Comments of Edwards Lifesciences LLC
on the NCA for TAVR
(CAG-00430R)
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1. Clinical Evidence Demonstrates Effectiveness of Transcatheter Aortic Heart Valves

1.1 Aortic Stenosis Disproportionately Impacts Medicare Beneficiaries

1.1.1 Aortic Stenosis Is an Insidious Disease

Overview

Aortic stenosis (AS) is a relatively common type of valvular heart disease that presents as a narrowing of the aortic valve opening. This narrowing results in reduced blood flow from the left ventricle to the aorta and to the rest of the body. AS is a degenerative condition that is associated with debilitating symptoms and complications such as angina (chest pain), syncope (fainting), and heart failure.[1,2] These manifestations lead to significantly reduced survival, poor quality of life (QoL) and functioning, and high healthcare costs.

Etiology & Pathophysiology

AS is predominantly an age-related condition that results from the deposition of calcium on the aortic valve leaflets.[3] In most patients, the tissue of the aortic valve becomes scarred, inflamed, or thickened as collection of calcium reduces the flexibility of the valve's leaflets. This loss in flexibility makes it harder to push blood through the valve leading to decreased blood flow across the valve, which causes the muscles of the heart chamber wall to stretch and thicken. This degenerative process places stress on the heart and leads to an increased likelihood of cardiovascular complications such as heart failure.

Epidemiology

AS is a common, public health problem in the United States (US) and a major cause of cardiovascular morbidity and mortality in elderly individuals.[4] Approximately 2.5 million people in the US—12.4% of the population ages 75 years or older—suffer from AS.[5,6] The prevalence of moderate or severe disease is approximately 2.8% in individuals aged ≥ 75 years.[7,8] AS is the principle cause of thousands of deaths in the US each year and a contributing factor to many more.[7,9]

Natural History

The progression of AS can be even more insidious in patients with medical conditions and/or cardiovascular abnormalities that result in an elevated surgical risk. Among medically managed patients with AS who are inoperable, predicted survival is only about 3% at 5 years and is lower than that of many associated metastatic cancers (Figure 2.1).[10] Among medically managed patients with AS who are at high surgical risk, survival has been reported at approximately 40–65% at 1 year[11,12] and 5.1% at 5 years.[11]

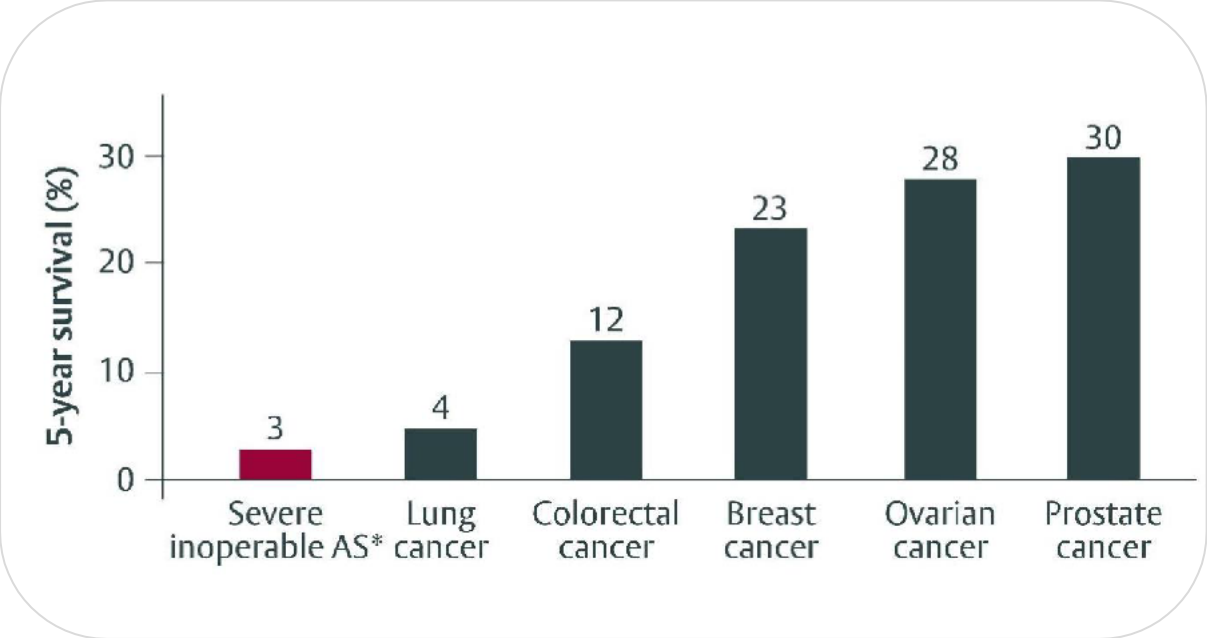

Figure 2.1: Comparison of five-year survival in patients with severe symptomatic inoperable AS or different cancer types with distant metastases.
*Constant hazard model.
Key: AS = aortic stenosis.
Source: Data on file, Edwards Lifesciences LLC. Analysis courtesy of E.M. Tuzcu, MD, Cleveland Clinic.[10]

Humanistic & Economic Burden

Patients with severe symptomatic AS (SSAS) experience significantly compromised QoL related to the physical, social, and psychological impact of the disease.[13,14] Patients often suffer from fatigue, palpitations, or shortness of breath, even while at rest.[15] Many patients are classified as either New York Heart Association (NYHA) functional class III or IV, indicating they have important limitations in their ability to undertake daily activities.[15] Class IV patients suffer from cardiac insufficiency at rest and are unable to undertake any physical activity without discomfort; further, many of these patients are bedridden.[15] These manifestations lead to significant reductions in QoL, as demonstrated by studies of patient-reported outcomes. For example, a study of inoperable patients with SSAS found that baseline scores on the physical component of the Short Form-12 (SF-12) health survey were, on average, at least two standard deviations below that of the US population norm, indicating significantly compromised physical well-being.[13] Highly similar SF-12 results were also shown in a study of patients at high risk for surgery.[14] Moreover, a study of transcatheter aortic valve replacement (TAVR) in patients with intermediate surgical risk found that the mean baseline Short Form-36 (SF-36) physical summary score was about 1.5 standard deviations below that of the US population.[16]

In addition to reduced QoL, patients who receive medical management for AS incur substantial end-of-life costs. In a study of Medicare beneficiaries, the annual medical expenditure of patients receiving medical management for AS was approximately $30,000 per patient, and average health care spending was 3.4 times higher than that of the average beneficiary.[11]

Therapeutic Treatment Goals

According to the American College of Cardiology/American Heart Association guidelines, the main goals of valvular intervention in patients with severe symptomatic AS include improvement of survival and symptoms and minimization of AS-related complications.[2] Recent evidence further suggests that maintenance or improvement of QoL and functionality are also important goals of therapy. In a retrospective study of treatment goals in patients with severe AS, being able to perform a specific activity was the most common preferred outcome (48%) when patients considered undergoing TAVR.[17] Other preferred outcomes included maintaining independence (30%), reducing/eliminating pain or symptoms (15%), and staying alive (7%).

1.1.2. Valve Replacement Is the Only Effective Treatment Option

Three primary treatment options are available for AS patients: medical management, surgical aortic valve replacement (SAVR), and TAVR. Medical management consists of pharmacologic treatment to alleviate symptoms and, in certain cases, balloon aortic valvuloplasty (BAV) to enlarge the aortic valve opening. However, these treatments have not been found to provide sustained symptom relief, alter the disease course, or improve survival in patients with severe symptomatic AS. Studies of medical management and/or BAV in inoperable and high surgical risk patients report mean survival rates of only 54%, 35%, and 20% at one, two, and three years follow-up, respectively.[18-31], medical therapy remains an option for patients who cannot undergo AVR (e.g., because of comorbidities). As no medical therapy is available that can alter disease progression in patients with severe symptomatic AS, standard treatment options currently include SAVR and TAVR. SAVR involves replacement of the native aortic valve with a bioprosthetic or mechanical valve during open-heart surgery in which the patient is put on cardiopulmonary bypass and is a proven option for some patients. However, for patients with severe symptomatic AS who are at intermediate or greater surgical risk, TAVR is becoming the preferred and less invasive treatment option. TAVR allows a new valve to be inserted within the native disease aortic valve without the need for open-heart surgery. Both SAVR and TAVR are associated with prolonged survival and durable improvements in disease-related symptoms compared with medical management.

1.1.3. Summary

Taken collectively, severe symptomatic AS is a relatively common form of heart disease that is associated with high rates of mortality, poor QoL, and a high economic burden. Aortic valve replacement (AVR) is the only treatment option that can improve symptoms and QoL and prolong survival in patients with this condition. TAVR is recommended as an effective, minimally invasive, and well-tolerated form of AVR for patients with severe symptomatic AS who are elderly and/or inoperable, or who have an intermediate or higher surgical risk.

1.2. TAVR Has Dramatically Improved the Care of Medicare Patients with Aortic Stenosis

1.2.1. TAVR Has Allowed Thousands of Untreated Patients to Receive Treatment

Since its US introduction in 2011, more than 100,000 patients have received TAVR for the treatment of their SSAS. The vast majority (over 75%) of these procedures have been for Medicare beneficiaries who would likely never been treated **(Figure 2.2)**, as TAVR has significantly changed the risk-benefit proposition of AVR.[32] In fact, the number of patients receiving *any* AVR treatment has more than doubled between 2012 and 2017, indicating substantial improvements in access to care for Medicare patients suffering from SSAS (**Appendix A: Medicare**).

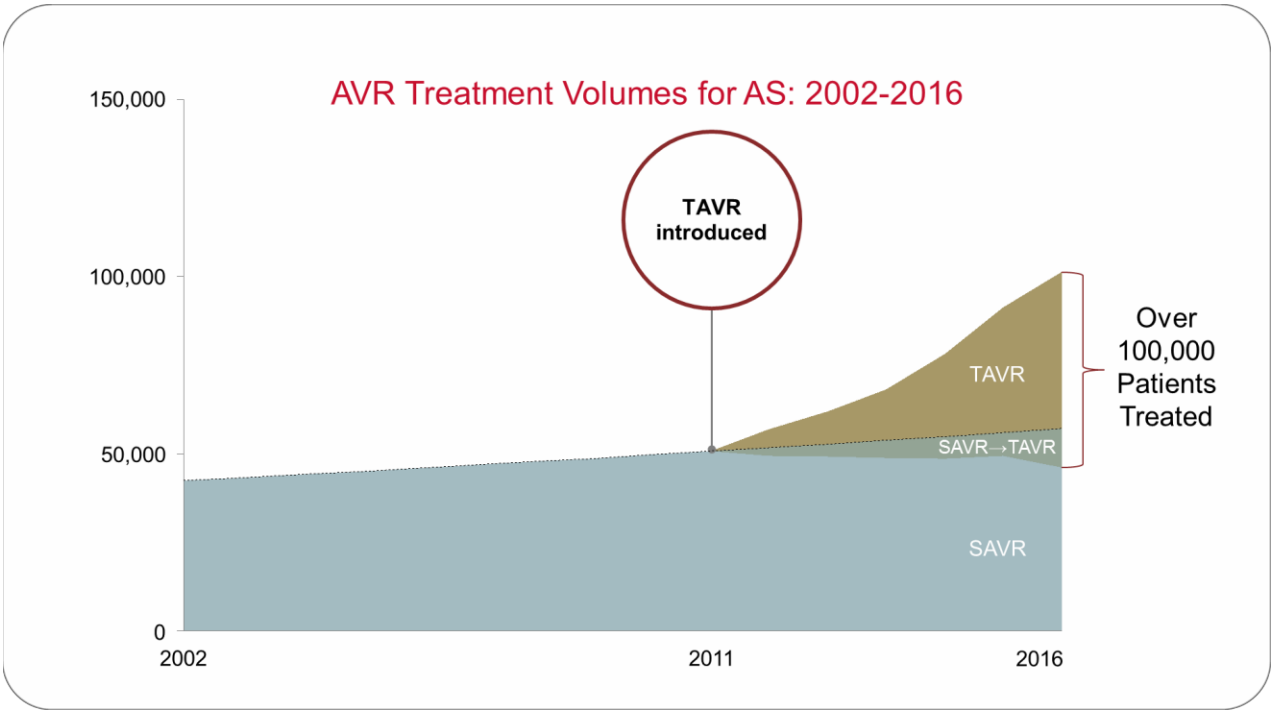

Figure 2.2. Growth of SAVR and TAVR since 2002. SAVR and TAVR volumes were obtained from Medicare/HCUP. Over 100,000 TAVR procedures have been performed since introduction. SAVR conversion to TAVR (vs. new procedures) was determined by projecting expected SAVR volumes based on the 2002–2011 SAVR CAGR and comparing them to the observed procedure number.

1.2.2. The Addition of TAVR Centers Has Been Associated with Higher Diagnosis Rates, Higher AVR Treatment Rates, and Lower Mortality Rates

The increase in TAVR facilities over the last several years has been accompanied by remarkable improvements in health outcomes for SSAS patients. An electronic health record-based cohort study, which compared SSAS patients in 2016 (when there were 470 operating TAVR centers in the United States) to patients in 2014 (when there were only 370 operating TAVR centers), found that, in 2016 SSAS patients had an 8% higher diagnosed incidence rate and a 19% relative reduction in 1-year mortality relative to AS patients in 2014 (**Appendix B: Optum**). Published research has also commented on this increase in diagnosis and decrease in untreated mortality secondary to TAVR growth.[33]

However, given the high mortality of untreated SSAS, the public health benefits of TAVR are strongest with timely and readily accessible care. In a review of electronic health care records from multiple systems,

SSAS patients with faster times to TAVR had 50% lower 1-year mortality rates than their counterparts with longer wait times (**Appendix B: Optum**). These findings align with patient-level findings in the academic literature, which demonstrated that patients' probability of death waiting for TAVR increased to nearly 15% over the course of 12 weeks.[34] Given that these patients poorly tolerate waiting due to the deadly nature of SSAS, ensuring adequate access to TAVR should be a key goal to maximize the outcomes of these Medicare beneficiaries.

1.3. TAVR Outcomes Have Evolved and the Evidence Base Is Robust

1.3.1. The Evidence Has Evolved Significantly Since the Initial TAVR NCD

When the TAVR NCD process was initiated in 2011, the available clinical trial data was largely based on the original PARTNER Trial. This study was conducted 10 years ago with inoperable and high-risk patients enrolled between May 2007 and August 2009.[22,35,36] Much was learned about TAVR during that period, and it may be more appropriate to consider the results as a landmark, proof of concept study, rather than as a benchmark for gauging current outcomes.[37]

Following the PARTNER Trial, a much larger Non-Randomized Continued Access Registry (NRCA) enrolled 1,023 high-risk and inoperable transfemoral patients and 975 high-risk transapical patients between September 2009 and January 2012. The NRCA cohort demonstrated significant improvements in procedural and longer-term outcomes when compared with the PARTNER 1A results.[38,39] Among patients receiving transfemoral access (TF-TAVR), mortality at 1 year was significantly lower in the NRCA group (19.0% vs. 25.3%, p=0.009) as compared to the TF-TAVR PARTNER A group.[38] The 1-year mortality of the SAVR patients in PARTNER A was 26.8%.[36] While speculative, the 1-year mortality of 19% in the NRCA registry would reflect a 29% relative reduction in mortality compared with this historical control group.[40]

As part of the PARTNER 2 Trial, 583 high-risk and inoperable patients receiving the SAPIEN 3 valve were enrolled between October 2013 and September 2014. A transfemoral approach was used in 491 patients (84.2%). In the transfemoral cohort, mortality was 12.3% at 1 year. Across all patients, the rates of all and major (disabling) stroke at 30 days were 1.4% and 0.9%, respectively. The authors note the strikingly low rates of complications and mortality support the use of TAVR as the "preferred therapy" in high-risk and inoperable patients with aortic stenosis.[41]

In the PARTNER IIA Trial, surgery in intermediate-risk patients was compared to TAVR with the SAPIEN XT valve in a randomized fashion and with the SAPIEN 3 valve through a propensity score analysis. A total of 2,032 patients were enrolled between December 2011 and November 2013 for the randomized portion (surgery vs. SAPIEN XT valve) and 1077 patients were enrolled in a single-arm SAPIEN 3 valve cohort between February 2014 and September 2014. SAPIEN XT valve patients achieved similar 2-year all-cause mortality and disabling stroke outcomes as compared to surgery patients (18.9% vs. 21.0%, p=0.18). However, in transfemoral patients (as treated), SAPIEN XT valve was associated with significantly lower all-cause mortality and disabling stroke (16.3% vs. 20.0%, p=0.04).

When evaluating the results of SAPIEN 3 valve TAVR versus surgery the advantage was more pronounced, with SAPIEN 3 valve patients achieving clinical and statistical superiority to surgery in the (primary) composite endpoint of death, stroke and moderate or greater aortic regurgitation (p<0.001) and in its components of death (p<0.001) and stroke (p=0.004).

A significant factor facilitating improvements in outcomes over time is the rapid advancements in THV technologies:

- THVs now come in a full range of sizes, allowing for better anatomical fit and tailoring of the device to the patient's anatomy.

- THV systems now have reduced insertion profiles allowing more patients to be treated through the transfemoral route while experiencing lower rates of vascular complications.
- THVs commercially available in the US now have added features to reduce the rates of paravalvular leak (PVL). Current THVs have reduced significant PVL to such an extent that in some of the latest clinical trials there were no longer significant associations between even moderate/severe PVL and mortality.[42]
- The association of smoother and more flexible delivery systems that allow for smoother traversing of the aortic arch, easier crossing of the stenotic valve, positioning of the THV and predictable deployment have also greatly reduced the rates of peri-procedural stroke experience by TAVR patients.[43-45]

Additionally, significant improvements have been made in patient assessment and peri-procedural management:

- The pre-procedural assessment now routinely includes CT assessment of peripheral arteries for access and a thorough review of the aortic valve and root anatomy including intensive sizing characterization of the annulus, LVOT, calcium deposit distribution, etc. CT[46] (or 3D Echo[47]) can better inform THV size determination than 2D Echo, which was used in the first PARTNER Trial. The PARTNER II S3i Trial was the first to require mandatory CT core lab assessment. After the introduction of this requirement, annular rupture (a dreaded complication) was reduced to zero[48].
- More intensive pre-procedural assessment has also helped in improving patient selection for TAVR, providing treating physicians with the information to choose the best therapeutic option for each patient.[49]
- A more streamlined procedure with concomitant reduction in procedural complications has enabled many centers to perform TAVR under conscious sedation instead of general anesthesia, often without the use of a TEE probe. This allows for a speedier recovery, sometimes obviating the need for stay in the ICU, ambulation just 4 hours after the procedure and discharge home in 1-3 days after TAVR[50-52].

Finally, results from the Medicare program demonstrate a continuous improvement in TAVR outcomes since its initial introduction. Between 2012 and 2017, TAVR in-hospital mortality declined from 4.7% to 1.5% (2012-2017 MedPAR), which is numerically lower than in-hospital mortality for SAVR in contemporary practice.

Table 2.1 SAVR/TAVR Mortality Trends Over time

	Procedure Type	2012	2013	2014	2015	2016	2017
N	SAVR	26,321	26,287	26,066	25,310	32,318	29,183
	TAVR	3,964	6,426	10,112	17,385	26,615	33,618
Age	SAVR	76	76	75	75	74	73
	TAVR	83	83	83	83	82	81

Charlson Index	SAVR	2.23	2.22	2.22	2.24	2.17	2.33
	TAVR	3.3	3.24	3.32	3.25	3.1	3.13
In-hospital mortality	SAVR	3.90%	3.70%	3.60%	3.70%	3.80%	4.00%
	TAVR	4.70%	3.80%	3.30%	2.40%	1.90%	1.50%

1.3.2. Overview of Key Study Outcomes, Stratified by Surgical Risk

Overview

A substantial body of evidence demonstrates the safety and efficacy of Edwards SAPIEN transcatheter heart valves (THV) in patients with SSAS who are inoperable or have an elevated risk for surgery. Clinical outcomes data for the SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valves are available from the landmark Placement of AoRtic TraNscathetER valves (PARTNER) Trial,[13,14,22,36,53-56] the PARTNER II Trial,[57] PARTNER continued access studies,[38,58-64] the PARTNER II S3HR[41,43] and S3i Trials/analyses,[43,65] and the SAPIEN 3 valve CE Mark Trial.[66,67] Evidence for TAVR is also available from the US CoreValve Extreme Risk[68,69] and High Risk Trials,[70,71] the SURTAVI study,[45] and evaluations of other valve types.

The SAPIEN valve Transcatheter Heart Valve Trials

Edwards has played a pioneering role in generating evidence for TAVR through the PARTNER clinical trial program. The landmark PARTNER Trial (NCT00530894) was initiated in 2007 and is the first and longest-running prospective randomized controlled trial (RCT) to investigate the safety and efficacy of TAVR. The trial assigned more than 1,000 severe symptomatic AS patients to one of two independently powered arms according to their baseline characteristics: “inoperable” (Cohort B) and “high surgical risk” (Cohort A). Patients in Cohort B were randomized to receive the Edwards SAPIEN valve (delivered transfemorally) or medical management. Patients in Cohort A were randomized to receive the Edwards SAPIEN valve (delivered transfemorally or transapically) or SAVR.

After randomized enrollment was completed for both study cohorts in the PARTNER Trial, sites could enroll patients under a non-randomized continued access (NRCA) protocol. Enrollment in this cohort was initiated in September 2009 and was completed in 2011.[59,62-64] The results of the PARTNER Trial contributed to the establishment of the first TAVR guidelines in Europe.[72] (Details on the trial are described below)

The next PARTNER Trial, PARTNER II (NCT01314313), was initiated in 2011 and enrolled more than 3,300 patients in two individually powered cohorts (“inoperable”—Cohort B; “high/intermediate surgical risk”—Cohort A) and in nested registries. Cohort B compared the first-generation SAPIEN valve with the second-generation SAPIEN XT valve in inoperable patients, while Cohort A compared the SAPIEN XT valve with SAVR in intermediate and high surgical risk patients.[73] Alongside study of SAPIEN XT valve, the PARTNER II Trial included a study of Edwards’ newest device, the SAPIEN 3 valve,[43,74] a prospective, non-randomized cohort of inoperable and high surgical risk patients (PARTNER II S3HR),[41,43] and intermediate surgical risk patients (PARTNER II S3i).[43,65] Accordingly, because of the ethical issues associated with randomizing patients to a less efficacious treatment, and to avoid delays in patient access, outcomes from

the PARTNER II S3i study were tested for non-inferiority against historical controls using propensity score analysis.[65] Patients in the PARTNER II S3HR and S3i studies were followed for 1 year, and results for both the SAPIEN XT valve and SAPIEN 3 valves became available at the same time.

Clinical Study Results: Randomized-Controlled & Single-Arm Trials

Inoperable Patients: TAVR vs. Medical Management

As highlighted above, the efficacy and safety of TAVR in inoperable patients with AS have been evaluated in the following clinical studies: the PARTNER B pivotal trial (SAPIEN valve vs. medical management), a study of pooled PARTNER A and B RCT data versus NRCA data (SAPIEN valve), the PARTNER IIB RCT (SAPIEN valve vs. SAPIEN XT valve), the PARTNER II S3HR study (SAPIEN 3 valve), and the non-randomized single-arm CoreValve US Extreme Risk Trial (CoreValve).[13,22,38,41,43,54,55,68,75-77]* The results of these studies are summarized below, with follow-up durations ranging from 30 days to 5 years.

Efficacy

Survival: TAVR with the Edwards SAPIEN valves provides a significant survival benefit compared with medical management to inoperable patients with AS (**Table 2.2**).[22,54,55] In the PARTNER B RCT, SAPIEN valve was associated with significantly prolonged survival (lower all-cause mortality) compared with medical management starting at 1-year follow-up.[22,54,55] Survival remained significantly higher with SAPIEN valve throughout 5 years of follow-up. Median survival was 29.7 months in the SAPIEN valve arm and 11.1 months in the medical management arm (p [log rank] <0.0001), reflecting an 18.6-month extension with SAPIEN valve.[55] Importantly, cardiovascular mortality was also significantly reduced in TAVR patients compared with medically managed patients at 1 year (19.6% vs. 41.9%, respectively; p<0.001) and 5 years (57.5% vs. 85.9%; p<0.0001).[22,55]

Table 2.2: Survival of inoperable patients with AS treated with TAVR or medical management

	Survival					
	30 days	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**
***PARTNER B Randomized Cohort*[22,54,55]**						
SAPIEN valve	95%	69.3%	57.0%	45.9%	35.9%	28.2%
Medical Management	97.2%	49.2%	32.0%	19.1%	12.5%	6.4%
p-value	0.41	<0.001	HR (95%CI)=0.50 (0.39-0.65), p(log rank)<0.0001			
***PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts*[38a]**						

* The CoreValve US Extreme Risk Trial used an objective performance goal as a control, as well as data from prospective or retrospective comparative studies.

SAPIEN valve (TF-TAVR) NRCA	95.7%	81%	-	-	-	-
SAPIEN valve (TF-TAVR) Pooled PARTNER A & B RCTs	95.2%	74.7%	-	-	-	-
p-value	0.68	0.009	-	-	-	-
PARTNER IIB Randomized Cohort[73,78]						
SAPIEN valve	94.9%	76.7%	65.1%	-		
SAPIEN XT valve	96.5%	77.7%	63.5%	-		
p-value	HR (95%CI) = 0.93 (0.66-1.33), p(log rank) = 0.706					
PARTNER II S3HR: Inoperable Cohort[41,43]						
SAPIEN 3 valve	97.8%[a]	82.3%	-	-	-	-
TF	98.4%[a]	84.3%	-	-	-	-
CoreValve US Extreme Risk Trial (non-randomized, single-arm study)[68,69,75-77]						
CoreValve	91.6%	75.7%	63.4%	-	-	-

[a] Pooled data for inoperable and high surgical risk patients; individual results not reported.

Key: AS = aortic stenosis, CI = confidence interval, HR = hazard ratio, NRCA = non-randomized continued access, TAVR = transcatheter aortic valve replacement, US = United States.

In the PARTNER IIB Trial, the SAPIEN XT valve was associated with comparable survival to that of SAPIEN valve at 30-day, 1-year, and 2-year follow-up in inoperable patients with AS (**Table 2.2**).[73,78] In addition, SAPIEN XT valve expanded the eligible treatment population by offering a 29 mm valve size to patients who were previously excluded from the PARTNER Trials because of a large annulus size.[57] Further, the SAPIEN XT valve showed better survival than the SAPIEN valve from the original PARTNER B Trial at 1 year and 2 years (**Table 2.2**).

In the inoperable cohort of the PARTNER II S3HR Trial, SAPIEN 3 valve was associated with a high survival rate (82.3%) at 1-year follow-up; an even higher rate was observed in the TF arm (84.3%; **Table 2.2**).[41] As shown in **Figure 2.3**, evolution of the SAPIEN valve platform has led to steady improvement of survival at 30-day and 1-year follow-up.

