR patients consider most important, collect quantitative data about how patients weigh the benefits and risks associated with TAVR and SAVR, and to use this data to evaluate patients’ preferences for SAVR or TAVR.

Methods
Overview
Patients’ preferences for TAVR or SAVR were assessed using a quantitative benefit-risk assessment (BRA). This involved identifying attributes that distinguish TAVR and SAVR, measuring TAVR and SAVR performance on these attributes, eliciting patients’ preferences for these attributes, and combining performance and preference in a BRA to determine what proportion of patients prefer TAVR or SAVR. The patient-preference survey upon which the BRA is based was fielded in July–August 2018.

Attribute selection
A long list of potential attributes was identified by reviewing the attributes highlighted in previous patient preference studies for heart valve surgical interventions, published meta-analyses and clinical studies, and regulators’ assessments of related products. Additional attributes were identified based on consultation with TAVR and SAVR clinical experts and from patient input. The final attributes used in the study were selected based on clinical and regulatory relevance, whether or not the attribute distinguishes between TAVR and SAVR, and to comply with the attribute set properties required of an additive BRA. For example, to avoid overlap with ‘mortality’, the ‘stroke’ attribute was defined as ‘disabling, non-fatal strokes.’

Descriptions of the final attributes included in the BRA are summarized in Table 1.

Performance measurement
TAVR and SAVR performance against the final attributes were identified from the published literature and from clinical data (Table 2), focusing on data that had a high degree of reference and use within the clinical community. Available data for stroke risk, defined as “all stroke” (both fatal and non-fatal) in the literature, and independence, defined by Kansas City Cardiomyopathy Questionnaire (KCCQ) score, required transformation to estimate performance as defined by the final study attributes. To estimate the risk of non-fatal stroke only, available stroke risk data was adjusted using the mortality rate among patients with severe aortic stenosis enrolled in the PARTNER trial who suffered a stroke compared to the mortality rate among those in the trial who did not suffer a stroke. ‘Independence’ was defined as the probability of achieving relief from AS symptoms within a month of a procedure. Given available data, this was estimated as the probability of achieving a total score of 75 on KCCQ. The KCCQ is a standard patient reported outcome measure used in clinical trials of surgical and transcatheter heart valves. Estimated mean KCCQ score and variation in this measure were transformed into the proportion of patients achieving a KCCQ total score of 75 at 1 month using procedures previously described in Marchini.

Survey methodology
An adapted swing weighting (ASW) exercise was administered online to elicit patients’ preferences for treatment attributes. The objective of the ASW exercise was to identify the level of change in an attribute that patients would be willing to accept.
### Table 1. Selected attributes for the patient-centered benefit-risk analysis of transcatheter aortic valve replacement vs surgical aortic valve replacement.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Definition</th>
<th>Description provided to participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of procedure</td>
<td>Type of procedure</td>
<td>The invasiveness of the procedure is described by three characteristics: The length and depth of the incision Whether you heart is stopped There are two types of procedure: A minimally invasive procedure requiring, on average, 8 days in hospital. A small incision is made near your groin, and a valve is inserted and guided to your heart using a long tube through an artery. The tube is used to implant a new valve in the heart to replace the diseased aortic valve. An invasive procedure, requiring, on average, 12 days in hospital. A large cut about 25 cm long is made in your chest to access your heart. Then, your heart is stopped while a machine takes over your heart and lung function. A new valve is implanted to replace the damaged valve. Your heart is started again, and your chest is stitched closed.</td>
</tr>
<tr>
<td>Mortality</td>
<td>Number of patients out of 100 who will die within 1 month</td>
<td>The numbers of patients who will die from any cause within 1 month of having the procedure. Death could be due to complications from the procedure, from complications of aortic stenosis, or as a result of disabling stroke.</td>
</tr>
<tr>
<td>Disabling non-fatal stroke</td>
<td>The number of patients out of 100 who will experience a non-fatal disabling stroke within 1 month</td>
<td>The number of patients who will experience a non-fatal but disabling stroke within one 1 of having the procedure. If you experience a stroke, you will be hospitalized. If the stroke is severe, it may lead to temporary or permanent disability, such as paralysis, reduced mobility, and problems with thinking, memory and speech.</td>
</tr>
<tr>
<td>Independence</td>
<td>Number of patients out of 100 who experience greater independence within 1 month</td>
<td>The number of patients who experience improvement in daily activities (greater independence) following relief from aortic stenosis symptoms within 1 month of the procedure. The symptoms of aortic stenosis (shortness of breath, fatigue, chest pain, and dizziness), physical function, and quality of life are improved to an extent that you experience improvements in your degree of independence and ability to engage in activities of daily living.</td>
</tr>
<tr>
<td>New permanent pacemaker</td>
<td>The number of patients out of 100 who will require a pacemaker within 1 year</td>
<td>The number of patients that will need to have a pacemaker permanently implanted as a result of the procedure. Typically, a pacemaker is implanted under local anesthetics and you may be discharged the same day if you get your pacemaker in the morning.</td>
</tr>
<tr>
<td>Requirement for dialysis</td>
<td>The number of patients out of 100 who will require dialysis within 1 year</td>
<td>The number of patients that will experience kidney function damage that will need dialysis as a result of the procedure. A machine is used to do the kidney's job of cleaning the blood. If you need dialysis, you will need to go to the hospital three times a week, with each visit lasting 4 hours.</td>
</tr>
<tr>
<td>Time over which the procedure has been proven to work</td>
<td>The number of years for which your procedure has been available and proven to work</td>
<td>The number of years the procedure has been available and is proven to keep symptoms of aortic stenosis from coming back. Following this period, it is currently not known whether you will experience aortic stenosis symptoms again.</td>
</tr>
</tbody>
</table>

