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Transcatheter vs. surgical aortic valve replacement in patients at intermediate surgical risk

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Abstract

- **Objective:** To compare the safety and efficacy of transcatheter aortic valve replacement (TAVR) to surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic stenosis at intermediate surgical risk.
- **Design:** Systematic literature review.
- **Methods:** Literature searches were done in PubMed and Scopus search engines using key terms: TAVR, trans-catheter aortic valve replacement, SAVR, surgical aortic valve replacement, severe aortic stenosis, and intermediate risk. Filters included primary research only. Inclusion criteria were articles which studied an intermediate risk patient population (STS-PROM 3-15%), primary research, and compared outcomes of TAVR and SAVR in patients with severe aortic stenosis requiring replacement.
- **Results:** Two randomized control trials were identified (Reardon et al & Leon et al). One propensity matched retrospective cohort study was identified (Brennan et al).
- **Conclusion:** The side effect profile for both TAVR and SAVR are very different. TAVR shows higher rates of major vascular complications, pacemaker implantation, and risk of valvular regurgitation while patients undergoing SAVR experience greater rates of blood loss, kidney injury, atrial fibrillation and longer stays in the hospital and ICU. In patients at intermediate risk for surgery, the decision to undergo TAVR or SAVR should be based on the individual patient's desired outcome. Both procedures show improved quality of life however TAVR has less risk for serious intraoperative complication and reduced recovery time while SAVR shows greater efficacy with less frequent paravalvular regurgitation, need for reintervention and pacemaker implantation.

Introduction:

Aortic stenosis is a condition which affects up to 9.8% of the 80-89 year old patient population.[1] Stenosis of the aortic valve is most commonly caused in the US by a process of inflammation and eventual calcification of the aortic valve leaflets.[2] Patients can be asymptomatic for a long period however once the non-compliant valve causes enough narrowing it can lead to increased outflow obstruction of the left ventricle and eventual left ventricular hypertrophy. Once patients become symptomatic, they commonly complain of dyspnea on exertion, angina and syncope.[2] Valve replacement is a necessity at this point as rates of mortality are as high as 25% and average survival time only 2-3 years if left untreated.[3]

Severe aortic stenosis is defined as aortic stenosis with a maximum aortic transvalvular velocity of ≥ 4 m/s with aortic valve area ≤ 1 cm^2. Symptomatic aortic stenosis is defined as aortic stenosis which is causing cardiac symptoms including decreased exercise tolerance, dyspnea with exertion, anginal

chest pain, syncope and heart failure.[4] After the onset of cardiac symptoms, the prognosis for severe aortic stenosis is very poor and has a high mortality rate.[5] It is therefore recommended that all patients with severe aortic stenosis undergo aortic valve replacement.[6,7]

Trans-catheter aortic valve replacement (TAVR) is a relatively new procedure which has been shown to have comparable outcomes and decreased rates of complications compared to surgical aortic valve replacement (SAVR) in patients considered to be at high surgical risk.[8-10] TAVR is less invasive than surgical valve replacement as a catheter is placed percutaneously either through the femoral artery or via trans-thoracic approach to the aorta where a new aortic valve is deployed.[11] As compared to SAVR which requires median sternotomy with cardiac bypass.[12] In 2017 the American Heart Association and American College of Cardiology updated guidelines so that both TAVR and SAVR were equally acceptable options for aortic valve replacement in high risk patients (class I).[13] The standard of care for intermediate risk patients however is less clear. The guidelines recommend SAVR (class I) and offer consideration of TAVR (Class IIa).[13] The aim of our study is to examine available research to determine if TAVR is non-inferior to SAVR in terms of primary outcomes including death from any cause, disabling stroke or serious complications in intermediate risk patients.

Case:

Mr. J is a 75 year old male, whom you have followed in your practice for many years. He is a generally healthy adult male with a PMHx of HTN, HLD and mild aortic stenosis which has up to this point been asymptomatic. Recently Mr. J came to the clinic complaining of increasing exertional dyspnea as well as chest pain that worsens with activity. Transthoracic echocardiogram was performed and revealed a left ventricular ejection fraction of 40% indicative of left ventricular dysfunction likely due to progression of aortic valve stenosis. Aortic transvalvular velocity is determined to be 4 m/s with aortic valve area of 1 cm^2 and mean transvalvular pressure gradient of 40 mmHg. Mr. J will require aortic valve replacement to reduce symptoms and prevent progression of heart failure. He states that his father had his aortic valve replaced surgically years ago and died in the hospital “from complications”. He has heard that there is now a less invasive option called the trans-catheter aortic valve replacement (TAVR) procedure and is wondering if he would be a candidate for this procedure instead of surgery. This scenario poses the clinical question in adult male patients who present an intermediate surgical risk, does TAVR provide comparable clinical outcomes as surgical valve replacement in patients with severe aortic stenosis.

