07/28/2025

VIA ELECTRONIC MAIL TO NCDREQUEST@CMS.HHS.GOV

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Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR) 20.32

Dear Ms. Syrek-Jensen,

Edwards Lifesciences would like to formally request that the Centers for Medicare and Medicaid Services (CMS) reconsider the national coverage determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR) 20.32.

We believe that this reconsideration is needed to reflect new published evidence demonstrating improved outcomes with the use of TAVR for asymptomatic patients that are beyond the scope of the current NCD, as well as additional evidence supporting the removal of coverage with evidence development (CED) and other outdated requirements in the current NCD.

Introduction

For more than six decades, Edwards Lifesciences ("Edwards") has been driven by a passion to improve patient lives to become a leading global structural heart company at the forefront of patient-focused medical innovations. These lifesaving and life-enhancing innovations include the Edwards SAPIEN family of transcatheter heart valves used in transcatheter aortic valve replacement (TAVR) procedures. The Edwards SAPIEN transcatheter heart valves are one of the most studied and widely used TAVR valves around the world, having been implanted in more than 1,000,000 patients worldwide.

TAVR procedures have revolutionized the practice of medicine for the treatment of aortic stenosis (AS), estimated to affect over 2 million Americans aged over 65 years [1]. In just over a decade, TAVR indications have expanded from treating a niche population of inoperable patients to now being a treatment option for most AS patients across all surgical risk levels [2]. TAVR provides substantial value to patients and the healthcare system by improving both the patient care experience and population health overall, while simultaneously improving the affordability of AS treatment for the Medicare program [3, 4].

AS is a deadly condition with up to 50% mortality at 1 year without treatment [5]. CMS approval of the 2012 TAVR NCD allowed initial patient access to lifesaving treatment as technology, evidence and clinical experience evolved. In 2019, CMS updated the TAVR NCD to better reflect available evidence and clinical practice at that time to appropriately expand beneficiary access and available sites qualified to perform lifesaving TAVR procedures. In addition, CMS' quick action to provide NCD flexibilities during the COVID-19 Public Health Emergency (PHE) has been recognized by the greater healthcare community for saving patient lives and not compromising care [6]. Despite these efforts, today's AS patients experience significant delays and hurdles to access TAVR and AS remains largely undertreated, with less than half of indicated patients receiving AVR [7].

Summary of Reconsideration Request and Rationale

Edwards requests CMS update the TAVR NCD to address new evidence supporting asymptomatic indications not currently covered, as well as the totality of evidence now available supporting a determination that the current NCD CED requirements have been met and TAVR is reasonable and necessary for Medicare beneficiaries.

Updates to the TAVR NCD are needed to include asymptomatic patients not addressed under the current policy. Current TAVR NCD criteria specify coverage for symptomatic AS; however, asymptomatic patients should be included for coverage based upon a body of evidence demonstrating patient harm when relegated to a conservative strategy of clinical surveillance (CS). Observational studies and randomized controlled trials (RCTs) demonstrate superior outcomes for AVR in patients with clinically significant asymptomatic AS compared to CS, including results from the EARLY TAVR randomized controlled clinical trial for asymptomatic AS presented at the Transcatheter Cardiovascular Therapeutics (TCT) Conference on October 27, 2024, and also published simultaneously in the *New England Journal of Medicine* [8-23]. Findings from the trial were also highlighted in a notable recent meta-analyses in the *Journal of the American College of Cardiology,* the *International Journal of Cardiology,* and the *Journal of the Society for Cardiovascular Angiography & Interventions* [24].

Cumulative evidence demonstrates that TAVR no longer requires CED and is reasonable and necessary for the benefit category of inpatient hospital services and physician services in the treatment of AS. CED requirements for TAVR were established by CMS through its NCD process in 2012 and updated again in 2019. However, practice patterns, patient selection criteria, indications, and technological innovations have evolved significantly. This is evidenced by excellent procedural outcomes overall, and a rate of conversion to surgery during TAVR of under 0.4%, comparable to percutaneous coronary intervention (PCI) in contemporary practice [25, 26]. In addition, all CED questions posed by CMS under CED have been satisfactorily answered by an abundance of clinical trials and registry studies published within the past decade. We review this evidence in detail, below. In summary: (1) Published registry outcomes across all surgical risk levels describe excellent performance of TAVR procedures outside of pivotal clinical trials [27]. (2) TAVR has excellent, well-evidenced, long-term outcomes, including established long-term device durability through 10 years [28]. (3) There is considerable understanding of what morbidity and procedure related factors impact TAVR outcomes, and procedural factors have been incorporated in a 30-day composite performance measure, obviating the need for proxy measures for quality [29].