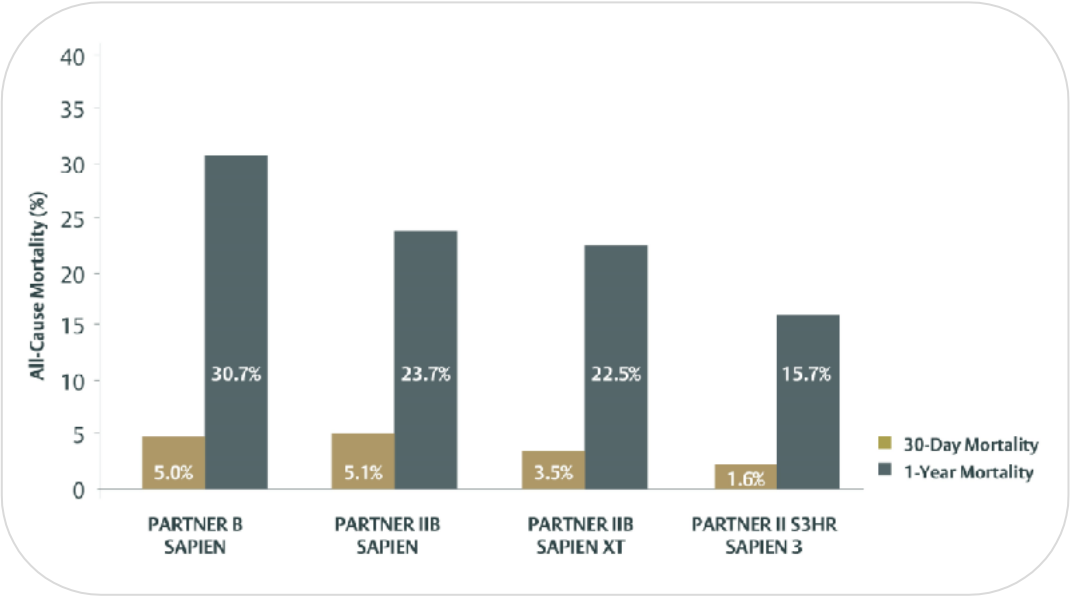

Figure 2.3: All-cause mortality in inoperable patients with AS after TAVR with SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valve, transfemoral approach.

Note: 30-day data from PARTNER II S3HR represent pooled data for inoperable and high-risk patients.
Key: AS = aortic stenosis, CI = confidence interval, HR = hazard ratio, TAVR = transcatheter aortic valve replacement.

Source: Leon et al., 2010[22]; Leon et al., 2013[73]; Kodali et al., 2016[43]; Herrmann et al., 2016[41]; Webb et al., 2015.[78]

Overall, the high mortality rate observed in medically managed patients in the PARTNER B Trial (at 1 year and beyond) underscores the dismal prognosis of patients with AS who are inoperable and do not receive valve replacement. The SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valves provide significant and durable improvement of survival in this population.

Safety

Major Stroke: Results from the PARTNER B RCT of inoperable patients with AS showed that rates of major or disabling stroke did not differ significantly between SAPIEN valve and medical management, but trended higher with SAPIEN valve at both 30 days (5.0% vs. 1.1%, respectively; p=0.06) and 1 year (7.8% vs. 3.9%,

p=0.18) (**Table 2.3**). In the inoperable cohort of the PARTNER II S3HR Trial, the rate of major stroke was low, at 1.3% at 1-year follow-up.[41]

Table 2.3: Rates of major stroke in inoperable patients with AS treated with TAVR or medical management

	Rates of Major Stroke	
	30 days	**1 year**
PARTNER B Randomized Cohort[22,54,55]		
SAPIEN valve	5.0%	7.8%
Medical Management	1.1%	3.9%
p-value	0.06	0.18
PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts[38a]		
SAPIEN valve (TF-TAVR) NRCA	2.4%	3.6%
SAPIEN valve (TF-TAVR) Pooled PARTNER A & B RCTs	3.6%	5.3%
p-value	0.20	0.14
PARTNER IIB Randomized Cohort[73,78]		
SAPIEN valve	3.0%	5.5%
SAPIEN XT valve	3.2%	4.8%
p-value	0.85	0.76
PARTNER II S3HR: Inoperable Cohort [41,43]		
SAPIEN 3 valve	0.9%[a]	1.3%
TF	0.8%[a]	-
CoreValve US Extreme Risk Trial (non-randomized, single-arm study)[68,69,75-77]		
CoreValve	2.3%	4.3%
[a] Pooled data for inoperable and high surgical risk patients; individual results not reported.		

	Rates of Major Stroke	
	30 days	**1 year**
Key: CI = confidence interval, HR = hazard ratio, NRCA = non-randomized continued access, TAVR = transcatheter aortic valve replacement, US = United States.		

In the PARTNER IIB Trial, rates of major stroke were similar between the SAPIEN valve and SAPIEN XT valves at 30 days and 1 year[73], and were lower with both valves than with SAPIEN valve in the PARTNER B Trial (**Table 2.3**, **Figure 2.4**). Notably, rates of major stroke were also considerably lower with SAPIEN 3 valve than with SAPIEN valve and SAPIEN XT valve, as reported in the PARTNER B,[22] PARTNER IIB,[73] and PARTNER II S3HR[41] Trials (**Table 2.3**, **Figure 2.4**).

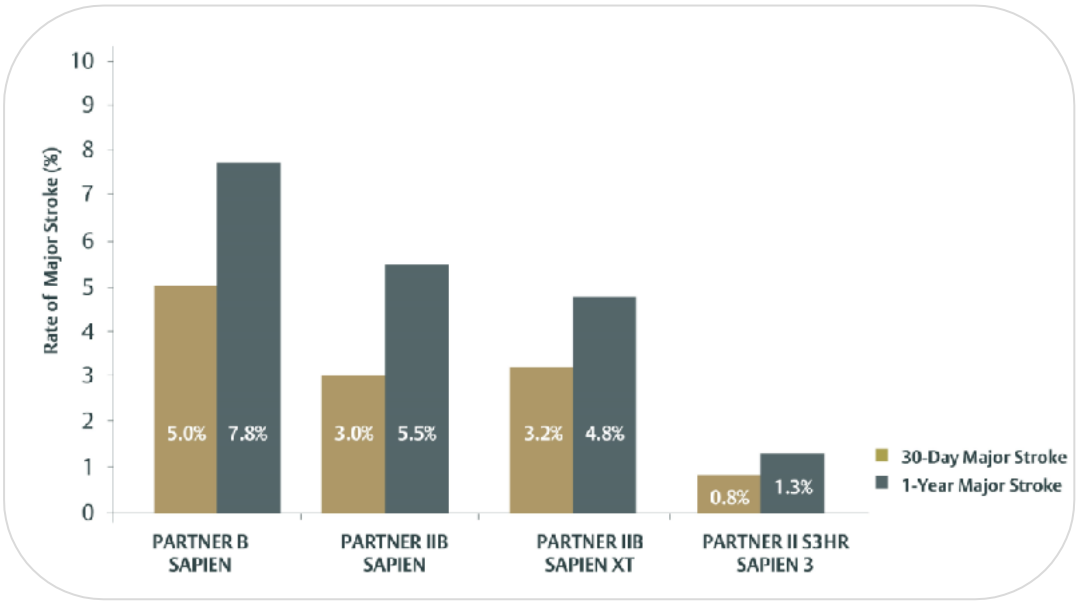

Figure 2.4: Comparison of major stroke rates at 30 days and 1 year with SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valve in inoperable patients with AS, transfemoral approach.

Note: 30-day results for PARTNER II S3HR are from a pooled population of inoperable and high surgical risk patients.

Key: AS = aortic stenosis, RCT = randomized controlled trial, THV = transcatheter heart valve.

Source: Leon et al., 2010[22]; Leon et al., 2013[73]; Kodali et al., 2016[43]; Herrmann et al., 2016.[41]

Moderate-to-Severe AR: In the PARTNER B RCT of inoperable patients with AS, the rate of moderate-to-severe AR was 11.8% at 30 days after implantation of SAPIEN valve and generally decreased over time (**Table 2.4**).[22,79] The incidence of transvalvular AR, an AE typically experienced by patients who are medically managed, was lower in SAPIEN valve patients than in medically managed patients at 30 days (1.3% vs. 16.9%, respectively) and 1 year (4.2% vs. 15.2%).[22] Comparison of the pooled PARTNER A and B RCT cohort with the NRCA cohort showed similar rates of moderate-to-severe AR at 30-day follow-up.[38] Further, in the PARTNER IIB Trial, similar rates of moderate-to-severe AR were reported for patients

randomized to SAPIEN valve or SAPIEN XT valve at 30 days and 1 year.[73] This outcome was not reported in the PARTNER II 3HR study.

Table 2.4: Rates of moderate-to-severe AR[a] in inoperable patients with AS treated with TAVR

	Rates of Moderate-to-Severe AR	
	30 days	**1 year**
***PARTNER B Randomized Cohort*[22,54,60]**		
SAPIEN valve	11.8%	8.7%
p-value	-	-
***PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts*[38b]**		
SAPIEN valve (TF-TAVR) NRCA	11.3%	-
SAPIEN valve (TF-TAVR) Pooled PARTNER A & B RCTs	10.8%	-
p-value	0.78	-
***PARTNER IIB Randomized Cohort*[73,78]**		
SAPIEN valve	17.1%	21.1%
SAPIEN XT valve	24.2%	27.5%
p-value	NR	NR
***PARTNER II S3HR: Inoperable Cohort*[41,43]**		
SAPIEN 3 valve	NR	NR
***CoreValve US Extreme Risk Trial (non-randomized, single-arm study)*[68,69,75-77]**		
CoreValve	10.9%	4.3%

[a] Paravalvular AR unless otherwise indicated.

[b] Pooled data for inoperable and high surgical risk patients; individual results not reported.

Key: AR = aortic regurgitation, AS = aortic stenosis, NR = not reported, NRCA = non-randomized continued access, TAVR = transcatheter aortic valve replacement.

New-onset AF: Conduction abnormalities such as AF can occur after prosthetic AVR procedures.[80] However, in the PARTNER B study of inoperable patients, the rate of new-onset AF was similar in the SAPIEN valve and medical management groups at 30 days (0.6% vs. 1.1%, respectively; p=1.00) and 1 year (0.6% vs. 1.7%, p=0.62).[22] The occurrence of this outcome is not well reported in other studies of TAVR.

Major Vascular Complications: In inoperable patients with AS in the PARTNER B Trial, implantation of SAPIEN valve was associated with significantly higher rates of major vascular complications than medical management at 30 days through 3 years of follow-up (**Table 2.5**).[22] However, significantly fewer TF-TAVR patients in the NRCA cohort experienced major vascular complications than in the pooled PARTNER A and B RCTs cohort at 30 days through 1 year of follow-up.[38] Introduction of the SAPIEN XT valve and a new delivery system significantly reduced the rate of major vascular complications compared with SAPIEN valve at 30 days and 1 year, as shown by the results of the PARTNER IIB Trial.[73] Rates of major vascular complications were even lower with the introduction of SAPIEN 3 valve at 30-day follow-up as reported in a pool of inoperable and high-risk patients in the PARTNER II S3HR Trial.[43]

Table 2.5: Rates of major vascular complications in inoperable patients with AS treated with TAVR or medical management

	Rates of Major Vascular Complications	
	30 days	**1 year**
PARTNER B Randomized Cohort[22,54,81]		
SAPIEN valve	16.2%	16.8%
Medical Management	1.1%	2.2%
p-value	≤0.001	<0.001
PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohort[38a]		
SAPIEN valve (TF-TAVR) NRCA	8.0%	8.4%
SAPIEN valve (TF-TAVR) RCT Pooled PARTNER A & B RCTs	15.7%	15.7%
p-value	<0.0001	<0.0001
PARTNER IIB Randomized Cohort[73,78]		
SAPIEN valve	15.2%	16.1%
SAPIEN XT valve	9.5%	10.3%

p-value	0.04	0.04
PARTNER II S3HR: Inoperable[43]		
SAPIEN 3 valve	5.1%[a]	-
TF	5.5%[a]	-
CoreValve US Extreme Risk Trial (non-randomized, single-arm study)[68,69,75,77]		
CoreValve	-	8.4%
[a] Pooled data for inoperable and high surgical risk patients; individual results not reported. Key: AS = aortic stenosis, RCT = randomized controlled trial, TAVR = transcatheter aortic valve replacement, US = United States.		

High Surgical Risk Patients: TAVR vs. SAVR

The efficacy and safety of TAVR in high surgical risk patients with AS have been evaluated in the following clinical studies/patient groups: the PARTNER A RCT (SAPIEN valve vs. SAVR), the PARTNER A NRCA cohort (SAPIEN valve), a pre-marketing approval (PMA) cohort (SAPIEN valve), the PARTNER IIA S3HR study (SAPIEN 3 valve), the single-arm SAPIEN 3 valve CE Mark Trial, and the CoreValve US Pivotal High Risk Trial (CoreValve vs. SAVR).[38,41,43,56,62,67,82] Results from these studies/groups are summarized below, with follow-up durations ranging from 30 days to 5 years.

Efficacy

Survival: Evidence from several clinical studies indicates that TAVR provides similar or improved survival compared with SAVR in high surgical risk patients with AS. For example, at 30 days through 5 years of follow-up in the PARTNER A landmark RCT, survival rates were comparable for patients randomized to the SAPIEN valve or SAVR (**Table 2.6**).[36,53,56] Median survival was longer in the TAVR group (44.5 months; IQR 13.7, 63.7) than in the SAVR group (40.6 months; IQR 10.1-not assessable; p=0.76).[56]

Table 2.6: Survival rates in high surgical risk patients with AS treated with TAVR or SAVR

	Survival Rates			
	30 days	**1 year**	**2 years**	**5 years**
PARTNER A Randomized Cohort[36,53,56]				
SAPIEN valve (TAVR)	96.6%	75.8%	66.7%	32.2%
SAVR	93.5%	73.2%	65%	37.6%
p-value	HR=1.04, 95% CI 0.86-1.24, p=0.76			

	Survival Rates			
	30 days	**1 year**	**2 years**	**5 years**
PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts[38]				
SAPIEN valve (TF-TAVR) NRCA	95.7%	81.0%	-	-
SAPIEN valve (TF-TAVR) RCT (PARTNER A & B Pooled)	95.2%	74.7%	-	-
p-value	0.68	0.009	-	-
PARTNER A NRCA vs. PMA Transapical TAVR[62]				
SAPIEN valve (TA-TAVR) NRCA	91.2%	77.9%	-	-
SAPIEN valve (TA-TAVR) PMA	89.4%	71.0%	-	-
SAVR	88.0%	74.7%	-	-
p-value	0.54	0.27	-	-
PARTNER II S3HR Trial: High-risk Cohort[41,43]				
SAPIEN 3 valve	97.8%[a]	87.3%	-	-
TF	98.4%[a]	89.3%	-	-
SAPIEN 3 valve CE Mark Trial[66,67]				
SAPIEN 3 valve (TF)	97.9%	91.6%	-	-
CoreValve US Pivotal High-risk Trial[70,82]				
CoreValve (all)	-	85.9%	77.8%	-
SAVR (all)	-	81.1%	71.4%	-
p-value	-	1- and 2-yr: log-rank p=0.04		-

[a] Pooled data for inoperable and high surgical risk patients; individual results not reported.

Key: AS = aortic stenosis, NRCA = non-randomized continued access, PMA = post-marketing approval, RCT = randomized controlled trial, SAVR = surgical aortic valve replacement, TA = transapical, TAVR = transcatheter aortic valve replacement, TF = transfemoral.

Additional data show that the survival of high surgical risk patients improved considerably with the introduction of the SAPIEN 3 valve (**Table 2.6**; **Figure 2.5**): the PARTNER II S3HR Trial of high surgical risk and inoperable patients had the highest reported 30-day survival rate in a study of TAVR.[43] In the full cohort of patients who received the SAPIEN 3 valve, survival in as-treated patients was 97.8% and freedom from cardiovascular mortality was 98.6% at 30 days; at 1 year, survival was 85.6%.[41,43] When stratified by delivery routes, TF delivery was associated with a survival rate of 98.4% and freedom from cardiovascular mortality was 99.0% at 30 days; transapical/transaortic delivery was associated with rates of 94.6% and 96.7% for these outcomes, respectively.[41,43] Similarly, survival in the as-treated TF patient group in the SAPIEN 3 valve CE Mark Trial was also higher than that in the PARTNER A Trial at 30 days (97.9%) and 1 year (91.6%) (**Table 2.6**; **Figure 2.5**).[66,67]

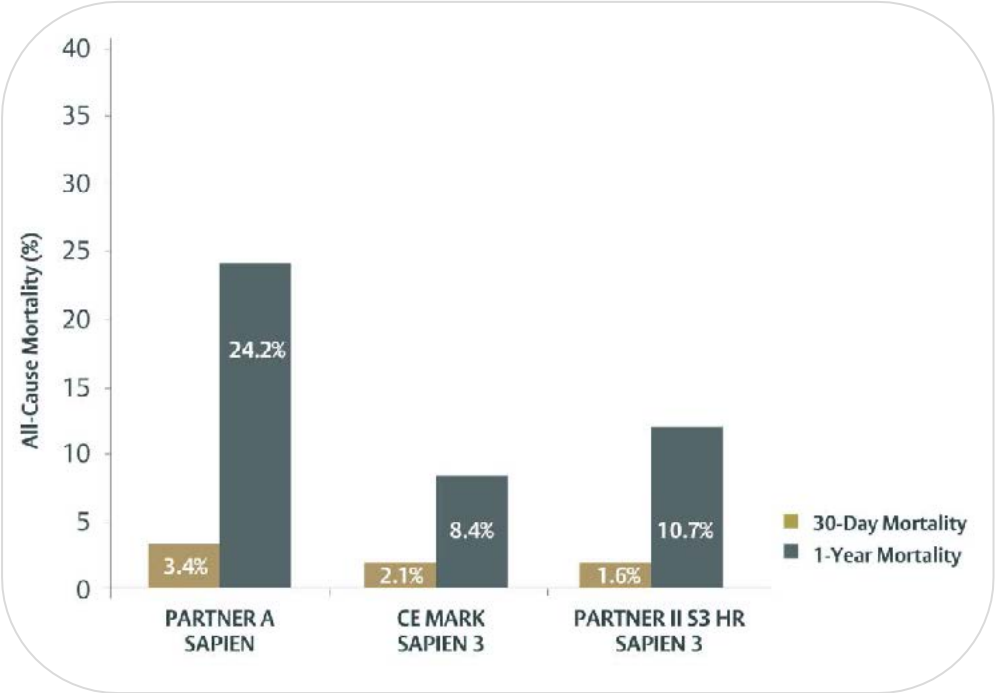

Figure 2.5: Reduction of all-cause mortality at 30 days and 1 year with the introduction of next-generation SAPIEN valve devices in high surgical risk patients with AS, transfemoral approach.

Note: 30-day results for PARTNER II S3HR are from a pooled inoperable and high-risk patient population.

Key: AS = aortic stenosis, RCT = randomized controlled trial, THV = transcatheter heart valve.

Sources: Smith et al., 2011[36]; Webb et al., 2014[67]; Webb et al., 2015[66]; Kodali et al., 2016[43]; Herrmann et al., 2016.[41]

Safety

Major Stroke: In the PARTNER A Trial of high surgical risk patients with AS, rates of major stroke were similar between the SAPIEN valve and SAVR groups at 30 days (3.8% vs. 2.1%, respectively, p=0.20) (**Table 2.7**); at 1 year, there was a trend towards a higher rate with SAPIEN valve (5.1% vs. 2.4% with SAVR; p=0.07).[36] In the comparison of PARTNER NRCA and pooled PARTNER A & B RCT data, rates of major stroke in SAPIEN valve-TF patients were similar between groups at 30 days (2.4% vs. 3.6%, respectively; p=0.20) and 1 year (3.6% vs. 5.3%, p=0.14) (**Table 2.7**).[38]

Table 2.7: Rates of major stroke in high surgical risk patients with AS treated with TAVR or SAVR

	Rates of Major Stroke	
	30 days	**1 year**
PARTNER A Randomized Cohort[36,53,56]		
SAPIEN valve (TAVR)	3.8%	5.1%
SAVR	2.1%	2.4%
p-value	0.20	0.07
PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts[38]		
SAPIEN valve (TF-TAVR) NRCA	2.4%	3.6%
SAPIEN valve (TF-TAVR) RCT (PARTNER A & B Pooled)	3.6%	5.3%
p-value	0.20	0.14
PARTNER II S3HR: High-risk Cohort[41,43]		
SAPIEN 3 valve (TAVR)	0.9%[c]	3.0%
TF-TAVR	0.8%[c]	-
SAPIEN 3 valve CE Mark Trial[66,67]		
SAPIEN 3 valve (TF-TAVR)	0%	1.1%
CoreValve US Pivotal High-Risk Trial[70,82]		
CoreValve	3.9%	5.8%
SAVR	3.1%	6.9%
p-value	-	-

[a] Paired comparison between NRCA and PMA (TA).

[b] Paired comparison between NRCA and SAVR (TA).

[c] Pooled data for inoperable and high surgical risk patients; individual results not reported.

Key: AS = aortic stenosis, NRCA = non-randomized continued access, PMA = post-market approval, SAVR = surgical aortic valve replacement, TA = transapical, TF = transfemoral, TAVR = transcatheter aortic valve replacement, US = United States.

As observed for survival, advancements in TAVR technology led to a decrease in rates of stroke in high surgical risk patients with AS. In the PARTNER II S3HR Trial, rates of major stroke in high surgical risk and inoperable patients who received SAPIEN 3 valve were 0.9% at 30 days and 3% at 1 year.[41,43] These rates are lower than those observed with SAPIEN valve in the PARTNER A Trial (**Table 2.7**, **Figure 2.6**).[36,66,67] Similarly, in the SAPIEN 3 valve CE Mark Trial, patients who received SAPIEN 3 valve-TF had no occurrences of major stroke at 30 days and rates remained low at 1 year (1.1%).[66,67]

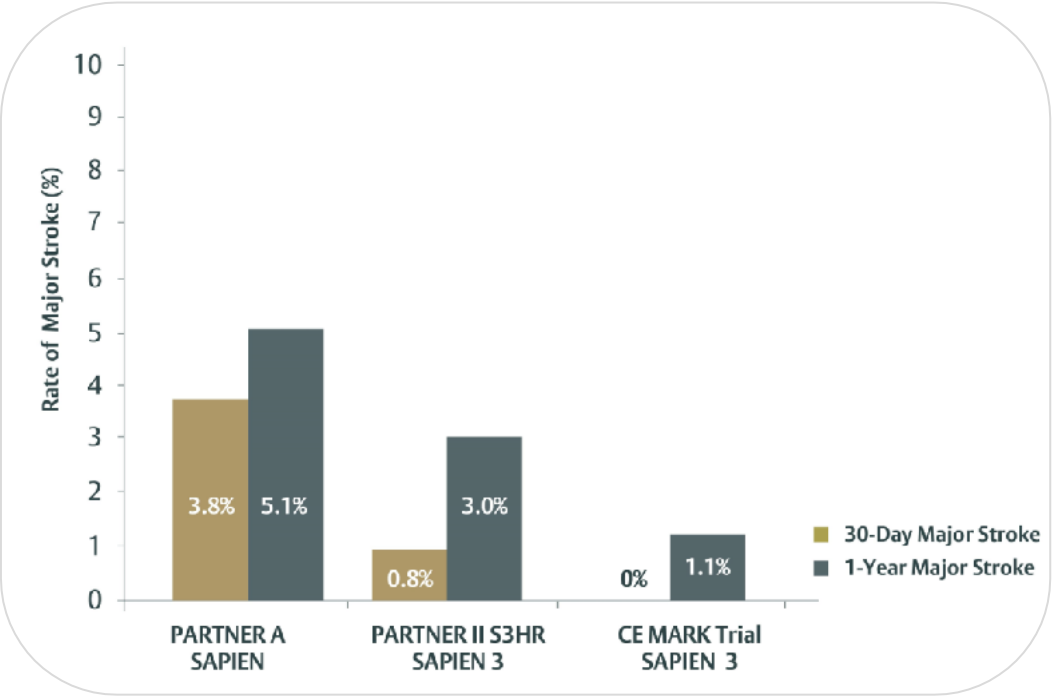

Figure 2.6: Comparison of major stroke rates at 30 days and 1 year with SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valve in high surgical risk patients with AS, transfemoral approach.

Note: 30-day results for PARTNER II S3HR are from a pooled population of inoperable and high surgical risk patients.

Key: AS = aortic stenosis, RCT = randomized controlled trial, THV = transcatheter heart valve.

Sources: Smith et al., 2011[36]; Kodali et al., 2016[43]; Herrmann et al., 2016[20]; Webb et al., 2014[67]; Webb et al., 2015.[66]

Moderate-to-severe AR: Rates of moderate-to-severe AR in high surgical risk patients with AS have also improved with the introduction of next-generation TAVR devices. In the PARTNER A Trial, the risk of this AE was significantly higher in the SAPIEN valve group than in the SAVR group between 30 days and 2 years (**Table 2.8**).[36,53,56] These elevated rates were attributed, in part, to the design of this first-generation device, as well as imaging practices and limitations in valve size.[36,37,53,56]

Introduction of the SAPIEN 3 valve has resulted in lower rates of moderate-to-severe AR. In the PARTNER II S3HR Trial, the rate of this AE was 1.2% at 1 year after implantation of SAPIEN 3 valve (**Table 2.8**).[43]

Table 2.8: Rates of moderate-to-severe AR in high surgical risk patients with AS treated with TAVR or SAVR

	Rates of Moderate-to-severe AR	
	30 days	**1 year**
PARTNER A Randomized Cohort[36,53,56]		
SAPIEN valve (TAVR)	12.2%	7.0%
SAVR	0.9%	1.9%
p-value	<0.001	<0.001
PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts[38]		
SAPIEN valve (TF-TAVR) NRCA	11.3%	-
SAPIEN valve (TF-TAVR) RCT (PARTNER A & B Pooled)	10.8%	-
p-value	0.78	-
PARTNER II S3HR: High-risk Cohort[41,43]		
SAPIEN 3 valve (TAVR)	NR[a]	1.2%[b]
SAPIEN 3 valve CE Mark Trial[66]		
SAPIEN 3 valve (TAVR)	3.4%	2.0%
CoreValve US Pivotal High Risk Trial[70,71]		
CoreValve[c] (TAVR)	9.0%	6.1%
SAVR[c]	1.0%	0.5%
p-value	<0.001	<0.001

[a] Kodali reports 6.5% for pooled population of inoperable and high and intermediate surgical risk patients.

[b] Pooled data for inoperable and high surgical risk patients; individual results not reported.

[c] Rates for paravalvular AR.

Key: AR = aortic regurgitation, AS = aortic stenosis, NRCA = non-randomized continued access, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement, US = United States.

New-onset AF: In the PARTNER A Trial, new-onset AF was significantly less frequent in patients who received SAPIEN valve than in those who underwent SAVR at 30 days; however, rates of this AE did not differ significantly between groups at 1 year (**Table 2.9**).[36,53,56] The SAPIEN 3 valve CE Mark Trial showed that patients who received SAPIEN 3 valve via TF access had rates of new-onset AF that were lower but still similar to those in the PARTNER A RCT at both 30 days and 1 year.[66,67]

Table 2.9: Rates of new-onset AF in high surgical risk patients treated with TAVR or SAVR

	Rates of New-onset AF	
	30 days	**1 year**
PARTNER A Randomized Cohort[36,53,56]		
SAPIEN valve (TAVR)	8.6%	12.1%
SAVR	16%	17.1%
p-value	0.006	0.07
SAPIEN 3 valve CE Mark Trial[66,67]		
SAPIEN 3 valve (TF-TAVR)	7.3%	7.3%
SAPIEN 3 valve (TA-TAVR)	20.7%	23%
CoreValve US Pivotal High Risk Trial[70,71]		
CoreValve (TAVR)	11.7%	15.9%
SAVR	30.5%	32.7%
p-value	<0.001	<0.001

Note: the NRCA cohort and the S3HR do not reported new-onset AF.
Key: AS = aortic stenosis, NRCA = non-randomized continued access, SAVR = surgical aortic valve replacement, TA = transapical, TAVR = transcatheter aortic valve replacement, TF = transfemoral, US = United States.