Methods:

A literature search was conducted on PubMed and Scopus search engines in September 2019. Key search terms included TAVR, trans-catheter aortic valve replacement, SAVR, surgical aortic valve replacement, severe aortic stenosis, and intermediate risk. This search yielded 376 results. These results were further filtered to include only primary research, excluding meta-analyses and systematic reviews. This resulted in 20 articles which were screened for inclusion or exclusion. Examination of the literature determined that most studies defined surgical risk with consideration of the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scoring system. Studies which did not utilize this scoring system were excluded to promote homogeneity of the included studies. Patient populations defined to be at high risk included those with risk of death within 30 days after surgery of ≥ 15%[8] and populations at low risk were determined to have risk of death <3% within 30 days after surgery.[14,15] Studies with predominantly low or high surgical risk patient populations were excluded. The final 3 selected articles met inclusion criteria of intermediate risk patient population (STS-PROM score 3-15%), primary research, and with the purpose of comparing outcomes between TAVR and SAVR procedures in patients with severe, symptomatic aortic stenosis requiring replacement.

Results:

Study #1:

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *Reardon et al.*[16]

Objective: To compare the safety and efficacy of TAVR with surgical aortic valve replacement in patients with severe, symptomatic aortic stenosis at intermediate surgical risk

Study design: Patients were recruited from 87 centers in the United States, United Kingdom, Switzerland, Spain, Germany and Denmark. They underwent randomization in a 1:1 ratio to either receive TAVR or SAVR. Inclusion criteria are listed in Table 1. Most notably, they include an estimated risk of surgical death within 30 days between 3 and 15%. This risk was calculated using criteria from the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) as well as the presence of co-existing illness, frailty and disability. Patients were considered to be eligible if they had severe aortic stenosis, defined as the presence of any of the criteria listed in Table 2. Inclusion in the study also required that patients be symptomatic due to their aortic stenosis, this was determined by requiring the patients be classified as New York Heart Association Class II or greater. Exclusion criteria are extensive

and listed in the supplementary appendix available with the original article on the New England Journal of Medicine website (Table S3).

Table 1: Inclusion Criteria
STS PROM score ≥3% and < 15%
Eligible for both TAVR and SAVR
Presence of severe aortic stenosis
Subject is symptomatic: NYHA Functional Class II or greater
Subject and physician agree to required follow up
Subject meets legal minimum age to provide informed consent

Table 2: Criteria used to determine the presence of severe aortic stenosis
Initial aortic valve area of ≤ 1 cm^2
Aortic valve area index of < 0.6 cm^2 per square meter of body surface area and a mean gradient of > 40 mm Hg
Maximum aortic velocity of > 4 m/s at rest or with dobutamine provocation in patients with LVEF < 55%
Doppler velocity index of < 0.25 on resting echocardiogram

Patients were randomized at each clinical site considering the need for coronary revascularization as determined by the multi-disciplinary heart team at each location. Patients in the surgical group underwent coronary revascularization at the time of aortic valve replacement. The majority of patients in the TAVR group underwent transfemoral access. Subclavian or direct aortic approach was only utilized in patients who had iliofemoral anatomy which prohibited femoral access. Post-operatively, patients in the surgical group received 81 mg of aspirin daily while patients in the TAVR group received dual antiplatelet therapy with 81-100 mg of aspirin in combination with 75 mg of Clopidogrel for 3 months following the procedure.

Primary end points included death from any cause or disabling stroke at 24 months. Each patient was evaluated by a trained neurologist or stroke specialist to determine this. All neurological events were reported and evaluated by a neurologist on the clinical events committee. Secondary end points included cardiovascular events such as myocardial infarction, cerebrovascular events such as TIA or CVA, as well as any need for re-intervention. Serial echocardiograms were completed at an independent laboratory to measure aortic valve hemodynamics following the procedure through 24 months. Health related quality of life assessments were also evaluated through 24 months.

Bayesian statistical methods were used to compare outcomes in the TAVR and SAVR groups. The primary and secondary endpoints were evaluated using a modified intention to treat population. To account for missing data (lost to follow up or patients who had withdrawn from the study), a sensitivity analysis was performed. Bayesian analogue of a two sample t-test was used to compare continuous variables as means. Categorical variables were compared as frequencies and percentages using a Bayesian version of comparison proportions. Event rates are given as Bayesian posterior medians with 95% credible intervals. Kaplan Meier survival analyses were also performed.