### Table 2. Transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) performance against benefit-risk analysis attributes.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Measure</th>
<th>TAVR Mean</th>
<th>TAVR 95% CI</th>
<th>SAVR Mean</th>
<th>SAVR 95% CI</th>
<th>Performance Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (all cause)</td>
<td>One-month risk</td>
<td>0.011</td>
<td>0.005-0.017</td>
<td>0.040</td>
<td>0.028-0.053</td>
<td>0.005-0.053</td>
</tr>
<tr>
<td>Disabling non-fatal stroke</td>
<td>One-month risk</td>
<td>0.008</td>
<td>0.002-0.013</td>
<td>0.033</td>
<td>0.021-0.044</td>
<td>0.002-0.044</td>
</tr>
<tr>
<td>Independence</td>
<td>Probability of having relief from AS symptoms that have an effect on daily life</td>
<td>0.479</td>
<td>0.454-0.500</td>
<td>0.249</td>
<td>0.227-0.276</td>
<td>0.227-0.500</td>
</tr>
<tr>
<td>New permanent pacemaker</td>
<td>One-year risk</td>
<td>0.123</td>
<td>0.103-0.142</td>
<td>0.090</td>
<td>0.072-0.108</td>
<td>0.072-0.142</td>
</tr>
<tr>
<td>Requirement for dialysis</td>
<td>One-year risk</td>
<td>0.032</td>
<td>0.021-0.042</td>
<td>0.047</td>
<td>0.034-0.060</td>
<td>0.021-0.060</td>
</tr>
<tr>
<td>Time over which the Procedure has been Proven to Work</td>
<td>Years</td>
<td>10</td>
<td>20</td>
<td>5 - 30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; AS, aortic stenosis.
in exchange for improving their procedure from ‘invasive’ to ‘minimally invasive’ (see Table 1 for definitions). The ASW exercise consisted of a series of pairwise comparisons of attributes—the ‘invasiveness’ attribute and one other attribute. Participants were shown ‘current’ and ‘improved’ levels on each attribute and asked which improvement they would prefer to make (an example choice question is shown in Figure 1). The ‘current’ levels were chosen to reflect the attribute performance levels of TAVR and SAVR (Table 2), to ensure they had credibility with patients, adjusted to ensure that patients had sufficient range to indicate the change in the attribute that would have the equivalent value as reducing invasiveness. Therefore, the exercises were not designed to directly elicit patients’ willingness to tolerate the actual change observed with TAVR.

Each set of pairwise comparisons included five iterations of the choice question. Depending on the answer to the choice question, the level of improvement offered on the non-procedure attribute was updated in the direction that made the value of improvements on the two attributes more similar than in the previous question. The levels used in each of the five iterations, and how these changed depend on previous responses are shown in extended data, Appendix 1.

A pilot of the survey among five AS patients, carried out over a 4-week period in June 2018, ensured acceptable cognitive burden, clarity of the instructions, and ease of use of the elicitation software. Before completing the ASW exercises, participants were introduced to the attributes and their definitions. Participants also completed two ASW practice questions; interpretation of their response to these practice questions was tested to ensure participants understood how to complete each of the pairwise comparisons. Only six participants incorrectly interpreted the meaning of their response to the first practice question, and no participants incorrectly interpreted their response to the second practice question. Each participant completed a proportion of the possible pairwise question—either 3 or 4 sets of pairwise comparison questions. Participants also completed clinical and demographic questions, and health literacy and numeracy questionnaires, available as extended data.

### Participants

Potentially eligible participants were recruited from the membership of Heart Value Voice and Mended Hearts patient organizations through e-mails and advertisements on social media platforms. Patients from the American Heart Association membership who had given prior permission to receive mailings were also invited to participate. Potential participants were directed to an online screening tool, where their eligibility for the survey was determined. Participants had to meet specific inclusion/exclusion criteria to participate (Box 1). There were no predefined enrollment targets or stratification by other demographic characteristics. Following completion of the online screening tool, eligible participants were directed to the web survey. They were also sent a link to the web survey, available as extended data, via e-mail so that they were able to complete the study at a time that was convenient for them.

