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Is transcatheter aortic valve replacement associated with a decreased mortality rate when compared to surgical aortic valve replacement in patients with severe aortic stenosis?

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Abstract

Objective: The objective of this selective EBM was to investigate the question, "Is the transcatheter aortic valve replacement associated with a decreased mortality rate when compared to the surgical aortic valve replacement method in patients with severe aortic stenosis?"

Study Design: systematic review of 3 English language primary studies, published between 2013 and 2015.

Data Sources: Three Randomized Controlled Trials (RCT's) published on or after 2010 were selected based on their relevance to the proposed questions via PubMed. All three RCT's compared transcatheter aortic valve replacement (TAVR) vs. surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis.

Outcomes Measured: The outcomes measured in these studies include death from any cause at 1 year, quality of life, physical and social limitations, improvement of left ventricular ejection fraction (LVEF) at 1 year following the procedure, and effect of LVEF on the outcome of the procedure. This was accomplished using three separate techniques depending on the study using either a chi-squared test, fischer exact test, or a combination of both tests.

Results: Thyregod et. al. found that the composite death rate from any cause, stroke or MI at 1 year was similar between TAVR vs. SAVR (13.1% vs 16.3%, repectively; p=0.43). Arnold et. al. demonstrated that at 1 year the rates of favorable outcomes, as defined by this study, did not differ significantly between TAVR vs. SAVR (58% vs 51%; p=0.143). Elmariah et. al. found similar outcomes, death from any cause, stroke, or MI, were observed between TAVR and SAVR in patients who had LVEF < 50% and those with a LVEF of >50% at 1 year (TAVR with LVEF <50% vs LVEF > 50%: 25.9% vs 22.9%, p= 0.56; SAVR with LVEF < 50% vs LVEF > 50% 23.3% vs 25.2%, p=0.79). This study also observed similar outcomes between TAVR with LVEF of < 50% and SAVR with LVEF < 50% at 2 years following the procedure (36.2% vs 31.3%, p=0.826)

Conclusions: Based on these studies, there is no significant decrease in the rate of overall mortality, improvement of LVEF, or improvement of quality of life and symptoms between patients who received TAVR vs SAVR. Further research should be conducted investigating the long term follow up of these procedures to determine appropriate rates of mortality and improvement of symptoms following these procedures.

Key Words: Transcatheter aortic valve replacement, surgical aortic valve replacement, severe aortic stenosis, left ventricular dysfunction, mortality

Introduction

Aortic Stenosis (AS) is defined as a narrowing of the aortic valve opening that results in restricted blood flow from the left ventricle (LV) to the aorta.[2] Although some people may suffer from congenital abnormalities, this condition most commonly develops from aging as calcium or scar tissue damages the valve restricting its motion.[4] The impeded motion of the aortic valve leads to a decrease in blood flow from the LV to the aorta and, therefore, the rest of the cardiovascular system. [2,3,4] This restriction of blood flow can result in many symptoms ranging from shortness of breath, chest pain, syncope and decreased exercise tolerance.[2] An estimated 610,000, or 1 out of every 4, people die of heart disease in the United States every year.[5] When looking specifically at valvular disease, approximately 25% of the general population ≥ 65 years of age are affected by aortic sclerosis. Of these, 2-9% suffer from aortic stenosis.[6] According to the Frankel Cardiovascular Center at Michigan Medicine, as many as 300,000 people in the US are diagnosed each year with severe AS.[3] The initial finding of AS is a harsh systolic, crescendo/decrescendo mumur heard over the 2nd right intercostal space. Accompanied with symptoms of AS, this murmur warrants the use of further diagnostic testing. The diagnostic test of choice is a transthoracic echocardiogram (TTE) with doppler.[3] This test allows for the assessment of aortic jet velocity, mean gradient, and aortic valve area, furthermore classifying the severity of stenosis at the aortic valve.[3] Severe AS is classified as an aortic jet velocity of > 4 m/sec, mean gradient > 40 mmHg, and an aortic valve area of < 1 cm^2.[3] According to a study done by Osnabrugge et. al., there are approximately 290,000 elderly patients who meet these criteria and are currently candidates for the TAVR procedure. They continued by stating that approximately 27,000 patients become eligible for the procedure annually.