Results: Between June 19, 2012 and June 30, 2016 1746 patients underwent randomization. The modified intention to treat population included 1660 patients. 864 patients were assigned to undergo TAVR procedure and 796 to surgical valve replacement. The mean age of the patients in the study was 79.8 ± 6.2 years. All patients were considered to be at intermediate surgical risk with the mean STS PROM score 4.5 ± 1.6%.

Differences in procedural outcomes showed an increased risk of acute kidney injury, new or worsening atrial fibrillation, and need for blood transfusion in the surgical group while the TAVR group showed an increased risk of major vascular complications and required pacemaker implantation. Major vascular complications are listed in Table S4 of the supplementary appendix and include complications such as aortic dissection, new apical aneurysm, access site or access related vascular injury (dissection, stenosis perforation, hematoma, etc.), non-cerebral distal embolization, and new ipsilateral lower extremity ischemia. These early post-procedural (≤ 30 day) outcomes are shown in Table 3.

Table 3: Procedure Related Complications at 30 days (Modified Intention to Treat Population)*[16]

Complication	TAVR (N=864)	Surgery (N=796)	95% Credible Interval for Difference
Life-threatening or major bleeding — %	12.2	9.3	–0.1 to 5.9
Transfusion of red cells — no. (%)			
0 units	756 (87.5)	469 (58.9)	24.4 to 32.5
1 unit	29 (3.4)	90 (11.3)	–10.5 to –5.5
2 to 4 units	48 (5.6)	136 (17.1)	–14.5 to –8.5
>4 units	31 (3.6)	101 (12.7)	–11.7 to –6.5
Acute kidney injury stage 2 or 3 — %	1.7	4.4	–4.4 to –1.0
Coronary-artery obstruction — %	0.2	0.0	–0.2 to 0.8
Major vascular complication — %	6.0	1.1	3.2 to 6.7
Cardiac perforation — %	1.7	0.9	–0.2 to 2.0
Cardiogenic shock — %	1.1	3.8	–4.2 to –1.1
Permanent pacemaker implantation — %	25.9	6.6	15.9 to 22.7
Atrial fibrillation — %	12.9	43.4	–34.7 to –26.4

* Values are estimated incidence (median of the posterior probability distribution, as calculated by means of Bayesian analysis), except for transfusion values, which are the numbers of patients and percentages. For all the values, 95% credible intervals were calculated for the difference between groups. Percentages may not total 100 because of rounding.

At 24 months, the primary endpoint (composite of death from any cause and stroke) was similar between TAVR (12.6%) and SAVR (14.0%) groups. In the intention to treat population, similar results were found (13.2% in the TAVR group and 14.1% in the SAVR group). The rate of death from any cause (TAVR 11.4% vs. SAVR 11.6%) as well as disabling stroke (TAVR 2.6% vs. SAVR 4.5% with 95% CI -4.0,0.1) were also similar in both groups at 24 months. There is no significant difference in other outcomes assessed, all of which are presented in Table 4. Both groups also showed significant improvement in NYHA symptoms throughout the 24 month follow up period. Echocardiographic findings showed improved hemodynamics in both the TAVR and SAVR groups. Paravalvular regurgitation however was more prevalent in the TAVR group (5.3%) than the SAVR group (0.6%). Whether the incidence of paravalvular regurgitation was clinically significant requiring reintervention was not reported however TAVR showed a significantly elevated requirement for valve reintervention (2.8% vs 0.7%) as well as hospitalization for valve related disease (13.2% vs 9.7%) when compared to the SAVR group.

Table 4: Clinical Outcomes at 30 days, 12 months, and 24 months (Modified Intention To Treat Population)*[16]