### Analysis

Participant responses to the ASW questions identified the level of change in an attribute that patients would be willing to accept in exchange for improving their procedure from ‘invasive’ to ‘minimally invasive.’ For instance, a participant might assign the same value to a 2% reduction in mortality risk as reducing the invasiveness of the procedure. Inverting this relationship, responses we’re used to estimate the maximum acceptable increase in risks (MIR) or the maximum acceptable reduction in benefits (MRB) that participants would be willing to tolerate in exchange for moving from an invasive procedure to a minimally invasive procedure. In the above example, the participant would

![Figure 1](image)

**Figure 1.** Example adapted swing weighting question presented to study participants. ‘Type of Procedure’ was used in every pairwise comparison. Only the comparison attribute was varied across different attributes and performance levels.
Participants’ MIR/MRB was converted into an attribute weight ($w_i$) by setting the weight for ‘type of procedure’ to 1, and then dividing the range in performance between TAVR and SAVR on that attribute (Table 2) by the MIR/MRB. For instance, if patients were willing to tolerate a 2% increase in mortality risk in exchange for a reduction in invasiveness, and reducing invasiveness is given a weight of 1, then the 4.8% change in mortality risk covered by the benefit-risk model (0.5%–5.3% range identified in Table 2) would be given a weight of 1.4 (4.8%/2%). Weights across all attributes in the model were then normalized to sum to 100.

Four outputs were generated from the benefit-risk model to evaluate patients’ preferences for TAVR and SAVR. First, the incremental overall value generated by TAVR:

$$U_{\text{increment}}(\text{TAVR}) = U(\text{TAVR}) - U(\text{SAVR})$$

(Equation 2)

Second, the incremental partial value on each attribute generated by TAVR:

$$PV_{\text{increment}}(i) = w_i(v_i(x_{\text{TAVR}}) - v_i(x_{\text{SAVR}}))$$

(Equation 3)

Where

- $x_{\text{TAVR}}$ is the performance of TAVR on attribute $i$
- $x_{\text{SAVR}}$ is the performance of SAVR on attribute $i$

Third, a threshold analysis was undertaken, estimating the level of performance (minimum acceptable benefit or maximum acceptable risk) on each attribute that would leave patients indifferent between TAVR and SAVR. More specifically:

$$MAR_a \text{ or } MAB_a = TAVR_a + ((U(\text{TAVR}) - U(\text{SAVR}))/w_i v_i(x_{\text{unit,a}}))$$

(Equation 4)

Where

- $MAR_a$ or $MAB_a$ is the maximum acceptable risk or minimum acceptable benefit of attribute $a$
- $TAVR_a$ is the performance of TAVR on attribute $a$ (see Table 2).
- $x_{\text{unit,a}}$ is a single unit of performance on attribute $a$

Table 3 outlines the definitions of MIR, MRB, MAR, and MAB.

Fourth, a Monte Carlo Simulation (MCS) was run to explore uncertainty in model inputs. That is, the benefit-risk model was run 10,000 times for both TAVR and SAVR. In each instance, the model drew from the distribution around both performance and weight inputs. Specifically, performance inputs were drawn from the distribution around TAVR and SAVR performance data (Table 2). Weight inputs were drawn in a manner that reflected the probability that participants identified different MIR/MRBs in their responses to the survey. For each iteration of the MCS, TAVR and SAVR, we’ve ranked based on $U$ (Equation 2) and the proportion of instances that TAVR ranked first was estimated.
**Table 3. Benefit-risk analysis definitions.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIR</td>
<td><strong>Maximum Acceptable Increase in Risk:</strong> The maximum acceptable increase in risk for a single attribute that patients would tolerate in exchange for reducing procedure invasiveness.</td>
</tr>
<tr>
<td>MRB</td>
<td><strong>Maximum Acceptable Reduction in Benefit:</strong> The maximum acceptable reduction in benefit for a single attribute that patients would tolerate in exchange for reducing procedure invasiveness.</td>
</tr>
<tr>
<td>MAR</td>
<td><strong>Maximum Acceptable Risk:</strong> The maximum acceptable risk that would make patients indifferent between TAVR and SAVR.</td>
</tr>
<tr>
<td>MAB</td>
<td><strong>Minimum Acceptable Benefit:</strong> The minimum acceptable benefit that would make patients indifferent between TAVR and SAVR.</td>
</tr>
</tbody>
</table>

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

**Ethics**

In accordance with ethical practice, Institutional Review Board (IRB) approval was obtained through Advarra (approval MOD00300398) to comply with human participants research requirements prior to initiation of participant recruitment or administration of measures in the pilot or main studies. Informed consent was recorded electronically via the online survey platform. Any change to the protocol and/or informed consent form was resubmitted to the IRB for review and approval prior to implementation. The study was available for monitoring, auditing, IRB review, and regulatory inspection as applicable.

**Results**

**Demographic characteristics of participants**

A total of 93 patients completed the survey (Table 4). Raw data are available from Open Science Framework24. The majority of patients were 60 years old or older (n=69, 74.3%). More than half of the respondents were female (n=53, 57.0%) and almost all participants were white (n= 87, 93.5%). Over half of the sample was retired (n=57, 61.3%) and completed a college degree or higher (n=61, 65.6%). Most of the participants lived with a partner/spouse, family, or friends (n =74, 79.6%). No participants reported experiencing severe limitations to their physical activity. Very few patients demonstrated low health literacy (n=3, 3.2%) or numeracy (n=6, 6.5%), and no patients were low on both scales.