CED guidance recognizes that CED should be "time-limited to facilitate the timely generation of sufficient evidence to support a Medicare coverage determination." [30] This comprehensive evaluation of TAVR under the existing CED questions demonstrates "sufficient evidence to inform patient and clinician decision-making and to support a Medicare coverage determination" that TAVR has satisfied the standard for "reasonable and necessary" for AS and no longer requires CED [31]. In the case of TAVR, CED has successfully demonstrated that TAVR has met the "reasonable and necessary" standard for Medicare beneficiaries based on additional follow-up from pivotal trials and published registry data supporting consistent and excellent outcomes with this therapy.

Finally, updates to the TAVR NCD are needed to streamline and remove outdated and burdensome requirements that create barriers to patient care. Today, outdated TAVR coverage requirements exacerbate barriers to patient access, leading to delayed patient care and poor outcomes [32, 33]. Increased patient need and widespread AS undertreatment, as well as a growing demand for structural heart procedures overall, delay timely treatment under existing NCD requirements [7, 34, 35]. Flexibilities to outdated TAVR coverage criteria are needed to empower hospitals and Heart Teams to make appropriate care decisions that will enable patient access to treatment locally.

Conclusion

Edwards is proud of the transformative changes to care delivery that TAVR procedures have achieved for patients with AS. We urge CMS to prioritize this reconsideration to ensure patients with AS will have timely access to this lifesaving technology in the future. Edwards appreciates CMS' consideration of this request and provides full details of our request,

rationale, and supporting evidence in the following pages. We look forward to continuing to engage with CMS to ensure high quality and appropriate access for all Medicare beneficiaries in need of treatment for structural heart disease.

Sincerely,

Larry Wood
Corporate Vice President and Group President
Transcatheter Aortic Valve Replacement and Surgical Structural Heart
Edwards Lifesciences

Contents

1. Introduction

1.1 Background of disease and treatment

Heart disease is the leading cause of death among Americans aged 65+, and approximately 1 in 10 of those individuals have moderate or severe valvular heart diseases like aortic stenosis [36]. Aortic stenosis (AS) describes a condition when the heart's aortic valve narrows, affecting normal blood flow. Medicare patients with AS can suffer up to 50 percent mortality at 1 year without treatment, yet this disease remains substantially undertreated, with less than half of indicated patients ever receiving an aortic valve replacement (AVR) [5, 7]. Many patients with AS are candidates for both surgical aortic valve replacement (SAVR), a traditional open heart surgery procedure, as well as transcatheter aortic valve replacement (TAVR), a minimally invasive, non-surgical procedure. However, some patients may only be eligible for one of the two procedures due to patient-specific factors and appropriateness. For example, a patient who is deemed to be too high-risk for surgery may still be a candidate for TAVR, while a patient in need of concomitant coronary procedures may be a better candidate for SAVR.

As compared to SAVR, TAVR shortens hospital stays, reduces complications, and achieves cost savings for the Medicare program [4]. TAVR provides substantial value to our healthcare system by improving both the experience of receiving treatment and population health overall, while simultaneously reducing healthcare costs [3]. Because TAVR is less invasive than SAVR, patient recovery is often faster, hospital stays are shorter, and resource utilization is reduced. Compared to SAVR patients, TAVR patients may experience improved quality of life due to a faster, less painful recovery process following treatment as well as a return to normal heart valve function that allows for a more active lifestyle [37-40].

1.2 TAVR NCD reconsideration history

TAVR procedures were first approved by the Food and Drug Administration (FDA) for inoperable-risk severe symptomatic AS patients in 2011. Approved for coverage by CMS through a national coverage decision (NCD) with coverage with evidence development (CED) in 2012, hospital program eligibility was based on volumes of SAVR procedures, cardiac catheterizations, and percutaneous coronary interventions (PCIs). Procedural volume was used as a surrogate for program quality due to limited provider and program experience with the TAVR procedure. Further, evaluation criteria for coverage required two independent evaluations by cardiac surgeons, due to a clinical need to assess patients for high surgical risk TAVR indications at the time. Many of the initial coverage criteria were based on the criteria established for the initial pivotal trial, the PARTNER trial, which began in 2007, and the limited evidence and clinical experience at that time. [38]

