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Emily Belz

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Belz, Emily, "Systematic Review Comparing All-Cause Mortality Rates Between TAVR and SAVR to Treat High Risk Surgical Patients with Severe Aortic Stenosis" (2021). *Physician Assistant Studies | Student Articles*. 13.
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Systematic Review Comparing All-Cause Mortality Rates Between TAVR and SAVR to Treat High Risk Surgical Patients with Severe Aortic Stenosis

By: Emily Belz, Physician Assistant Student, Dominican University of California
emilyobelz@gmail.com

Abstract

Background: Our goal was to conduct a systematic review of available randomized controlled trials to compare the safety and efficacy of TAVR to SAVR by looking at absolute risk reduction in all-cause mortality for high risk surgical patients with severe aortic stenosis at 1, 2 and 5 years post-intervention.

Methods/Results: The PubMed database was searched according to the PRISMA guidelines from inception until September 2020. 6 high quality randomized controlled trials analyzing all-cause mortality for TAVR versus SAVR in the CoreValve US High-Risk Clinical Study and Placement of Aortic Transcatheter Valves (PARTNER) Trial populations at 1, 2 and 5 years post-intervention were included (n = 1,446 participants, randomly assigned to undergo TAVR (738) or SAVR (708)). The CoreValve Trial found a statistically significant absolute risk reduction of 4.9% with TAVR compared to SAVR at 1 year (superiority P-value of 0.04 and non-inferiority P-value of <0.001). The Partner Trial also found a statistically significant risk reduction of 2.6% with TAVR compared to SAVR at 1 year (non-inferiority P-value of <0.001). Additionally, the CoreValve Trial found a statistically significant absolute risk reduction of 6.4% with TAVR compared to SAVR at 2 years (superiority P-value of <0.05). The Partner Trial at 2 years and the CoreValve Trial at 5 years found small, but not statistically significant risk reduction for TAVR compared to SAVR.

Conclusion: This systematic review showed lower or comparable all-cause mortality rates for TAVR compared to SAVR over 2 study populations from large, multicenter randomized controlled trials analyzed at 1, 2, and 5 years intervals, thus demonstrating the viability of TAVR for high risk surgical patients with severe AS. Based on these results, as well as the additional advantages of TAVR being less invasive, resulting in less acute blood loss, and having a shorter hospital stay and recovery time compared to SAVR, healthcare providers should recommend TAVR as a safe and viable alternative to SAVR to their patients with severe AS at high surgical risk due to its reduced or comparable all-cause mortality rates up to 5 years post-intervention. If feasible, a trans-femoral approach for TAVR is recommended due to lower mortality rates.

Introduction:

Aortic stenosis (AS) occurs when there is a narrowing of the aortic valve opening, usually due to degenerative calcification and scarring, impeding the effective passage of blood from the left heart ventricle to the aorta (About the Aortic), (Aortic Valve), (Crawford, 2017), (Problem: Aortic, 2016), (Xiushui, 2019). AS leads to reduced cardiac output and increased afterload, which overtime cause left ventricular hypertrophy, myocardial dysfunction, arrhythmias, MIs, heart failure and sudden cardiac death (About the Aortic), (Aortic Valve), (Otto, 2018), (Papadakis, 2020), (Problem:

Aortic, 2016), (Williams, 2016), (Xiushui, 2019). It is estimated that AS affects around 300,000 Americans, including 12.4% of people over age 75, making it the most common valvular heart disease in the elderly (About the Aortic), (Cover Story, 2017), (Nishimura, 2017). AS is the most common valvular disease requiring surgery as well as the most common cause of left ventricular outflow obstruction (Otto, 2018), (Papadakis, 2020), (Williams, 2016). It is estimated that aortic valve disease costs $10.2 billion in direct costs each year in the US (Moore, 2016).