**Responses to ASW questions**

When responding to the ASW questions, only a small proportion (10%) of participants ‘straight-lined’ on all questions—consistently choosing to improve either ‘procedure’ or the comparison attribute across all five iterations of the choice question. These responses may be a valid reflection of participants’ preference—suggesting a strong preference either for avoiding an invasive procedure, or a strong preference to prioritize improving other procedure attributes. Thus, these responses were included in the analysis. The impact of excluding these data were tested, and it was determined that results of the BRA were not sensitive to whether these data were included or excluded.

**Comparisons of TAVR and SAVR**

Table 5 shows the difference in performance of TAVR compared with SAVR on each attribute, and patients’ willingness to accept this difference in exchange for the lesser invasiveness of TAVR. The increase in risks or the reduction in benefits that patients are, on average, willing to accept in exchange for reducing procedure invasiveness is reported in the middle three columns. For instance, patients would be willing to tolerate a 6.55% increase in the probability of experiencing disabling, non-fatal stroke in exchange for the reduction in invasiveness associated with receiving TAVR instead of SAVR. In each case, patients were on average willing to accept TAVR’s performance on any attribute in exchange for its lower invasiveness. In the case of four attributes (mortality, disabling non-fatal stroke, independence, and dialysis), TAVR performs better than SAVR. Where SAVR performs better than TAVR (the need for new permanent pacemaker and time over which the procedure has been proven to work), patients would, on average, be willing to accept TAVR’s performance given its lower invasiveness. For example, patients are willing to tolerate a 7.6% increase in the risk of a new permanent pacemaker, while the probability of needing a new permanent pacemaker only increases by 3.3% with TAVR.

The standard errors in patients’ MIR/MRB suggests a substantial heterogeneity in patients’ responses to the ASW exercise (see extended data, Appendix S2 for more detail). Some of this heterogeneity was associated with participants’ age. MIR/MRB for three attributes—probability of having a new permanent pacemaker, probability of requiring dialysis, and period over which a procedure had been proven to work—were associated with whether patients are over or under 60 years old. Older patients were more willing to tolerate increases in risks/reductions in benefit to avoid having to undergo an invasive procedure. Younger patients (<60 years old) would, on average, still be willing to accept the increased risk of needing a new permanent pacemaker associated with TAVR, but had a tolerance for a reduction in the period over which a procedure had been proven to work for less than the 10 years. That is, everything else being equal, younger patients (<60 years old) may prefer to undergo a more invasive procedure to ensure the procedure had had been proven to work for 10 years or longer.

There were a large proportion of participants whose individual MIR/MRB was greater than the change in attribute performance achieved with TAVR (Table 5). For attributes where
Table 4. Demographic and clinical characteristics of aortic stenosis patients who completed the preference elicitation survey (N=93).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (43.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>53 (57.0%)</td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>93 (100.0%)</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
</tr>
<tr>
<td>19–39</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td>40–59</td>
<td>20 (21.5%)</td>
</tr>
<tr>
<td>60–74</td>
<td>39 (41.9%)</td>
</tr>
<tr>
<td>75–89</td>
<td>27 (29.0%)</td>
</tr>
<tr>
<td>90+</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Racial background</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87 (93.5%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Living Situation</td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>19 (20.4%)</td>
</tr>
<tr>
<td>Living with a partner or spouse, family, or friends</td>
<td>74 (79.6%)</td>
</tr>
<tr>
<td>Employment Status</td>
<td></td>
</tr>
<tr>
<td>Employed, full-time</td>
<td>19 (20.4%)</td>
</tr>
<tr>
<td>Employed, part-time</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Homemaker</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Student</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Retired</td>
<td>57 (61.3%)</td>
</tr>
<tr>
<td>Disabled</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>Highest level of education completed</td>
<td></td>
</tr>
<tr>
<td>Secondary/high school</td>
<td>8 (8.6%)</td>
</tr>
<tr>
<td>Some college</td>
<td>23 (24.7%)</td>
</tr>
<tr>
<td>College degree</td>
<td>30 (32.3%)</td>
</tr>
<tr>
<td>Postgraduate degree</td>
<td>31 (33.3%)</td>
</tr>
<tr>
<td>Other:</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>General health within past week</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>36 (38.7%)</td>
</tr>
<tr>
<td>Good</td>
<td>33 (35.5%)</td>
</tr>
<tr>
<td>Fair</td>
<td>18 (19.4%)</td>
</tr>
<tr>
<td>Poor</td>
<td>5 (5.4%)</td>
</tr>
</tbody>
</table>

Characteristics | Patients, n (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very poor</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>NYHA Classification</td>
<td></td>
</tr>
<tr>
<td>No limitation of physical activity</td>
<td>53 (57.0%)</td>
</tr>
<tr>
<td>Slight limitation of physical activity</td>
<td>25 (26.9%)</td>
</tr>
<tr>
<td>Marked limitation in physical activity</td>
<td>15 (16.1%)</td>
</tr>
<tr>
<td>Severe limitation in physical activity</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Health literacy and numeracy</td>
<td></td>
</tr>
<tr>
<td>Low literacy (1)</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Low numeracy (2)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Overall low literacy / numeracy (3)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

1 Responses were scored between 0 (always) and 4 (never). Each participants' scored responses were averaged for a composite score ranging from 0–4. A low score if ≤2.
2 Participants were given one point for each correctly answered question (maximum numeracy score = 5). A low score if given is ≤2 answered incorrectly. 3 Overall low: individuals who scored low on both educational level and objective health literacy.