Treatment of aortic stenosis depends on the severity of the disease and ranges from lifestyle modifications to valvular replacement. For patients with mild to moderate disease, lifestyle modifications (diet interventions, smoking cessation, exercise, etc.) and symptomatic control with the use of long-term anti-coagulation, hypertensive treatments, and long term antibiotics (prophylaxis for infective endocarditis) are the mainstay of treatment. However, in patients with more severe AS valve replacement using either the TAVR or SAVR method are the only definitive treatments.[3,5] These treatments do not come without cost. According to the American Heart Association (AHA), the estimated cost of a typical SAVR in the US ranges from $80,000- $200,000.[1,4] The cost of TAVR procedure in the US is typically higher due to the cost of the device used in the procedure, $32,500.[4]

Due to the fact that there are no pharmacological treatments that can reverse the damage to the valve that occurs in AS, the most definitive treatment for this disease is valve replacement. There are currently two methods to replace a damaged aortic valve: SAVR and TAVR. The surgical approach involves exposure via a midline sternotomy and the use of a cardiopulmonary bypass machine to access the diseased valve. The transcatheter approach allows for replacement of the valve via catheter using either iliofemoral, subclavian, or a direct aortic approach to gain access to the aortic valve.[3] In theory because this approach does not involve the use of cardiopulmonary bypass or a sternotomy, recovery time, length of hospital stay, and rate of overall mortality should be lower in patients who undergo the TAVR vs. SAVR.

Objective

The objective of this systematic review is to determine whether or not TAVR is associated with a decreased rate of mortality when compared to SAVR in patients with severe

AS. I selected three english language primary RCTs published between 2013 and 2015 for this review.

The studies included in this review: Randomized clinical trial of Transcatheter vs. Surgical Aortic Valve Replacement in patients with Severe AS by Thyregod et. al.[7](NOTION Trial); Outcomes of Transcatheter and Surgical Aortic Valve Replacement in High-Risk patients with AS and Left Ventricular Dysfunction by Elmariah et. al.[9] (PARTNER Trial Cohort A); Health Status After Transcatheter or Surgical Aortic Valve Replacement in Patients with Severe AS at increased Surgical Risk by Arnold et. al.[10] (CoreValve Trial). Inclusion criteria for selection of these studies were as follows: the comparison of TAVR vs. SAVR, a patient population with severe AS, and a primary outcome of either overall mortality, improved LVEF, or improved quality of life at least 1 year following the procedure. Studies were excluded from this review if follow-up time was less than 1 year, if study conducted was not a RCT, the population included in the study did not have a primary diagnosis of severe AS, if the study was conducted prior to 2010, if the procedures assessed within the study did not include TAVR and SAVR, or if the primary outcome addressed failed to include overall mortality. The inclusion criteria for each study varied for each study but typically included severe AS with physical limitations due to symptoms, NYHA class II + heart failure, and age ≥70 years. Exclusion criteria for these studies varied as well but included patients who did not meet the inclusion criteria, patients with another valvular or cardiac disease, prior cardiothoracic surgeries or interventions, or those with other comorbidities including severe renal disease or neurological events. Each study used a different type of measurement to determine clinical significance between TAVR and SAVR. These methods will be discussed in further detail below. The demographics and characteristics of the included studies are displayed in Table 1.