There is no effective medical therapy for AS, therefore surgical aortic valve replacement is the only definitive treatment for patients with severe AS, which is typically fatal within 2 to 5 years without valve replacement (About the Aortic), (Crawford, 2017), (Papadakis, 2020), (Williams, 2017) (Xiushui, 2019). The traditional approach to treating severe AS for the past 50 years has been a surgical aortic valve replacement (SAVR), a type of open heart surgery that requires the patient be placed on a heart-lung bypass machine (About the Aortic), (Miller, 2016). Transcatheter aortic valve replacement (TAVR) is a newer procedure first approved by the FDA in 2011, which provides a less invasive alternative to SAVR by using a catheter that is inserted most commonly into the femoral artery and guided to the heart using fluoroscopy, when it reaches the aortic valve, a new balloon expandable valve is deployed (About the Aortic). While the risks and costs of SAVR and TAVR are similar, the TAVR procedure is less invasive, results in less acute blood loss, a shorter hospital stay and recovery time, can be used to repair prosthetic aortic valves that have become dysfunctional, and gives patients for whom surgery poses a significant risk or is prohibitive another option (About the Aortic), (Crawford, 2017), (Mahmaljy, 2019), (Meduri, 2017), (Miller, 2016), (Papadakis, 2020), (Xiushui, 2019). Up to one third of the 300,000 Americans with aortic stenosis are considered too old or too sick to undergo surgery, so TAVR provides a crucial, lifesaving option for these patients who previously had no alternative (About the Aortic). TAVR is currently approved by the FDA for patients with severe aortic stenosis at high or intermediate surgical risk. (Cover Story, 2017), (Xiushui, 2019). The 2017 ACC/AHA guidelines gave a Class 1 recommendation for TAVR for patients with severe AS who are high risk surgical patients or patients where the risk of surgery is prohibitive and state that it is also a reasonable alternative for intermediate risk surgical patients (STS-PROM 4-8%) (Papadakis, 2020), (Cover Story, 2017), (Xiushui, 2019).

Prior research has found conflicting results on all-cause mortality rates of TAVR compared to SAVR. The majority of studies have found significantly lower mortality rates for TAVR compared to SAVR (Adams, 2014), (Deeb, 2016), (Reardon, 2015), (Smith, 2011). Other studies have found comparable mortality rates (Gleason, 2018), (Kodali,

2012) while one study found worse mortality rates (Mack, 2015). In 2016, Siontis et al. published a similar metanalysis that looked at the primary outcome of all-cause at 2 years. More research is needed on the durability of TAVR by looking at all-cause mortality at 5- and 10-years post-intervention. This research will incorporate more recent studies since the publication of this previous metanalysis in 2016 and will also examine all-cause mortality at 5 years, to elucidate a more clear picture of mortality rates of TAVR procedure compared to SAVR.

The purpose of this paper is to conduct a systematic review of published randomized controlled trials (RCTs) examining the safety and efficacy of the TAVR and SAVR procedures. We will look at all-cause post-interventional mortality rates at 1, 2 and years after TAVR or SAVR in high risk surgical patients with severe AS. This project will provide a more definitive conclusion on the mortality rate and durability of TAVR compared to SAVR in order to allow providers and their patients to make a more informed decision about the risks and benefits of TAVR compared to SAVR.

Methods

Database Search Strategy

In order to compare all-cause mortality of the TAVR to the SAVR procedure, a systematic review in PubMed was conducted using PRISMA guidelines with all available English-language articles through September 2020. We used the keywords "SAVR, TAVR, severe aortic stenosis, high risk surgical patients." The bibliographies of studies found from this search were also reviewed to find additional clinical trials. A further search using the above keywords was conducted in Google and Google Scholar to identify grey literature. Initial results were screened by title and abstract and the full-text results of all clinical trials were then evaluated by one researcher (EB) to ensure they met inclusion criteria.