Outcome	30 Days			12 Months			24 Months		
	TAVR	Surgery	95% Credible Interval	TAVR	Surgery	95% Credible Interval	TAVR	Surgery	95% Credible Interval
					percent				
Death from any cause or disabling stroke	2.8	3.9	−2.8 to 0.7	8.1	8.8	−3.5 to 2.1	12.6	14.0	−5.2 to 2.3
Death from any cause	2.2	1.7	−0.9 to 1.8	6.7	6.8	−2.7 to 2.4	11.4	11.6	−3.8 to 3.3
Cardiovascular	2.0	1.7	−1.0 to 1.6	4.8	5.5	−2.9 to 1.5	7.7	8.0	−3.3 to 2.6
Valve-related	0.1	0.1	−0.3 to 0.3	0.1	0.3	−0.7 to 0.3	0.2	0.4	−0.9 to 0.5
Aortic-valve reintervention	0.9	0.2	−0.1 to 1.4	2.1	0.5	0.4 to 2.7	2.8	0.7	0.7 to 3.5
All stroke and TIA	4.5	6.5	−4.2 to 0.3	8.2	8.6	−3.1 to 2.4	10.0	11.0	−4.2 to 2.2
All stroke	3.4	5.6	−4.2 to −0.2	5.4	6.9	−3.9 to 0.9	6.2	8.4	−5.0 to 0.4
Disabling	1.2	2.5	−2.6 to 0.1	2.2	3.6	−3.1 to 0.4	2.6	4.5	−4.0 to 0.1
Nondisabling	2.2	3.1	−2.5 to 0.6	3.7	3.9	−2.2 to 1.7	4.4	4.7	−2.6 to 1.9
TIA	1.5	1.1	−0.7 to 1.5	3.2	2.0	−0.4 to 2.8	4.3	3.1	−0.9 to 3.2
Myocardial infarction	0.9	1.0	−1.0 to 0.9	2.0	1.6	−0.9 to 1.8	2.8	2.2	−1.1 to 2.4
Hospitalization for aortic-valve–related disease	2.9	4.2	−3.1 to 0.5	8.5	7.6	−1.8 to 3.6	13.2	9.7	0.1 to 7.0
MACCE	5.7	7.4	−4.0 to 0.7	13.2	12.8	−2.9 to 3.7	18.6	18.6	−4.2 to 4.2

* Values are estimated incidence (median of the posterior probability distribution, as calculated by means of Bayesian analysis) with the 95% credible interval for the difference between groups. MACCE denotes major adverse cerebrovascular and cardiovascular events and includes death from any cause, myocardial infarction, all stroke, and reintervention.

Study Critique: Strengths of this study include that it is a randomized control trial with a large patient population. Weaknesses include the fact that this study was not only funded by Medtronic, the company that produces the prosthesis used in the TAVR procedure, but the protocol was developed by representatives of Medtronic and the sites where patients were recruited from were chosen by representatives of Medtronic. Medtronic was also responsible for monitoring data collection and management of the trial. This presents a clear conflict of interest in which a favorable outcome of the study directly benefits those who funded the study. It is also unclear from the article how the need for revascularization affected placement in either TAVR or SAVR groups. The article states that the need for revascularization was considered which would then impair randomization if certain patient characteristics determined which group the patient was assigned to. This may improve outcomes in the TAVR group if patients who required revascularization were placed into the SAVR group exclusively.

Another issue with the study is that two different prosthetic valves were utilized in the TAVR procedures, however the study did not present data for the TAVR group that stratified results by valve type. Additionally, the study did not stratify results by TAVR route, i.e. transthoracic or transfemoral, only offering combined data from both routes. Aggregating these results could artificially inflate the

safety of the TAVR procedure, as one access route or valve type may have had poorer outcomes than others, but this is masked in the combining of the data.

Study #2*:*

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. Leon et al.[17]

Objective: To compare the safety and efficacy of TAVR to SAVR in the treatment of severe, symptomatic aortic stenosis in patients considered to be at intermediate surgical risk.

Methods: Patients were selected from 57 centers in the United States and Canada. Inclusion criteria were the presence of severe aortic stenosis as well as cardiac symptoms. Intermediate risk was defined as an STS PROM score between 4% and 8% however patients could be included in the study if they had an STS PROM score of < 4% and any comorbidities not accounted for in the STS risk model. The SAPIEN XT heart valve was used for all TAVR procedures. Patients in the TAVR group underwent either trans-femoral or trans-thoracic (transapical or transaortic) placement of the SAPIEN valve. All patients in the TAVR group received ASA 81 mg and clopidogrel 300 mg prior to the procedure and heparin intra-operatively. ASA was continued indefinitely and clopidogrel for a minimum of 1 month in TAVR patients. Prior to randomization, all subjects underwent peripheral arterial evaluation to determine which patients would require trans-thoracic as opposed to trans-femoral TAVR approach. These patients were stratified into separate groups (eligible for transfemoral or transthoracic) and then randomized in a 1:1 fashion to the surgical or TAVR group to ensure equal distribution. Intention to treat analysis was used to evaluate primary and secondary endpoints. The primary endpoint evaluated was a composite of death from any cause or disabling stroke at 2 years. All patients were evaluated by a trained neurologist and any neurological event which occurred was evaluated by a neurologist who was blinded to which procedure the patient received.

Fisher's exact test was used to compare categorical variables. Continuous variables were compared using Student's t-test or Wilcoxon rank-sum test. Kaplan-Meier estimates were used to calculate time to event analyses. Hazard ratios were calculated to evaluate the relationship between subgroups and outcomes of interest.