Major Vascular Complications: In the PARTNER A Trial, patients in the SAPIEN valve group experienced significantly higher rates of major vascular complications than those in the SAVR group at 30 days and through 5 years (**Table 2.10**).[36,53,56] Further, comparison of the PARTNER NRCA and pooled PARTNER A and B RCT cohorts revealed that significantly fewer SAPIEN valve-TF patients in the NRCA cohort experienced major vascular complications than in the RCT cohort at both 30 days and 1 year (**Table 2.10**).[38]

Further reduction of major vascular complications was observed with the introduction of SAPIEN 3 valve. In the PARTNER II S3HR and SAPIEN 3 valve CE Mark Trials, 30-day rates of this AE were lower than those in the PARTNER RCT and in its cohorts, including in a TA subgroup (**Table 2.10**).[67,85]

Table 2.10: Rates of major vascular complications in high surgical risk patients treated with TAVR or SAVR

	Rates of Major Vascular Complications	
	30 days	**1 year**
***PARTNER A Randomized Cohort*[36,53,56]**		
SAPIEN valve (TAVR)	11%	11.3%
SAVR	3.2%	3.8%
p-value	<0.001	0.0002
***PARTNER NRCA vs. Pooled PARTNER A & B RCT Cohorts*[38]**		
SAPIEN valve (TF-TAVR) NRCA	8.0%	8.4%
SAPIEN valve (TF-TAVR) RCT (PARTNER A & B Pooled)	15.7%	15.7%
p-value	<0.0001	<0.0001
***PARTNER II S3HR: High-risk Cohort*[85]**		
SAPIEN 3 valve (TAVR-all)	5.1%[a]	-
TF-TAVR	5.5%[a]	-
***SAPIEN 3 valve CE Mark Trial*[67]**		
SAPIEN 3 valve (TAVR-all)	5.3%	-
TF-TAVR	4.2%	-

***CoreValve US Pivotal High Risk Trial*[70,71]**		
CoreValve (TAVR)	5.9%	6.2%
SAVR	1.7%	2.0%
p-value	0.003	0.004

[a] Pooled data for inoperable and high surgical risk patients; individual results not reported.

Key: AS = aortic stenosis, NRCA = non-randomized continued access, RCT = randomized controlled trial, SAVR = surgical aortic valve replacement, TA = transapical, TAVR = transcatheter aortic valve replacement, TF = transfemoral, US = United States.

Intermediate Surgical Risk Patients: TAVR vs. SAVR

The efficacy and safety of TAVR in intermediate surgical risk patients have been evaluated in the PARTNER IIA Trial (SAPIEN XT valve vs. SAVR) and the PARTNER II S3i Trial (SAPIEN 3 valve).[43,74] Outcomes with the SAPIEN 3 valve were also compared in a propensity score analysis of TF-TAVR outcomes from the PARTNER II S3i Trial versus outcomes with SAVR in the PARTNER IIA Trial.[65] Results in intermediate surgical risk patients are also available for the CoreValve in the SURTAVI study.[45]

Efficacy

Survival: Throughout two years of follow-up PARTNER IIA Trial, survival was slightly higher in patients who received the SAPIEN XT valve compared with patients who underwent SAVR (**Table 2.11**).[74] This finding was consistent across all study cohorts (e.g., overall, TF, and transthoracic)

Table 2.11: Survival in intermediate surgical risk patients with severe symptomatic AS treated with TAVR or SAVR

	Survival Rates		
	30 days	**1 year**	**2 years**
PARTNER IIA Trial[74a]			
SAPIEN XT valve (TAVR-all)	96.1%	87.7%	83.3%
TF-TAVR	97.0%	90.0%	85.8%
SAVR (all)	95.9%	87.1%	82.0%
TF cohort	95.9%	87.7%	82.8%
p-value for “all” comparison (TF)	0.78 (0.24)	0.69 (0.17)	0.45 (0.11)
PARTNER II S3i Trial[43]			
SAPIEN 3 valve (TAVR-all)	98.9% (95% CI: 0.5-1.7)	-	-
TF-TAVR	98.9% (95% CI: 0.4-1.7)	-	-
PARTNER II S3i Propensity Score Analysis[65b]			
SAPIEN 3 valve (TAVR-all)	98.9%	92.6%	-
SAVR	96.0%	87%	-

	Survival Rates		
	30 days	**1 year**	**2 years**
SURTAVI Trial[45] (mortality rate in brackets)			
CoreValve (TAVR)	97.8% (2.2%)	93.3% (6.7%)	88.6% (11.4%)
SAVR	98.3% (1.7%)	93.2% (6.8%)	88.4% (11.6%)
95% credible interval for mortality rate	-0.9 to 1.8	-2.7 to 2.4	-3.8 to 3.3

[a] Transthoracic data are available but were omitted for brevity.

[b] Propensity matching analysis; cumulative KM estimates.
Key: TF = transfemoral, KM = Kaplan–Meier, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.

In the TF-access patient subgroup, the incidence of the primary composite endpoint of all-cause mortality or disabling stroke was significantly lower in patients who received SAPIEN XT valve than in those who received SAVR at 30 days (4.9% vs. 7.7%, respectively; p<0.05) and at 1 year (12.3% vs. 15.9%, p<0.05). At 2 years, the incidence of this outcome was comparable between treatment groups (16.8% vs. 20.4%, p=0.07). The occurrence of all-cause mortality or disabling stroke was also comparable between the SAPIEN XT valve and SAVR groups overall (19.3% vs. 21.1%, p=0.25) and in the transthoracic-access subgroups (27.7% vs. 23.4%, p=0.29) at 2 years, as well as at earlier 30-day and 1-year time points (p>0.05 for both comparisons).

In the propensity score analysis of PARTNER II data, all-cause mortality rates were lower with the SAPIEN 3 valve than with SAVR (**Table 2.11**).[65] Notably, survival rates were also higher with SAPIEN 3 valve in the S3i study than with SAPIEN XT valve in the PARTNER IIA Trial.[43,65,74]

Safety

Major Stroke: At 30 days in the PARTNER IIA Trial, the rate of major/disabling stroke was significantly lower in the SAPIEN XT valve (TF-TAVR) group than in the SAVR group (TF cohort; 2.3% vs. 4.2%; p=0.04).[74] After this time point, rates of major stroke were generally comparable between groups. In the PARTNER II S3i propensity score analysis, the rate of major/disabling stroke with SAPIEN 3 valve was lower than that with SAVR and was also lower than that observed with SAPIEN XT valve in the PARTNER IIA Trial.[65]

	Rate of Major/Disabling Stroke	
	30 days	**1 year**
PARTNER IIA Trial[74]		
SAPIEN XT valve (TAVR-all)	3.2%	5.0%
TF-TAVR	2.3%	4.3%
SAVR (all)	4.3%	5.8%
TF cohort	4.2%	6.0%
p-value for "all" comparison (TF)	0.20 (0.04)	0.46 (0.13)
PARTNER II S3i Trial[43]		
SAPIEN 3 valve (TAVR-all)	1.0 (95% CI: 0.4-1.6)	-
TF-TAVR	0.7 (95% CI: 0.2-1.3)	-
PARTNER II S3i Propensity Score Analysis[65]		
SAPIEN 3 valve (TAVR-all)	1.0%	2.3%
SAVR	4.4%	5.9%
SURTAVI Trial[45]		
CoreValve (TAVR)	1.2%	2.2%
SAVR	2.5%	3.6%
95% credible interval	-2.6 to 0.1	-3.1 to 0.4
Key: AS = aortic stenosis, CI = confidence interval, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

	Rate of Major/Disabling Stroke	
	30 days	**1 year**
PARTNER IIA Trial[74]		
SAPIEN XT valve (TAVR-all)	3.2%	5.0%
TF-TAVR	2.3%	4.3%
SAVR (all)	4.3%	5.8%
TF cohort	4.2%	6.0%
p-value for “all” comparison (TF)	0.20 (0.04)	0.46 (0.13)
PARTNER II S3i Trial[43]		
SAPIEN 3 valve (TAVR-all)	1.0 (95% CI: 0.4-1.6)	-
TF-TAVR	0.7 (95% CI: 0.2-1.3)	-
PARTNER II S3i Propensity Score Analysis[65]		
SAPIEN 3 valve (TAVR-all)	1.0%	2.3%
SAVR	4.4%	5.9%
SURTAVI Trial[45]		
CoreValve (TAVR)	1.2%	2.2%
SAVR	2.5%	3.6%
95% credible interval	-2.6 to 0.1	-3.1 to 0.4
Key: AS = aortic stenosis, CI = confidence interval, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Table 2.12: Rates of major/disabling stroke in studies of intermediate surgical risk patients with AS treated with TAVR or SAVR

	Rate of Major/Disabling Stroke	
	30 days	**1 year**
PARTNER IIA Trial[74]		
SAPIEN XT valve (TAVR-all)	3.2%	5.0%
TF-TAVR	2.3%	4.3%
SAVR (all)	4.3%	5.8%
TF cohort	4.2%	6.0%
p-value for "all" comparison (TF)	0.20 (0.04)	0.46 (0.13)
PARTNER II S3i Trial[43]		
SAPIEN 3 valve (TAVR-all)	1.0 (95% CI: 0.4-1.6)	-
TF-TAVR	0.7 (95% CI: 0.2-1.3)	-
PARTNER II S3i Propensity Score Analysis[65]		
SAPIEN 3 valve (TAVR-all)	1.0%	2.3%
SAVR	4.4%	5.9%
SURTAVI Trial[45]		
CoreValve (TAVR)	1.2%	2.2%
SAVR	2.5%	3.6%
95% credible interval	-2.6 to 0.1	-3.1 to 0.4
Key: AS = aortic stenosis, CI = confidence interval, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Moderate-to-Severe AR: In the PARTNER IIA Trial and the PARTNER II S3i propensity score analysis, comparison of the SAPIEN XT valve and SAPIEN 3 valves with SAVR suggested that rates of moderate-to-severe AR are similar between treatment groups and SAPIEN valve types across all follow-up periods (**Table 2.13**).[65,74]

Table 2.13: Rates of moderate-to-severe AR in studies of intermediate surgical risk patients with AS treated with TAVR or SAVR

	Rate of Moderate-to-Severe AR	
	30 days	**1 year**
PARTNER IIA Trial[74][a]		
SAPIEN XT valve (TAVR-all)	0.5%	0.5%
SAVR (all)	0.1%	0.0%
p-value	NR	NR
PARTNER II S3i Propensity Score Analysis[65]		
SAPIEN 3 valve (TAVR-all)	-	1.5%[a]
SAVR	-	NR
SURTAVI Trial[45][b]		
CoreValve (TAVR)	-	5.3%
SAVR	-	0.6%
95% credible interval	-	2.8 to 6.8

[a]Results from the valve implanted (non-ITT) population.

Key: AS = aortic stenosis, ITT = intention to treat, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.

New-onset AF: At 30 days in the PARTNER IIA Trial, the risk of new-onset AF was significantly lower with SAPIEN XT valve than with SAVR in both the overall cohort (9.1% vs. 26.4%, respectively; p<0.001) and in the TF cohort (4.9% vs. 26.7%, p<0.001) (

Table 2.14).[74] This significant difference was observed through 2 years of follow-up. Similar results were observed in the PARTNER II S3i propensity score analysis, where new-onset AF rates were lower with SAPIEN 3 valve than SAVR at both 30 days and 1 year.[65]

Table 2.14: Rates of new-onset AF in studies of intermediate surgical risk patients with AS treated with TAVR or SAVR

	Rate of New-onset AF	
	30 days	**1 year**
***PARTNER IIA Trial*[74]**		
SAPIEN XT valve (TAVR-all)	9.1%	10.1%
TF-TAVR	4.9%	5.9%
SAVR (all)	26.4%	27.2%
TF cohort	26.7%	27.6%
p-value (both "all" and TF comparisons)	<0.001	<0.001
***PARTNER II S3i Propensity Score Analysis*[65]**		
SAPIEN 3 valve (TAVR-all)	5.0%	5.9%[a]
SAVR	28.3%	29.2%
***SURTAVI Trial*[45b]**		
CoreValve (TAVR)	12.9%	-
SAVR	43.4%	-
95% credible interval	-34.7 to -26.4	-

[a] Site-reported data.

[b] New or worsening AF.

Key: AS = aortic stenosis, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.

Major Vascular Complications: Throughout 2 years of follow-up in the PARTNER IIA Trial, rates of major vascular complications were significantly higher with SAPIEN XT valve than with SAVR in both the overall and TF cohorts (

Table 2.15).[74] In the PARTNER II S3i propensity score analysis, the 30-day rate of this outcome was slightly higher with SAPIEN 3 valve than with SAVR, but was lower than that observed at 30 days in the PARTNER IIA Trial.[65]

Table 2.15: Rates of major vascular complication in studies of intermediate surgical risk patients with AS treated with TAVR or SAVR

	Rate of Major Vascular Complications	
	30 days	**1 year**
PARTNER IIA Trial[74]		
SAPIEN XT valve (TAVR-all)	7.9%	8.4%
TF-TAVR	8.5%	8.8%
SAVR (all)	5.0%	5.3%
TF cohort	3.9%	4.3%
p-value for “all” comparison (TF)	0.008 (<0.001)	0.007 (<0.001)
PARTNER II S3i Trial[43]		
SAPIEN 3 valve (TAVR-all)	6.1% (95% CI: 4.7-7.6)	-
TF-TAVR	6.3% (95% CI: 4.9-8.0)	-
PARTNER II S3i Propensity Score Analysis[65]		
SAPIEN 3 valve (TAVR-all)	6.1%	-
SAVR	5.4%	-
SURTAVI Trial[45b]		
CoreValve (TAVR)	6.0%	-
SAVR	1.1%	-
95% credible interval	3.2 to 6.7	-

	Rate of Major Vascular Complications	
	30 days	**1 year**
Key: AS = aortic stenosis, CI = confidence interval, TF = transfemoral, S3 = SAPIEN 3 valve, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Summary of RCTs

The efficacy and safety of the SAPIEN valve THV platform have been studied in a comprehensive clinical program including RCTs, non-randomized studies, and propensity score analysis. These studies have evaluated outcomes in inoperable and/or elevated surgical risk patients with severe symptomatic AS. Across all patient groups, the initially favorable results with the SAPIEN valve have improved further over time as a result of evolving valve designs (i.e., SAPIEN XT valve and SAPIEN 3 valve), improved operator experience, and optimization of best practices for imaging, and valve sizing.[37] Further, health outcomes with the SAPIEN valve THV platform have improved alongside valve innovation, with clinically meaningful improvements observed in rates of all-cause mortality (**Figure 2.7**), major/disabling stroke (**Figure 2.8**), and complications. In particular, the outcomes achieved with SAPIEN 3 valve exemplify the progress in Edwards' valve design and challenge the current gold standard therapy, SAVR, in the care of patients with severe symptomatic AS.

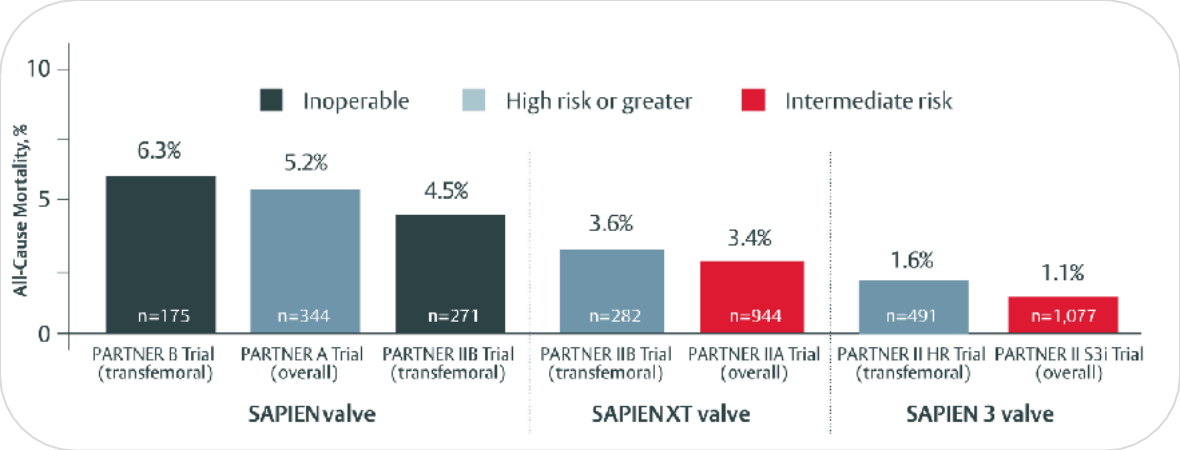

Figure 2.7: Evolution of 30-day all-cause mortality outcomes across the PARTNER Trials and the SAPIEN valve THV platform.

Note: some endpoints were not reported in the published literature but have been sourced from Edwards data on file.
Key: HR = high risk, S3i = SAPIEN 3 valve intermediate, THV = transcatheter heart valve.

Source: Edwards, Data on file.

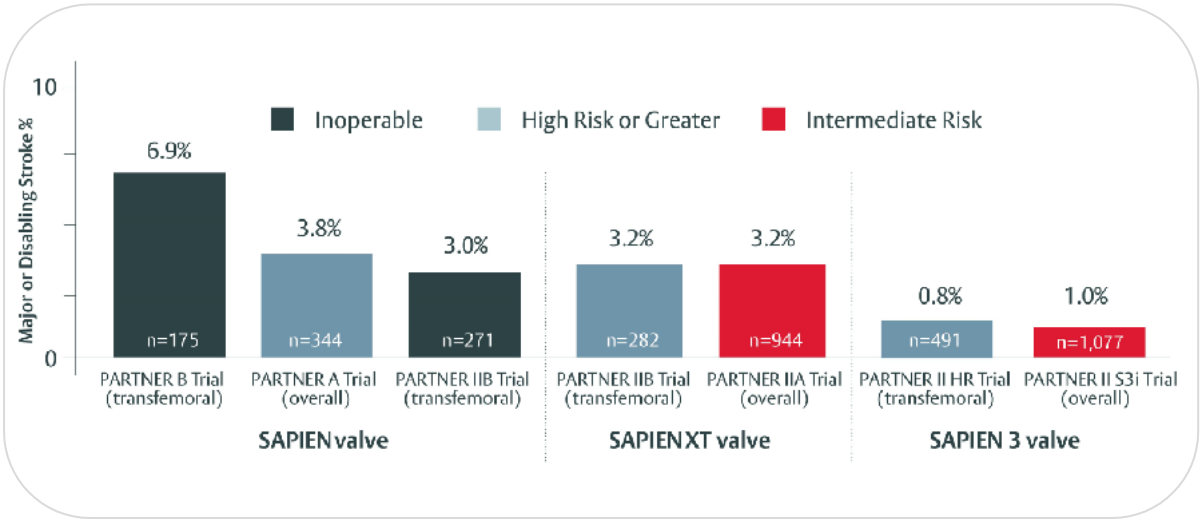

Figure 2.8: Evolution of 30-day major or disabling stroke outcomes across the PARTNER Trials and the SAPIEN valve THV platform.

Note: Some endpoints were not reported in the published literature but have been sourced from Edwards data on file.
Key: HR = high risk, THV = transcatheter heart valve.

Source: Edwards, Data on file.

Real-World Evidence

Real-world outcomes with the SAPIEN valve THVs and other TAVR devices have been evaluated in numerous registry, observational and case series studies. Specifically, the safety and effectiveness of SAPIEN valve, SAPIEN XT valve, and SAPIEN 3 valve have been assessed in five prospective continued access registry studies (N=22 publications), while 21 national and regional registry studies (N=41 publications) have evaluated the SAPIEN valve THVs and/or other valve types.

Collectively, the real-world studies of TAVR have captured the contemporary US and European experience in a broad population of patients with SSAS. As described below, these studies generally show results that are similar to those reported in the randomized-controlled and single-arm trials.

Registry Studies: TAVR Only

Procedure Success

In the national and regional registry studies of TAVR that reported on procedure success (N=27 publications),[86-109] this outcome was consistently high and ranged between 93.1% in the Global Valve-in-Valve Registry[100] and 100% in the Athens[86] and German TAVI registries[95].

Survival

Registry studies of the SAPIEN valve THVs provide support for the beneficial survival outcomes observed in the RCTs and single-arm studies of these devices. For example, at 30-day follow-up in the PARTNER and SOURCE registry studies of SAPIEN valve THVs, survival rates ranged from 91.8% to 97.8% in the "all" and TF groups (**Table 2.16**).[41,43,110-124] Survival in the PARTNER A[36,53,55,125] and CHOICE RCTs[126,127] was highly similar at this time point, at 94.6% with SAPIEN valve (all) and 95.9% with SAPIEN XT valve, respectively. At 1- and 2-year follow-up, survival was also similar or higher in the registry studies of the SAPIEN valve THVs[41,43,110-124] compared with that in the RCTs[36,53,56,126,127]. In contrast, real-world data for CoreValve from the Italian CoreValve Registry[101-103,128,129] showed slightly lower survival rates than those reported in the CoreValve US Pivotal High Risk Trial[70,82] and the CHOICE RCT[43,44] at all time points (**Table 2.16**). Long-term data from national and regional studies of TAVR (SAPIEN valve and/or other THVs) generally show similar results to those in the RCTs, reporting survival rates ranging from 69.7% to 92.6% at 1 year and 67% to 83.0% at 2 years ("all" and "TF" groups).[86-89,95-100,105-107,130-150]

Registry studies of the SAPIEN valve THVs also show that patient survival after TAVR has increased over time and varies among patient subgroups. In the PARTNER Continued Access Registry, 30-day survival improved from 94.6% in 2009/10 to 97.2% in 2011/12. This trend of improvement was also observed at 1- and 2-year follow-up. Similar to the RCTs, the registry studies have also shown variations in patient survival according to access route, gender, and baseline surgical risk.

Table 2.16: Comparison of survival rates in RCTs and registry studies of the SAPIEN valve THVs and other device types

Study Device (access route)	Survival Rates			
	30 days	1 year	2 years	5 years
SOURCE Registry[121,122]				
SAPIEN valve (all)	-	76.11%	-	-
SAPIEN valve (TA)	88.8%	73.8%	65.1%	-
PARTNER EU Registry[120]				
SAPIEN valve (TF)	91.8%	78.7%	-	-
SAPIEN valve (TA)	81.2%	49.3%	-	-
SOURCE XT Registry[110-119]				
SAPIEN valve (all)[110-118]	92.7%- 97.8%	72.9%-85%	65.6%- 76.5%	-
SAPIEN XT valve (all)[118,119]	93.7%	80.6%	72.3%	-
TF[118,119]	95.8%	85.0%	77.6%	-
PARTNER Continued Access Registry[123,124,152]				
SAPIEN valve (TF)[123] March 2009-July 2010 July 2010-March 2011 March 2011-January 2012	 94.6% 94.9% 97.2%	 77.3% 78.6% 85.6%	 65.1% 67.4% 75.8%	 - - -
SAPIEN valve (all)[124] SR at baseline and discharge Baseline SR, discharge AF AF at baseline and discharge	 - - -	 84.2% 64.3% 70.1%	 - - -	 - - -
SAPIEN valve (all)[152] Females Males	 93.5% 94.1%	 81.0% 74.1%	 - -	 - -
PARTNER Adjudicated Registry[41]				
SAPIEN 3 valve (all) Overall High surgical risk patients Inoperable patients	97.4% - -	85.6% 87.3% 82.3%	- - -	- - -
National and Regional Registries				
Athens TAVR Registry,[86] TAVR (all)	99.47%	-	-	-

Study Device (access route)	Survival Rates			
	30 days	1 year	2 years	5 years
Belgian TAVR Registry,[87] TAVR (all)	89	74%	-	-
Brazilian TAVI registry,[130] TAVR (all)	93.1%	81.0%	-	-
Canadian TAVI Registry,[88] SAPIEN valve (all)	89.4%	76%	67%	-
European SENTINEL Registry,[89] TAVR (all)	92.6%	-	-	-
FRANCE, FRANCE2 Registries,[90-94,153] TAVR (all)	87.3%-91.4%	72%-78%	-	-
German TAVI Registry (GARY),[95-99,131-135] TAVR (all)	89.9%-99.0%	69.7%-72.6%	-	-
Global Valve-in-Valve Registry,[100] TAVR (all)	91.6%	85.8%	-	-
Italian CoreValve Registry,[101-103,128,129] CoreValve (all)	93.9%-94.7%	83%	73.8%	-
Italian OBSERVANT registry,[136] TAVR (all) TF TA	 96.0% 92.0%	 - -	 3-yr: 69.1% 3-yr: 57.0%	 - -
Italian Registry of Trans-apical Aortic Valve Implantation,[137,154] SAPIEN valve (TA)	91%-93%	81.7%	76.1%	-
Italian Transcatheter Balloon-Expandable TAVI Registry (ITER),[107] SAPIEN valve, SAPIEN XT valve (all) TF TA	95.6% 96.2%	92.6% 89.5%	 - -	 - -
Nordic Lotus-TAVR registry,[138] Lotus Valve (all), intermediate-risk patients	98.1%	-	-	-
Polish Transcatheter Aortic Valve Implantation Registry (POL-TAVI)[139] TAVR (all)	93.4% (in-hospital)	-	-	-
Swiss Bern TAVI Registry,[140] TAVR (all) No myocardial injury (troponin ≤ 15 x normal limit) Myocardial injury (troponin > 15 x normal limit)	 99.2% 91.7%	 - -	 83.0% 68.1%	 - -

Study Device (access route)	Survival Rates			
	30 days	1 year	2 years	5 years
Swiss TAVI Registry,[155] TAVR (all)	90.5%-96.4%	-	-	-
UK TAVI Registry,[104,141,143] TAVR (all)	92.9%-93.4%	78.6%-81.7%	72.8%-73.7%	5-yr: 46.9% 6-yr: 37.3%
US STS/ACC TVT Registry,[105,144-148,156] SAPIEN valve, SAPIEN XT valve, and CoreValve (all)	Overall (2012-2015): 94.3% 2015: 95.4%	Overall (2012-2015): 77.4% 2014: 78.4%	-	-
US Virginia Cardiac Surgery Quality Initiative (VCSQI) registry,[149] TAVR (all)	89.9% (operative)	-	-	-
Women's International Transcatheter Aortic Valve Implantation (WIN-TAVI) registry,[150] TAVR (all)	96.6%	-	-	-

Note: As TF is the preferred access approach for TAVR, TA outcomes were excluded from studies that presented both overall and approach-specific outcomes to increase brevity. Key: ACC = American College of Cardiology, AF = atrial fibrillation, EU = Europe, OBSERVANT = Observational Study of Effectiveness of avR-taVi procedures for severe Aortic stenosis Treatment, RCT = randomized controlled trial, SR = sinus rhythm, STS = Society of Thoracic Surgeons, TA = transapical, TAVI = transcatheter aortic valve implantation, TAVR = transcatheter aortic valve replacement, TF = transfemoral, THV = transcatheter heart valve, UK = United Kingdom, US = United States, WIN-TAVR = Women's International Transcatheter Aortic Valve Implantation, yr = year

Adverse Events

Stroke: In the vast majority of registry studies of TAVR, rates of all stroke are lower than those in RCTs of THVs. In the PARTNER and SOURCE registry studies of the SAPIEN valve THVs, 30-day rates of all stroke ranged from 1.4% to 3.6% across the "all" and TF patient groups (Table 2.17).[41,43,110-124] In contrast, rates of all stroke were slightly higher in the PARTNER A[36,53,55,125] and CHOICE RCTs,[45,46] at 4.7% and 5.8% in the SAPIEN valve (all) and SAPIEN XT valve (TF) arms, respectively. At 1- and 2-year follow-up, rates of all stroke in the PARTNER and SOURCE registry studies[41,43,110-124] remained lower than those in the PARTNER A and CHOICE RCTs.[36,53,55,125-127] A similar trend is observed for CoreValve, where a lower rate of all stroke was reported in the Italian CoreValve Registry[101-103,128,129] than in the CHOICE[43,44] and US Pivotal High Risk Trials[50,51] (Table 2.17).