By 2019, TAVR FDA approved indications had expanded to include intermediate-risk patients and TAVR procedures were considered a common, safe procedure with excellent outcomes. In the 2019 NCD reconsideration, patient evaluation criteria were relaxed to require evaluation by one cardiac surgeon, and provider and program volume requirements for non-TAVR procedures were lowered. CED questions regarding outcomes in subpopulations and demographics of registry patients were retired. In addition, CMS stated that developing a periprocedural composite metric incorporating relevant patient health outcomes was a priority. An additional CED question was added, stating, “What morbidity and procedure-related factors contribute to TAVR patients’ outcomes? Specifically, this must be addressed through a composite metric.”[41]

Due to the challenges of maintaining care during the COVID-19 Public Health Emergency (PHE), several waivers were implemented by CMS from April 2020 to May 2023 that allowed flexibilities to the TAVR NCD. Flexibilities included a waiver of face-to-face requirements for evaluations, flexibility for the chief medical office of a facility to authorize another physician specialty to meet physician specialty requirements, and waiver of volume requirements for facilities and practitioners [42] [43]. Waivers in place for 3 years demonstrated that flexibilities to NCD requirements did not compromise patient care, as the technologies, procedural aspects, and role of the Heart Team, had reached significant maturity whereby rigid NCD requirements were no longer necessary [44].

2. Rationale for Reopening the TAVR NCD

We believe that this reconsideration is needed to reflect new published evidence demonstrating improved outcomes with the use of TAVR for asymptomatic patients that are beyond the scope of the current NCD, as well as additional evidence supporting the removal of coverage with evidence development (CED) and other outdated, burdensome requirements in the current NCD.

Consistent with CMS' conditions for requesting Reconsideration of an Existing NCD (78 FedReg 48164), Edwards is presenting scientific evidence that was not considered during the most recent review of the TAVR NCD in 2019. TAVR is a rigorously studied procedure for the treatment of AS. Of the 27 therapies with CMS' CED determinations from 2005 to 2022, TAVR has the highest total number of trials and registries. With 34 studies, TAVR has more than double the number of studies compared to other therapies subject to CED [45]. The PARTNER randomized clinical trials (1, 1A, 2A, and 3) included 4,089 patients total and demonstrated the safety of TAVR for all surgical risk levels [37-40]. The TVT Registry includes data from all U.S. states, including 276,316 TAVR cases from 2011 to 2019 [25]. There are 10+ years of TAVR patient-level data in healthcare claims, which have been used in publications pertaining to longer-term outcomes [2]. Notably, results from the EARLY TAVR trial, the largest randomized trial assessing the role of early intervention among patients with asymptomatic severe AS compared to clinical surveillance (CS), are now available [22].

Findings from this ground-breaking trial, along with the robust evidence base for TAVR further necessitate that substantive changes to TAVR coverage policy [46] are required. Specifically, we present evidence to support the following justifications for reconsideration of the TAVR NCD:

a) **Expanding Indications:** Updates to the TAVR NCD are needed to include asymptomatic patients not covered under the current policy.

b) **Sunset CED:** Cumulative evidence demonstrates that TAVR no longer requires CED and is reasonable and necessary for the benefit category of inpatient hospital services and physician services in the treatment of AS.

c) **Remove Barriers to Access:** Updates to the TAVR NCD are needed to streamline and remove outdated and burdensome requirements that create barriers to patient care.

2.1 Updates are needed to include asymptomatic patients.

A growing body of evidence has expanded our understanding of the optimal timing of AVR, particularly in asymptomatic patients with severe AS not covered under the current TAVR NCD. This body of evidence has prompted a reevaluation of conservative management strategies in asymptomatic AS and supports a reconsideration of current practice patterns. Results from the most recent (and largest) RCT demonstrated that asymptomatic severe AS patients randomized to TAVR experienced superior outcomes compared to guideline-recommended clinical surveillance (CS). Compared to CS, prompt intervention with TAVR reduced the composite risk of death, stroke, or unplanned cardiovascular hospitalization. Early AVR also reduced the composite risk of death, stroke, or heart failure hospitalization alone [22, 23]. Additionally, the trial helps foster a better understanding of the clinical presentation and progression of AS and how patients convert to symptoms, in some cases, rapidly and unpredictably. We believe these results will help change future clinical guidelines and transform the treatment paradigm for AS patients.