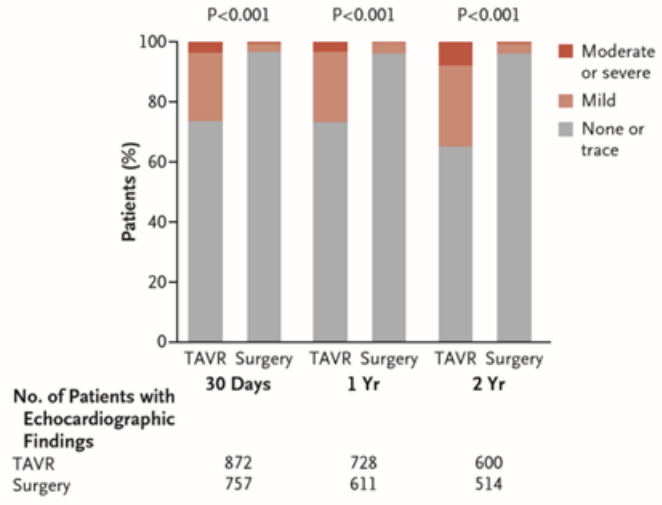
2032 patients underwent randomization with 1011 assigned to the TAVR group and 1021 assigned to surgery. 236 patients in the TAVR group underwent transthoracic as opposed to transfemoral valve placement. The mean STS PROM score was 5.8% in both the TAVR and SAVR groups.

Results: Evaluation of the primary endpoint of death from any cause or disabling stroke at 2 years showed no statistically significant difference between the TAVR and SAVR cohorts (HR 0.89; 95% CI 0.73, 1.09, p = 0.25). Patients who were treated via trans-femoral access in the TAVR group showed a lower rate of death from any cause or disabling stroke than those in the SAVR cohort (HR 0.79; 95% CI 0.62-1.00; p = 0.05) while there was no difference in the rate of these outcomes seen in those who were treated via transthoracic access and those treated surgically (HR 1.21; 95% CI 0.84, 1.74, p = 0.47).

Treatment with TAVR showed an increased risk of major vascular complications at 30 days (7.9% vs. 5.0%, p = 0.008). Major vascular complications are listed in Table S2 of the supplementary appendix and include complications such as aortic dissection, new apical aneurysm, access site or access related vascular injury (dissection, stenosis perforation, hematoma, etc.), non-cerebral distal embolization, and new ipsilateral lower extremity ischemia. Life threatening bleeding (10.4% vs. 43.4%, p<0.001), acute kidney injury (1.3% vs. 3.1%, p = 0.006) and new onset atrial fibrillation (9.1% vs. 26.4%, p < 0.001) were all significantly increased in those undergoing surgical intervention. There was no significant difference in repeat hospitalizations (19.6% and 17.3%, p = 0.22) or rate of valvular reintervention (1.4% vs. 0.6%, p = 0.09) between TAVR and SAVR groups at 2 years. The TAVR cohort had a significantly reduced duration of stay in the ICU (median 2 vs. 4 days, p < 0.001) and hospital (6 vs. 9 days, p < 0.001) compared to the SAVR cohort.

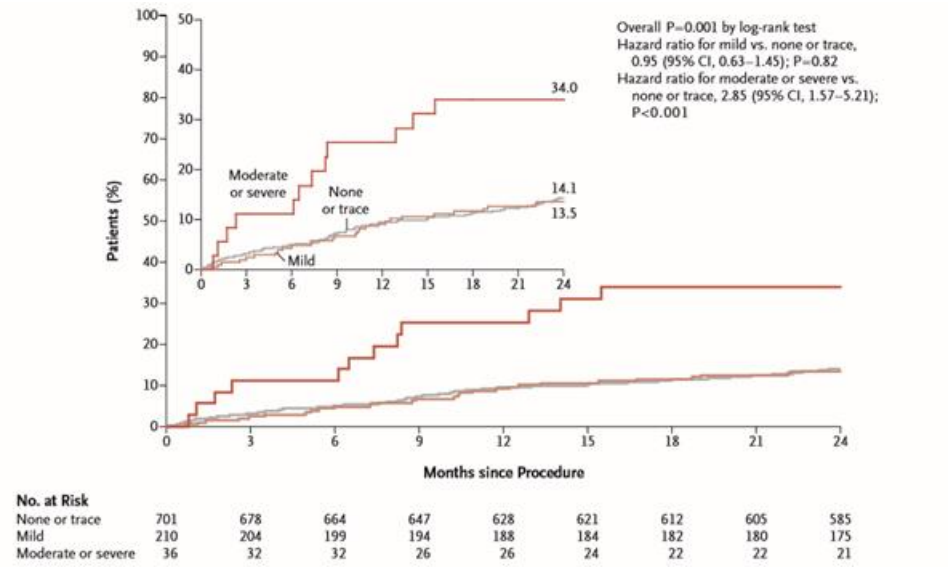
Both groups showed significant reduction in NYHA Class following treatment (p<0.001 for all comparisons). Echocardiographic findings common to both cohorts include improved ejection fraction, increased aortic valve areas and decreased aortic valve gradients. TAVR however showed superior improvement over SAVR in aortic valve area and gradient. Patients who underwent TAVR showed a statistically significant increased frequency and severity of aortic regurgitation when compared to SAVR (Figure 1). Patients who had moderate or severe paravalvular aortic regurgitation at 30 days had a higher mortality rate (Figure 2) during the 2 year follow up period than patients without regurgitation (p< 0.001).