Table 1- Demographics and Characteristics of included studies

Study	Type	# of Pts	Age	Inclusion	Exclusion	W/D	Interventions
Arnold, 2015 (1)	RCT	795	76-90	Severe aortic stenosis with substantial functional limitations d/t heart failure symptoms (NYHA II+)	Pts who did not meet the inclusion criteria (no dx of Severe aortic stenosis/ not receiving interventions)	7	SAVR TAVR
Elmariah, 2013 (2)	RCT	699	76-90	Severe aortic stenosis, NYHA II+	Bicuspid or noncalcified aortic valve, coronary artery disease, LVEF of < 20%, aortic annulus diameter of < 18 or > 25mm, severe mitral or aortic regurg (4+) severe renal insufficiency, recent cardiac/ neuro event	43	SAVR TAVR
Thyregod, 2015 (3)	RCT	280	79.1 (mean age)	70+ y/o, severe aortic stenosis, NYHA II+, decreasing LVEF	Another severe heart valve disease, coronary artery disease requiring intervention, previous CT surgery, MI/ CVA w/in 30 d	4 due to mortality	SAVR TAVR

Methods

The following is a systematic review of three English language primary RCT's published on or after 2010 that were selected based on their relevance to the proposed questions via PubMed. All three RCT's compared TAVR vs. SAVR in patients with severe aortic stenosis. Keywords used in the search include transcatheter aortic valve replacement, surgical aortic valve replacement, severe aortic stenosis, left ventricular dysfunction, and mortality.

Outcomes Measured

In the PARTNER Trail, 699 patients from 25 sites who met the inclusion criteria, determined by experienced surgeons, were randomly assigned to undergo either TAVR or SAVR. The primary endpoint of this study was all-cause mortality at 1 year following the procedure. Secondary end points included cardiovascular mortality, stroke, repeat hospitalization, acute kidney injury, vascular complications, bleeding events, and NYHA functional class. This study also evaluated the effect of LVEF on these outcomes. For this study LV dysfunction was determined as an LVEF < 50% and improvement of LVEF was classified as ≥10% improvement in LVEF at 30 days. Analysis was performed using intention-to-treat data, which began at the time of randomization, and as-treated data, beginning at the time of induction of anesthesia. To measure the true effect of the included procedures, only as-treated data was included in the statistical analysis of this study. Categorical variables were compared using Fisher exact test. Continuous variables were compared using Student t-test. Survival curves for time-to-event variables were compared using log-rank tests. Paired t tests were used to assess changes in LVEF following the procedure. Other variables were measured in this study however, they are not relevant to the question addressed in this systematic review. Statistical significance was determined by a P value of <0.05.[9]

In the CoreValve Trial, patients who met the inclusion criteria, as determined by 2 cardiac surgeons and 1 interventional cardiologist were randomly assigned in a 1:1 ratio to treatment with either TAVR or SAVR. Disease specific and generic health status was assessed at baseline, 1 month, 6 months, and 1 year following the procedure. Disease specific health status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). This questionnaire was a 23-item self-administered questionnaire that has been shown to be a reliable measure of symptoms, functional status, and quality of life in patients with heart failure symptoms, including those with symptomatic AS. Generic health status was evaluated with the Medical Outcomes Study Short-Form 12 (SF-12) and the EuroQOL 5-dimension questionnaires. Acceptable and favorable outcomes after TAVR were also measured using definitions that combined mortality and quality of life into a single outcome. An acceptable outcome was defined as the presence of all the following at 6 months after the procedure: alive, KCCQ score of ≥ 45 (roughly equal to NYHA class III+), and stability or improvement of the patients KCCQ score from baseline to 6 months (decrease <10 points). A favorable outcome was defined as all the following at 1 year following the procedure: alive, KCCQ score ≥ 60 (equal to NYHA class I-II), stability or improvement of KCCQ score from baseline to 6 months (decrease < 10 points). Baseline characteristics were compared using 2-sample Student t-test for continuous variables and x^2-tests for categorical variables. Follow-up health status scores at 1 month, 6 months, and 1 year were compared using paired Student t-tests. Rates of acceptable and favorable outcomes at 6 months and 1 year were compared using x^2-tests. In addition to the analysis of these variables longitudinal random-effects growth curves were used to examine the relative effect of TAVR vs AVR over time. Statistical significance was determined by a P value <0.05.[10]