In national and regional registries, results for all stroke are almost consistently lower than those in the SAPIEN valve RCTs and range from 0% to 4.5% at 30 days and 4% to 5% at 1 year (when reported).[86-89,95-100,105-107,130-150,156] However, the Brazilian TAVR Registry (all THV types and access routes) reported a higher risk of all stroke at 30-day follow-up, at 8.6%.[130]

Table 2.17: Comparison of rates of all stroke in RCTs and registry studies of the SAPIEN valve THVs and other device types

Study Device (access route)	Rates of All Stroke	
	30 days	1 year
SOURCE Registry[121,122]		
SAPIEN valve (all)	-	4.5%
TA	2.5%	4.8%
PARTNER EU Registry[120]		
SAPIEN valve (TF)	3.3%	5.1%
SAPIEN valve (TA)	1.5%	7.6%
SOURCE XT Registry[118,119]		
SAPIEN XT valve (all)	3.6%	6.3%
TF	3.4%	5.6%
PARTNER Continued Access Registry[152]		
SAPIEN valve (all)[152] Females Males	 3.8% 2.9%	 5.2% 4.5%
PARTNER Adjudicated Registry[41]		
SAPIEN valve Overall High surgical risk patients Inoperable patients	 1.4% - -	 4.3% 5.6% 1.8%
National and Regional Registries		
Athens TAVR Registry,[86] TAVR (all)	0%	-
Belgian TAVR Registry,[87] TAVR (all)	-	5.0%
Brazilian TAVI registry,[130] TAVR (all)	8.6%	-
Canadian TAVI Registry,[88] SAPIEN valve (all)	2.3%	-
European SENTINEL Registry,[89] TAVR (all)	1.8%	-
FRANCE, FRANCE2 Registries,[90-94,153] TAVR (all)	2.7%-3.6%	4.1%
German TAVI Registry (GARY),[95-99,131-134] TAVR (all)	2.7%- 3.2%	4.0%

Study Device (access route)	Rates of All Stroke	
	30 days	1 year
Global Valve-in-Valve Registry,[100] TAVR (all)	2.0%	-
Italian CoreValve Registry,[101-103,128] CoreValve (all)	1.8%	-
Italian OBSERVANT registry,[136] TAVR (all) TF TA	 1.0% 2.0%	 - -
Italian Registry of Trans-apical Aortic Valve Implantation,[137,154] SAPIEN valve (TA)	1.2%-2.5%	-
Nordic Lotus-TAVR registry,[138] Lotus (all), intermediate surgical risk patients	3.2%	-
Swiss Bern TAVI Registry,[140] TAVR (all) No myocardial injury (troponin ≤15 x normal limit) Myocardial injury (troponin >15 x normal limit)	 1.7% 4.5%	 - -
Swiss TAVI Registry,[155] TAVR (all)	3.3%	-
UK TAVI Registry,[104,141] TAVR (all)	4.1%	-
US STS/ACC TVT Registry,[144,148,156] SAPIEN valve, SAPIEN XT valve, CoreValve (all)	2015: 1.9%	Overall (2012-2015): 3.8%
WIN-TAVI registry,[150] TAVR (all)	1.3%	-

Note: As TF is the preferred access approach for TAVR, TA outcomes were excluded from studies that presented both overall and approach-specific outcomes to increase brevity.
Key: ACC = American College of Cardiology, EU = Europe, RCT = randomized controlled trial, STS = Society of Thoracic Surgeons, TA = transapical, TAVI = transcatheter aortic valve implantation, TAVR = transcatheter aortic valve replacement, TF = transfemoral, THV = transcatheter heart valve, UK = United Kingdom, US = United States.

Summary

Considered collectively, the results of real-world studies of TAVR provide strong support for the favorable outcomes observed in randomized clinical studies such as the PARTNER Trials. These studies also highlight the evolution of best practices over time as patient outcomes have continued to improve since the introduction of TAVR.

2. Quality of Life (QoL) Evidence Demonstrates Significant Improvements in TAVR Patients

2.1. QoL Study Results for TAVR

2.1.1. Inoperable Patients: TAVR vs. Medical Management

Quality of Life

As described below, results from an RCT and a single-arm study show that TAVR is associated with significant improvement of QoL from baseline in inoperable patients with severe symptomatic AS. Further, improvement of QoL is significantly greater with TAVR than with medical management.[13,22,55,68,69,157]

SAPIEN valve/SAPIEN XT valve

In the PARTNER B Trial that compared TAVR using the SAPIEN valve versus medical management, patients in the SAPIEN valve group experienced a statistically significant 24.8-point improvement from baseline on the KCCQ overall summary (-OS) score at 30 days.[13,22,55,158] This improvement was maintained at 6 months (+33.5 points) and 1 year (+31.8 points) and was substantial (i.e., ≥20-point change) at all timepoints. When compared with medical management, use of the SAPIEN valve was also associated with a significantly higher mean KCCQ-OS score at 30 days (+13.3-point difference), 6 months (+20.8 points), and 1 year (+26.0 points) (all p<0.001) (**Figure 2.1**, left panel). EQ-5D utility scores were also significantly higher for patients who received the SAPIEN valve than for those who received medical management at 1 month (+0.07-point difference), 6 months (+0.04 point), and 1 year (+0.10 point) (all p<0.001) (**Figure 2.1**, right panel).[13] The difference at 1 year was clinically important (MCID=0.074).

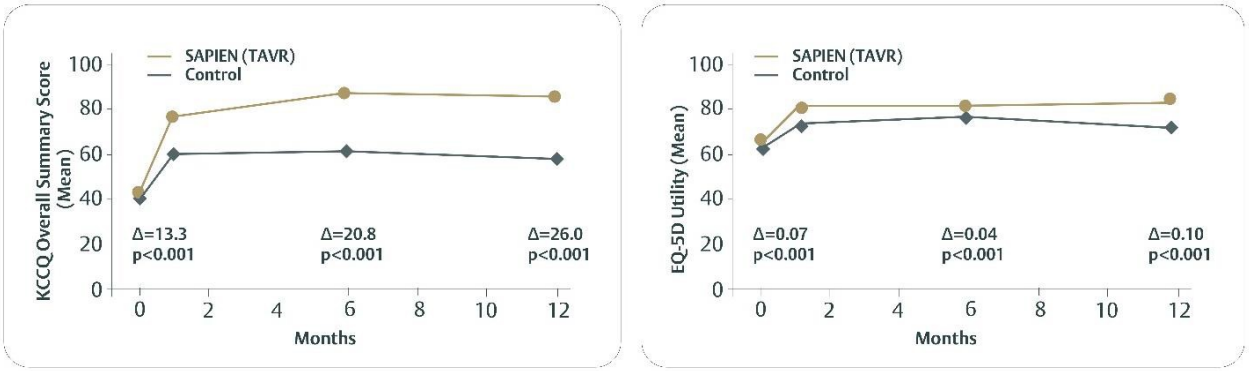

Figure 2.1: Mean KCCQ-OS (left panel) and EQ-5D (right panel) scores in inoperable patients with AS who received the SAPIEN valve (TAVR) or medical management, PARTNER B Trial.
Note: KCCQ small MCID = 5 points; EQ-5D MCID = 0.074.
Key: AS = aortic stenosis, EQ-5D = EuroQol 5 dimensions, KCCQ-OS = Kansas City Cardiomyopathy Questionnaire overall summary, MCID = minimal clinically important difference, TAVR = transcatheter aortic valve replacement.
Source: Reynolds et al., 2011.[13]

Results from the PARTNER B Trial also showed increased physical and mental functioning with TAVR that corresponded to clinically important improvements (MCID=2). Significantly better SF-12 physical scores were observed in patients who received the SAPIEN valve than in medically managed patients at 30 days (+4.5-point difference, p<0.001), 6 months (+4.7 points, p=0.001), and 1 year (+4.7 points, p=0.006).[13] SF-12 mental scores were also significantly higher in the SAPIEN valve group than in the medical management group at 6 months (+4.3 points, p=0.005) and 1 year (+5.9 points, p=0.001).[13]

SAPIEN 3 valve

In the PARTNER II S3HR registry of the SAPIEN 3 valve, mean overall results on the KCCQ increased significantly from 47.8 at baseline to 67.8 at Day 30 in inoperable/high-risk patients (p<0.0001).[43] In a separate analysis of follow-up data, the overall KCCQ score improved significantly from 46.9 at baseline to 72.4 at 1 year (p<0.0001).[41]

CoreValve

Similar improvements in QoL were observed after TAVR in the single-arm CoreValve US Extreme Risk Trial.[157] Compared with baseline, patients who received the CoreValve showed a significant increase in KCCQ-OS scores at 1 month (+23.9 points), 6 months (+27.4 points), and 1 year (+27.4 points) (all p<0.001). Further, EQ-5D utility scores were significantly higher than those at baseline at 1 month (+0.084 points, p<0.001), 6 months (+0.092, p<0.001), and 1 year (+0.058, p=0.003); these improvements were clinically meaningful at 1 and 6 months. CoreValve patients also had significant improvements from baseline in SF-12 physical (1 month, +5.8 points; 6 months, +5.0 points; 1 year, +5.1 points) and mental scores (1 month, +3.9 points; 6 months, +4.5 points; 12 months, +5.1 points) at all timepoints (all p<0.001).

Functional Status

Randomized and non-randomized studies show that TAVR also leads to improvements in functional status compared with both baseline and medical management in inoperable patients with severe symptomatic AS.[12,22,55,68,69,159]

SAPIEN valve/SAPIEN XT valve

Among survivors in the PARTNER B Trial, significantly fewer patients who received the SAPIEN valve experienced NYHA class III/IV heart failure symptoms than medically managed patients at 1 year (23.7% vs. 60.8%, respectively; p<0.001); this difference remained numerically but not significantly lower in the SAPIEN valve arm at 3 years (30% vs. 50%) and 5 years (14.3% vs. 40.0%).[55] Significant improvements from baseline were also observed on the 6MWT for patients who received the SAPIEN valve (p=0.002), whereas medically managed patients did not experience an improvement in this outcome.[22]

The PARTNER IIB study of SAPIEN valve versus SAPIEN XT valve also showed improvements in functional status in inoperable patients with AS.[78] At 30 days and 1 year, there was a significant improvement in NYHA symptoms compared with baseline in both study groups (p=NR); no differences were observed between groups. Nearly 85% of all patients had an improvement of at least one NYHA functional class at 30 days, and 91% had this improvement by 1 year. At 1 year, patients in both study groups also experienced improved 6MWT results compared with baseline (p=NR); no significant differences were observed between groups.

SAPIEN 3 valve

At day 30 in the PARTNER II S3HR registry of inoperable and high-risk patients who received SAPIEN 3 valve, considerably fewer patients had class III/IV NYHA status compared with baseline (13.3% vs. 90.1%, respectively; p=NR). Further, 6MWT results were significantly prolonged (176.7 feet [53.86 m] at Day 30 vs. 138.2 feet [42.12 m] at baseline; p<0.0001).[43] In a separate analysis of 1-year follow-up data, the percentage of patients in NYHA class III/IV decreased further to 7.7% (p<0.0001 vs. 90.1% at baseline) and 6MWT results continued to be significantly prolonged (179 m vs. 134 m at baseline; p<0.0001).[41]

CoreValve

Similar functional status results were reported with TAVR in the CoreValve US Extreme Risk Trial. The proportion of inoperable patients classified as NYHA class III/IV was reduced after CoreValve implantation, lowering from 89.9% at baseline to 12.6% at 1 month and 6.1% at both 1 and 2 years.[68,69]

2.1.2. Patients at High Surgical Risk: TAVR vs. SAVR

Quality of Life

The results of randomized and non-randomized trials show that QoL is significantly improved after both TAVR and SAVR in patients with AS who are at high surgical risk.[14,67,70,71,160] However, patients who undergo TAVR through a TF approach experience these improvements earlier than those who undergo SAVR.

SAPIEN valve/SAPIEN XT valve

The PARTNER A Trial compared outcomes with SAPIEN valve (TAVR) and SAVR in high surgical risk patients.[14] In the TF cohort, patients who received TAVR experienced improvements from baseline in all QoL indicators, including the KCCQ-OS, physical limitations, total symptoms, QoL, and social limitation scores; SF-12 physical and mental scores; and EQ-5D utilities at 1 month, 6 months, and 1 year.[14] Importantly, TF-TAVR patients experienced improvements earlier than SAVR patients, showing a significantly greater improvement in KCCQ-OS scores than SAVR patients at 1 month (+9.9-point increase, p≤0.001). This change corresponded to a moderate clinical improvement, although similar improvements were observed between patients who received SAPIEN valve or SAVR at 6 months and 1 year.[14,158] In the TA cohort of PARTNER A, patients in the SAPIEN valve and SAVR groups experienced a significant improvement of KCCQ-OS scores at 30 days, 6 months, and 1 year compared with baseline.[14] However, a short-term QoL advantage of SAPIEN valve over SAVR was not observed on the KCCQ, SF-12, or EQ-5D surveys.

SAPIEN 3 valve

Significant improvement of QoL has also been reported in patients with high surgical risk who received the SAPIEN 3 valve. In the SAPIEN 3 valve CE Mark study, high-risk patients who received SAPIEN 3 valve reported significantly higher mean Visual Analog Scale (VAS)[†] EQ-5D scores at 1 month than at baseline (64.7 vs. 56.9, respectively; p<0.0001).[66,67] Inoperable and high surgical risk patients in the PARTNER II S3HR registry also reported significant improvements in KCCQ scores from baseline to 30-day and 1-year follow-up (both p<0.0001).[41,43]

CoreValve

In the CoreValve US Pivotal High Risk study, patients who received the CoreValve had a mean 23.2-point increase in KCCQ-OS score from baseline to 1 year that was non-inferior to the increase observed in SAVR patients (+21.88 points).[67,70,160] Analysis by access site revealed that CoreValve patients in the iliofemoral cohort experienced significant improvements from baseline earlier than SAVR patients across all health status measures.[160] Specifically, health status improvements were significantly greater with the CoreValve than with SAVR at 1 month for KCCQ OS (+16.7-point improvement), physical limitations (+17.8 points), total symptoms (+9.9 points), QoL (+19.0 points), and social limitation (+18.6 points) scores (all p<0.001); SF-12 physical (+4.9-point improvement) and mental (+6.1 points) scores (both p<0.001); and EQ-5D scores (+0.117-point improvement, p<0.001). However, no difference in health status was observed between the CoreValve and SAVR groups at 6-month and 1-year follow-up. For patients in the non-iliofemoral subcohort, no significant differences were observed for any health status measure at any timepoint.

Functional Status

Similar to the results for QoL, evidence suggests that both TAVR and SAVR improve the functional status of patients with AS who are at high surgical risk, but that improvements may be observed earlier with TAVR than with SAVR.[12,36,53,67,71,159]

[†] VAS scoring: 0 = worse health imaginable; 100 = best health imaginable.

SAPIEN valve/SAPIEN XT valve

In the PARTNER A Trial, a greater proportion of patients who received the SAPIEN valve had less severe heart failure symptoms (NYHA class I/II) than patients who underwent SAVR at 1 month after treatment (p<0.001).[36] Such delays in functional improvement immediately after SAVR have been attributed to the relatively longer recovery period associated with open-heart surgery than with the TF-TAVR approach. By 1[36] and 2 years[53], the proportion of patients with NYHA class I/II symptoms was similar among SAPIEN valve and SAVR survivors. The study additionally showed that patients who received the SAPIEN valve had better 6MWT results than SAVR patients at 1 month (median distance: 128 m vs. 75 m, respectively; p=0.002); the two groups performed equally well at 1 year (152 m vs. 175 m; p=0.76).

SAPIEN 3 valve

Similar improvements in the functional status of high surgical risk patients have been reported with the SAPIEN 3 valve.[66,67] In the SAPIEN 3 valve CE Mark study, patients who received SAPIEN 3 valve experienced significant functional improvements, with nearly all patients having NYHA I/II symptoms at 1 month (95.2%) and 1 year (94.6%) in contrast to only 16.1% at baseline. By 1 month, patients could also walk significantly further than at baseline, as demonstrated by results on the 6MWT (241.6 m vs. 201.9 m, respectively; p=0.0031). Similarly, as described above, the PARTNER II S3HR registry of inoperable and high-risk patients reported significant improvements from baseline in NYHA functional status and 6MWT at 30-day and 1-year follow-up after implantation of SAPIEN 3 valve.[41,43]

CoreValve

In the CoreValve US Pivotal High Risk study, the improvements observed in NYHA class heart failure symptoms with the CoreValve THV were non-inferior to those observed in SAVR patients at 1 month, 1 year, and 2 years.[66,67,71]

2.1.3. Patients at Intermediate Surgical Risk: TAVR vs. SAVR

Quality of Life

Evidence from the PARTNER II clinical program also shows that patients with severe symptomatic AS who are at intermediate surgical risk experience substantial QoL benefits after TAVR.[43,161,162] As shown in other patient populations, these improvements occur earlier with TAVR than with SAVR.

SAPIEN XT valve

In the PARTNER IIA Trial of SAPIEN XT valve (TAVR) versus SAVR, intermediate surgical risk patients in both groups experienced substantial improvements in QoL at 1 and 2 years compared with baseline.[161] However, differences were observed between treatment groups when outcomes were examined by approach. In the TF cohort, improvements in QoL were experienced significantly earlier by patients who received SAPIEN XT valve than those who received SAVR. At 1 month, significantly better results were observed with SAPIEN XT valve than with SAVR on the KCCQ-OS (mean adjusted difference: +14.1 points; **Figure 2.2**), SF-36 physical (+4.6 points), SF-36 mental (+5.5 points), and EQ-5D (+0.066 point) scores (all p<0.001). At 1- and 2-year follow-up, no differences in QoL scores were observed between SAPIEN XT valve and SAVR. In contrast, in the transthoracic cohort (i.e., transapical or transaortic approach), SAPIEN XT valve and SAVR were associated with similar QoL benefits at 1 month, 1 year, and 2 years.

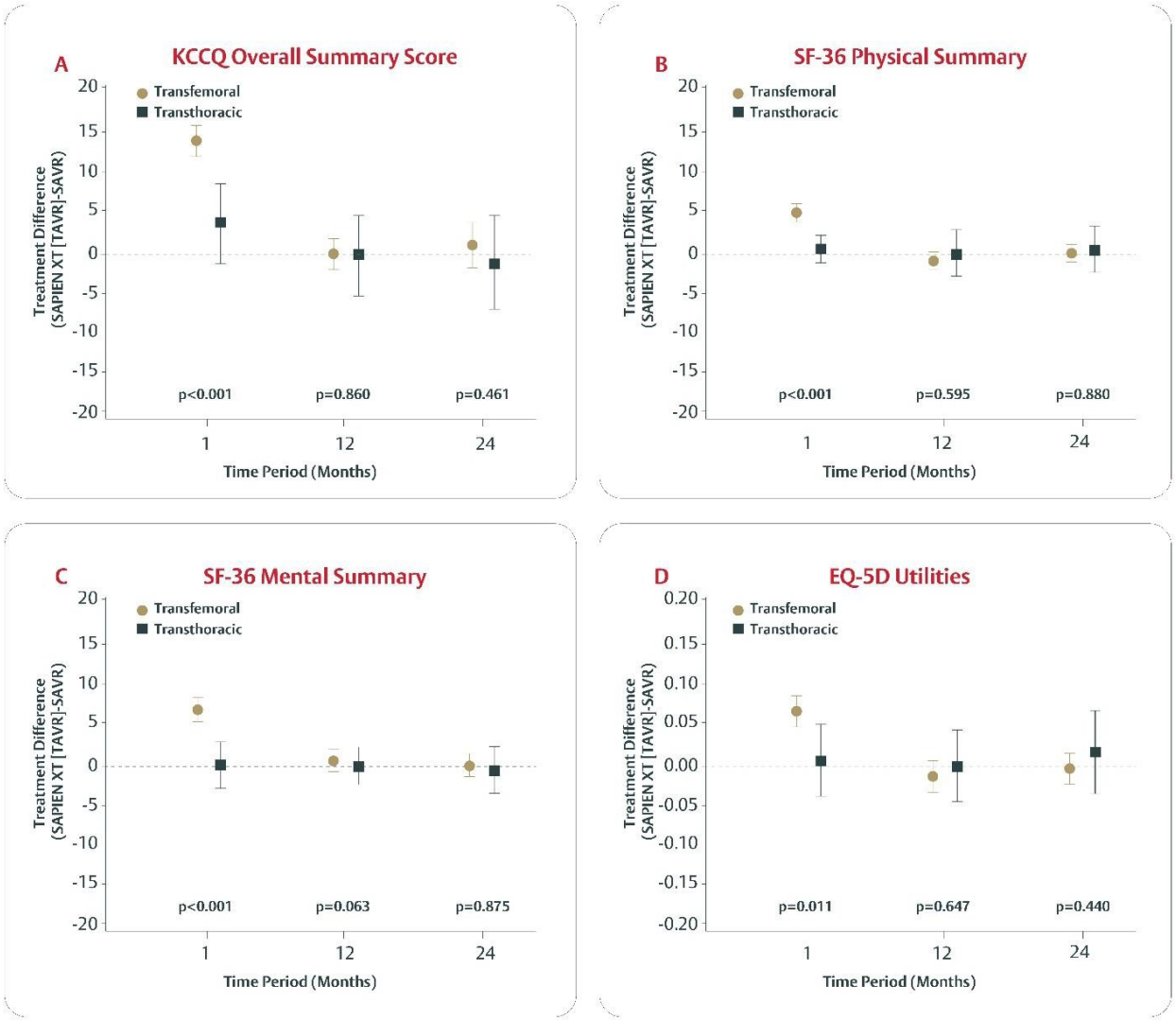

Figure 2.2: Mean differences in (A) KCCQ-OS, (B) SF-36 physical, (C) SF-36 mental, and (D) EQ-5D utility scores for SAPIEN XT valve (TAVR) versus SAVR in AS patients with intermediate surgical risk, PARTNER IIA Trial, transfemoral and transthoracic subcohorts.
Key: AS = aortic stenosis, EQ-5D = EuroQoL 5 dimensions, KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary, M = months, SAVR = surgical aortic valve replacement, SF-36 = short form 36, TAVR = transcatheter aortic valve replacement.
Source: Baron et al., 2017.[161]

Notably, these health status results only apply to surviving patients at each time point. When both survival and the magnitude of QoL improvement are considered together—with death as the worst possible outcome—treatment with TF-TAVR results in a statistically significant benefit compared with SAVR at both early (1 month; p<0.001) and late (1 and 2 years; p=0.04) timepoints

SAPIEN 3 valve

The PARTNER II S3i Trial was a propensity score analysis of SAPIEN 3 valve, SAPIEN XT valve, and SAVR in severe symptomatic AS patients with intermediate surgical risk.[162] The study showed that patients who received the SAPIEN 3 valve experienced a 19-point improvement at 1 month and a 23-point

improvement at 12 months compared with baseline on the KCCQ-OS score (**Figure 2.3**). At 12 months, this difference corresponded to a large, clinically important improvement (i.e., ≥ 20-point change).[158] TAVR with SAPIEN 3 valve also resulted in earlier significant improvements in patient QoL than SAVR in the S3i Trial.[162] At 1 month, patients treated with SAPIEN 3 valve had a significantly improved mean overall KCCQ score (+15.6 points) compared with those who received SAVR (p<0.001). By 12 months, the improvement with SAPIEN 3 valve remained statistically significant compared with SAVR (p=0.04). Similarly, when health status was assessed using the SF-36, treatment with SAPIEN 3 valve was associated with a 4.7-point improvement on the physical component summary score compared with treatment with SAVR (p<0.001) at 1-month follow-up.

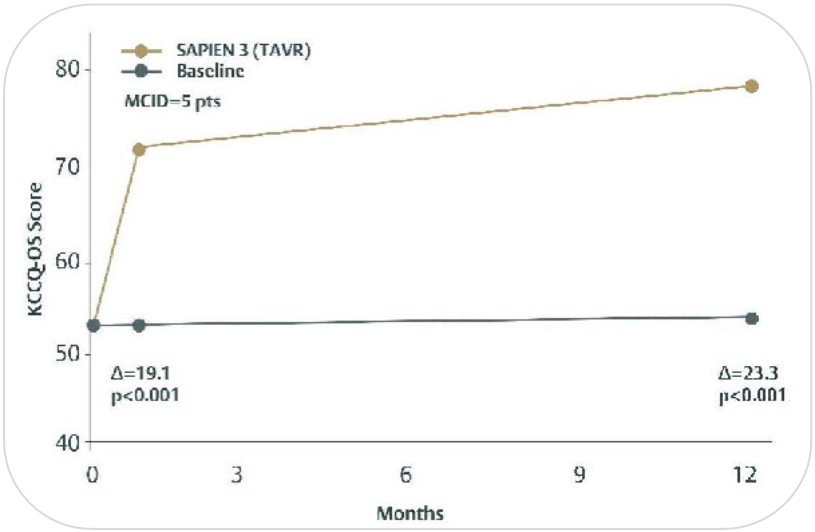

Figure 2.3: Change in KCCQ-OS score from baseline for AS patients with intermediate surgical risk who received the SAPIEN 3 valve (TAVR), PARTNER II S3i Trial.
Key: AS = aortic stenosis, KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary, MCID = minimal clinically important difference, S3i = SAPIEN 3 valve intermediate, TAVR = transcatheter aortic valve replacement.
Source: Baron et al., 2016.[162]

Finally, the PARTNER II S3i registry study of SAPIEN 3 valve also showed positive results on the KCCQ in AS patients with intermediate surgical risk.[43] Mean overall scores increased from 54.7 at baseline to 74.0 at 30 days (p<0.0001).

Functional Status

SAPIEN XT valve

The PARTNER IIA RCT of SAPIEN XT valve (TAVR) versus SAVR reported on the functional status of intermediate-risk patients.[74] From baseline to 30 days, there was a significant reduction in symptoms with both TAVR and SAVR, as a greater proportion of patients had NYHA class I/II status (p<0.001). The proportion of patients with NYHA class I/II was maintained for 2 years in both treatment groups (p<0.001). Patients in the SAPIEN XT valve group had significantly fewer cardiac symptoms than did those in the SAVR group at 30 days (p=0.001), but the frequency of these symptoms did not differ significantly at later time points.

SAPIEN 3 valve

The PARTNER II S3i registry study also reported on the functional status of intermediate-risk patients who had received SAPIEN 3 valve.[43] From baseline to day 30 after intervention, the proportion of patients with

class I/II NYHA status increased from 27.5% to 93.8% (p=NR). Mean 6MWT also improved significantly from baseline to day 30, increasing from 197.0 to 231.3 feet (p<0.0001).

2.1.4. Real-World Patient Populations Undergoing TAVR

The impact of TAVR on QoL was also evaluated in the STS/ACC Transcatheter Valve Therapy Registry, which included a population of 31,636 (N at 30 days) patients.[163] At baseline, the median STS predicted risk of operative mortality score was 6.3 (IQR: 4.2-9.6) and the mean (SD) baseline KCCQ-OS score was 42.3 (23.7), indicating substantial impairment of health status. On average, surviving patients had large improvements in health status after TAVR, with mean increases on the KCCQ-OS score of 27.6 points at 30 days and 31.9 points at 1 year.

2.2. Summary

In summary, the QoL and functioning of patients with severe symptomatic AS is an important consideration after AVR. Disease-specific and generic measures show that patients experience important improvements in QoL after TAVR: in inoperable patients, these improvements are significantly greater than those achieved with medical management; in patients with high or intermediate surgical risk, improvement of QoL occurs earlier with TAVR than with SAVR.

3. Economic Evidence Demonstrates that TAVR Produces Benefits for Patients and the Medicare Program

3.1. Cost-effectiveness Analyses

3.1.1. Inoperable Patients

The cost effectiveness of TAVR in patients with severe symptomatic AS who are inoperable was assessed in a cost effectiveness analysis (CEA) that was conducted alongside the PARTNER B Trial.[164] The economic value of TAVR in this population has also been assessed in other studies that used outcomes data from PARTNER B and other sources.[142,165-168] Overall, the results of these analyses indicate that TAVR is a cost-effective option for patients who are not eligible for SAVR. Their findings are summarized below.

PARTNER B CEAs

A health economic study was conducted alongside the PARTNER Trial to understand the incremental costs and cost effectiveness of TAVR with the SAPIEN valve (TF approach) compared with standard medical therapy among inoperable patients with severe AS (cohort B).[164] Data on survival, QoL, healthcare resource utilization, and hospital charges were collected through the first 12 months of follow-up for all patients and were used to estimate the incremental cost effectiveness of SAPIEN valve from the perspective of the US healthcare system. Survival analyses were performed using data collected through ≥12 months of follow-up (mean follow-up duration: 18 months; maximum: 30 months). To estimate life expectancy beyond the trial period, parametric survival models were used to extrapolate survival probabilities.