Figure 1: Percentage of Patients with paravalvular aortic regurgitation [17]



No. of Patients with Echocardiographic Findings	30 Days	1 Yr	2 Yr
TAVR	872	728	600
Surgery	757	611	514

Figure 2: Death from Any Cause, According to Severity of Paravalvular Aortic Regurgitation[17]



No. at Risk									
None or trace	701	678	664	647	628	621	612	605	585
Mild	210	204	199	194	188	184	182	180	175
Moderate or severe	36	32	32	26	26	24	22	22	21

Critique: Strengths of this study include that it is a randomized control trial that is well powered with a large sample size. The study design was unique in the pre-operative evaluation of peripheral arteries and randomization process considering transfemoral and transthoracic approach. Blinding of neurologists who evaluated possible strokes was another advantage of the study design.

Weaknesses include that the study was funded by Edwards Life Sciences and only utilized the valve type which the company produced. The study sites, methods and data collection were all chosen and overseen by Edwards Life Sciences. This presents a significant conflict of interest.

Study #3:

Transcatheter versus Surgical Aortic Valve Replacement: A Propensity-Matched Analysis from Two United States Registries. Brennan et al. [14]

Objective: The objective of this study was to compare the safety and efficacy of TAVR and SAVR in a large patient population thought to be more representative of the average patient than those included in previously conducted randomized control trials.

Study Design: This was a propensity matched retrospective cohort study which reviewed Medicare insurance claims of patients who had either undergone SAVR or TAVR. SAVR data was collected from the society of thoracic surgeons (STS) national database. More than 90% of cardiac surgery programs in the US participate in this database. TAVR data was collected from the STS/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry. Participation in this registry is required for Medicare reimbursement in the U.S. Records identified from these databases were then linked to the Centers for Medicare & Medicaid Services (CMS) fee-for-service administrative insurance claims files in order to create a chronological record of events including vital status and any rehospitalization occurrences. 25,786 records were available from TAVR cases performed between January 1, 2014 and September 30, 2015 while 198,077 SAVR records were available for cases performed between July 1, 2011 and December 31, 2013. Patients included in the study were older patients with severe, symptomatic aortic valve stenosis who were considered to be at intermediate or high surgical risk, were candidates for both TAVR and SAVR and who eventually underwent either TAVR or SAVR. Exclusion criteria included patient characteristics that would seem to favor one treatment strategy over the other. These criteria are listed in Table 5.

Table 5: Exclusion Criteria – Brennan et al.
• Patient age < 65 or > 90 • Other major cardiac operations • History of endocarditis • Emergency salvage status • Primary aortic insufficiency • Hostile chest or porcelain aorta • Moderate to severe mitral stenosis • STS-PROM < 3% • Subsequent aortic valve replacement procedures during the initial aortic valve replacement admission • Hospitals submitting < 10 total SAVR or TAVR records during the study interval

Primary outcomes which were assessed were decided through consensus by a panel of patients, caregivers, clinicians, health science researchers and statisticians. These outcomes included: death, stroke, days alive out of acute care hospital facility (DAOH) to 1 year as well as discharge to home. Stroke and mortality were evaluated to 30 days and 1 year.

Propensity score matching was conducted to balance the covariates between the SAVR and TAVR groups. Propensity score was defined as the probability of receiving TAVR given measured covariates. These were calculated using logistic regression. Covariates were defined as patient characteristics which would favor one treatment plan over the other and they were identified by the expert panel mentioned previously. Distribution of covariates between the study groups were assessed and patients who fell under 5% or over 95% of propensity distribution were excluded due to overwhelming likelihood of receiving one treatment over the other. Propensity score matching was completed in a 1:1 ratio by greedy matching using a caliper of 0.2 standard deviations.