Observational evidence published over the last decade suggests that the progression of AS might not be benign. Studies have shown that the risk of sudden cardiac death in asymptomatic patients may be higher than initially estimated; further, while the rate of sudden cardiac death in asymptomatic patients is low, it is still higher than in the general population [14, 16, 47]. The sustained pressure overload during watchful waiting is also associated with structural and functional impairment of the left ventricle, which are associated with an increased likelihood of heart failure and death [21, 22, 47-49]. Additionally, several studies exploring the different stages of cardiac damage have suggested that irreversible cardiac

damage that develops during the asymptomatic phase may not necessarily be corrected or reduced with later AVR [48-51]. Généreux and colleagues recently evaluated the economic implications of cardiac damage in patients with AVR, noting that treating AS before worsening cardiac damage is associated with a $35,663 savings per patient over 1 year, as well as lower healthcare resource utilization [51]. The findings reinforce the importance of timely intervention in AS and suggest that strategies to mitigate cardiac damage may improve both clinical and economic outcomes [14, 51].

Previous meta-analyses including mostly observational studies have suggested a benefit from timely AVR among patients with asymptomatic severe AS, demonstrating that timely intervention with AVR is associated with improved survival and lower rates of heart failure (HF)-related hospitalizations compared to CS [8-14, 16, 17, 19].

Subsequently, two RCTs provided the research community with a better understanding of the role of AVR in asymptomatic severe AS: The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY; NCT01161732) trial and the Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR; NCT02436655) trial. Both studies demonstrated a clinical benefit from early SAVR among younger patients with asymptomatic severe or very severe AS and normal left ventricular ejection fraction [20, 21].

More recently, results from the Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis (EARLY TAVR; NCT03042104) trial, and the Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS (EVoLVeD; NCT03094143) trial suggest that the timing of AVR after diagnosis of severe AS strongly influences the expected benefit of intervention, especially in older patients with asymptomatic severe AS and multiple comorbidities. These 4 RCTs provide the strongest level of evidence in support of AVR in this patient population [20-23].

Importantly, the EARLY TAVR trial provided unique insights into the role of TAVR and the significance of a less invasive approach in maximizing the potential benefits of timely intervention in elderly patients with asymptomatic severe AS [22]. **Results from the trial published in the *New England Journal of Medicine* showed that timely AVR with TAVR:**

- Resulted in a **significant reduction of the primary endpoint** (death, stroke, or unplanned CV hospitalization)- at 2 years as well as a median follow-up of 3.8 years, occurring in **35.1%** in the TAVR group versus **51.2%** in the CS group (hazard ratio (HR): 0.50; 95% CI: 0.40-0.63; p<0.001);
- Resulted in a 68% **lower risk of hospitalization** for heart failure through 5 years (5.3% versus 12.0%; HR:0.32; 95% CI: 0.18-0.58; p<0.0001);
- Prevented clinically meaningful and rapid decline in **quality of life** in patients in the CS group who subsequently converted to AVR;
- Improved measures of **left ventricular and left atrial health** at 2-year follow-up (48.1% versus 35.9%, Abs Δ: 12.2% (4.4%, 19.4%), p=0.001); and
- Resulted in numerically **lower rates of stroke** for patients with TAVR (4.2% vs. 6.7% at a median follow-up time of 3.8 years).

These results were further supported by several meta-analyses published prior to the release this data, highlighting evidence from the AVATAR trial, the RECOVERY trial, and several observational studies evaluating the role of AVR versus CS in patients with asymptomatic severe AS [52-57]. The studies showed significant reductions in all-cause mortality and heart failure hospitalizations with AVR compared to CS. AVR was also associated with a reduction in cardiovascular mortality [54, 56, 57], though the benefit was non-significant in some reviews [52, 53, 55]. Finally, the majority of these studies found no differences between AVR and CS in terms of stroke, although conflicting results have since then been reported in more recent reviews [52-56].

A recently published meta-analysis in the *Journal of the American College of Cardiology* includes the latest randomized evidence evaluating outcomes of AVR in asymptomatic severe AS patients, including, notably, new data from the EARLY TAVR and EVoLVeD trials, as well as updated 5-year results from the AVATAR trial. This study-level meta-analysis was the first to synthesize evidence emerging from the 4 RCTs assessing the effects of timely AVR (TAVR or SAVR) against a strategy of CS in these patients. The benefits of timely intervention observed in the meta-analysis of 1,427 asymptomatic patients included:

- **Significant reductions in rates of HF hospitalizations** (pooled rate: 3.0% in the AVR group versus 10.9% in the CS group; pooled HR: 0.28; 95% CI: 0.17-0.47; p<0.01);
- **Significant reductions in rates of unplanned cardiovascular or HF hospitalizations** (pooled rate: 14.6% in the AVR group versus 31.9% in the CS group; pooled HR: 0.40; 95% CI: 0.30-0.53; p<0.01);
- **Significantly lower rates of stroke** (pooled rate: 4.5% in the AVR group versus 7.2% in the CS group; pooled HR: 0.62; 95% CI: 0.40-0.97; p=0.03); and
- **Trends in favor of timely AVR in terms of all-cause mortality** (pooled rate: 9.7% in the AVR group versus 13.7% in the CS group; pooled HR: 0.68; 95% CI: 0.40-1.17; p=0.17) and **cardiovascular mortality** (pooled rate: 5.1% in the AVR group versus 8.3% in the CS group; pooled HR: 0.67; 95% CI: 0.35-1.29; p=0.23) that did not reach statistical significance [24].

These findings were consistent with results from several meta-analyses which were published shortly thereafter also highlighting the role of early AVR in significantly reducing HF hospitalizations and stroke, with favorable effects on all-cause mortality and cardiovascular mortality compared to CS [58-61]. **Notably, a meta-analysis of Kaplan–Meier-derived reconstructed time-to-event data of the four RCTs demonstrated that early AVR:**

- **Significantly reduces all-cause mortality** (HR: 0.72; 95 % CI: 0.53-0.97, p=0.031), **cardiovascular mortality** (HR: 0.56; 95 % CI: 0.36-0.89, p=0.014), **and heart failure hospitalizations** (HR: 0.31, 95 % CI: 0.18-0.53, p<0.001) compared to CS in asymptomatic patients with severe AS [62].

Another meta-analysis in the *Journal of the Society for Cardiovascular Angiography & Interventions* highlighting the latest randomized and non-randomized evidence has characterized the totality of the evidence assessing the effects of timely AVR (TAVR or SAVR) against a CS strategy in asymptomatic severe AS. When considering data from existing observational studies combined with RCTs, the study offers additional insight supporting a strategy of timely AVR over CS for these patients, including:

- **Significantly lower rates of all-cause mortality** (IRR: 0.36; 95% CI: 0.27 – 0.49; p<0.001), **cardiovascular mortality** (IRR: 0.33; 95% CI:0.16 - 0.70; p<0.01), and **unplanned cardiovascular or HF hospitalization** (IRR: 0.27; 95% CI: 0.10-0.76; p=0.01) with AVR compared with a strategy of CS across **observational studies,** as well as
- **Significantly lower rates of all-cause mortality** (IRR: 0.42; 95% CI:0.31-0.58; p<0.01), **cardiovascular mortality** (IRR: 0.46; 95% CI 0.28-0.78; p<0.01)**,** and **unplanned cardiovascular or HF hospitalization** (IRR: 0.34; 95% CI: 0.21-0.55; p< 0.01) with AVR compared with a strategy of CS in **pooled analyses combining observational studies and RCTs**.

No significant differences in stroke overall (IRR: 0.82; 95% CI: 0.54-1.24; p=0.35), with **significant reductions observed with early intervention in RCT data** (IRR: 0.63; 95% CI: 0.40-0.98; p=0.04) [63]. Furthermore, a recent publication in *Structural Heart* further emphasizes the potential benefits of timely intervention among patients with moderate or severe AS, both to prevent the progression of AS and to improve outcomes post-AVR. Results from this large, real-world study of 17,838 patients undergoing AVR for moderate or severe AS (78.6% TAVR, 21.4% SAVR) showed that:

- More than **half (51.7%) of patients presented with advanced or acute signs and symptoms** prior to undergoing AVR; and

- Outcomes for these patients was associated with a **~3-fold significant increase in mortality** (5.8% versus 17.5%; p<0.0001) and a **~4-fold significant increase in hospitalization for heart failure** (11.1% versus 41.5%; p<0.0001) at 2 years post-AVR compared to patients treated when **asymptomatic** [64].

Considering the results of the RECOVERY, AVATAR, EVoLVeD, and EARLY TAVR randomized trials taken together with observational studies and meta-analyses, the findings are consistent and uniformly highlight the benefit of timely intervention and support evolving the current standard of care for patients with asymptomatic AS.

We believe that the increasingly well-established role of TAVR and the recently published data demonstrating excellent outcomes for TAVR in asymptomatic patients reinforces the need to amend the current TAVR NCD language to meet future patient treatment needs. For patients to maintain access and to preserve flexibility for new FDA-approved indications, the coverage policy should be amended to cover "aortic valve stenosis" rather than "symptomatic" aortic valve stenosis.