Studies deemed eligible were randomized controlled trials, enrolling men and women, with a study design that compared TAVR to SAVR in hig- risk surgical patients with severe aortic stenosis. Included papers had a primary outcome of all-cause mortality at 1, 2, or 5 years post-intervention. Excluded trials compared TAVR to medical therapy, included low or medium risk surgical patients or patients with moderate aortic stenosis, did not include both sexes, and reported only short-term mortality outcomes.

Data Extraction and Analysis

Reviewers extracted the data regarding baseline study characteristics (study objectives, study design, length of study, year of publication, number of participating centers, number of randomized patients, number of patients assigned to each treatment group), baseline patient demographics (sex, age, Society of Thoracic Surgeons Predicted Risk Of Mortality

(STS) estimate), quality data and outcomes of interest (absolute risk reduction, superiority or non-inferiority P-values for TAVR compared to SAVR). A P-value of <0.05 was considered statistically significant.

Risk of Bias and Quality Assessment

The Cochrane Collaboration Tool was used to assess the risk of bias and all studies included were of high quality per the 12-question article critique.

Outcome

This paper will describe all-cause mortality and absolute risk reduction for TAVR compared to SAVR using superiority or non-inferiority P-values at 1, 2 and 5 years post-intervention with the study populations from the CoreValve US High-Risk Clinical Study and Placement of Aortic Transcatheter Valves (PARTNER) trial.

Results

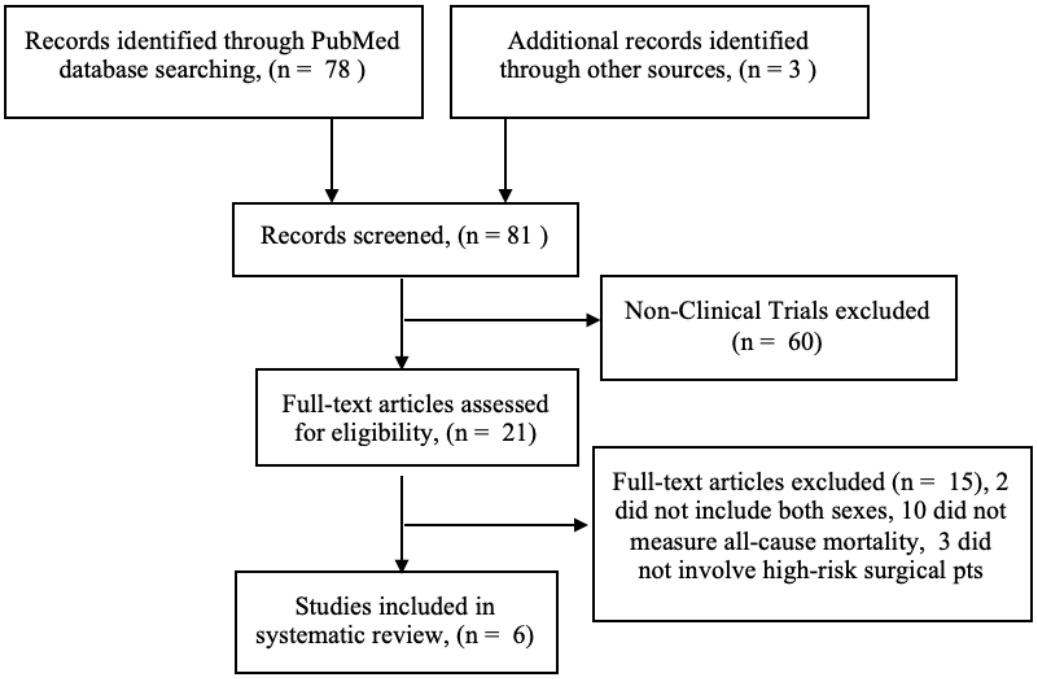

Figure 1: PRISMA flow diagram of literature review and study selection

As demonstrated in Figure 1, the initial keyword search of the PubMed database resulted in 78 articles, which were narrowed to 18 studies by including only clinical trials. These 18 studies along with 3 additional studies identified through bibliographies were retrieved and reviewed via full-text to ensure they met inclusion criteria. Fifteen studies were excluded for various other reasons: 2 did not include both sexes, 10 did not measure the outcome of all-cause mortality,

and 3 did not involve high risk surgical patients). Searching reference lists of selected papers and reviews identified 3 additional studies that met inclusion criteria.