COX proportional hazard models were used to compare outcomes in the TAVR and SAVR groups by hazard ratios (HRs) with 95% confidence intervals (CIs). DOAH was modeled as count data using generalized estimating equations with a long link and fixed offset to obtain rate ratios (RRs) with 95% CI. Statistical significance was defined as $p < 0.1$. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results: The propensity matched cohorts included 4,732 SAVR patients and 4,732 TAVR patients. The median age was 82 years (interquartile range (IQR): 77, 85), 47.9% women and median STS PROM of 5.6% (4.2%, 8.2%). Transfemoral access was utilized in 76% of TAVR patients with 33% utilizing the CoreValve prosthesis (Medtronic) and 67% utilizing the SAPIEN valve prosthesis (Edwards LifeSciences).

During the initial visit, TAVR patients spent an average of 31 (IQR: 24, 57) hours in the intensive care unit (ICU) and 4 (IQR 3,6) days in the hospital while SAVR patients spent an average of 68 (IQR: 37, 119) hours in the ICU and 8 (IQR: 6, 11) days in the hospital. In hospital mortality was found to be lower in patients who received TAVR than SAVR (3.0% vs. 5.0%, $p<0.001$) with no significant difference in the incidence of stroke (2.5% vs. 2.7%, $p=0.4$). TAVR patients showed an increased incidence of new pacemaker/implantable cardioverter defibrillator placement (12.8% vs. 6.3%, $p < 0.001$) as well as a higher rate of major vascular complications (4.2% vs. 0.4%, $p< 0.001$). TAVR patients did show a lower incidence of blood transfusions (packed red blood cell units: TAVR 0 [0,0], SAVR 2 [0,4], $p<0.001$) as well as a decreased requirement for hemodialysis following the procedure (1.7% vs. 3.2%, p,0.001) during the initial hospitalization. TAVR patients had a higher rate of discharge to home (69.9% vs. 41.2%) while those who received SAVR were more likely to be discharged to an extended care facility, transitional care unit, or rehabilitation unit (41.2% vs. 20.5%, $p < 0.01$).

There was no difference in mortality at 1 year between TAVR and SAVR cohorts (17.3% vs. 17.9%, $p=0.40$), stroke during the first 30 days (2.8% vs. 2.8%, $p = 0.13$) or at 1 year (HR 1.18 95% CI 0.95-1.47). Days alive out of hospital (DAOH) were similar between TAVR and SAVR groups (RR 1.0, 95% CI 0.98-1.02).

A stratified analysis was performed looking at key outcomes at 1 year including death, stroke, discharge to home and DAOH in subgroups determined by STS PROM scores: 3-5%, 5-8%, ≥ 8%. There was no significant difference in these key outcomes based on treatment strategy (TAVR or SAVR). The results of this are depicted in Table 6.

Table 6: Clinical Outcomes to 1 Year, Stratified by Surgical Risk (STS PROM) [14]

	Overall n=9,464			STS PROM (≥3%, 5%) n=3,803			STS PROM (≥5%, <8%) n=3,141			STS PROM (≥8%) n=2,520			
Outcome	SAVR n=4,732	TAVR n=4,732	HR (95% CI)	SAVR n=1,850	TAVR n=1,953	HR (95% CI)	SAVR n=1,545	TAVR n=1,596	HR (95% CI)	SAVR n=1,337	TAVR n=1,183	HR (95% CI)	p-interaction
Death	17.9	17.3	0.93 (0.83, 1.04)	11.2	12.6	1.06 (0.86, 1.31)	16.2	15.3	0.92 (0.75, 1.13)	28.7	27.4	0.91 (0.78, 1.08)	0.50
Stroke	3.3	4.2	1.18 (0.95, 1.47)	3.3	3.8	1.06 (0.73, 1.54)	3.5	4.5	1.22 (0.83, 1.79)	3.1	4.4	1.33 (0.87, 2.03)	0.73
Discharge to home	41.2	69.9	3.19 (2.84, 3.58)†	49.5	77.5	3.33 (2.83, 3.92)†	41.9	70.4	2.37 (2.00, 2.80)†	29.0	56.8	1.32 (1.13, 1.55)†	0.89
% DAOH, median	100	100	1.00 (0.98,1.02)*	100	100	0.99 (0.97,1.01)*	98.9	99.3	0.99 (0.95,1.04)*	95.6	96.9	0.93 (0.83,1.05)*	0.598

*A rate ratio was calculated to compare treatment effects for the proportion (%) of days alive and out of an acute care hospital to 1 year.

†An odds ratio was calculated to compare treatment effects for the probability of discharge to home.