NYHA, New York Heart Association.

Performance is better with TAVR compared to SAVR (mortality, disabling non-fatal stroke, independence, and dialysis), 100% of patients would prefer the improved performance and reduced invasiveness of TAVR. For the two attributes on which attribute performance is better with SAVR compared to TAVR, 61% of patients would be willing to accept the increased risk of needing a new permanent pacemaker, and 38% of participants would be willing to accept the shorter period for which TAVR had been proven to work in order to experience TAVR’s reduced invasiveness.

The above analysis compares the performance of TAVR on each attribute separately. A complete comparison of TAVR and SAVR should do so across all attributes simultaneously and take into account observed heterogeneity (in this case across age groups). This objective is accomplished by means of the benefit-risk model (see Equation 2 and Equation 3). Figure 2 and Figure 3 show the incremental value of TAVR (overall and by attribute) observed among patients 60 years old or older (Figure 2) and among patients less than 60 years old (Figure 3). These figures reveal that, overall, TAVR is of greater value to patients than SAVR. Specifically, patients placed greater value on TAVR based on a lower short-term mortality rate, reduced procedural invasiveness, and a quicker time to return to normal quality of life (independence) offsetting the value patients placed on longer period over which the procedure has been proven to work and reduced risk of needing a pacemaker generated by SAVR. Similar patterns were observed among younger and older patients, though younger patients place a lower value on reducing the invasiveness of their procedure, the speed with which they return to a normal quality of life, and a higher value on the period over which the procedure has been proven to work compared to older patients.
Table 5. Patients Maximum Acceptable Increase in Risk (MIR)/Minimum Acceptable Reduction in Benefit (MRB) in Exchange for Reducing Procedure Invasiveness from ‘Invasive’ to ‘Minimally Invasive’.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Impact of TAVR compared with SAVR†</th>
<th>Maximum Acceptable Increase in Risk/Maximum Acceptable Reduction in Benefit [Mean, (SD, n)]</th>
<th>Proportion of participants MIR/MRB &gt; TAVR impact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Whole sample</td>
<td>&lt;60yrs old</td>
</tr>
<tr>
<td>Mortality (1 Month)</td>
<td>-2.9%</td>
<td>-2.9% (3.44, 46)</td>
<td>2.9% (3.0, 12)</td>
</tr>
<tr>
<td>Disabling Non-Fatal Stroke</td>
<td>-2.5%</td>
<td>-2.5% (6.32, 47)</td>
<td>4.7% (5.3, 12)</td>
</tr>
<tr>
<td>Independence</td>
<td>+23.0%</td>
<td>15.38% (13.41, 56)</td>
<td>13.4% (12.6, 16)</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>+3.3%</td>
<td>8.37% (6.70, 56)</td>
<td>5.4% (5.7, 12)</td>
</tr>
<tr>
<td>Requirement for Dialysis</td>
<td>-1.5%</td>
<td>6.42% (6.74, 55)</td>
<td>3.7% (5.5, 15)</td>
</tr>
<tr>
<td>Proven to Work</td>
<td>-10yrs</td>
<td>14.79yrs (18.04, 56)</td>
<td>8.3yrs (14.1, 16)</td>
</tr>
</tbody>
</table>

†See Table 2 for source of data

* p<0.1

Figure 2. Incremental value transcatheter aortic valve replacement vs. surgical aortic valve replacement in patients ≥60 years old.

Figure 3. Incremental value transcatheter aortic valve replacement vs. surgical aortic valve replacement in patients <60 years old.
TAVR threshold analysis

Table 6 reports a threshold analysis, which shows the minimum amount of benefit that patients would accept before preferring TAVR, or the maximum amount of risk that patients would tolerate before preferring TAVR. For example, given the incremental value that patients attach to TAVR (as reflected in Figure 2 and Figure 3) they would be willing to tolerate a mortality risk of 12.4% following TAVR before they would be indifferent between TAVR and SAVR.

The MCS shows that 75.1% of patients would prefer TAVR over SAVR. When the analysis is run separately for patients less than and greater than 60 years old, the proportions of patients preferring TAVR are 78.3% and 73.9% respectively. Removing patients who ‘one-lined’ in response to ASW exercises does not impact the results of the MCS, with 75.3% of patients still preferring TAVR.