In the NOTION Trial, patients who met the inclusion criteria, as determined by a team consisting of an imaging cardiologist, an interventional cardiologist, and a cardiac surgeon, were randomized in a 1:1 ratio to treatment with either TAVR or SAVR. The primary outcomes assessed in this study included death from any cause, stroke or MI at 1 year following the procedure. The analysis for these outcomes was performed using logistic regression by adjusting for age, trial site, and history of coronary artery disease (CAD) with a 2-sided alpha level of 5%. Categorical variables were compared using the Fisher exact test or x^2-test. Continuous variables were compared with the use of student t-tests.[7]

Results

In the study performed by Elmariah et. al., a total of 657 patients were included in the as-treated cohort. Of these, 332 patients underwent TAVR and 304 underwent SAVR.[9] In both groups a similar number of patients with LV dysfunction died at 30 days and at 1 year when compared with those without LV dysfunction.[9] In the TAVR group, 25.9% of patients with LV dysfunction died by 1 year compared to 22.9% of patients with normal LV function (p=0.56).[9] In the SAVR group, 23.3% of patients with LV dysfunction died at 1 year compared to 25.2% of patients with normal LV function (p=0.79).[9] More importantly this study observed similar rates of all-cause mortality at 2 years following the procedure in patients with LVEF < 50% who underwent their assigned procedure (TAVR 36.2% vs. SAVR 31.3%, p=0.826).[9] A similar trend was observed in patients with normal LVEF at 2 years following their procedure (TAVR 31.8% vs. SAVR 30.9%, p=0.826).[9] Analysis for this systematic review was performed using the 2-year data in the patient group classified as having LV dysfunction as these patients were more likely to fit the inclusion criteria of this review. Table 2 contains the control event rate, experimental

event rate, relative benefit increase, absolute benefit increase, and number needed to treat

analysis for this study.

Table 2: Analysis data comparing all-cause mortality at 2-years following TAVR vs. SAVR as reported by the PARTNER Trial.

Patients	CER	EER	RBI	ABI	NNT
657	.313	.362	15.65%	4.9%	21

In the study conducted by Arnold et. al., 795 patients with severe symptomatic AS from

45 US centers met the inclusion criteria. Of those 394 were randomized to undergo TAVR and

401 were randomized to undergo SAVR. This study also stratified patients based on the site of

access used for the procedure.[10] The access sites included either iliofemoral or non-iliofemoral

(subclavian or direct aortic) access.[10] According to Arnold et. al. the iliofemoral TAVR (IF-

TAVR) group had a greater earlier improvement in health status when compared to the SAVR

group, with 16.7- point higher KCCQ overall summary scores at 1 month (CI=95%: 12.0 vs 21.3

pts, p= <0.001).[10] This trend was not observed between these two groups at 6 months and 1

year.[10] An acceptable outcome which, in this study, is a combination of survival status and health

status at 6 months occurred in 73% of TAVR patients vs 64% of SAVR patients (p=0.022). This

difference was confined to the IF-TAVR cohort (75% vs 63%, p=0.005), with no differences

between the two groups in patients with noniliofemoral (NIF) access.[10] At 1 year, the rates of

favorable outcomes did not differ significantly, regardless of access site (overall population

TAVR vs SAVR: 58% vs 51%, p=0.143).[10] In concordance with the inclusion criteria of this

systematic review the data including the overall population collected at 1 year was analyzed.

Table 3 displays control event rate, experiment event rate, relative benefit increase, absolute

benefit increase, and number needed to treat.

Table 3: Analysis data comparing favorable outcomes between TAVR and SAVR in the overall population included in a study conducted by the CoreValve Trial.

Patients	CER	EER	RBI	ABI	NNT
795	.51	.58	13.73%	7.0%	15

In the study done by Thyregod et. al, 276 patients met the inclusion criteria and were included in the as-treated cohort. Of those selected, 142 patients underwent TAVR and 134 patients underwent SAVR.[7] Two patients who were assigned SAVR did not undergo this procedure (1 treated with an apico-aortic conduit and 1 with apical TAVR); 3 TAVR patients were converted to SAVR because of complications during the procedure.[7] No patients were lost to follow-up in this study.[7] In the intention-to-treat analysis, the primary outcome (composite rate of death from any cause, stroke, or MI at 1 year) was similar between the 2 groups (13.1% vs 16.3%, p=0.43).[7] These results did not change for the as-treated analysis (11.3% vs 15.7%, p=0.30).[7] The as-treated data at 1-year found in this study was analyzed and the results are represented in table 4. Table 4 includes control event rate, experiment event rate, relative benefit increase, absolute benefit increase, and number needed to treat.