CI = confidence interval; DAOH = days alive and out of hospital; HR = hazard ratio (TAVR vs. SAVR); SAVR = surgical aortic valve replacement; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement

Study Critique: Strengths of this study include its large sample size of 9,464 patients, that it is independently funded by the Patient Centered Outcomes Research Institute (PCORI) award, and that it includes both the Edwards LifeSciences and Medtronic valve prostheses. The fact that records were linked to Medicare insurance claims allowed for creation of a chronological log of events and ensured inclusion of the patient population most commonly affected by aortic stenosis (> 65 years). Propensity matching allowed for even distribution of potential cofounding variables between the TAVR and SAVR groups. Weaknesses of this study include that it was a retrospective cohort study that is not randomized. Additionally, different time frames were utilized for TAVR (2014-2015) and SAVR cases (2011-2013) however this is unlikely to significantly alter results as significant changes in SAVR are unlikely to have occurred during this period. Certain exclusion criteria may have altered results including exclusion of cases requiring subsequent aortic valve replacement procedures during the initial valve replacement admission. Exclusion of these cases may have ignored cases in which TAVR procedure was ineffective and required surgical replacement. Exclusion of hospitals submitting < 10 total SAVR or TAVR records during the study interval may have altered results by only examining high volume centers with interventional cardiologists who have a high level of expertise in the TAVR procedure.

Discussion:

The first two studies (Reardon et al, Leon et al) were very similar in the outcomes they assessed and study design. They were also both funded by the companies responsible for producing the prosthetic valve used in the TAVR procedure. This represents a definite conflict of interest however

given the novelty of the procedure there are not any randomized control trials we could find that were not funded by medical device companies which focused on an intermediate surgical risk patient population. Both studies had similar findings which showed better immediate outcomes and less serious complications associated with the TAVR procedure when compared to SAVR. They both showed a reduced risk of acute kidney injury, serious bleeding as well as new onset or worsening atrial fibrillation with the TAVR procedure. Patients who underwent TAVR also spent less time in the ICU and the hospital than patients who underwent SAVR. Where the TAVR procedure was inferior to SAVR in the immediate post-operative period was an increased incidence of major vascular complications and requirement for pacemaker or defibrillator implantation. Both studies also compared outcomes at 2 years. Most of these showed TAVR to be non-inferior to SAVR including composite incidence of death and stroke, all-cause mortality, stroke alone, as well as improved quality of life as measured by NYHA classification. Key differences at 2 years include an increased rate of required re-intervention, re-hospitalization as well as paravalvular regurgitation in patients who underwent the TAVR procedure.

The third study which was included (Brennan et al) was different than the first two in that it was not a randomized control trial. This study was designed as a retrospective cohort which had a large sample size and linked patients records to the Medicare & Medicaid fee for service database in order to create a chronological record of events in patients who had received either TAVR or SAVR. Benefits of this study include that it was funded by an independent educational grant and not a medical device company. It included both the Medtronic and Edwards LifeSciences devices which reduced likelihood for bias. This study supported findings of the previous two including increased risk of blood loss as well as time spent in the ICU and hospital following SAVR as well as increased rate of major vascular complications and required pacemaker implantation in patients who underwent TAVR. It also found that the rate of mortality, stroke and days alive out of hospital (DAOH) were unaffected by SAVR or TAVR procedure. Additional findings of this study which were not reported in the previous two included increased rate of hemodialysis and in hospital mortality in patients who underwent SAVR.

Conclusion:

Overall, the studies show a similar rate of long-term efficacy and complications between TAVR and SAVR, with similar rates of all-cause mortality and stroke as far as 24 months as well as an improved quality of life following both procedures. The side effect profile for each is different, with patients undergoing SAVR experiencing greater rates of blood loss, kidney injury, new onset or worsening atrial fibrillation and longer stays in the hospital or ICU. TAVR patients however experience greater rates of

major vascular complications, pacemaker implantation, and significantly increased risk of valvular regurgitation requiring re-intervention.

Given the significant side effects of both TAVR and SAVR and the relative lack of available research conducted in intermediate risk patients, it's difficult to suggest one treatment option over the other. The choice would depend on the patient and what outcome they desire. If it is a younger patient with fewer comorbidities, SAVR would likely be the better option due to less frequent need for re-intervention and regurgitation. However, if it were an older patient who only wishes to improve quality of life for a few more years, TAVR would be a superior option due to less recovery time and serious intraoperative risks.

Case Resolution:

Mr. J is a 75-year-old male with past medical history of hypertension and hyperlipidemia who has just recently progressed to severe aortic stenosis requiring intervention. He is younger than the average age of the patient population included in all three studies and has relatively few comorbidities. At this point the recommended intervention for this patient would be surgical aortic valve replacement (SAVR). If the patient were resistant to surgical intervention, TAVR could be considered however it should be explained to the patient that although TAVR has less immediate post-operative complications and shorter recovery it does increase risk for required reintervention at a later point in time. Therefore, SAVR would provide a better chance at definitive treatment of his severe aortic stenosis.

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