The study found that the mean admission cost of TAVR with the SAPIEN valve was $73,563 (median: $62,934) excluding physician fees; when physician fees were included, the mean cost rose to $78,542 (median: $67,551). Over the first 12 months of follow-up, per-patient hospital care costs were $26,025 higher in the standard therapy group than in the SAPIEN valve group ($p<0.001$). Including the initial admission for TAVR, the total first-year medical care cost per patient was approximately $52,000 higher in the SAPIEN valve group than in the standard therapy group ($p<0.001$). Lifetime medical care costs beyond 1 year were approximately $43,664 per patient in the SAPIEN valve group and $16,282 per patient in the standard therapy group. These results were largely attributable to the low survival rate in medically managed patients. Based on the survival models, total life expectancy was estimated to be 3.1 years in the SAPIEN valve group and 1.2 years in the standard therapy group, a difference of 1.9 years (1.6 years after discounting) in favor of SAPIEN valve.

Over a lifetime time horizon, the ICER for TAVR with the SAPIEN valve compared with standard therapy was estimated at $50,200 per LYG (2010 USD) or approximately $62,000 per QALY gained. The study authors concluded that among inoperable patients with severe AS, TAVR with SAPIEN valve provides a substantial survival benefit at a reasonable incremental cost.

3.1.2. High Surgical Risk Patients

The cost effectiveness of TAVR in patients with severe symptomatic AS who are at high surgical risk was assessed in a CEA conducted alongside the PARTNER Trial[169] as well as in studies that used outcomes data from PARTNER A or other sources.[170-173] Overall, these studies generally showed TAVR to be a cost-effective therapy in this population. The results of these studies are summarized below.

PARTNER A CEAs

Using data from Cohort A of the PARTNER Trial, Reynolds and colleagues conducted an analysis to establish the cost effectiveness of TAVR with the SAPIEN valve compared with SAVR in high surgical risk patients.[169] SAPIEN valve was compared to SAVR by stratifying outcomes and costs for the SAPIEN valve

arm by access site over a one-year time horizon. For TF-TAVR and SAVR, mean index admission costs were $71,955 and $74,452, respectively (difference=$2,496; p=0.53); after excluding physician fees, the mean costs were $67,213 and $68,679. For TA-TAVR and SAVR, mean index admission costs were $90,548 and $79,540, respectively (difference=$11,008; p=0.08); after excluding physician fees, the mean costs were $85,055 and $73,410. Over the first 12 months after treatment, total follow-up costs were comparable between TAVR and SAVR.

Over 12 months, TF-TAVR with the SAPIEN valve was associated with a small but significant gain in QALYs (0.068 QALYs) compared with SAVR. Similarly, TF-TAVR was associated with a gain in life-years of 0.065 versus SAVR. In contrast, the gain in QALYs and life-years was slightly higher for SAVR than for TA-TAVR (0.07 QALYs and 0.015 life-years).

Among patients eligible for a TF approach, TAVR with the SAPIEN valve was less expensive (by approximately $1,250) and more effective than SAVR as measured in QALYs. This led to an estimated ICER where TF-TAVR was dominant compared with SAVR (**Figure 3.1**, left panel). In contrast, among patients eligible only for a TA approach, the incremental cost of TAVR with the SAPIEN valve was approximately $10,000 higher per patient, with no increase in QALYs compared to SAVR. In this analysis, TA-TAVR was dominated by SAVR (**Figure 3.1**, right panel).

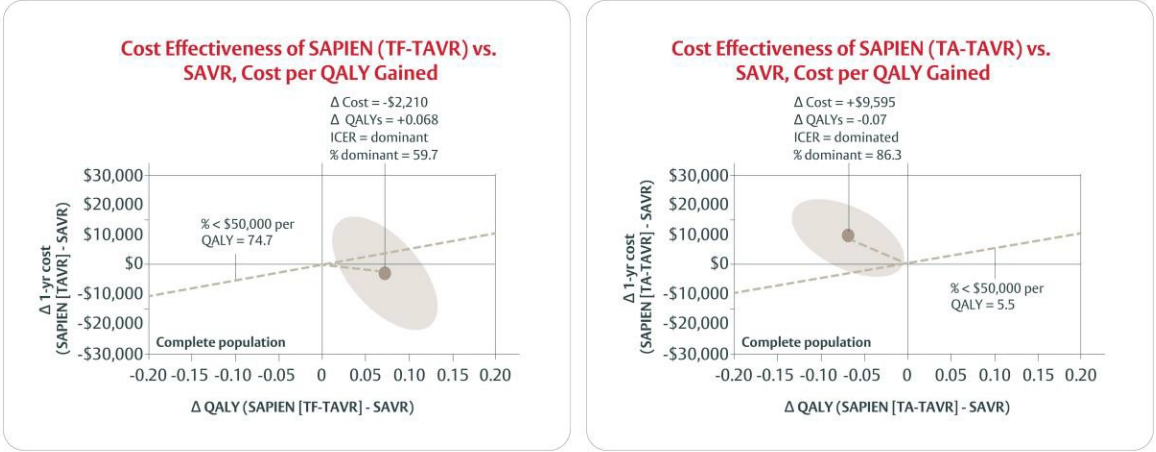

Figure 3.1: Cost effectiveness of TF-TAVR (left panel) and TA-TAVR (right panel) with the SAPIEN valve versus SAVR, cost per QALY gained, high surgical risk patients, PARTNER A Trial.
Key: ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, SAVR = surgical aortic valve replacement, TA = transapical, TAVR = transcatheter aortic valve replacement, TF = transfemoral, yr = year. Source: Reynolds et al., 2012.[169]

The study showed that the differences in cost effectiveness by TAVR access site were driven by differences in hospital resource utilization and short-term clinical outcomes. That is, TF-TAVR with SAPIEN valve was associated with substantial reductions in hospital length of stay and significant early QoL benefits, thereby providing both economic and clinical benefits compared with SAVR. In contrast, TA-TAVR with SAPIEN valve was associated with a smaller reduction in length of stay that was not great enough to offset the higher procedural costs and did not improve QoL compared with SAVR.

Another CEA of TAVR with the SAPIEN valve versus SAVR using PARTNER A data was conducted from the perspective of the UK healthcare system.[170] The analysis did not stratify TAVR by access site. Its results showed SAPIEN valve to be the dominant treatment strategy, being less costly and more effective than SAVR over a 10-year time horizon. In a probabilistic analysis, SAPIEN valve had a 65% likelihood of being cost effective at a threshold of £20,000.

Other CEAs

In 2016, Reynolds and colleagues conducted another CEA of TAVR versus SAVR in high surgical-risk patients using clinical data derived from the CoreValve US High Risk study (NCT01240902[174]). The study was conducted from the perspective of the US healthcare system. TAVR with the CoreValve was associated with a higher lifetime cost than SAVR (difference = $17,849; 2013 USD) but a gain of 0.32 QALYs (0.41 Lys). [173] The lifetime ICER for TAVR versus SAVR was $55,090 per QALY gained ($43,114 per LYG). Sensitivity analyses indicated that a reduction in the initial cost of TAVR by ~$1,650 would lead to an ICER of <$50,000/QALY gained. Notably, the study also reported greater procedural efficiency with TAVR. [173]

3.1.3. Intermediate Surgical-risk Patients

PARTNER IIA and S3i CEAs

The cost effectiveness of TAVR versus SAVR in patients with severe symptomatic AS who are at intermediate surgical risk was assessed in two CEAs that used data from the PARTNER IIA and S3i Trials.[175] Both analyses were conducted from the perspective of the US healthcare system. The PARTNER IIA CEA included as-treated patients (SAPIEN XT valve, n=994; SAVR, n=944) while the S3i analysis included the valve-implanted population (SAPIEN 3 valve, n=1,068; SAVR, n=936). Both CEAs included an in-trial (24 month) analysis based on observed data, followed by patient-level lifetime projections of survival, quality-adjusted life expectancy (QALE), and costs. All future costs and benefits were discounted at 3% per year. Probabilistic matching was used to link trial patients with Medicare claims data. Index hospitalization costs were calculated using a combination of resource-based accounting (for TAVR/SAVR procedures) and hospital billing data (from Medicare claims); all other costs were based on Medicare claims*. In the SAVR group in each analysis, observed mortality between 6 and 24 months was compared with age- and gender-specific mortality from US life tables; recalibrated life tables were used to project patient-level survival beyond 24 months. In the TAVR group of each analysis, the HR for TAVR versus SAVR was derived from a 6- to 24-month landmark analysis of trial data. As the observed HR (1.07, 95% CI: 0.78-1.45) did not differ from unity, the base-case analysis assumed an HR equal to 1.0. Utilities were measured at baseline, 1, 6, 12, and 24 months using the EQ-5D and were used to calculate within-trial and lifetime QALYs.

PARTNER IIA CEA Results

The results of the PARTNER IIA CEA showed that procedural efficiency (procedure time and hospital LOS) was significantly better with SAPIEN XT valve than with SAVR; still, index hospital costs† were significantly higher with SAPIEN XT valve (trimmed means: $61,433 vs. $58,545 with SAVR; difference: $2,888, p=0.014).[175] However, from discharge to 12 months, follow-up costs were lower with SAPIEN XT valve than with SAVR, and from 12 to 24 months, follow-up costs were only slightly higher with TAVR (+$668). Overall, total 2-year costs‡ were significantly lower with SAPIEN XT valve than with SAVR ($107,716 vs. $114,132, respectively; difference: $6,416, p=0.014). The in-trial change in QALYs was 0.07. Projected life expectancy (undiscounted) was 7.80 years with SAPIEN XT valve and 7.64 years with SAVR (difference: 0.16 years). The change in QALE was 0.18 QALYs. The study showed that with a change in cost of -$7,949 and a change in QALYs of 0.15 years (both discounted), SAPIEN XT valve had an 84% probability of being dominant over SAVR. Further, SAPIEN XT valve had a 100% probability of being a cost-effective treatment option (i.e., ICER <$50,000/QALY) for AS patients with intermediate surgical risk.

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* See S3i CEA results section below for slight variations in cost inputs.

† Included medical doctor fees and procedural and non-procedural costs.

‡ Iincluded index hospitalization and follow-up costs.

In summary, although the procedural costs associated with the SAPIEN XT valve were higher than those associated with SAVR, use of SAPIEN XT valve led to substantial reductions in hospital LOS that resulted in total medical care costs that are lower at 2 years of follow-up. Over a lifetime horizon, SAPIEN XT valve was projected to be an economically dominant treatment strategy, providing both longer QALE and lower long-term costs than SAVR with a high degree of confidence.

S3i CEA Results

The S3i CEA included a few differences compared with the PARTNER IIA CEA: complete Medicare claims were only available through 1-year of follow-up; Year 2 costs were estimated based on regression analysis; and all comparisons were adjusted for imbalances in baseline characterisitics using propensity score stratification (for clinical outcomes) or propensity bin bootstrapping (for costs).[175]

As in the PARTNER IIA CEA of SAPIEN XT valve, the S3i analysis showed that procedural efficiency was significantly better with the SAPIEN 3 valve than with SAVR. However, unlike the PARTNER IIA CEA, index costs (**Figure 3.2**), follow-up costs (**Figure 3.3**), and total 1-year costs (

Figure 3.4) were all lower with SAPIEN 3 valve than with SAVR.

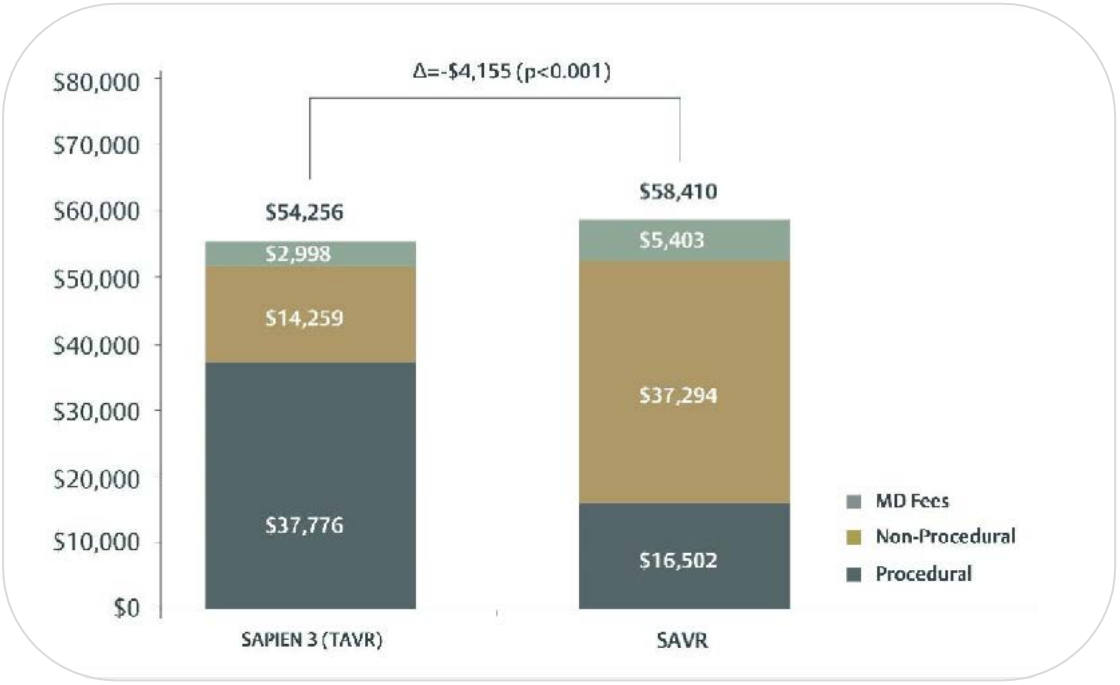

Figure 3.2: Index hospital costs with SAPIEN 3 valve (TAVR) and SAVR, intermediate surgical risk patients, S3i Trial.
Note: Trimmed means; all costs are propensity-adjusted.
Key: MD = medical doctor, S3i = SAPIEN 3 valve intermediate, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.
Source: Cohen, 2017.[175]

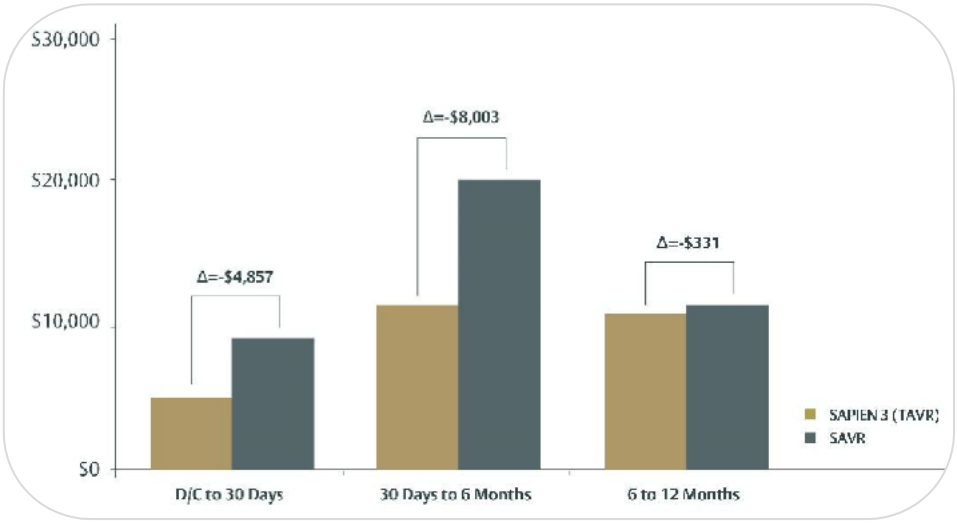

Figure 3.3: Follow-up costs by time interval with SAPIEN 3 valve (TAVR) and SAVR, intermediate surgical risk patients, S3i Trial.
Note: Trimmed means; all costs are propensity-adjusted.
Key: D/C = discharge, S3i = SAPIEN 3 valve intermediate, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.
Source: Cohen, 2017.[175]

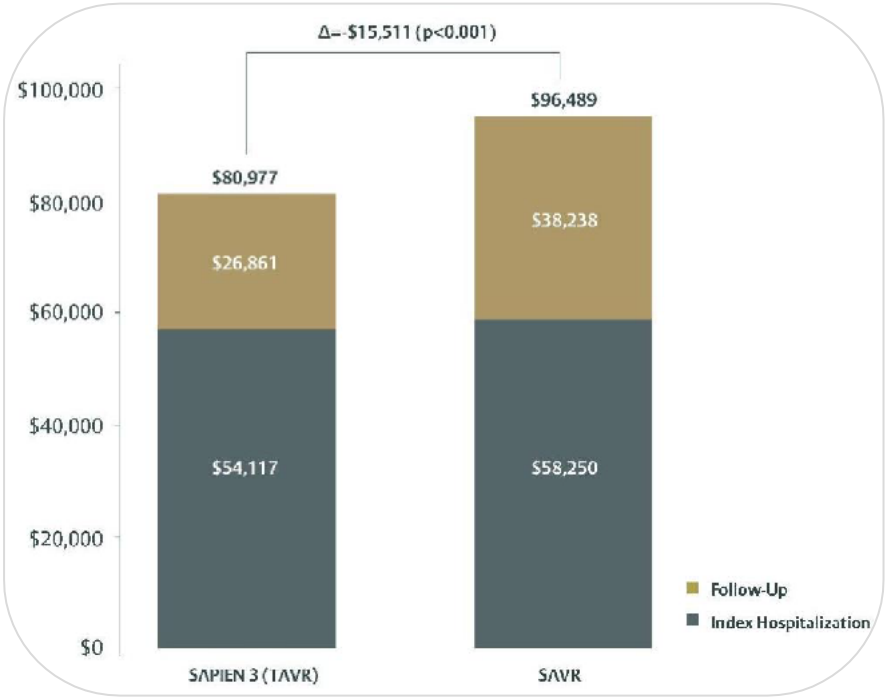

Figure 3.4: Total 1-year costs with SAPIEN 3 valve (TAVR) and SAVR, intermediate surgical risk patients, S3i Trial.

Note: Trimmed means.
Key: S3i = SAPIEN 3 valve intermediate, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.
Source: Cohen, 2017.[175]

Within the trial, there was a 0.09 change in Lys and a 0.11 change in QALY. Projected changes in life expectancy and QALE (undiscounted; risk-adjusted) were increased with SAPIEN 3 valve compared with SAVR (+0.34 years and +0.32 QALYs, respectively). The analysis showed that with a change in cost of -$9,692 and a change in QALE of 0.27 QALYs (discounted), SAPIEN 3 valve had a 97% probability of being dominant over SAVR (**Figure 3.5**). Further, similar to the PARTNER IIA CEA, SAPIEN 3 valve had a 100% probability of being a cost-effective treatment option (i.e., ICER <$50,000/QALY) for AS patients with intermediate surgical risk.

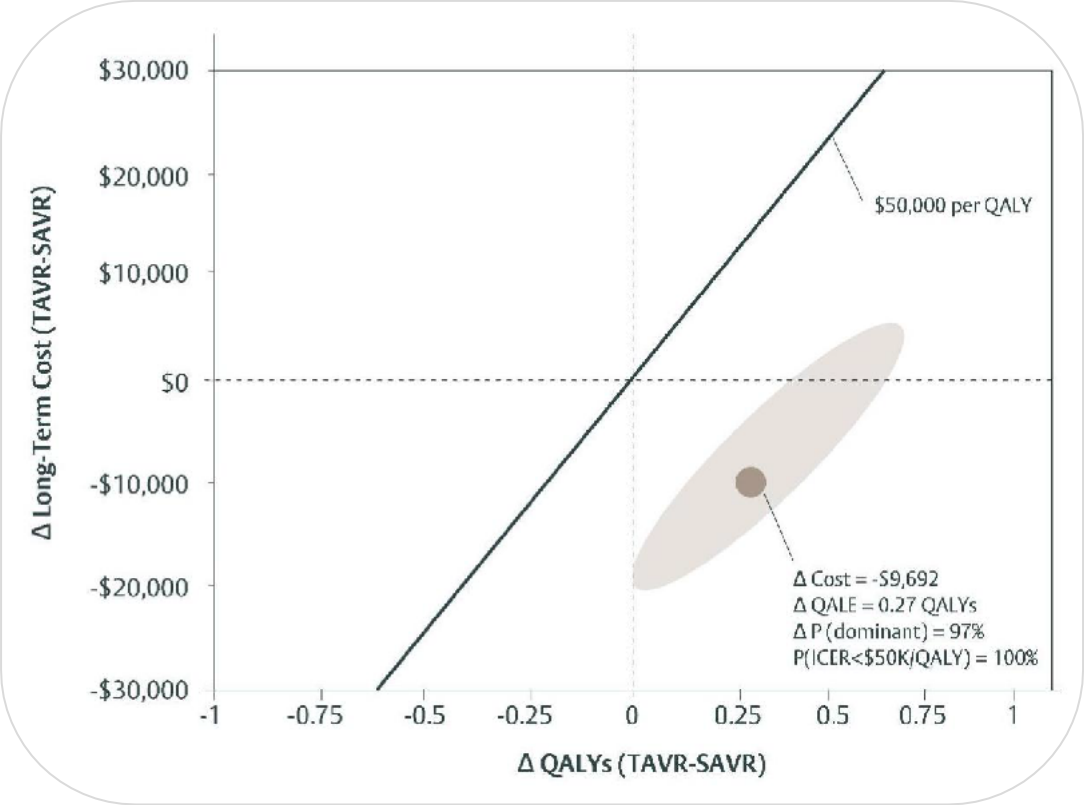

Figure 3.5: Cost effectiveness of SAPIEN 3 valve (TAVR) versus SAVR in intermediate surgical risk patients, S3i Trial.
Key: ICER = incremental cost-effectiveness ratio, P = probability, QALE = quality-adjusted life expectancy, QALY = quality-adjusted life years, S3i = SAPIEN 3 valve intermediate, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.
Note: costs and benefits discounted at 3%.
Source: Cohen, 2017.[175]

In summary, the cost effectiveness results for the SAPIEN 3 valve (with more contemporary care patterns) were even more favorable than those for SAPIEN XT valve in severe AS patients who are at intermediate risk for surgery. SAPIEN 3 valve was found to be a dominant strategy compared with surgery, meaning that it improves both clinical outcomes (e.g., life years and QALYs) and lowers costs. The CEA showed a lifetime cost savings of ~$10,000 per patient and a significant gain in QALYs. Taken collectively, the clinical and economic results for SAPIEN XT valve and SAPIEN 3 valve suggest that TAVR is not only cost effective but cost saving for severe symptomatic AS patients with intermediate surgical risk. These findings are extremely favorable, particularly given that prior CEAs for SAPIEN valve and CoreValve have not shown statistically significant differences in follow-up costs. The results are also favorable when compared with those for other technologies used in the US—TAVR with SAPIEN 3 valve is one of few therapies that has the potential to generate substantial cost savings while improving clinical outcomes.

3.1.4. Summary

As described above, several studies have evaluated the cost effectiveness of TAVR with the SAPIEN valve or other THVs compared with medical management or SAVR in patients with severe symptomatic AS. These studies are associated with some limitations that should be considered while reviewing their results:[176]

- The majority of these trial- and model-based analyses used inputs from studies of first-generation TAVR technologies; however, newer and improved generations are available (e.g., SAPIEN 3 valve).
- Model inputs for high surgical risk patients were derived from randomized controlled trials that compared the early clinical experience with TAVR (i.e., learning curve cases) to a more well-established surgical therapy.
- Model results for TAVR versus SAVR are notably better for TF-TAVR than for non-TF access routes; however, some analyses included both approaches. TF-TAVR is the preferred route in current practice.
- Various methodological approaches were used in the models to project long-term survival that can substantially impact their results.
- Practices in clinical trials may differ from those in routine clinical care and lead to different clinical outcomes.
- The results of analyses conducted in one region/country/health system do not easily translate to those in others.

Despite these limitations, overall the results of CEAs suggest that TAVR with the SAPIEN valve can be a cost-effective option for patients with severe symptomatic AS who are inoperable or at high surgical risk. Further, TAVR with the SAPIEN XT valve or SAPIEN 3 valves is a dominant (improved clinical outcomes and lower costs) strategy over SAVR in patients with intermediate surgical risk.

4. The Requestor's Recommended NCD

On October 25, 2017, CMS received a request from Dr. Pelikan et al. to reconsider the TAVR NCD 20.32. In the letter, Dr. Pelikan indicates that current TAVR NCD requirements are obsolete and overly restrictive, limiting the ability of low volume centers to provide key services to Medicare beneficiaries. The letter conveys four key points: 1) NCD determinations can adversely affect patient care and outcomes, 2) there is no data to support the procedural volume criteria for TAVR in the initial NCD, 3) procedural volume is not an absolute predictor of quality and, 4) TAVR growth results in significant reduction in surgical AVR volume.

In support of these key points, Dr. Pelikan states that TAVR has evolved into a streamlined, "commonplace and safe procedure" and that strict procedural volume requirements – initially intended to ensure quality when few hospitals and operators had experience with the procedure – are no longer relevant. In addition, Dr. Pelikan asserts there is no evidence to support the use of non-TAVR procedural volume criteria (PCI, SAVR) as a surrogate for TAVR quality. Two options are proposed for CMS consideration: 1) retire the NCD or 2) remove the volume criteria from the NCD and instead base coverage on direct quality measurement.

Edwards commends Dr. Pelikan for raising a number of relevant and timely issues. We agree that updating the NCD is important; however, we do not envision a current scenario in which the NCD is eliminated. We provide detailed recommendations in Sections 5-6 for areas in which we believe the NCD can and should be revised. Briefly, given the state of the evidence for TAVR and the urgent patient need, we believe it is now appropriate for CMS to expand the NCD to all AVR and to permit carefully controlled TAVR expansion to additional hospitals based on clinical need, patient access and the assurance of high quality outcomes. Similar to Dr. Pelikan, we contest the notion that only high-volume TAVR centers produce excellent results, since the evidence clearly demonstrates that many low-volume, quality centers are delivering excellent care. As an alternative to using volume as a surrogate for quality, we believe CMS should directly measure quality at TAVR centers as the basis for ongoing coverage by using the established quality-tracking infrastructure available in national prospective audited registries.

Another relevant document, with important implications for the NCA, is the recently published 2018 Multisociety Expert Consensus Systems of Care Document.[177] Tables summarizing the Societies recommended requirements for new and existing TAVR programs are included in **Appendix C: 2018 Multisociety Expert Consensus Systems of Care Document Tables**

For new programs, Edwards supports the use of a multidisciplinary approach to all forms of therapy for aortic valve disease and an SDM process. Edwards also supports appropriate site infrastructure and quality assessment. We believe having an active SAVR and PCI program as well as the capacity to perform vascular and pacemaker interventions are necessary prerequisites. However, we believe there is insufficient evidence to establish minimum volume thresholds for SAVR, PCI, or TAVR to start a new program as an assurance of better outcomes.

For existing programs, Edwards supports the establishment and use of minimum quality requirements. We believe a quality focus will ensure high performance and obviate the need for less precise measures such as volume. Additionally, we are concerned that other requirements, such as the need for ≥2 hospital based cardiac surgeons who both spend ≥ 50% of their time at the hospital are arbitrary and unnecessarily burdensome.

4.1. Volume Is Not an Appropriate Surrogate for Quality

There is limited relevant evidence in the literature on the relationship between TAVR outcomes and both non TAVR or TAVR volumes (**Appendix D: Literature Review)**. In a review of 2,893 articles:

- No studies were identified that directly assess the impact of SAVR and/or PCI volumes on the set-up of new TAVR programs. Thus, there is no evidence that a certain threshold of SAVR and/or PCI procedure volumes would predict quality or outcomes for TAVR procedures performed in new TAVR programs without prior TAVR experience.
- Only two studies assessed the relationship between annual SAVR procedure volumes and outcomes (mortality) in patients undergoing TAVR in hospitals with TAVR programs; both these studies reported that there was no statistically significant association between annual SAVR procedure volume and TAVR mortality. [178,179]
- There is only one study that specifically examined PCI volume and TAVR outcomes using the Nationwide Inpatient Sample (NIS) database.[180] No association was found regarding outcomes of in-hospital mortality, vascular complications, bleeding complications, or neurological complications.