Discussion

The choice between TAVR and SAVR for the treatment of AS involves making trade-offs between procedure invasiveness; the period over which the procedure has been proven to be effective; mortality, stroke and independence outcomes; and risks such as the need for a new pacemaker or dialysis. This study elicited patients’ preferences for AS procedure attributes to determine how they make these trade-offs, and thus whether they prefer TAVR or SAVR. Results suggest that, given the potential benefits and risks of TAVR and SAVR, on average, patients attach more value to TAVR, and the majority of patients would prefer TAVR. Patients placed a greater value on the lower invasiveness, quicker speed of recovery, and reduced risk of mortality, stroke and need for dialysis associated with TAVR than they did on longer period over which the procedure has been proven to work and reduced risk of needing a pacemaker associated with SAVR.

Current guidelines from the American Heart Association for the procedural treatment of AS do not take into account recent clinical data supporting the use of TAVR. Based on the recent clinical results of TAVR and the findings of this study, regulators may reach different conclusions about the need to protect patients from risks historically associated with TAVR. For instance, TAVR may not result in the increased risk of stroke that regulators might expect it to, and patients may be willing to tolerate the greater need for a permanent pacemaker in order to experience the benefits of TAVR.

The BRA revealed substantial heterogeneity in patient preferences for AS treatment. Some preference heterogeneity is explained by patient age, with older patients being less willing to tolerate the invasiveness of SAVR, instead preferring to accept greater potential risks associated with other procedure attributes in order to reduce the invasiveness. However, preference heterogeneity raises concerns about the attendance of participants to the preference elicitation tasks. A small proportion (10%) of participants straight-lined on all questions. While this might indicate a lack of attendance, it may also be capture strong preferences for/against the invasiveness of SAVR. Furthermore, all participants interpreted their response to the practice questions correctly, and a very small proportion of respondents demonstrated low health literacy or numeracy. This provides some reassurance that the preference heterogeneity observed in this study reflects a genuine difference in preference, rather than being the result of patients failing to complete the survey in a meaningful way.

Two other studies that used ASW to elicit patient preferences have been published\cite{36,27}. Both studies also observed substantial preference heterogeneity. One of these studies\cite{36} provided evidence supporting the validity and reliability of the preference outputs, both by replicating the results of the ASW with a thresholding exercise, and by comparing participants’ responses with their qualitative statements on the basis for their answers. This provides some reassurance about the validity of responses to the ASW exercise used for the current study. This may suggest that methods such as ASW, which elicit individual-level patient preferences, capture more preference heterogeneity than population-level methods, such as discrete choice experiments. Further work could usefully continue to validate the results of ASW exercises and test the hypothesis that individual-level preferences method captures greater heterogeneity in patient preferences.

<table>
<thead>
<tr>
<th>Minimum Acceptable Benefit/Maximum Acceptable Risk</th>
<th>Outcome with TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Population</td>
<td>&lt;60 years old</td>
</tr>
<tr>
<td>Mortality (1 Month)</td>
<td>12.4%</td>
</tr>
<tr>
<td>Disabling Non-Fatal Stroke</td>
<td>18.8%</td>
</tr>
<tr>
<td>Independence</td>
<td>5.7%</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>35.3%</td>
</tr>
<tr>
<td>Requirement for Dialysis</td>
<td>21.0%</td>
</tr>
<tr>
<td>Proven to Work</td>
<td>0yrs</td>
</tr>
</tbody>
</table>

Table 6. Threshold Analysis.
Only one other study of AS patients’ treatment preferences has been published to date\(^6\). The study design was sufficiently different to the current study—focusing on patients’ willingness to accept the mortality risk associated with interventions—that it is not possible to directly compare the results. However, the study by Hussain \textit{et al.}\(^6\) did reveal a higher risk tolerance among patients with greater disease burden (defined as weekly incidence of restricting symptoms, perceived change in health compared with 1 year earlier, EQ-VAS scores, and the New York Heart Association (NYHA) classification). Our study failed to identify an association between patient preferences and NYHA classification, though this might be due to the limited sample size and the small proportion of the sample in the more severe stages of the NYHA classification. Further research could usefully gather data from a larger sample of AS patients to determine if NYHA classification is associated with preferences.

While a majority of patients in the current study preferred TAVR, a number of patients (around 25%) preferred SAVR. This, and the underlying heterogeneity in patient preferences, support the need for a shared decision-making (SDM) tool that will help patients and surgeons choose procedures based on both clinical indications and patient risk tolerance. The Patient-Centered Outcomes Research Institute (PCORI) has developed a SDM tool to support patients choose between SAVR and TAVR\(^6\). However, this tool includes a narrower range of treatment attributes—stroke risk, mortality risk and discharge home—than those included in the analysis reported in this study. Furthermore, the tool does not include a component to elicit a patient’s preferences.

Finally, the current study is based on a relatively small sample of patients, and the sample is healthier and younger than the population currently eligible for TAVR and SAVR\(^6\). Further AS patient preference research should replicate this study in a larger sample of patients, including more patients with more severe disease burden.