All-cause mortality and absolute risk reduction for TAVR versus SAVR at 1, 2 and 5 years post-intervention was compared between the CoreValve US High-Risk Clinical Study and Placement of Aortic Transcatheter Valves (PARTNER) trial study populations. Table 1 summarizes the characteristics of these trials and their patient populations. Both studies were multicenter randomized controlled trials. The CoreValve US High-Risk Clinical Study included 750 patients from 45 US centers with a mean age of 83 years, 53% males, and a mean STS score of 7.4. Placement of Aortic Transcatheter Valves (PARTNER) trial included 699 patients from 25 centers (22 in US, 2 in Canada and 1 in Germany) with a mean age of 84 years, 57% males and a mean STS score of 11.7. Patients in the TAVR group of the CoreValve study were treated with the CoreValve self-expanding prosthesis (Medtronic Inc). Patients in the PARTNER trial TAVR group received the SAPIEN heart-valve system (Edwards Lifesciences).

Table 1 – Characteristics of trials, study populations and interventions of included randomized controlled trials

Authors	Single or Multicenter	Population	Distribution of SAVR vs. TAVR	All-Cause Mortality Outcome
Studies involving the CoreValve US High Risk Clinical Study Population				
Adams et al.	45 US centers	Mean age – 83 years 53% males STS score – 7.4	TAVR - 390 SAVR - 357	1 year
Reardon et al.			TAVR - 390 SAVR - 357	2 years
Gleason et al.			TAVR - 391 SAVR - 359	5 years
Studies involving the Placement of Aortic Transcatheter Valves (PARTNER) Trial Population				
Smith et al.	25 centers: 22 in US, 2 in Canada, 1 in Germany	Mean age – 84 years 57% males STS score – 11.7	TAVR - 348 SAVR - 351	30 days and 1 year
Kodali et al.				2 years
Mack et al.				5 years

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons Predicted Risk of Mortality

Table 2 presents the primary outcomes of all-cause mortality at 1, 2, and 5 years of TAVR compared to SAVR for the CoreValve and Partner Trail study populations. The CoreValve Trial found a statistically significant absolute risk reduction of 4.9% with TAVR compared to SAVR at 1 year (superiority P-value of 0.04 and non-inferiority P-value of <0.001). The Partner Trial also found a statistically significant risk reduction of 2.6% with TAVR compared to SAVR at 1 year (non-inferiority P-value of <0.001). Additionally, the CoreValve Trial found a statistically significant absolute risk reduction of 6.4% with TAVR compared to SAVR at 2 years (superiority P-value of <0.05). The Partner Trial at 2 years and the CoreValve Trial at 5 years found small, but not statistically significant risk reduction for TAVR compared to SAVR.

Table 2 - Comparison of All-Cause Mortality of TAVR Compared to SAVR at 1, 2 & 5 Years

	1-year All-Cause Mortality					2-year All-Cause Mortality				5-year All-Cause Mortality			
	TAVR	SAVR	Absolute Risk Reduction	Superiority P-value	Non-Inferiority P-value	TAVR	SAVR	Absolute Risk Reduction	Superiority P-value	TAVR	SAVR	Absolute Risk Reduction	Superiority P-value
CoreValve Trial	14.2%	19.1%	**4.9%**	**P = 0.04**	**P < 0.001**	22.2%	28.6%	**6.4%**	**P <0.05**	55.3%	55.4%	0.1%	P = 0.5
PARTNER Trial	24.2%	26.8%	**2.6%**	P = 0.44	**P < 0.001**	33.9%	35.0%	**1.1%**	P = 0.78	67.8%	62.4%	none	P = 0.76

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

Based on previously referenced Cochrane Collaboration Tool, the risk of bias in all included studies was found to be low and all studies included were of high quality per the 12-question article critique.