2.2 TAVR no longer requires CED and is reasonable and necessary for coverage.

CMS states that, when evidence is insufficient to demonstrate that the items and services are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Act, CED can be used to support evidence development for items and services that are likely to show benefit for the Medicare population [65].

In the case of TAVR, coverage under CED successfully expedited Medicare beneficiary access to innovative AS treatment under National Medicare coverage while ensuring safeguards were in place to protect patient safety and quality outcomes through the maturation of TAVR procedures. Over the past decade, more than 30 clinical trials, alongside robust registry data collection, have generated a comprehensive body of evidence to inform patient and clinician decision making that supports a Medicare coverage determination under section 1862(a)(1)(A) of the Act. Therefore, the evidence is now sufficient for CMS to determine that CED should no longer be required as a condition of coverage and TAVR is reasonable and necessary for aortic stenosis.

2.2.1 The CED questions from the 2019 TAVR NCD have been answered.

All CED questions posed by CMS have been satisfactorily answered by an abundance of clinical trials and registry studies for TAVR published within the past decade.

CED Question	Summary
When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?	TVT Registry 30-day outcomes are clinically similar to outcomes from pivotal clinical studies.
What is the long-term durability of the device?	TAVR has demonstrated excellent durability through 5 years for high, intermediate, and low-risk patients from the PARTNER trials. Additionally, the excellent durability of TAVR valves in a real-world population of Medicare beneficiaries has been demonstrated through 10 years.
What are the long-term outcomes and adverse events?	TAVR has excellent, well-evidenced long-term outcomes in pivotal clinical studies.

CED Question	Summary
What morbidity and procedure-related factors contribute to TAVR patients' outcomes? Specifically, this must be addressed through a composite metric.	A published composite performance measure incorporating mortality and serious complications is now available.

2.2.1.1"When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?" (p. 2)

TVT Registry 30-day outcomes are clinically similar to outcomes from pivotal clinical studies. Carroll et al. included the 30-day outcomes of TAVR patients with balloon-expandable or self-expanding THVs by risk level from 2011 to 2019 from the US Transcatheter Valve Therapy (TVT) Registry, which resolves questions regarding how outcomes in clinical practice compared to clinical trial experience. The findings were an early indication of registry outcomes paralleling pivotal clinical trial outcomes in low-risk patients [27]. In an unmatched sample, stratified by surgical risk category (High-risk: n=31,598; Intermediate-risk: n= 2,697; Low-risk: n=8,395), the 30-day registry outcomes are clinically similar to outcomes from the PARTNER trials, apart from a major vascular complications rate, which has decreased by 9.4 percentage points from the PARTNER 1 results in the high-risk population (**Table 1**). For all risk levels, the median length of stay and 30-day major vascular complication rates were lower in 2019 than in the PARTNER trials [40, 66, 67].

Table 1. 30-Day Registry & PARTNER Outcomes

Risk Category	Sample	STS PROM, Mean (SD)*	Median LOS	Mean 30-Day Outcomes			
				All-Cause Mortality	Stroke	New PPMI	Major Vascular Complications
High	**Registry** [25]	6.06	2	3.8%	2.7%	11.8%	1.8%
	PARTNER 1 [38]	11.8 ± 3.3	8	5.2%	4.7%	4.4%	11.2%
	Difference	-5.7	-6	-1.4%	-2.0%	7.4%	-9.4%
Intermediate	**Registry**	3.89	2	1.4%	1.9%	10.3%	1.4%
	PARTNER 2 S3i [67]	5.2 (4.3 - 6.3)	4	1.1%	2.7%	10.2%	6.1%
	Difference	0.3	-2	0.3%	-0.8%	0.1%	-4.7%
Low	**Registry**	2.31	1	1.0%	1.9%	8.2%	0.8%
	PARTNER 3 [40]	1.9 ± 0.7	3	0.4%	0.6%	6.5%	2.2%
	Difference	0.3	-2	0.6%	1.3%	1.7%	-1.4%

PROM: Predicted Risk of Mortality; SD: standard deviation; LOS: length of stay: PPMI: permanent pacemaker implantation

2.2.1.2 "What is the long-term durability of the device?" (p. 2)

TAVR has demonstrated excellent durability through 5 years for high, intermediate, and low-risk patients from the PARTNER trials. When the TAVR NCD was last reopened, the "excellent longitudinal durability" of a first-generation THV

through 5 years had been demonstrated in the core lab evaluation of 2,482 high surgical risk patients from the PARTNER trial [68]. Since then, durability data for all risk levels has been published from randomized controlled trials (RCTs) of balloon-expandable and self-expanding valves showing similar or lower rates of structural valve deterioration for TAVR compared to SAVR. **Additionally, the excellent durability of TAVR valves in a real-world population of Medicare beneficiaries has been demonstrated through 10 years** [28].