**Conclusions**

Most AS patients are willing to tolerate sizable increases in clinical risk in exchange for the benefits associated with TAVR. A BRA incorporating data from patients’ preferences for the attributes of AS treatments revealed a strong preference for TAVR compared to SAVR. The analysis also revealed substantial heterogeneity in individual patient preferences, partly associated with patient age. Further work is required to understand this heterogeneity, and whether additional patient characteristics such as NYHA class are associated with different preferences. In the meantime, SDM tools should incorporate the factors identified in this model to assist patients and clinicians in achieving a more patient-centered treatment decision.

**Data availability**

**Underlying data**

Open Science Framework: AS patient preference data. https://doi.org/10.17605/OSF.IO/RTDS6\(^6\).

This project contains the following underlying data:

- TAVR Manuscript_Full Dataset.csv (full dataset of patient responses).
- TAVR Manuscript Datamap.xlsx (codebook for the dataset).

**Extended data**

Open Science Framework: AS patient preference data. https://doi.org/10.17605/OSF.IO/RTDS6\(^6\).

This project contains the following extended data:

- TAVR Manuscript Appendices S1_S2.docx (contains S1 Appendix, including S1 Table 1 and legends for S1 Figures 1-6; and S2 Appendix, including legends for S2 Figures 1-6).
- TAVR Manuscript Figures.docx (Figures 1–Figure 3, S1 Figures 1-6 and S2 Figures 1-6).
- TAVR Survey Contents.docx (a copy of the questionnaire given to each participant).

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Grant information**

Funding for this project was provided by Edwards Lifesciences, Washington D.C., US.

**Acknowledgements**

The authors would like to thank Heart Value Voice and Mended Hearts for their support with the design of the survey, and their support recruiting patients.

### References

6. Bach DS: Prevalence and characteristics of unoperated patients with severe

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  Published Abstract | Publisher Full Text

  Published Abstract | Publisher Full Text

  Published Abstract | Publisher Full Text | Free Full Text

  Published Abstract | Publisher Full Text | Free Full Text

15. Patient-Centered Outcomes Research Institute (PCORI): Optimizing Health Outcomes in Patients with Symptomatic Aortic Valve Disease. Reference Source

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Open Peer Review

Current Referee Status: ?

Version 1

Referee Report 25 April 2019

https://doi.org/10.5256/f1000research.20591.r46833

Ross Jaffe
Versant Ventures, San Francisco, CA, USA

This article by Marsh et al assesses patient preferences regarding the important medical decision about whether to undergo traditional surgical aortic valve replacement (SAVR) versus the newer transcatheter aortic valve replacement (TAVR) for aortic stenosis. This is an important effort to understand what attributes of benefit and risk from aortic valve replacement are most important to patients and understand how patients tradeoff those attributes in deciding which therapy to choose. With shared decision-making becoming increasingly used as our US healthcare system evolves to be more patient-centric, studies such as this one are important to expanding our understanding of how best to provide the information needed by patients to make informed decisions about their care. This study confirms a belief that many clinicians have that most patients prefer TAVR to SAVR because it is less invasive, providing evidence that about 75% patients prefer the less invasive approach. These patients are willing to tolerate a somewhat higher risk of stroke, pacemaker placement, and dialysis, and less evidence of long-term duration for the benefits of less invasiveness. It also identifies that younger patients (<60 yo) perspectives may differ from those of older patients (>60 yo) somewhat, although both groups generally prefer the less invasive procedure.

I support the publication of this study. While this study is not perfect from my point of view, it is an important contribution to the literature, both about how to treat aortic stenosis and about patient preference assessment more generally. Understanding what treatment attributes are most important to patients and how patients trade off benefits and risks is important to understanding how best to inform patients about their treatment options and help them make decisions that best reflect their individual preferences. As the paper notes on p. 11, there has only been one other, more limited study of patient preferences in aortic stenosis, so this study is an important expansion of our understanding of patient preferences that clinical area.

Additionally, from a methodological perspective and as also noted in the paper, there are only a few other studies that use adapted swing weights (ASW) to assess patient preferences. Swing weighting is one of only fourteen methods identified in the Medical Device Innovation Consortium (MDIC) review of preference assessment methodologies. (See: MDIC Patient Centered Benefit Risk Project Report, Appendix A: Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies, May 2015, available at: https://mdic.org/resource/patient-centered-benefit-risk-pcb-framework/). This study is an important contribution to the literature about swing weighting methods, and should allow comparison to studies of patient preference using other methods to help researchers and clinicians better understand how best to assess patient preferences.
This study does have a few issues that should be highlighted to help put the results in context. I also note an area for further assessment of the data as well as areas for future research focus. Please note that I come at this study as someone with an interest in patient preferences from clinical and regulatory policy perspective, and do not have the expertise to comment on the specific methodology or statistical analysis, which I will leave to experts in those areas.

Major concerns:

1. **The mixing of treated and untreated patients in the participant population:** In Box 1 on p. 6, the inclusion criteria describe that patients in the study could have already had a procedure within the last 10 years or could be untreated. From a shared decision making point of view, patients express their preferences prior to treatment – so it is most important to understand the benefit-risk attributes that are most important to patients not yet treated and how such patients trade off such risks. The mixing of both untreated and treated patients may make it hard to understand how the pre-procedure patients view these issues.