Furthermore, there is also limited support of the relationship between TAVR volumes and outcomes. A recent review of currently available literature identified 26 studies that comment on TAVR volumes and their relationship to outcomes,[154,178,181-204] 19 papers show an inverse correlation with volumes and outcomes with only nine papers showing inpatient or 30-day mortality with appropriate risk adjustment for patient factors. However, overall, all of these studies had significant limitations including small sample size and/or single institution setting, conducted OUS, and/or had an early time bias given that these studies primarily focused on volume-outcomes data up to 2015, prior to the introduction of current generation, widely-used devices. Thus, these data represent historical TAVR practice and technology and are not relevant to practice today where current evaluation of Medicare or TVT volumes shows no association between volumes and outcomes. (**Appendix D: Literature Review**)**.** Given the dearth of relevant and timely published evidence, we have performed original analyses of the most updated available data from sources such as Medicare and the TVT Registry.

4.1.1. There Is No Data to Support Minimum Volume Threshold for PCI and SAVR to Start or Maintain a TAVR Program

In the establishment of requirements to open or maintain a TAVR center, the NCD 20.32 criteria for individual hospital program approval was based on non-TAVR procedural volume including number of SAVR, cardiac catheterizations, and coronary interventions (PCIs). At the time of the original NCD, few hospitals had TAVR experience and so expert opinion on program requirements was considered reasonable. However, TAVR has now passed the introductory phase and there is insufficient evidence to continue using non-TAVR volumes as criteria for TAVR program initiation or continuation.

To examine the potential correlation between non-TAVR procedural volume and TAVR outcomes, Medicare data from 2012-2016 were analyzed (**Appendix A: Medicare**). All outcomes underwent risk adjustment to ensure centers were not unfairly penalized for higher risk patients. The resulting analysis showed no significant correlation between SAVR volumes in the year prior to TAVR program establishment and TAVR in-hospital mortality in the first year of the program (p=0.79, **Figure 4.1.A**). Additionally, the data also showed no significant correlation between PCI volumes in the year prior to TAVR program establishment and TAVR in-hospital mortality in the first year of the program (p=0.59, **Figure 4.1.B**). These analyses demonstrate that non-TAVR volumes should not be used as criteria for the initiation of a TAVR program.

In examining the relationship between non-TAVR volumes and TAVR outcomes, 2016 SAVR volumes showed no correlation with TAVR in-hospital mortality (p=0.52, **Figure 4.1.C**) or TAVR 30-day mortality (p=0.75). Similarly, 2016 PCI volumes show no relationship to TAVR in-hospital mortality (p=0.84, **Figure 4.1.D**) or TAVR 30-day mortality rates (p=0.62).

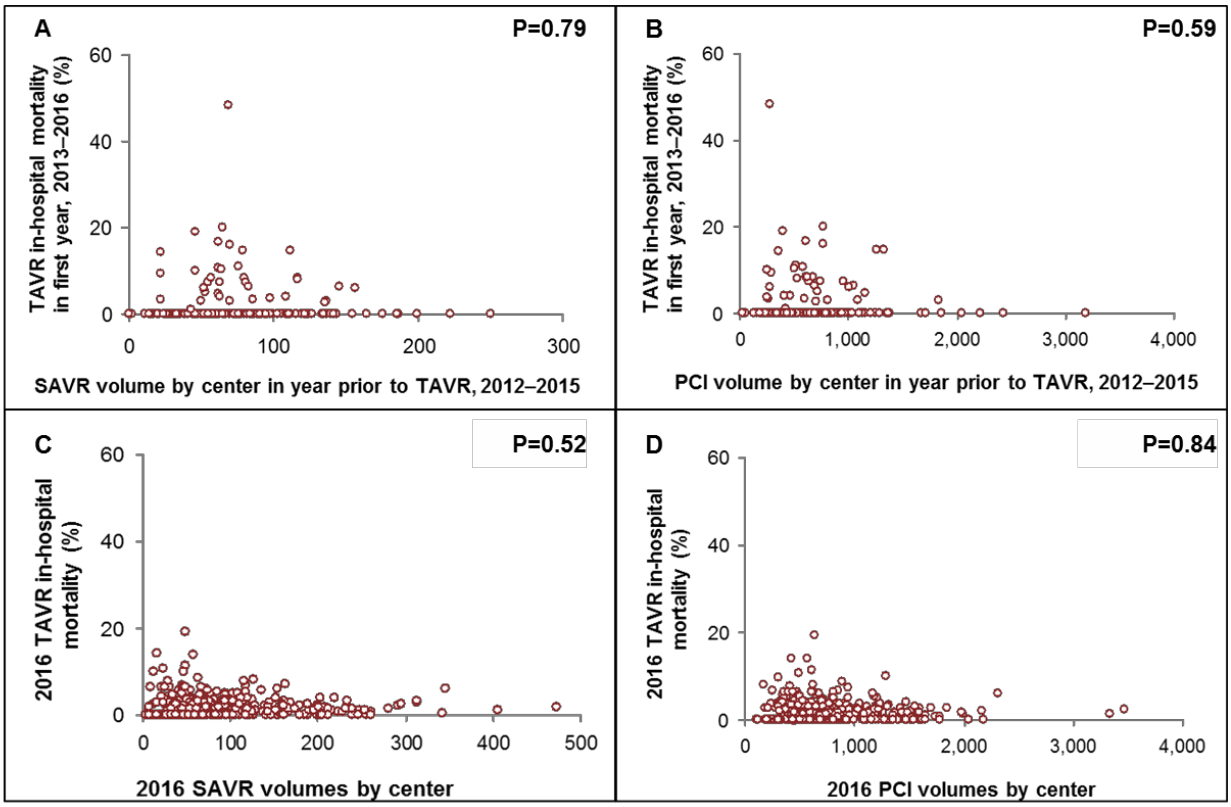

Figure 4.1: **Non-TAVR procedural volumes vs TAVR in-hospital mortality rates A.** Prior SAVR volume not correlated with TAVR mortality in the first year, **B.** Prior PCI volumes not correlated with TAVR mortality in the first year, **C.** Current SAVR volumes not correlated with TAVR mortality, **D.** Current PCI volumes not correlated with TAVR mortality

Additional published research has also shown similar results. One recent study specifically examined PCI volume and TAVR outcomes using the Nationwide Inpatient Sample (NIS) database.[180] No association was found regarding outcomes of in-hospital mortality, vascular complications, bleeding complications, or neurological complications (**Table 4.1**). The authors concluded that the CMS requirement of 400 PCIs per year does not seem to be necessary to warrant optimal TAVR outcomes as the skill sets required may not fully translate to TAVR.

Similarly, as TAVR is an interventional procedure, not an open surgical technique, there is limited correlation between TAVR outcomes and SAVR volumes and performance. Although concern for the need to convert to open procedures was valid in the early experience with TAVR, today, less than 1% of procedures convert to an open surgery. Overall, there is limited evidence to support the use of non-TAVR volumes as requirements for TAVR programs.

Table 4.1. Patel et al. on the association between PCI thresholds and TAVR outcomes

Annual Hospital PCI Volume	Overall	< 400	≥ 400	P-value
In-hospital mortality	4.9	5.2	4.7	0.124
Unadjusted OR (95% CI)		Referent	0.89 (0.78-1.02)	0.124
Adjusted OR (95% CI)		Referent	0.98 (0.62-1.54)	0.923
Vascular complications	6.7	6.9	6.6	0.514
Unadjusted OR (95% CI)		Referent	0.96 (0.85-1.08)	0.514
Adjusted OR (95% CI)		Referent	1.13 (0.78-1.63)	0.519
Bleeding requiring transfusion	13	13.3	12.9	0.52
Unadjusted OR (95% CI)		Referent	0.97 (0.89-1.06)	0.52
Adjusted OR (95% CI)		Referent	1.01 (0.64-1.58)	0.975
Neurological complications	1.5	0.9	1.7	<0.001
Unadjusted OR (95% CI)		Referent	1.85 (1.36-2.49)	<0.001
Adjusted OR (95% CI)		Referent	1.91 (0.90-4.06)	0.09

4.1.2. There Is No Data to Support a Relationship between Other Structural Heart Procedural Volumes and TAVR Outcomes

In the letter by Dr. Pelikan, there is mention of the potential use of other structural heart procedure volumes as surrogates for TAVR quality.[205] He highlights the similarities of TAVR with several procedures including MitraClip, Watchman, and septal repairs and states that these would be better indictors of a facility's TAVR abilities. To evaluate further, Medicare data from 2011 to 2016 were analyzed to assess any correlation between procedural volumes of MitraClip, Watchman, or septal repairs and TAVR risk-adjusted outcomes for 30-day mortality, 30-day stroke rate, bleeding complication rates, and vascular complication rates (**Appendix A: Medicare**). No significant correlation was found between any of these procedure volumes and TAVR outcomes (p>0.05 for all analysis) (**Figure 4.2**) providing no evidence to support this new recommendation from Dr. Pelikan.

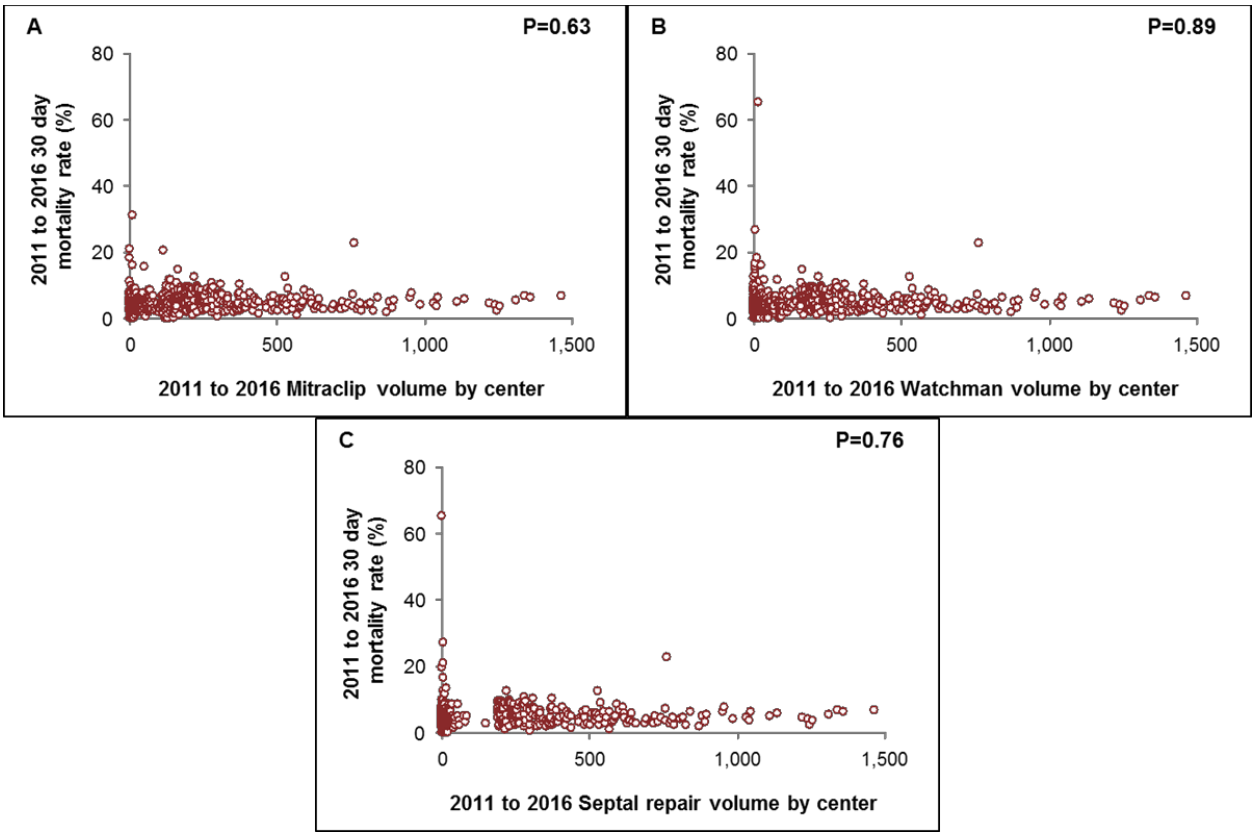

Figure 4.2: Non-TAVR procedural volumes versus 2011 to 2016 30-day mortality rate. A. No significant correlation between Mitraclip volumes **B.** No significant correlation between Mitraclip **C.** No significant correlation between septal repair volumes and TAVR 30-day mortality

4.1.3. There Is Limited Evidence to Support an Association between TAVR Volumes and Outcomes and Establish Minimum TAVR Volume Thresholds

In addition to the aforementioned literature review described in Section 4.1.1, Medicare data and TVT findings were used to evaluate the relationship between TAVR volumes and outcomes. Both sources found no strong evidence to support a relationship between TAVR volumes and outcomes. Specifically:

- **Medicare shows no significant relationship between TAVR volumes and outcomes:** An analysis of 2016 Medicare data showed no significant correlation between current TAVR volumes and risk adjusted 30-day mortality rate (p=0.37, **Figure 4.3.A**). 2011-2016 Medicare data showed similar results for rates of 30-day mortality (**Figure 4.3.B**), stroke, bleeding complications, and vascular complications (all p-values > 0.05). Additionally, no predictive relationship between TAVR volumes and any of these endpoints could be established using iterative mixed models (**Appendix A: Medicare**).

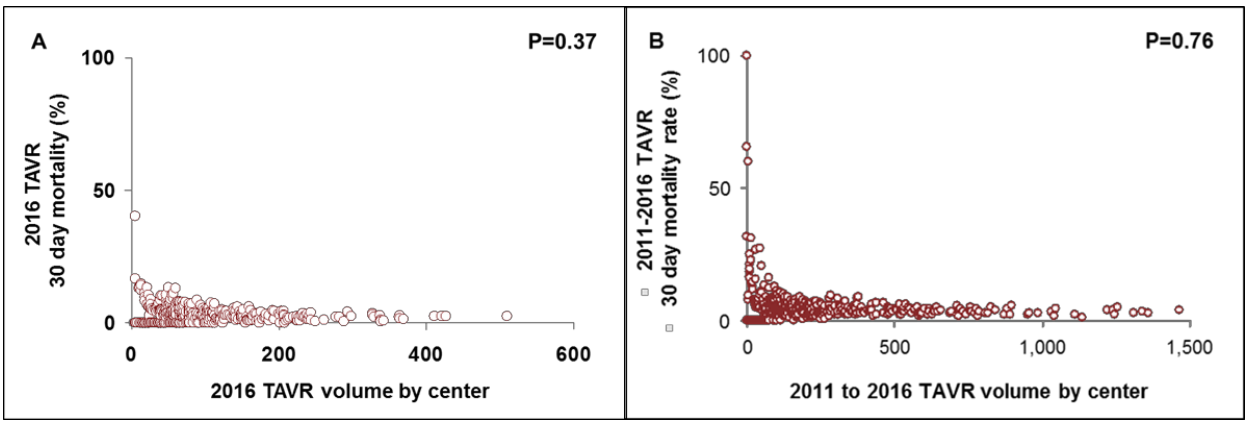

Figure 4.3: TAVR procedural volumes versus mortality outcomes measures. **A.** Current TAVR volumes not correlated with TAVR in-hospital mortality, **B.** No correlation between 2011-2016 TAVR volumes by center and 30-day mortality rate

- **TVT Registry data shows no relationship between TAVR volumes and outcomes:** In evaluating 61,295 SAPIEN 3 valve cases in the TVT Registry, there was no significant association between annualized procedure volume and TAVR outcomes including mortality, stroke, major vascular complications and major bleeding ($p>0.05$ for all, **Figure 4.4**). Furthermore, 111 low-volume centers (SAPIEN 3 valve annual volume < 50 cases/year) reported 0% in-hospital mortality (**Appendix E: TVT Registry**).

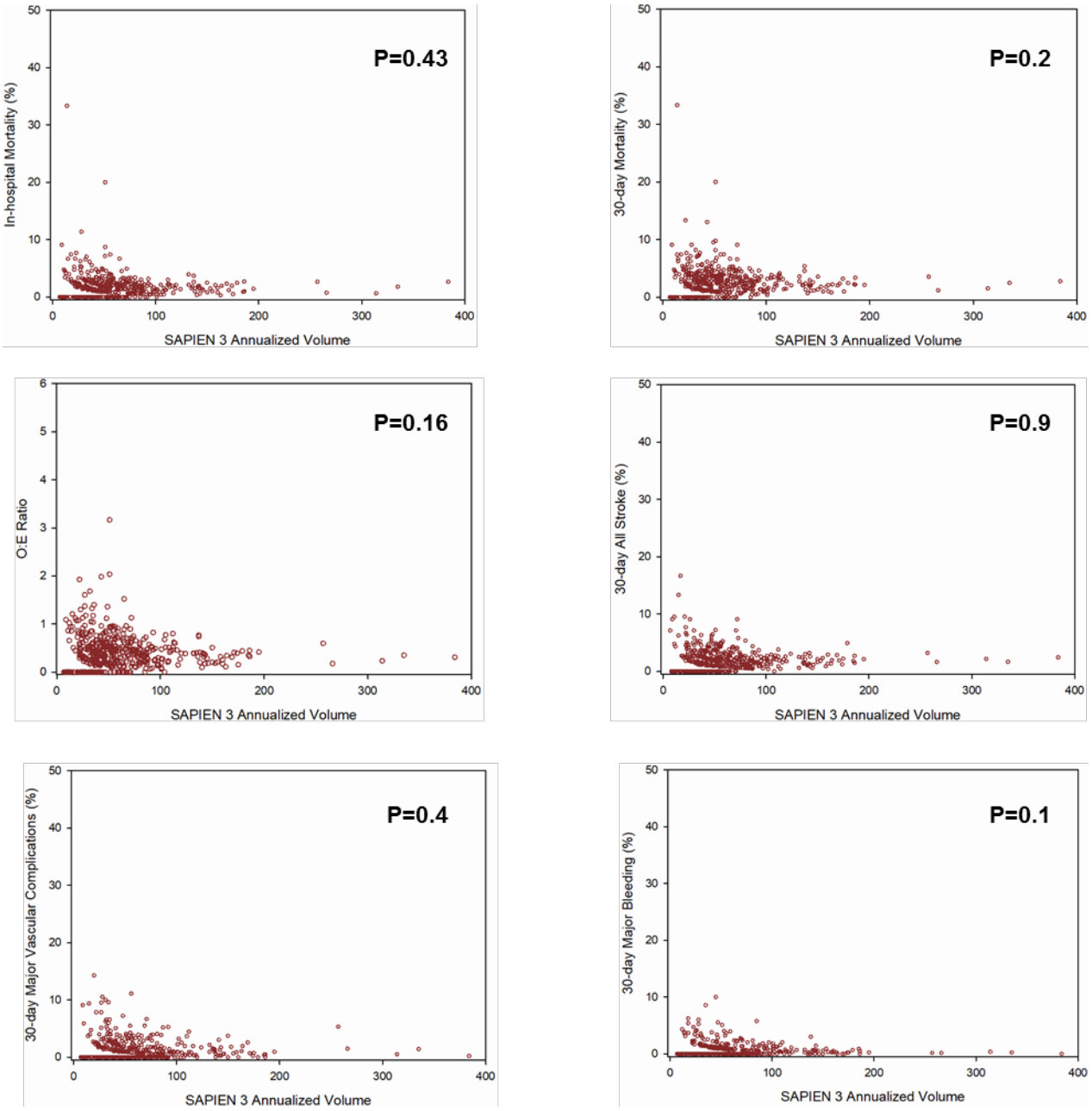

Figure 4.4: SAPIEN 3 valve outcomes versus annualized volumes shows no significant volumes outcomes relationship.

Specific attention must be given to address concerns related to John Carroll's recent publications and presentations. In a recent TVT publication, increasing site volume was associated with improved in-hospital risk-adjusted outcomes, including lower mortality ($p < 0.02$).[187] The findings of this paper, however, reflect a learning curve for the procedure that exists across *all* TAVR facilities, regardless of prior volume as demonstrated in an analysis of Medicare data recreating Carroll's findings (**Appendix A: Medicare**). When repeating case sequence analysis stratified by centers above and below the median procedure volume, no meaningful difference in learning curve was identified (**Figure 4.5**). This was further tested with interaction terms and nesting volume within facility, both of which showed no relationship to volume. Therefore, as

high and low volume centers show similar learning curves, the data do not support excluding low volume centers. Outcomes will be equally strong over time.

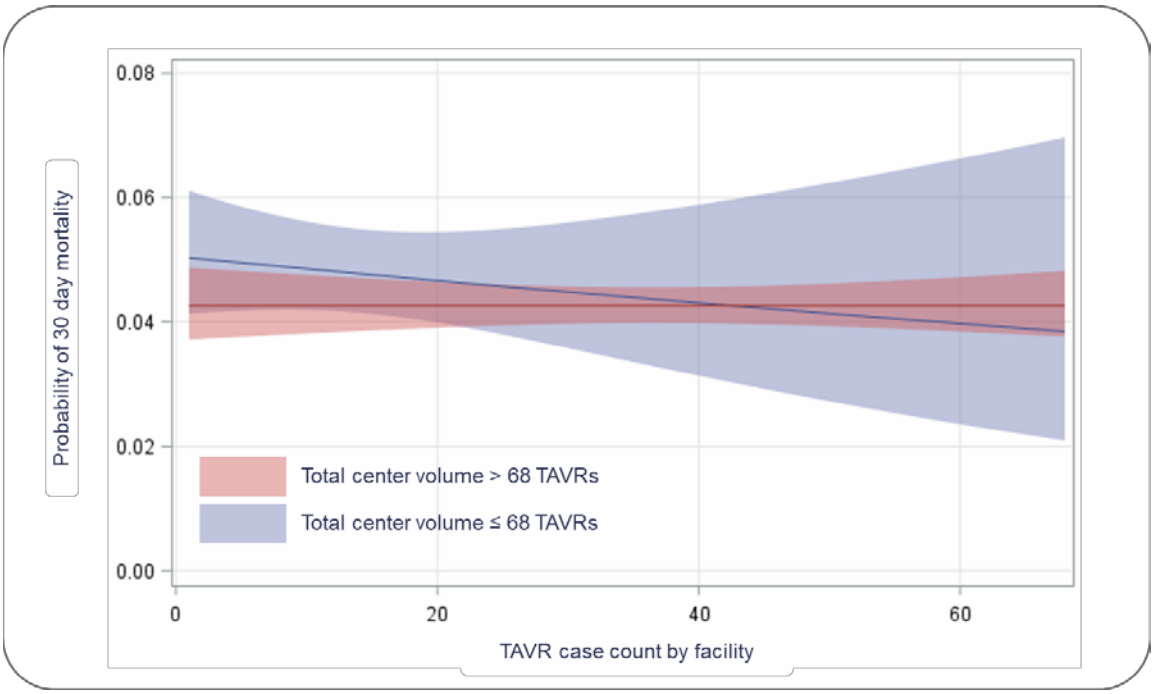

Figure 4.5: Mortality risk by case sequence (learning curves) for low volume and high volume TAVR centers. No difference for learning curves between low- and high-volume centers. Methodology for learning curves based on Carroll study.[187]

Carroll also recently presented data from the TVT Registry examining the relationship between annual TAVR volume and 30-day mortality.[208] The study analysis appears to use the means for the box plot analysis as opposed to the more conventional use of medians for this type of descriptive statistic. Data sets with observations rather distant from the main body of data have a long tail and therefore the mean can be unduly influenced by these few unusual observations. It is most appropriate to therefore use a median which is more resistant to outlier values.[209]

When the aforementioned analysis was recreated using the appropriate statistical test comparing the medians for adjusted 30-day mortality across the volume cohorts for the Medicare population there was no correlation between volumes and outcomes (**Appendix A: Medicare**). Box plots for results are shown in **Figure 4.6** with summarized statistics showing high overlap between the center volume groups presented in **Table 4.2.**

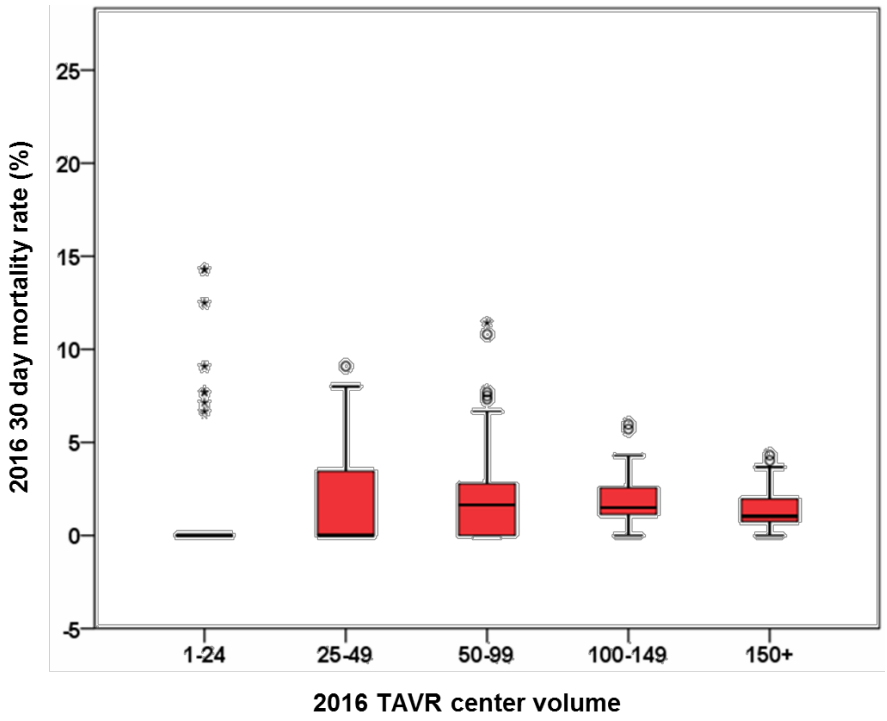

Figure 4.6: 30-day mortality rates stratified by center volumes from Medicare.

Table 4.2. Outcomes were excellent across centers regardless of case volume. No significant correlation between volumes and outcomes was observed.

Center Volume	# of Sites	# of Implants	% sites with zero mortality	30-day mortality rate			
				Median	Mean	10th Percentile	90th Percentile
1-24	81	1,033	80%	0.00%	2.60%	0.00%	2.60%
25-49	109	4,155	56%	0.00%	2.20%	0.00%	2.20%
50-99	143	10,011	33%	3.00%	3.30%	0.00%	3.30%
100-149	66	8,002	11%	2.90%	2.90%	0.50%	2.90%
150+	94	22,924	4%	2.00%	2.00%	0.70%	2.00%

4.1.4. Many Low Volume Centers Achieve Excellent Outcomes and There Are Higher Volume Sites with Suboptimal Outcomes

Most TAVR centers have achieved excellent outcomes with little difference noted between high- and low-volume centers. In fact, the median 30-day mortality at the lower volume centers was lower than that of the highest volume (**Table 4.2** above). Furthermore, in comparing the percentage of centers with 0% 30-day

mortality in 2016, 80% of sites with < 25 cases achieved this rate compared to only 4% of sites with > 150 procedures.

That said, there may be questions about the consistency of results at low volume centers. To address this, the outcomes of centers that remained low volume over time (<50 annual TAVR cases) were analyzed from 2014 to 2016 using Medicare data. The results demonstrate that these centers (n=72) all achieve excellent outcomes over time and there was no decrement to quality as additional case observations accumulated (**Table 4.3**).

The inclusion of more stringent volume criteria raises concerns that centers with proven quality and excellent outcomes may not be in compliance with revised policy requirements. We believe focusing directly on patient outcomes is the most appropriate way to improve patient care.