In the pooled analysis of the CoreValve High-risk RCT and SURTAVI trial at 5 years, intermediate or high-risk patients treated with TAVR (n=1,123) had statistically significantly lower rates of hemodynamic valve deterioration, defined as an increase in mean aortic gradient ≥10 mmHg or aortic valve reintervention for stenosis > 30 days post-procedure (2.95% vs. 5.46%; HR: 0.47; 95% CI: 0.29-0.77; p=0.003). The group treated with TAVR also had no significant difference in rates of SVD using VARC-3 definitions than patients treated with SAVR (n=964) (1.82% vs. 2.67%; HR: 0.59; 95% CI: 0.31-1.12; p=0.10) [69]. The PARTNER 2 S3i study of 5-year outcomes demonstrated similarly low rates of structural valve deterioration (SVD)-related using VARC 3 definitions for TAVR with SAPIEN 3 (stage 2 & 3 hemodynamic valve deterioration: 0.6 per 100 exposure years; BVF: 0.6 per 100 exposure years) and SAVR through 5 years. Among 783 propensity matched pairs of patients from the PARTNER 2 S3i study, there were no significant differences in the rates of aortic valve or surgical reintervention between SAVR and S3 TAVR at 5 years (1.3% vs. 0.8%; OR: 1.67; 95% CI: 0.61-4.56; p=0.31) [70].

Among low-risk patients in the 5-year follow-up of the PARTNER 3 Trial with 496 SAPIEN 3 recipients, aortic valve durability according to VARC-3 definitions of BVF (the occurrence of valve reintervention, valve-related death, or deterioration in hemodynamic valve function) were similar for SAVR and TAVR at 5 years (3.3% vs. 3.8%; HR: 0.86; 95% CI: 0.42-1.77). Low rates of aortic valve reintervention (2.2% vs. 2.6%) and SVD (stage 3 structural or hemodynamic valve deterioration: 1.1% vs. 1.0%) were demonstrated through 5 years for TAVR and SAVR [71]. In the ten-year NOTION trial follow-up of low-risk TAVR patients with first generation self-expanding valves, TAVR and SAVR patients had similarly low rates of aortic valve reintervention (4.3% vs. 2.2%; p=0.3). Additionally, TAVR patients showed no significant difference in SVD, defined as echo-gradient $\geq$ 20 mmHg and an increase of $\geq$ 10 mmHg after 3 months post-procedure or $\geq$ moderate AR, compared to SAVR patients (15.3% vs. 21.6%; HR: 0.71; 95% CI: 0.39-1.27; p=0.25) and had significantly lower bioprosthetic valve deterioration compared to SAVR patients (67.8% vs. 81.2%; p=0.007) [72].

Importantly, one recent observational study of 230,644 Medicare beneficiaries who underwent TAVR between 2011 and 2020 demonstrated low valve reintervention rates after TAVR (crude 10-year reintervention rate: 0.59%; adjusted 10-year reintervention incidence rate: 1.63%) and decreasing risk-adjusted rates of reintervention over time (0.85% in 2011-2016 vs. 0.51% in 2017-2020) [28]. Two observational single-center studies further support the long-term durability of the device in high-risk patients. Among 235 high-risk patients who underwent TAVR with early generation THVs (Cribier-Edwards (20.9%), Edwards SAPIEN (77.4%) or CoreValve (1.7%)), the cumulative incidence of SVD/BVF was 6.5% at 10 years and aortic valve reintervention was rare (n=2) [73]. In an early population of 378 very high-risk balloon expandable THV recipients, the incidence of SVD and BVF (which includes aortic valve reintervention) at 8 years was 3.2% and 0.6%, respectively [74].

2.2.1.3 "What are the long-term outcomes and adverse events?" (p. 2)

TAVR has excellent, well-evidenced long-term outcomes in pivotal clinical studies (**Table 2**).