   Prior treatment could significantly influence a patient’s preference for one treatment option or another, but it is hard to know *a priori* how treatment would influence a patients preferences. Prior treatment may introduce a confirmation bias that patients tend to prefer the procedure that they chose to have, and therefore require much greater benefit or much less risk from the alternative procedure compared to treatment naïve patients. Alternatively, if patients had a negative experience with their prior procedure, they may find the benefit/risk profile of the alternative procedure much more attractive than that of the procedure that they had. Additionally, their experience of specific benefits or risks from their procedure may skew their weighting of those specific attributes compared to other patients.

   For this study, it would be important in Table 4 to add a breakdown of the patient treatment history, specifically the number and percentage of patients that have had SAVR, TAVR, or were untreated.

   Additionally, it would be helpful to add a comparison of the preferences of patients in each of these categories to show how prior treatment affects the MIR/MRB for each attribute, perhaps in a table similar to Table 5 except substituting treatment category for age. One concern is that with a sample size of 93 patients, sub-categorization by treatment status may result in too few patients in any one category to have confidence in the results. If this is a problem, it should be acknowledged that future studies may be needed to better understand the effect of prior treatment on preferences in aortic valve replacement.

2. **Representativeness of patients involved in member organizations:** The study recruited participants from two member organizations (Heart Value Voice and Mended Hearts). While it is understandable why the membership of these organizations facilitated identifying patients with aortic valve disease. However, patients who are motivated enough to join such organizations may have different preferences than the broader population of patients with the disease eligible for treatment of their aortic valve disease. There is no way to assess this potential difference in this study, but the authors could acknowledge this potential source of bias in the sample population in their discussion of the results and encourage future study in one or more different aortic valve disease populations.

3. **Lack of clarity in the attribute of “Time over which the procedure has been proven to work”:** From the definition of this attribute in the paper, it is difficult to know whether patients interpreted this attribute as a measure of how long they could expect benefit, i.e., duration of effect, or whether patients also viewed this as how much clinical experience there was with a treatment, i.e., uncertainty in the knowledge about the effect. (See section 2 of the MDIC Patient Centered Benefit Risk Report for a nice discussion of
uncertainty and how it relates to patient preferences.). This ambiguity raises the question about whether this attribute as described elicited preferences about expected duration, or elicited preferences about patient tolerance of uncertainty about the effect of TAVR, or some combination of the two. Showing an example of how this “proven to work” attribute was shown to patients akin to Figure 1 might clarify this ambiguity. Future studies might try to separate these attributes, particularly comparing an established therapy like SAVR with a newer treatment like TAVR.

Minor issues and typos:
1. Introduction, last paragraph of left column, p. 3: the beginning of the second sentence is awkward: “However, little is known about the weights that patients assign to which attributes, . . . .” I would suggest “However, little is known about the weights that patients assign to each attribute. . . . .”
2. Methods, Attribute selection, last sentence (p.3): note “was were”. I would remove the were.
3. Table 1, p. 4: Disabling non-fatal stroke: in the description, first sentence, note the “one 1” – should be “one month”.
4. Table 2, p. 4, description of “independence” attribute: the description of the measure of this attribute does not mention that this is measured at one month, whereas all the other measures note the time frame of the measure.
5. Analysis, p. 6, top right column, first paragraph: there looks to be a calculation error in the next to the last sentence. 4.8%/2% = 2.4, not 1.4 as written.
6. Comparisons of TAVR and SAVR, p. 7: right column, top paragraph – “In each case, patients. . . . .” should be “In each case, patients. . . . .”
7. Figures 2 and 3, p. 9: Each x-axis should be labeled with what the unit of measurement is. This will help the figures be more self-explanatory.

I hope that these comments are helpful. Given my interest in the use of patient preferences in the FDA regulatory process and increasing shared decision making in medicine broadly, I am pleased that the authors undertook this study to better understand patient preferences in aortic stenosis treatment, and I support its publication. It should be a nice addition to both the aortic stenosis treatment literature and the patient preference literature.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I was asked to speak to the senior management of Edwards Lifesciences, which provided the grant for this study, in August 2017 about the use of patient preference information in FDA
regulatory approval of medical devices. I was not paid for the talk, but was reimbursed travel expenses. Additionally, one of the authors, Barry Liden, has served with me on the Steering Committee for the MDIC Patient Centered Benefit Risk (PCBR) Project, where I was the MDIC Board member leading that project. Barry now chairs the MDIC Science of Patient Input (SPI) Steering Committee, where I am also a member.

**Reviewer Expertise:** Internal medicine physician with prior experience in outcomes research and shared decision making. Not actively involved in research in my present role as a venture capitalist, but I led the MDIC Patient Centered Benefit-Risk Project that developed a framework for incorporating patient preferences into FDA medical device regulation and developed the first catalog of patient preference methodologies included as an appendix to that report.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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