Table 4.3. From 2014 to 2016, sites with less than 50 annual cases for 3 consecutive years have shown excellent outcomes

		2014	2015	2016
Average TAVR procedures per center	**Centers with <50 TAVR cases** *(n=72)*	**17**	**26**	**32**
Average risk-adjusted in-hospital mortality rate (%)	**Centers with <50 TAVR cases** *(median , 10th %tile, 90th %tile)*	**3.7%** *(0.0, 0.0, 10.6)*	**1.3%** *(0.0, 0.0, 5.1)*	**1.7%** *(0.0, 0.0, 5.5)*

4.1.5. Nearly 40% of Existing TAVR Centers Would Be at Risk of Noncompliance with Revised Volume Requirements

Implementing volume thresholds would have a significant impact on CMS's ability to provide adequate care to Medicare beneficiaries with SSAS. If volume requirements were to be increased to 50 TAVR cases and 30 SAVR cases to maintain a TAVR program, of the 540 TAVR centers in operation, 40% of centers would be at risk of non-compliance (n=208) based on an analysis of 2017 Medicare data (**Appendix A: Medicare**). 161 centers would be below the TAVR threshold (< 50 TAVR cases), 8 centers would be below the SAVR threshold (< 30 SAVR cases), and 39 centers would be below both SAVR and TAVR thresholds (< 50 TAVR cases and < 30 SAVR cases), resulting in the potential displacement of ~6500 patients who would have to seek care at alternate sites. With 208 fewer centers, there will also be a significant challenge adequately addressing the more than 250,000 patients who develop SSAS every year (**Appendix B: Optum**).

4.1.6. Few Non-TAVR Centers Would Have the Opportunity to Open in The Future

New NCD volume requirements would also have implications for the current SAVR only centers. Based on 2017 Medicare data, if a 40 SAVR procedural volume threshold is imposed, less than 25% of current "SAVR only" centers would meet requirements (**Appendix A: Medicare**). This situation would only be exacerbated if TAVR growth in the future causes the conversion of open to interventional procedures.

Furthermore, SAVR centers have also showed the strongest outcomes when they have the ability to also offer TAVR. A 2016 Medicare analysis showed that SAVR centers with TAVR have an in-hospital mortality of 4.4% versus 6.7% at "SAVR only" centers. Thus, the inability to open new TAVR programs to pair with SAVR may result in higher risk patients inappropriately receiving SAVR with excess morbidity and mortality.

4.1.7. Volume Requirements May Create Perverse Incentives

Volume thresholds may also create perverse incentives throughout the healthcare system, which could impact patient care beyond just patients with SSAS:

- **Hospitals could be perversely incentivized to perform inappropriate PCIs:** Given the PCI requirement for TAVR eligibility, centers could be incentivized to increase PCI volumes to ensure they meet volume requirements.
- **Hospitals could be incentivized to perform high-risk or non-indicated SAVRs:** Given the relationship between TAVR and SAVR, a volume requirement for SAVR would have significant patient impact. Centers may inappropriately limit patient choice to ensure surgical volumes are met. Likewise, centers may perform SAVR on higher risk patients to be TAVR eligible or maintain TAVR eligibility, potentially encouraging patients to undergo a significantly more invasive, higher mortality risk procedure.
- **Hospitals could be incentivized to perform more TAVRs as opposed to high-quality TAVRs:** Hospitals may focus on performing more procedures as opposed to emphasizing the delivery of high quality, high outcome interventions. This could lead to some patients who would be better surgical candidates inappropriately directed to TAVR. A volumes-focused system is likely to drive volumes—it could incentivize, instead of prevent—potentially inappropriate use of interventions and reward centers for doing more as opposed to improving care.

Overall, focusing on volumes may incentivize inappropriate utilization and drive the system towards inefficiencies, higher cost, and poorer patient care.

4.2 We Can and Should Measure TAVR Quality Directly

When the initial TAVR NCD was implemented, experience with the therapy was limited to sites participating in the early regulatory approval trials.[210] As questions remained about how the promising early clinical data would generalize in commercial practice, it made sense to take a cautious approach. Requirements in the form of minimum volumes mirroring the structural heart experience, infrastructure and processes of early trial sites were adopted in an effort to safely broaden the clinical use of TAVR. In the intervening years, careful monitoring in the form of annual Registry updates and quarterly hospital-specific reports has demonstrated national outcomes for TAVR comparable with prior published trial data[144,148] and significant improvements in clinical outcomes over time despite substantial TAVR center growth.[207]

The NCD also mandated hospital participation in a nationally audited prospective registry to track outcomes. The STS and ACC developed the TVT Registry in collaboration with the FDA, CMS and industry manufacturers to satisfy the reporting requirement and support performance improvement initiatives.[207] To date, more than 150,000 commercial TAVR cases have been submitted.[211] The Registry provides standardized clinical information on consecutive TAVR cases across the US and enables each hospital to compare its results to national and peer group averages for quality improvement.[207]

The ideal infrastructure and process is already in place to measure program outcomes and quality directly. These learnings can and should be used to disseminate best practices and improve patient care. As John Carroll has stated, "the bottom line is not volume, but the actual outcomes achieved at a center."[206] The availability of robust measures of quality through the Registry should obviate the need to rely on less precise measures such as volume. We are concerned a volume-based policy would distract from the true goal of promoting high standards of care for all patients with aortic stenosis. It would penalize low volume centers

with excellent outcomes. Therefore, Edwards supports measuring TAVR center quality directly through the TVT Registry and using this as the basis for ongoing CMS approval and reimbursement.

To this end, Edwards recommends that CMS establish AVR (TAVR ± SAVR) performance targets based on a hospital's observed/expected (O/E) in-hospital mortality using the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) score. This risk model has undergone peer-reviewed validation[212] and was described by the National Quality Forum as "scientifically valid and NQF-endorsed."[213] The risk model has been used in all the US TAVR pivotal trials and is broadly applicable to all AVR approaches (TAVR or SAVR). Furthermore, the STS National Database is used for quality reporting to CMS and is a key part of the quality category for cardiac surgery for CMS Merit-Based Incentive Payment System (MIPS) program.[214]

4.2.1. There Is Well Established Precedent for Measuring Provider Performance Even at Facilities with a Small Sample Size

Cardiac surgery has measured outcomes for quality improvement and has developed multiple surgical registries and risk models over the past several decades.[215] The STS, for example, uses risk-adjusted performance reports for participants in the STS National Adult Cardiac Surgery Database.[212] Recognizing the need for robust provider performance estimates even among facilities that treat a small number of patients, Bayesian random-effects approaches have been developed and employed.[216] These approaches are especially advantageous when providers treat a small number of patients or the endpoints of interest are rare.[216] In fact, programs need to submit to the STS a total of only 10 surgical AVR cases over 3 years to receive a "star rating." Given that these approaches have been effectively used by the STS, we believe similar methods could be adopted to evaluate TAVR program quality in the TVT Registry.

CMS has also published methods for addressing small volume centers namely by using hierarchical generalized linear mixed models. As they state in their "FAQ for the Implementation and Maintenance of CMS Mortality Measures for AMI & HF," they "had a choice of excluding 'small' hospitals entirely from the report or including as many hospitals as possible while honestly reflecting the amount of certainty we had in the estimates. CMS adopted the latter strategy." Given that both CMS and STS have described methods for analyzing small volume centers, there is little justification for asserting that outcomes cannot be measured at low volume centers.

As an additional protective mechanism, and to help overcome any statistical challenges in the evaluation of low volume centers, we support a 3-year rolling time period to collect cases. This system will allow for a more complete profile of center outcomes to emerge. For low volume centers and new facilities in particular, we support interim assessments to look for signals and trends of poor quality that can be acted on immediately to enhance clinical performance.

4.2.2 At a Population Level, Policies Directly Mandating Quality Have a More Beneficial Effect Than Policies Focused on Volume

Although volumes might be easier to measure, quality-based metrics are the most effective means of improving patient care. They preserve small volume, high performing centers (versus volumes-based metrics) and they focus systems on what is most important: patient care.

The ability of outcomes-based targets to drive stronger improvements in patient care versus a volumes-based threshold can be demonstrated using scenario analyses. To evaluate the impact of a volume-based threshold versus an outcome-based threshold, we generated two scenarios using 2016 Medicare data with unadjusted-risk outcomes and analyzed the potential patient and center implications (**Appendix A: Medicare**). If volume thresholds of 50 TAVR procedures and 30 SAVR procedures were implemented, 65% of TAVR centers with 0% in-hospital mortality and 43% of centers overall would fall below the threshold (211 centers). Additionally, 16% of patients would be at below volume centers and potentially either

displaced to their next nearest TAVR centers or only given the option of SAVR. Furthermore, the impact of this policy overall would result in less than a 5% improvement in TAVR in-hospital mortality overall (2.0% to 1.97%) (**Figure 4.7.A**).

Importantly, the above analysis removes low volume providers and then recalculates the estimated in-hospital mortality among the remaining TAVR facilities. There is an inherent assumption that displaced patients will receive care consistent with the average hospital in this scenario. However, in practice, some patients could actually be sent to worse performing centers. For example, if a patient who would have been treated at a low volume center with 0% mortality is sent to the next nearest, higher volume center, there is no guarantee this patient will receive improved care. In fact, in a scenario analysis where all displaced patients were redirected to their next nearest TAVR center, the overall mortality of the displaced patients actually increased 25% (2.0% to 2.5%). Furthermore, in a volumes based scenario, the nearest remaining centers receiving displaced patients would have to increase their capacity by 62%. In short, volumes based requirements may not achieve the intended quality gains and may impose additional patient and center burdens.

In an outcomes based scenario, however, a patient could receive care at a high performing center and therefore, outcomes would improve not only for the system overall, but also for the displaced patients. In considering a policy based on an outcome target below 5.8% mortality (90th percentile), all centers with 0% TAVR in-hospital mortality would meet the criteria and only 10% of current centers would fall below the threshold (50 centers). Only 5% of patients would be at "below threshold" centers. This policy would result in a 15% overall improvement in TAVR in-hospital mortality (2.0% to 1.7% overall average) (**Figure 4.7.B**).

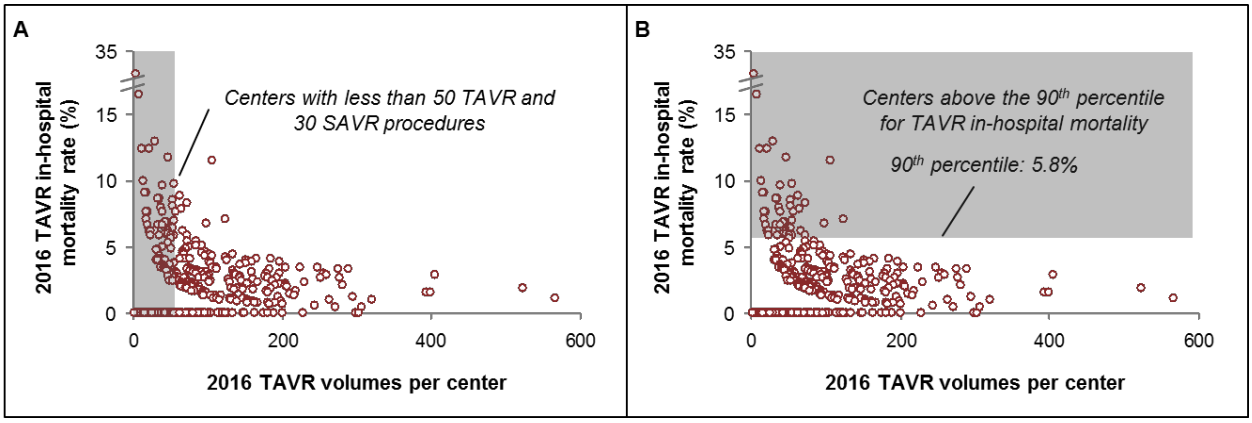

Figure 4.7: Outcome thresholds, not volume thresholds, will lead to better patient care. Outcomes thresholds keep all high performing centers, irrespective of volume.

Given that a registry is already established for the tracking and evaluation of outcomes in SSAS, outcomes should be the focus.

4.2.3. Multiple Examples of the Clinical Benefits of Directly Focusing on Outcomes

There are numerous real-world examples of the benefits of an outcomes-based approach. The Swedish Acute Myocardial Infarction Registry was established in 1991 to track key care outcomes. In 2006, the registry data was made publicly available resulting in poorer performing centers quickly taking notice of and remediating their performance. A Lancet study revealed a quick acceleration in adherence to guidelines after the results were made public with the poorest performers having the quickest rate of improvement.[217]

Overall systems outcomes in MI improved 22%. This example serves an illustration of the benefit of an outcomes-based evaluation system to drive improvements in patient care.

In another example of the benefits of focusing on outcomes-based approaches, two Swedish hospitals leveraged outcomes data to quickly and significantly decrease reoperation frequency in total hip replacements. In 2005, The Swedish Hip Arthroplasty Register reported the national average for reoperation frequency due to dislocation was 0.6%; however, Hospital Sundsvall reported 2.8% and Hospital Gavle reported 2.6%. Due to registry outcomes tracking, both hospitals realized the need for remediation with assistance from the registry and were able to drive significant improvements in surgical outcomes.[218] Within four years, Sundsvall lowered its reoperation frequency due to dislocation by 64% and Gavle lowered theirs by 58%.

In all of these examples, an outcomes-based focus was able to quickly and effectively improve patient care, resulting in strong improvements in overall system performance. As these examples illustrate, outcomes based systems can drive significant improvements in care.

4.3 Current Levels of Access Are Not Sufficient

4.3.1. Although Progress Has Been Made Since the Introduction of TAVR There Remains a Significant Treatment Gap Resulting in Excess Morbidity and Mortality

While most studies on treatment adequacy have focused on procedural outcomes, a broader examination of the full AS population, both treated and untreated, is required to understand the full extent of the unmet need.

The introduction of TAVR has resulted in a marked increase in the number of patients receiving life-saving care for SSAS; however, there is still a significant unmet need with less than 35% of the overall incident population treated in 2016 (**Figure 4.8**, **Appendix B: Optum and Appendix A: Medicare**). Even in states with the highest number of comprehensive facilities offering both TAVR and SAVR—California, New York, and Texas—the AVR treatment rates were all below 40% (**Figure 4.9**). In fact, in some areas of the country such as Wyoming, less than 8% of patients with newly developed SSAS received treatment. (**Appendix B: Optum and Appendix A: Medicare**).

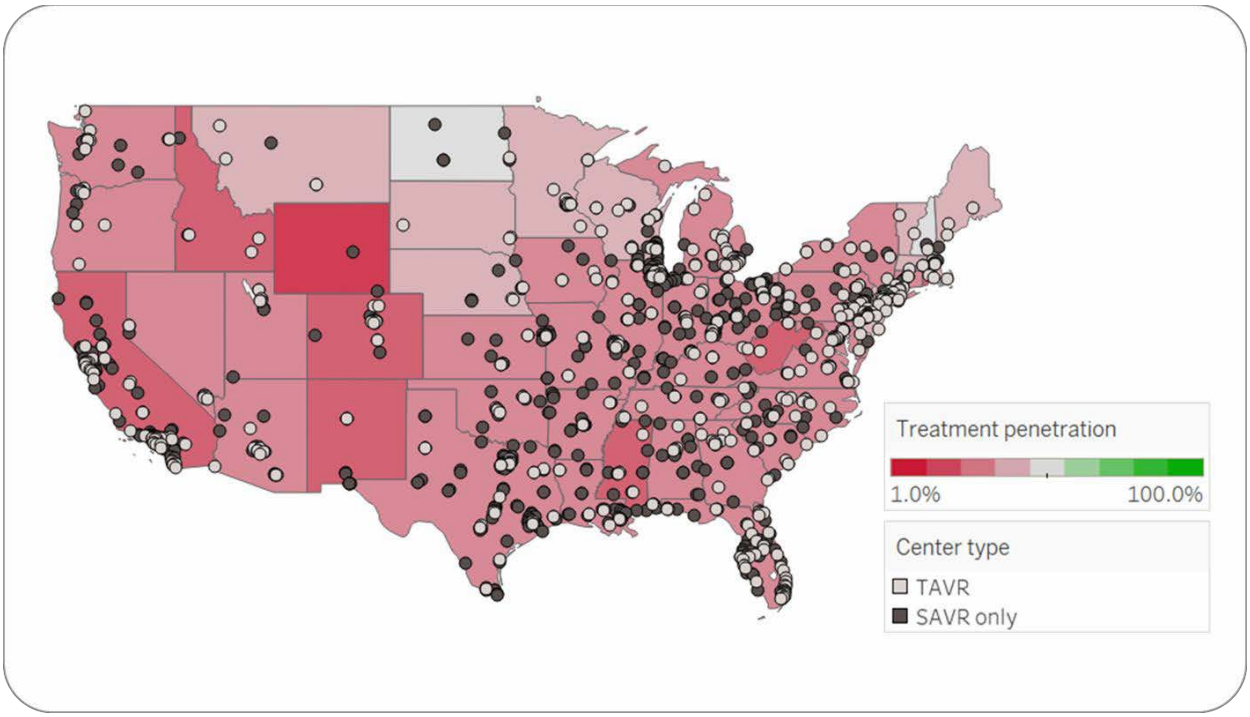

Figure 4.8: Treatment penetration in one year of patients with SSAS by comparing 2016 Medicare AVR volumes to overall incidence. Results are shown by state with the national average of AVR treatment penetration remaining at less than 35%.

Figure 4.9: Treatment penetration in one year of patients with SSAS in states with the highest number of TAVR centers. Despite having up to 44 centers, all of the states above have < 40% treatment rate

The continued impact of this low treatment penetration is significant: in the next two years, based on Optum data, it is estimated that more than 100,000 members of the incident population will die without treatment (**Appendix B: Optum)**. We believe the primary risk SSAS patients face today does not come from complications during AVR treatment—rather, it comes from not receiving treatment at all.

Underserved populations

While TAVR access has public health implications for the entire Medicare population, many of the more vulnerable and underserved Medicare patient subgroups have disproportionately gained from TAVR and therefore, stand to lose the most should access be curtailed.

1. *Elderly patients:* The prevalence of AS increases drastically with age. Patients 75 and older are nearly twice as likely as patients age 65-74 to have significant AS.[219] As a result, access to a less invasive intervention like TAVR has been critical to improving outcomes in elderly patients. In a cohort study examining outcomes in patients over 80, as the number of TAVR centers increased by more than 100 from 2014-2016, 23% more patients in this age group received an AVR resulting in a drop in mortality by 17% (**Appendix B: Optum and Appendix A: Medicare**).

   Despite these gains, elderly patients are still under-represented in AVR treatments given their share of the diagnosed SSAS population. In a review of a multi-institution EHR database, while elderly patients made up 47% of patients diagnosed with SSAS, they comprise only 36% of patients treated (**Appendix B: Optum**). This treatment gap likely persists for a number of reasons. Elderly patients are more likely to present with comorbidities that increase procedural risk of a procedure which could lead to more cautious treatment recommendations.[32] Also, elderly patients are significantly less willing to travel for surgery.[220] As a result, any further restriction in access to TAVR, may reverse the gains and exacerbate the original disparity.

2. *Women:* TAVR has also had a significant impact on the treatment of women with SSAS. Women have historically been less likely than men to receive SAVR and also more likely to have post procedural complications.[152] Women undergoing TAVR have been shown to realize stronger benefits from the procedure than their male counterparts[152] and thus access to this treatment for this patient group has significantly improved morbidity and mortality. That said, less than 25% of women who developed SSAS in 2016 received any form of valve replacement, and thus, despite these gains, there remains significant opportunity to improve outcomes for this patient population (**Appendix B: Optum and Appendix A: Medicare**).

3. *Minorities:* While nonwhite populations make up 25% of the Medicare population (Kaiser Family Foundation), they comprise only 6% of patients diagnosed with SSAS and only 4% of patients treated with AVR (either TAVR or SAVR) (**Appendix B: Optum**). Given this treatment rate, in 2016, less than 15% of all minority patients who developed SSAS were treated (**Appendix B: Optum and Appendix A: Medicare**).

   Specifically in African-Americans, TAVR rates have remained stagnant despite increasing incidence of SSAS among the population.[221] While one study suggested this may be due to lower prevalence of AS in the African-American population,[222] it was not a true prevalence study[221] and previous literature has found similar echocardiographic findings between elderly patients of different races,[223] suggesting that the condition is likely underdiagnosed in the African-American community.

   A recent study found that the most likely drivers of treatment disparities were socioeconomic disadvantages and poor cultural competency among some providers.[224] TAVR volume thresholds and center consolidation are likely to compound these factors. Socioeconomic barriers to care will place African-American patients at an even greater disadvantage if they need to travel farther to receive TAVR treatment. Likewise, there could be challenges in cultural competency and provider trust in an unfamiliar care setting.

   In a 2017 post titled “CMS’ Ongoing Commitment to Minority Health,” CMS Administrator Seema Verma emphasized the Center will “use every available tool…to promote the availability of high value and efficiently-provided care for all beneficiaries.”[225] Given the disparities that women, racial

minorities, and the elderly face, CMS should prioritize timely and efficient access to TAVR in order to carry out the agency's commitment.

4.3.2. More Stringent Volume Requirements Will Exacerbate Existing Access Barriers

As previously mentioned, more than 6500 patients at the current 540 U.S. TAVR centers could be displaced if more stringent volume thresholds are enforced (**Appendix A: Medicare**). Given the current average AVR treatment penetration of less than 35%, further consideration must be given to how treatment gaps may further be exacerbated by a volumes-based approach (**Appendix B: Optum**):

1. *Access to care could be delayed:*
   Limiting center growth or even closing centers under the volume threshold would require that existing centers significantly increase their capacity to address the growing pool of patients newly diagnosed and eligible for TAVR. This situation would either significantly increase wait times for TAVR patients, require hospitals to defer other non-TAVR procedures to increase TAVR capacity, or force 'approved' hospitals to build out new facilities. None of these options offers a simple solution. Patients with SSAS have a high risk of death due to their disease and just a few weeks of delay of care has been shown to significantly increase their risk of death.[34] Furthermore, a review of electronic health records from several health systems, showed that TAVR facilities with longer wait times had mortality rates up to 100% higher than their counterparts with shorter wait times (**Appendix B: Optum**). The ability of hospitals to displace other procedures or build new facilities would also require significant discussion and planning and would likely further delay treatment. Furthermore, curtailing the number of future TAVR centers that can open may further limit the growth of procedures needed improve the treatment rate and adequately address patients with SSAS.

2. *Patients may forego treatment:*
   Travel distance determines over 20% of the average Medicare aged patient's decision to seek surgical care,[226] and studies have consistently shown that older and lower income patients are less willing to travel for elective procedures.[220] Both of these findings suggest that many of the patients impacted by volume thresholds may choose to forego TAVR altogether, significantly increasing their risk of mortality due to SSAS (**Appendix A: Medicare**).

3. *Rural patients may be disproportionately impacted:*
   In reviewing Medicare data, we found that 76% of the facilities impacted by volume requirements would be non-academic/community facilities and that as many as 10 sole community hospitals would no longer be able to perform TAVR procedures (**Appendix A: Medicare**). Given that CMS' Rural Health Strategy lists "Improving Access to Care Through Provider Engagement and Support" as a core objective to improve care in rural areas,[17] adopting volume restrictions for TAVR would be counter to the agency's stated goals.

4. *Low income patients will be disproportionately impacted:*
   Income is already a significant predictor of whether a patient with SSAS receives TAVR treatment.[224] Imposing more stringent volume restrictions may compound this impact, as low income patients are significantly less able to travel for procedures than the general population[220] and the vast majority of facilities impacted by volume thresholds are in low-income states (≤15% of population below poverty line).[227]

Increasing volume thresholds could only further exacerbate the present treatment gap and disproportionally impact the groups least able to seek alternate sources of adequate care.

4.4 Policies Governing TAVR Should Be Flexible to Accommodate Changes in Practice Over Time

We believe the policy should remain flexible to accommodate appropriate changes in care over time. With this in mind, future treatment decisions should be based on specific valve pathology, comorbid conditions, and patient preferences.[228] We are concerned that mandating minimum procedure-specific volume requirements for TAVR and SAVR may interfere with personalized decision making as the appropriate mix of TAVRs and SAVRs in 2018 may look very different than the mix in 2020.

Accordingly, Edwards supports a minimum all AVR volume (TAVR or SAVR) of 30 procedures annually or 60 procedures over two years. We believe an all AVR volume minimum requirement is a reasonable baseline for sustaining a viable, high functioning heart team while at the same time preserving the ability to deliver the appropriate care, rather than prescribed care, as practice evolves.

Furthermore, although we do not believe sufficient evidence exists to establish minimum procedure volumes (SAVR, PCI or TAVR) to assure better outcomes, we recognize that procedural experience establishes technical proficiencies in cardiac surgery and interventional cardiology. As such, in section 5.4, we recommend minimum volume requirements to assure continued technical proficiency in both cardiac surgery and interventional cardiology and to maintain a viable heart team infrastructure.

1. Key Coverage Parameters

1.1. Certain Elements of the TAVR NCD Have Worked Exceptionally Well and Should Be Preserved

1.1.1. Maintain Coverage to Label When Other Conditions Are Met

As newer generation TAVR technologies and indications are likely to be assessed by the FDA in the coming years, maintaining TAVR coverage for FDA-approved indications ensures Medicare beneficiaries have timely and efficient access to appropriate care without having to reopen the policy for each newly approved indication. As CMS refines its coverage policy for TAVR, we urge CMS to maintain coverage for FDA approved indications.

1.1.2. Maintain Requirement for the Heart Team and Hospital to Participate in a Prospective, National, Audited Registry

Edwards recognizes the importance of TAVR Heart Teams and hospitals participating in a prospective, national, audited registry. More than 20 papers have been published using TVT Registry data and many more are in process or under evaluation.[207] As CMS refines its coverage policy for all AS therapies, we urge CMS to maintain requirements for registry participation, while also ensuring that efforts continue to appropriately streamline such registries.

In addition, we recommend adopting the following principles to enhance the value and governance of national registries. These are adapted from the recommendations of The Pew Charitable Trusts, the Blue Cross Blue Shield Association, and the Medical Device Epidemiology Network.

- Findings and reports should be publicly released on a regular basis.
- The workings of the system—its governance, operations, and financing—should be made publicly available.
- Registries should provide a clear, reasonable, and responsive process for providing data to outside researchers.
- Registry data should be limited to the data most relevant to the purpose of the registry and should not collect more data than necessary to answer the specific question or questions for which it was established.
- Stakeholder groups should work together to better understand and ultimately reduce unnecessary barriers to registry data collection and use.
- The amount of data collected should balance stakeholder interests with the workload placed on those who collect the data. In the TVT Registry, the time required for data extraction and input places a substantial burden—on average four hours per patient at the time of implant—on the clinical facility. Accordingly, all stakeholders involved in initiating registries should strive to limit the size and scope to minimize the time and cost of data collection and should work to create registries that can interact with other electronic sources of data.
- To improve public health and patient care, registry findings should be available to stakeholders, assuring that decision-makers—including regulators, clinicians, patients, and payers—have access to key information.
- Given the contribution that patients make in providing their data, an ethical obligation exists to ensure that they have access to registry information. For example, data from registries—written and presented at a lay level—should be available to patients to support informed choices about treatment.

1.1.3. Maintain TAVR Coverage for Uses That Are Not Expressly Listed as an FDA-Approved Indication When Performed Within a Clinical Study

Edwards remains firmly committed to continued rigorous evidence generation on TAVR. Coverage of TAVR in clinical trials ensures that additional Medicare patients can benefit in the near-term from improvements in this less-invasive approach. Clinical trials assist in growing the evidentiary base for the use of TAVR and other technologies used in the treatment of aortic valve disease that can inform improvements in clinical practice and help Medicare beneficiaries and providers make the most appropriate therapeutic decisions. As CMS refines its coverage policy for TAVR, we urge CMS to retain coverage for FDA-approved trials.