Table 4: Analysis data comparing the rate death from any cause, stroke or MI at 1-year between TAVR and SAVR included in a study conducted by NOTION Trial.

Patients	CER	EER	RBI	ABI	NNT
276	.157	.113	-28.02%	-3.57%	-28

Discussion

Although these three studies had similar results, each one had additional findings and limitations that should be mentioned within this review.

In addition to the results involving the primary outcome of their study, Elmariah et al. found an association of LV dysfunction with 30-day cardiac death after SAVR and with an increased risk of repeat hospitalization within the first year after TAVR.[9] This study observed

substantial improvements in NYHA functional class after both TAVR and SAVR, regardless of baseline LV function.[9] However, no difference in the rate or degree of LV functional recovery after either procedure was found.[9] This study did have several limitations including the exclusion of patients with severe LV dysfunction (<20% LVEF), and those with low gradient AS (aortic valve gradient < 40 mmHg).[9] The analyses done in this study were prone to survival selection bias given that follow-up LVEF was only available in those who survived.[9]

Arnold et. al. also had additional findings to those surrounding their primary outcomes as well as several limitations. When survival and quality of life outcomes were integrated into a single metric, Arnold et. al. found that patients treated with TAVR were more likely to have an acceptable outcome at 6 months when compared to those who underwent SAVR. A similar trend was observed at the 1-year time frame. There were 2 important limitations to this study. The first being the reported missing health status data over follow-up, particularly for the SAVR cohort. The second being the fact that this trial was unblinded, which could have impacted the manner in which the patients completed the health status assessments.

The NOTION Trial conducted by Thyregod et. al, had one of the lowest reported mortality rates for transcatheter therapy, as well as low stroke rates when compared to previous studies. Differences between the TAVR and SAVR were observed as procedure related outcomes. TAVR patients experienced more conduction abnormalities requiring pacemaker placement, and minor vascular complications. SAVR patients had more bleeding complications, cardiogenic shock, acute kidney injury, and new-onset or worsening atrial fibrillation. Patients who underwent SAVR also had a longer post-procedure hospital stay. One limitation of this study was the sample size. The authors of this study state that the sample size may have been too small to detect a potential difference in the effect of the treatment on the primary outcome. They

also stated that several outcomes assessed were unblended, particularly which procedure was conducted. Therefore, all outcomes addressed in this study, other than death, could be subject to bias.

Conclusions

This systematic review was conducted to determine if there was a decreased rate of mortality between patients with severe AS who received either TAVR or SAVR. After analyzing the studies included in this review there is no statistical difference found in mortality rates between the two groups. However, it is important to address one common finding between these studies. Both the PARTNER trial and the CoreValve trial found an early improvement in health status benefits at 30 days in the TAVR group. As stated above this trend was not observed at the 6 month and 1 year time mark. In both trials these early improvements were attributed to the less invasive nature of the TAVR procedure when compared to SAVR.

Due to the recent introduction of the TAVR procedure further research is required to investigate comparisons in long-term follow-up between TAVR and SAVR. This research should focus on outcomes including overall mortality rate, symptomatic and quality of life improvements, and improvements in LVEF in patients with severe AS. Further investigations should be conducted in order to compare the efficacy of devices used in the TAVR procedure (balloon expanding prosthesis vs self-expanding prosthesis).

Although no significant differences in mortality rates between the two procedures were found, these studies did confirm both the efficacy and safety of TAVR in patients with severe AS. Based on these studies, TAVR should be considered a feasible option in patients with severe AS who are considered to be at risk for SAVR.

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