Discussion

In this systematic review examining the results of 6 landmark RCTs, we compared all-cause mortality of TAVR to SAVR using between 2 large study populations of high-risk surgical patients with severe AS at 1, 2 and 5 year post-intervention. The main finding of our comparative efficacy trial was that TAVR had a statistically significant reduction in absolute risk or comparable risk at 1 and 2 years compared to SAVR, and comparable mortality in one study and worse mortality in another study compared to SAVR at 5 years. Mack et al. was the only included study to find higher all-cause mortality rates for TAVR compared to SAVR at 5 years post-intervention. However, sub-group analyses including only TAVR patients that underwent a transfemoral approach, excluding patients that underwent a transapical approach, found a

63% risk of all-cause mortality at 5 years compared to 64% in the SAVR group (p=0.41) (Mack, 2015). Therefore, we have concluded that all-cause mortality for TAVR is reduced or comparable compared to SAVR up to a period of 5 years post-intervention for high risk surgical patients with severe AS. Based on these results, as well as the additional advantages of TAVR being less invasive, resulting in less acute blood loss, and having a shorter hospital stay and recovery time compared to SAVR, healthcare providers should recommend TAVR as a safe and viable alternative to SAVR to their patients with severe AS at high surgical risk. If feasible, a trans-femoral approach for TAVR is recommended due to lower mortality rates.

A previous meta-analysis conducted by Siontis et al in 2016, similarly found a 13% relative reduction in all-cause mortality at 2 years for TAVR compared to SAVR (hazard ratio (95% CI): 0.87 (0.76–0.99); P = 0.038) in patients with severe aortic stenosis at intermediate or high surgical risk. Their subgroup analysis also found reduced mortality for TAVR compared to SAVR for patients undergoing a transfemoral access [0.80 (0.69–0.93); P = 0.004], but not transthoracic access [1.17 (0.88–1.56); P = 0.293] (Siontis, 2016).

Limitations for the studies using the CoreValve trial include the learning curve of providers and centers using TAVR for the first time compared to SAVR where all surgeons and centers had greater than 5 years' experience as well as their usage of the first generation CoreValve device, which has since been replaced by a third generation device (Adams, 2014), (Gleason, 2018), (Medtronic CoreValve, 2019), (Reardon, 2015). Limitations for studies using the PARTNER trail population include their usage of the first generation Sapien device, which has since been replaced by a fourth generation device, the learning curve of providers and centers using TAVR for the first time, and an average STS score of 11.7, indicating a very high risk population (Kodali, 2012), (Mack, 2015), (Smith, 2011), (Transcatheter Heart, 2020). Furthermore, only 6 RCTs were available for inclusion, limiting the power of this study. Additionally, 10 year post-interventional data comparing TAVR to SAVR is not yet available.

More research is needed to evaluate TAVR using the latest generations of the CoreValve (Evolut Pro) and Sapien (3 Ultra) devices compared to SAVR and with TAVR procedures performed by experienced surgeons (Medtronic CoreValve, 2019), (Transcatheter Heart, 2020). Additional research is also needed on the longer term durability and other complications of TAVR compared to SAVR and evaluation of all-cause mortality at 10 years post-intervention.

In conclusion, this systematic review described lower or comparable all-cause mortality rates for TAVR compared to SAVR over 2 study populations from large, multicenter RCTs analyzed at 1, 2, and 5 years intervals, thus

demonstrating the viability of TAVR for high risk surgical patients with severe AS. Based on this research and in accordance with existing FDA guidelines, TAVR should be recommended by healthcare providers to their patients with severe aortic stenosis and high surgical risk as a viable alternative to SAVR due to its reduced or comparable all-cause mortality rates up to 5 years post-intervention as well as additional benefits such as a shorter hospital stay and recovery time.

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