5.2. Certain Elements of the NCD Are No Longer Relevant and Should Be Removed or Amended

The Requirement That Two Cardiac Surgeons Have Independently Examined the Patients Suitability for Open AVR Should Be Retired

When the initial TAVR NCD was implemented, the intent was to mirror as closely as possible the clinical practices in the early trials.[210] In 2007, the PARTNER B study was initiated to evaluate patients who were not considered suitable candidates for surgery (i.e., inoperable). The protocol required that at least two surgeons had to agree that the patient was not a suitable candidate for surgery.[22] A similar requirement was adopted in the TAVR NCD. In subsequent trial experience, such as the PARTNER II B study,[78] these requirements were reduced to at least one surgeon personally examining the patient to make a determination of operability. Taken together with broadened indications over time, improvements in patient selection and the increasingly well-established role of TAVR in the management of aortic stenosis, the two-surgeon requirement is no longer necessary. As CMS refines its coverage policy for TAVR, we urge CMS to remove the two surgeon requirement. Instead, we recommend a cardiac surgeon and an interventional cardiologist at the TAVR-performing institution has examined the patient, evaluated the patient's suitability for SAVR, TAVR, medical or palliative therapy and has documented the rationale for their clinical judgment.

Coverage for the Treatment of "Symptomatic Aortic Valve Stenosis" Should Be Changed to "Aortic Stenosis"

Several clinical trials approved under section B of the existing TAVR NCD are underway to evaluate the safety and efficacy of TAVR in asymptomatic patients with severe aortic stenosis (EARLY TAVR) and heart failure patients with moderate aortic stenosis (TAVR UNLOAD). To preserve flexibility for future indications, Edwards urges CMS to change its coverage language from "symptomatic aortic valve stenosis" to "aortic stenosis."

5.3. Additional Elements Are Needed to Ensure Appropriate, High-Quality, and Timely Care for Medicare Beneficiaries with Aortic Stenosis

5.3.1. The Policy Should Focus on All AVR Therapies (Both TAVR and SAVR)

There are two forms of definitive treatment available for SSAS – TAVR and SAVR. A TAVR specific policy only provides half the solution. We believe that equitable policy and quality standards are necessary for all Medicare beneficiaries with SSAS regardless of treatment. At present, SAVR outcomes are only collected on a voluntary basis by the STS with limited public reporting and no national policy requirements on volume, infrastructure, heart team or quality to perform further SAVRs. We are concerned that the current disparity in policy standards may be leading to disparities in treatment and outcomes. SAVR currently has in-hospital mortality rates that are over twice as high as those for TAVR in the Medicare program. An analysis of the 2017 MedPAR file revealed that more than 1,100 hospitals currently perform SAVR, with more than 650

facilities performing less than 50 SAVRs annually, and more than 330 performing less than 20. Analyzing the 2016 Medicare SAF, we found that the adjusted 30-day mortality was 4.9% (**Appendix A: Medicare**) for SAVR facilities performing less than 20 procedures annually compared to 3.0% for TAVR facilities performing fewer than 20 procedures annually. These data support the need for a broader focus on quality and volume (beyond just TAVR). Using the same data sources, we also note that SAVR in-hospital mortality (unadjusted) was lower at comprehensive programs (offering TAVR and SAVR) as compared with SAVR only facilities (4.4% vs 6.7%, p<0.001). We encourage Medicare to establish a uniform policy across the continuum of AVR care to ensure high quality for all Medicare beneficiaries.

5.3.2. The Policy Should Include Shared Decision Making For All AVR Therapies

Additionally, the management of aortic valve disease should incorporate shared decision-making (SDM) based on a comprehensive understanding of the risk-benefit ratio of different treatment strategies and the integration of patient preferences and values.[229] To ensure that SDM is a benefit to patients and the healthcare system we believe CMS should:

- Apply the requirement to all aortic valve disease patients, not just patients at a TAVR center
- Not reference a specific patient decision aid as demonstrating SDM, but encourage providers to use tools that comply with standards for high quality, in alignment with NQF's performance measure #2962, NQF's National Standards for the Certification of Patient Decision Aids,[230] the National Quality Partners Playbook on Shared Decision-Making[231] and the Avalere/FasterCures' Patient Perspective Value Framework.[232]

High quality SDM is unlikely at centers that only offer one of the therapies or when there are large disparities in coverage policy. Today, less than half of centers that offer SAVR also have TAVR available. We are concerned that without aligned SDM requirements, patients may not be appropriately informed of all their treatment options when they are evaluated by physicians at hospitals that do not have a TAVR program. A review of national TAVR referral patterns using 2016 IQVia data reveals that only 5.8% of patients receiving TAVR were referred by physicians with a SAVR only center affiliation. Accordingly, we urge CMS to take specific steps to ensure all patients considering aortic stenosis treatment engage in SDM.

Currently available decision aids developed for TAVR, including one supported for development by the Patient-Centered Outcomes Research Institute (PCORI), are early in their development and therefore do not yet meet the NQF's standards and criteria. Resources are needed to further test the tool in real world settings and expand the engagement of patients to ensure that the outcomes being measured are understandable to patients who may not have deep health care literacy. To be consistent with the NQF's draft criteria for certification, patient decision aids must be rigorously developed and routinely updated.

Specific, validated tools to inform SDM need to be developed to facilitate the dissemination of information about the full spectrum of therapeutic options available to patients, regardless of the specific hospital they first visit.

We believe it should be the goal of each AVR program (surgical or transcatheter) to ensure that their patients be able to exhibit the following five behaviors to meaningfully participate in their health care decisions:

1. Well-informed regarding their treatment options;
2. Understand risk and benefits presented using data on treatment options that is as current, accurate and patient-specific as possible;
3. Articulate their goals related to treatment;
4. Identify their preferences and values relative to their care; and
5. Integrate these in order to make a final treatment choice

5.3.3. If the TAVR Policy Cannot Be Changed To Cover All AVR Therapies, Then A Comparable SAVR NCD Policy Should Be Implemented

5.4 Recommended AVR NCD

Benefit Category

Inpatient Hospital Services

Physicians' Services

Item/Service Description

A. Rationale for Reconsideration

Prior to transcatheter aortic valve replacement (TAVR) approval, surgical aortic valve replacement (SAVR) was available, performed, and covered without any procedure volume or quality requirements. The TAVR NCD has been in place for more than 6 years. During that time, significant advancements in technology have occurred, robust data have accumulated, and important lessons have been learned about valve replacement therapy in aortic stenosis patients. Substantial evidence has demonstrated the clinical, economic and quality of life benefits of TAVR across approved indications. Historically, procedure volume has been used as a surrogate for the quality of TAVR programs. TAVR has now become a mature procedure with safe and predictable results. Given the current state of the evidence, and to harmonize policy standards for all AVR therapies, the Centers for Medicare & Medicaid Services (CMS) expands the existing National Coverage Determination (NCD) for TAVR to include all aortic valve replacement.

B. General

1. SAVR is indicated in patients with aortic valve stenosis or aortic insufficiency. SAVR utilizes open-heart surgical placement of the valve, a heart-lung bypass machine, and temporary displacement of surrounding muscles and tissue.

2. TAVR is used in the treatment of aortic stenosis. A bioprosthetic valve is inserted percutaneously using a catheter and implanted in the orifice of the aortic valve, while the heart continues to beat.

Indications and Limitations of Coverage

C. Nationally Covered Indications

CMS covers aortic valve replacement (TAVR or SAVR) for the treatment of aortic valve disease when the following conditions are met:

1. The patient is under the care of a Heart Team—a cohesive, multi-disciplinary team of medical professionals. The Heart Team embodies collaboration across multiple specialties to offer optimal patient-centered care.

2. One cardiac surgeon and one interventional cardiologist with knowledge and experience in both TAVR and SAVR have examined the patient and evaluated the patient's suitability for AVR and both have documented the rationale for their clinical judgment and the rationale is available to the Heart Team.

3. A formal, shared decision-making encounter has occurred between the patient and the Heart Team using an evidence-based decision tool on the treatment options for aortic valve disease prior to AVR (either TAVR or SAVR) and been documented in the medical record. The encounter may involve at least one physician member of the Heart Team or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist) that is also a member of the Heart Team. Treatment decisions should be made using a shared decision-making process even in situations where the center may not offer both therapies and may need to refer the patient to another facility.

4. In the case of TAVR, the valve replacement is furnished with a complete aortic valve and/or a complete aortic valve implantation system that has received U.S. Food and Drug Administration (FDA) premarket approval (PMA) or clearance for that system's FDA approved indication; in the case of SAVR, the device and requisite supplies have received appropriate FDA approval or clearance.

5. The aortic valve replacement is performed at a hospital with the appropriate infrastructure that includes, but is not limited to:

    a. On-site interventional and surgical cardiac surgery program with appropriate accreditation,

    b. For TAVR, cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging. For SAVR, a cardiothoracic surgery suite and other necessary surgical equipment,

    c. Non-invasive imaging such as echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance (MR),

    d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications,

    e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone heart valve procedures,

There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR or SAVR experience and the second is for those with TAVR or SAVR experience.

Qualifications to begin a TAVR program for hospitals without TAVR experience:

The hospital must have the following:

a. Active cardiac surgery program and;
b. ≥50 open heart surgeries in the year prior to TAVR; and
c. Active interventional cardiology program, and;
d. ≥200 percutaneous coronary interventions (PCIs) in the year prior to TAVR

Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
    i. Professional experience with ≥50 open heart surgeries lifetime; or,
    ii. Professional experience with ≥50 left-sided structural procedures (including but not limited to TAVR, LAA, ASD, PFO, AAA, BAV) lifetime; and,
    iii. Board eligibility or certification in either interventional cardiology or cardiothoracic surgery

b. Interventional cardiologist with:
    i. Professional experience with ≥50 left-sided structural procedures (including but not limited to TAVR, LAA, ASD, PFO, AAA, BAV) lifetime; and,
    ii. Board eligibility or certification in interventional cardiology; and,
c. Device-specific training as required by the manufacturer

Qualifications to begin a SAVR program for hospitals without SAVR experience:

The hospital must have the following:

a. Active cardiac surgery program and;
b. ≥50 open heart surgeries in the year prior to SAVR

Qualifications to begin a SAVR program for heart teams without SAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
    i. Professional experience with ≥50 open heart surgeries lifetime;
b. The presence of a multi-disciplinary heart team

Qualifications for programs with TAVR and/or SAVR experience

The hospital must have the following:

a. Active cardiac surgery program and;
b. Active interventional cardiology program

The hospital program must maintain ≥30 AVRs (TAVR or SAVR) per year or ≥60 AVRs every 2 years. The aortic valve replacement is performed at a hospital meeting the following quality metrics:

a. The observed/expected (O/E) in-hospital mortality for AVR (TAVR ± SAVR) using the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) score is within an acceptable range as defined by expert consensus. Hospitals will be required to maintain records demonstrating compliance with an O/E ratio within national benchmarks of acceptable quality of care and certify with CMS annually.

    If a center fails to meet the national benchmark for a particular procedure for two consecutive years, Medicare will not cover future AVR procedures until the center successfully meets criteria for reinstatement. Centers can petition to CMS to reinstate their AVR program after successfully completing an approved training and accreditation program.

6. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls AVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least 1 year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner, and facility level variables that predict each of these outcomes:

    a. Stroke;
    b. All-cause mortality;
    c. Transient Ischemic Attacks (TIAs);
    d. Major vascular events;

e. Acute kidney injury;
f. Repeat aortic valve procedures;
g. Quality of Life (QoL).

7. The aortic valve replacement is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills the following requirements:

   a. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-AVR (minimum of 1 year), but must also address at least one of the following questions:
      - What is the incidence of stroke?
      - What is the rate of all-cause mortality?
      - What is the incidence of TIAs?
      - What is the incidence of major vascular events?
      - What is the incidence of acute kidney injury?
      - What is the incidence of repeat aortic valve procedures?

   b. The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed, and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity listed below. The information will be reviewed, and approved studies will be identified on the CMS Website. The clinical research study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
      - The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
      - The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
      - The research study does not unjustifiably duplicate existing studies.
      - The research study design is appropriate to answer the research question being asked in the study.
      - The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
      - The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the FDA, it also must be in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
      - All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
      - The research study has a written protocol that clearly addresses, or incorporates by reference; the standards listed as Medicare coverage requirements.

- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

D. Nationally Non-Covered Indications

AVR (TAVR or SAVR) is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis or aortic insufficiency.

6. Conclusion

Edwards thanks CMS for it consideration of our summary of the current state of the clinical evidence of TAVR and our recommendations for the NCD. We believe that our shared goals should be to ensure there is expanded and equitable access to TAVR so that all people with heart valve disease have the ability to consider all safe and effective treatment options with their clinicians at the appropriate time. We look forward to working closely with the CMS throughout the NCA process and to providing any additional information that CMS may require.

7. Appendices

Appendix A: Medicare

Methodology for adjusting Medicare volumes

TAVR and SAVR Medicare-Fee-For-Service volumes were first extracted from 2011-2016 from the inpatient file. Separately 2017 volumes were extracted from the SAF file. Volumes were then adjusted to account for Medicare Advantage patients using the reported volume splits from MEDPAR. Lastly, volumes were adjusted to account for private payer shares using HCUP. This same methodology was also used for MitraClip, Watchman, and septal repair procedural volume adjustments.

PCI volumes were adjusted in a similar manner; however, they were also additionally adjusted for outpatient share from a 5% Medicare sample.

Methodology for adjusting outcomes

To risk adjust center outcomes, inpatient primary and secondary claims and relevant cardiac procedures on the index admission were used to develop a risk adjusted model (RAM) for inpatient mortality. Model covariates were selected via lasso with forced demographic variables in order to incorporate as many predictors as possible to improve model fit, prediction and power. The hierarchical models were fitted to the data for TAVR, SAVR, and PCI. Standardization was utilized to adjust for outcomes including in-hospital mortality, 30 day mortality, 30 day stroke, bleeding complications, and vascular complications.[233] This approach also leveraged semi-Bayesian methods to adjust for small volumes with a clustered model. Results were validated with marginal GEE model to further control for small centers.[234]

Variables included in the final model were gender, race, region, age (categorical), CCI (categorical), CABG, MVR/r, TVR/r, MAZE, PCI, sepsis, metastatic cancer, protein calorie malnutrition, liver disease, immunity disorders, drug/alcohol dependence, MS, CHF, heart arrhythmias, vascular disease, COPD, chronic lung, renal disease, head injury, and facility (cluster). The ROC curve for the GLIMMIX model for 2014-2016 had an area under the curve =0.70 for mortality, 0.61 for stroke, 0.63 for bleeding complications, and 0.62 for vascular complications.

Methods for learning curve analysis

Medicare data was used to independently validate the analysis presented in the most recent TVT publication showing a case sequence-volumes relationship.[187] To briefly review the methods: case sequence was assigned to each TAVR patient based on procedure sequence within facility ID and modeled using restricted cubic splines with 4 degrees of freedom. Risk factors and demographic covariates were combined into a single risk score using logistic regression with predicted log odds to improve the probability of model convergence. This risk score was then used in the subsequent final hierarchical model that included reference date of TAVR, case sequence, random effect for facility id. The predicted probabilities of 30-day mortality outcomes by case sequence were plotted using generalized linear mixed models, which adjusted for risk factors, demographic factors, and time since TAVR approval. Site-specific effects were accounted for in the mixed model with a random effect for facility ID.

To explore the relationship between learning centers at small and large volume centers, a nested random effect with volume was also tested. A secondary analysis was also conducted by using an interaction term between case sequence and center volume to determine if there was a relationship between case sequence and outcome differs by center volume.

Appendix B: Optum

Optum Overview

Optum is a health database of over 80M electronic health records (EHR) from institutions across the United States. Patients with newly diagnosed SSAS within 1 year were identified in the data set via a physician report of SAS and a note of symptoms within the 6 months preceding diagnosis date with methodology similar to previously published studies.[235] Patients who did not die within the study period had to have at least one year of follow up documented in order to assess if treatments had taken place. Separate analysis had shown that 90% of patients were treated within a 1 year period of diagnosis.

The following analyses were conducted in Optum:

Methods: Outcomes over time

SSAS patient cohorts were identified in 2014 and 2016. Outcomes were tracked over time to evaluate treatment and mortality rate in a 1 year period. Diagnosed incidence was compared between 2014 and 2016 by comparing the number of newly diagnosed patients in a year period as compared to the number of patients touching the healthcare system at least once in the year period. All results were presented as a relative change.

Methods: Speed to TAVR analyses

Health care systems in 2016 were stratified based on their time to TAVR rate (median ~90 days). Systems with low time to TAVR ('fast' system) were compared to systems with an above median treatment time ('slow' system). Patients who did not die within the study period had to have at least one year of follow up. Patients were evaluated for treatment rate and untreated mortality within the year period.

Appendix C: 2018 Multisociety Expert Consensus Systems of Care Document Tables

Table 4: Requirements for New TAVR Programs 2018 Criteria
There should be documentation of a multidisciplinary approach and of patient access to all forms of therapy for aortic valve disease (TAVR, SAVR, and palliative and medical care using an SDM process. • For all patients with aortic stenosis meeting criteria for valve replacement, there should be documentation of the following: o Completion of an evaluation by both a cardiac surgeon and a cardiologist with knowledge and experience in both TAVR and SAVR o Education of patients regarding the treatment recommendations and options by the multidisciplinary team o Use of an SDM process incorporating patient preference • For patients undergoing TAVR, there should be documentation of evaluation by 1 surgeon involved in the TAVR program. o For this requirement to fulfill CMS coverage criteria, the NCD should be updated as it currently recommends evaluation by 2 surgeons for all patients having TAVR.
The proposed TAVR proceduralist for a new TAVR program should document the following: • Prior TAVR experience with participation in 100 transfemoral TAVRs lifetime, including 50 TAVRs as primary operator • Being board eligible or certified in either interventional cardiology or cardiothoracic surgery • Certification of device-specific training on device(s) to be used.
The TAVR sites must have: • The site must have documented expertise, state of the art technology and dedicated board certified imager that is a member of the MDT. • Echocardiography: TTE, TEE and 3D • CT Scan and MR imaging
The proposed TAVR surgeon for a new TAVR program should document the following: • 100 lifetime SAVRs or 25 per prior year or 50 over 2 years and ≥20 SAVRs in the year prior to TAVR program initiation Board eligible or certified by the American Board of Thoracic Surgery or equivalent
The institution should document the following prior to expanding into alternative-access TAVR (e.g., transapical, direct aortic, brachiocephalic arteries, transcaval): • Completion of 80 TAVRs using transfemoral access with an STS/ACC TVT Registry 30-day risk-adjusted TAVR all-cause mortality "as expected" or "better than expected"
The institution should document the following concerning its SAVR program: • ≥2 hospital-based cardiac surgeons who both spend ≥50% time at the hospital with the proposed TAVR program • Minimum hospital SAVR volume†: 40 per prior year or 80 over 2 years • Quality assessment/quality improvement program: o Active participation in the STS National Database or a validated state/multi-institutional consortium that gathers and reports risk-adjusted and benchmarked outcomes ** o Quality metric: STS 2- or 3-star rating for isolated AVR and AVR plus CABG in both reporting periods during the most recent reporting year
The institution should document the following resources and experience: • PCI o Minimum volume: 300 PCI/year o Active participation in the NCDR/Cath PCI Registry or a validated state/multi-institutional consortium that gathers and reports risk-adjusted and benchmarked outcomes o Quality metric: PCI in-hospital risk-adjusted mortality (NQF endorsed) above the bottom 25th percentile for the most recent 4 consecutive quarters. • Vascular interventions o Physicians experienced and competent in vascular arterial interventions* • Pacemaker capabilities o Experienced and competent physicians for temporary and permanent pacemaker placement and management o On-site services should be available 24 hours/day and 7 days/week to handle conduction disturbances as a result of TAVR
Program directors are responsible for accurate reporting of multidisciplinary team clinical volume and outcomes to the STS/TVT Registry and the STS National Database.**
Quality assessment/quality improvement program requirements: • Active participation of institution in STS/ACC TVT Registry and STS National Database or a validated state/multi-institutional consortium registry ** o Registry submission of all cases using FDA-approved TAVR/SAVR technology, including off-label uses‡ o Registry documentation that data submissions meet performance metrics for completeness and accuracy as defined by each registry • Multidisciplinary team quarterly meetings with documentation of the following: o Review of institutional reports for TAVR (quarterly) and SAVR (semi-annually) from the STS/ACC TVT Registry and STS National Database or an alternative approved registry o Assessment and proposed actions if site performance for TAVR and SAVR is suboptimal relative to volume and quality requirements, including national benchmarking of performance metrics as outlined in Tables 1 and 2 o Presentation of selected TAVR/SAVR cases at quarterly mortality/morbidity conferences o Documentation of incorporation of TAVR/SAVR AUC into patient selection process (23)
Continuing education requirements: • It is expected that the MDT will participate in appropriate CME.

*Vascular arterial interventions include TEVAR/EVAR, carotid stenting, renal artery stenting, iliac and femoral artery stenting, coarctation stenting, and acute limb ischemia related interventions.

** Or analogous if only reporting to other state or national database.

† For the purposes of this document, the hospital volume requirement for SAVR is defined to include all aortic valve replacement (mechanical, bioprosthesis, homograft, autograft [Ross], composite valve graft or root replacement) or aortic valve repair procedures, including concomitant valve resuspension for acute aortic dissection and valve-sparing aortic root replacement. Simple adjuvant aortic valve procedures, *e.g.*, suturing closed regurgitant aortic valves in an LVAD patient, excising a papillary fibroelastoma or thrombus, *etc.*, are not counted.

‡Does not include patients in ongoing clinical trials.

ACC indicates American College of Cardiology; AUC, appropriate use criteria; CMA, continuing medical education; NCD, National Coverage Decision; NQF, National Quality Forum; EVAR, endovascular aneurysm repair (or endovascular aortic repair); PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEVAR, thoracic endovascular aortic/aneurysm repair; TVT, Transcatheter Valve Therapies

Table 5: Requirements for Continued Certification for Existing TAVR Programs 2018 Criteria
Optimal program characteristics include documentation of multidisciplinary approach and patient access to all forms of therapy for aortic valve disease (TAVR, SAVR, and medical therapy) using an SDM process. • For all patients with aortic stenosis meeting criteria for valve replacement, there should be documentation of the following: o An evaluation completed by both a cardiac surgeon and cardiologist with knowledge and experience in both TAVR and SAVR; o Education of patients regarding the treatment recommendations and options; o The use of an SDM process incorporating patient preference. • For patients undergoing TAVR, there should be documentation of an evaluation by 1 surgeon involved in the TAVR program. o For this requirement to meet CMS coverage criteria, the NCD recommendation of evaluation by 2 surgeons for all patients having TAVR should be updated.
<u>TAVR Volume and Quality Requirements</u> To have optimal outcomes, a program will have: • ≥50 cases per year or 100 cases over 2 years • Minimum quality requirement: STS/ACC TVT Registry-reported 30-day risk-adjusted all-cause TAVR mortality above the bottom 10% for metrics outlined in Table 1.
To have optimal outcomes, a program will ensure program directors are responsible for accurately reporting MDT clinical volume and outcomes to the STS/TVT Registry and the STS National Database.
To have optimal outcomes an institution will have the following resources and experience: • PCI o ≥300 PCIs/year o Active participation in the NCDR/Cath PCI Registry or a validated state/multi-institutional consortium that gathers and reports risk-adjusted and benchmarked outcomes o PCI in-hospital risk-adjusted mortality (NQF endorsed) above the bottom 25th percentile for 4 consecutive quarters. • Vascular interventions * o Experienced and competent physicians in vascular arterial interventions • Pacemaker capabilities o Experienced and competent physicians for temporary and permanent pacemaker placement and management. o On-site services available 24 hours/day and 7 days/week to handle conduction disturbances as a result of TAVR
<u>SAVR Volume and Quality Requirements</u> To have optimal outcomes a program will have: • ≥2 hospital-based cardiac surgeons who both spend ≥50% of their time at the hospital with the proposed TAVR program • ≥30 SAVRs per prior year or 60 over 2 years† • quality assessment/quality improvement program:
o Active participation in STS National Database to monitor outcomes o Quality Metric: STS 2 or 3 star rating for isolated AVR and AVR + CABG in both reporting periods during the most recent reporting year
To have optimal outcomes, a program will have a quality assessment/quality improvement program that includes: • Active institutional participation in the STS/ACC TVT Registry and STS National Database or a validated state/multi-institutional consortium registry o Registry submission of all commercial cases using FDA-approved TAVR/SAVR technology, including off-label uses. o Registry documentation that data submissions meet performance metrics for completeness and accuracy as defined by each registry • MDT quarterly meetings, with documentation of the following: o Review of institutional reports for TAVR (quarterly) and SAVR (semiannually) from the STS/ACC TVT Registry or STS National Database or an alternative approved registry o Assessment and proposed actions if site performance for TAVR and SAVR is suboptimal relative to volume and quality requirements, including national benchmarking of performance metrics as outlined in Tables 1 and 2 o Presentation of selected TAVR/SAVR cases at quarterly mortality/morbidity conferences. • Documentation of incorporation of TAVR/SAVR AUC in the patient selection process (23)
To have optimal outcomes, all MDT members will participate in appropriate CME annually.

*Vascular arterial interventions include TEVAR/EVAR, carotid stenting, renal artery stenting, iliac and femoral artery stenting, coarctation stenting, and acute limb ischemia related interventions.

† For the purposes of this hospital volume requirement SAVR is defined to include all aortic valve replacement (mechanical, bioprosthesis, homograft, autograft [Ross], composite valve graft or root replacement) or aortic valve repair procedures, including concomitant valve resuspension for acute aortic dissection and valve-sparing aortic root replacement. Simple adjuvant aortic valve procedures, e.g., suturing closed regurgitant aortic valves in an LVAD patient, excising a papillary fibroelastoma or thrombus, etc., are not counted.

ACC indicates American College of Cardiology; AUC, appropriate use criteria; FDA, Food and Drug Administration; NCD, National Coverage Decision; NCDR, National Cardiovascular Data Registry; NQF, National Quality Forum; EVAR, endovascular aneurysm repair (or endovascular aortic repair); PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEVAR, thoracic endovascular aortic/aneurysm repair; TVT, Transcatheter Valve Therapies

Appendix D: Literature Review

Methods

A focused assessment of published literature was performed to evaluate the strength of evidence for the relationship between procedural volumes and patient outcomes of TAVR, SAVR, and PCI. The PubMed database was searched using the search filters of, “Year 2012 to present (June 5, 2018)” AND “Abstract Available” AND “Search terms present in Title/Abstract.” The following search terms were used:

- The primary terms were as follows:
  - *Percutaneous Coronary Intervention"[Mesh] OR "Balloon Angioplasty,*
  - *"SAVR" OR "SAVI" OR "Surgical Aortic Valve Implant" OR "Surgical Aortic Valve Replacement,*
  - *“TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant”*
- The secondary terms were as follows:
  - *"TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant"*
  - *"TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant”*
- The tertiary terms were as follows:
  - *"Volume" OR "Outcome*" OR "Volume-Outcome*" OR "Experience*" OR "Professional Competence" OR "Caseload" OR "Case-load" OR "Case load" OR "Learning curve" OR "Learning-curve" Or "Threshold"*

These search terms were used to find articles in PubMed (n=2,893) then results were filtered based on article titles and abstracts (n=64 remaining, n=2,829 eliminated).

An additional filter for English language was used (n=61 remaining, n=3 eliminated) followed by a filter for full-text articles only (n=30 remaining, n=31 excluded).

Of the 30 remaining articles, 26 studies were found to assess the relationship between institutional TAVR volumes and outcomes in patients undergoing TAVR (n=26 remaining, n=4 eliminated).

Appendix E: TVT Registry

The STS/ACC TVT Registry is the main repository for clinical data related to TAVR. The Registry, created by a collaboration between STS and the American College of Cardiology, monitors patient safety and real-world outcomes and has been approved by the Centers for Medicare and Medicaid Services (CMS) to meet the registry requirements outlined in the national coverage decision. All commercial SAPIEN 3 valve cases (n=61,295) captured in TVT Registry from June 2015 through February 2018 were analyzed in order to evaluate site volume-outcomes relationships. This included data from 509 sites (four centers had to be excluded as they were active for less than 30 days.) Event rates were determined for each site and Pearson correlation coefficient used to measure strength of association between annual volume and outcomes.

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