All-cause mortality

TAVR with a balloon-expandable or self-expanding device has demonstrated similar all-cause mortality rates as SAVR for high and intermediate and low-risk patients at 5 years. For high-risk patients in the PARTNER A randomized controlled trial (RCT) and the CoreValve U.S. Pivotal High-risk RCT, TAVR with a first generation device resulted in similar all-cause mortality rates as SAVR at 5 years (PARTNER A: 67.8% vs. 62.4%; HR: 1.04; 95% CI: 0.86-1.24; p=0.76; CoreValve: 55.3% vs. 55.4%; log-rank p=0.50) [75, 76]. For intermediate-risk patients with a third-generation device in the PARTNER 2 S3i study

and with a first- or second-generation device in the SURTAVI RCT, all-cause mortality was similar for TAVR and SAVR recipients at 5 years (PARTNER 2 S3i: 39.2% vs. 41.4%; HR: 0.90; 95% CI: 0.76-1.06; p=0.21; SURTAVI: 30.0% vs. 28.7%; HR: 1.06; 95% CI: 0.88-1.28; p=0.55) [70, 77]. For low-risk patients, all-cause mortality was similar at 5 years for TAVR and SAVR patients in the PARTNER 3 RCT (10.0% vs. 8.2%; HR: 0.79; 95% CI: 0.61-1.02), at 5 years for patients in the Evolut Low-risk RCT (13.5% vs 14.9%; p=0.39), and at 10 years for TAVR and SAVR patients in the NOTION trial (62.7% vs. 64%; HR: 0.97; 95% CI: 0.72-1.30; p=0.84) [72, 78, 79].

Stroke

Across 7 trials of TAVR and SAVR and all risk levels, TAVR and SAVR resulted in similar or reduced long-term rates of stroke. The risk of stroke or transient ischemic attack for high-risk patients in the PARTNER A Trial and the rate of major stroke for high-risk patients in the CoreValve U.S. Pivotal High-risk Trial were similar for TAVR and SAVR patients at 5 years (PARTNER A: 15.9% vs. 14.7%; HR: 0.82; 95% CI: 0.59-1.15; p=0.24; CoreValve: 12.3% vs. 13.2%; p=0.49) [75, 76]. Intermediate patients that underwent TAVR in the PARTNER 2 S3i study had reduced rates of disabling stroke and those from the SURTAVI RCT had similar rates of stroke at 5 years compared to SAVR patients (PARTNER 2 S3i: 5.8% vs. 7.9%; HR: 0.66; 95% CI: 0.43-1.00; p=0.046; SURTAVI: 4.1% vs. 5.8%; HR: 0.69; 95% CI: 0.43-1.10; p=0.12) [77, 80]. Compared to SAVR patients, low-risk TAVR patients had similar rates of disabling stroke at 5 years in the PARTNER 3 RCT, similar rates of disabling stroke at 5 years in the Evolut Low-risk RCT, and similar rates of any stroke at 10 years in the NOTION RCT (PARTNER 3: 2.9% vs. 2.7%; HR: 1.03; 95% CI: 0.46-2.30; Evolut: 3.6% vs. 4.0%; p=0.32; NOTION: 9.7% vs. 16.4%; p=0.11) [72, 79, 81].

New permanent pacemaker implantation

Across 7 RCTs and all risk levels, TAVR has demonstrated similar or higher rates of new permanent pacemaker implantation than SAVR. For high-risk patients, the need for new permanent pacemaker implantation (PPI) was similar for the TAVR and SAVR groups in the PARTNER A trial and higher for the TAVR group in the CoreValve U.S. Pivotal High-risk RCT at 5 years (PARTNER A: 9.7% vs. 9.1%; log-rank p=0.64; CoreValve: 33.0% vs. 19.8%; p<0.001) [75, 76] The 5-year incidence rate of new permanent pacemaker was higher in TAVR than SAVR among intermediate-risk patients in the PARTNER 2 S3i study and SURTAVI RCT (PARTNER 2 S3i: 16.2% vs. 11.7%; OR: 1.38; 95% CI: 1.08-1.77; p=0.01; SURTAVI: 39.1% vs. 15.1%; HR: 3.30; 95% CI: 2.61-4.17; log-rank p<0.001) [77, 80]. Among low-risk patients, the rates of new PPI were comparable between TAVR and SAVR at 5 years in the PARTNER 3 RCT, (13.5% vs. 10.4%; HR: 1.33; 95% CI: 0.90-1.96), and higher in TAVR than SAVR in patients with self-expanding valves at 4 years in the Evolut Low-risk RCT and 10 years in the NOTION trial (Evolut: 24.6% vs 9.9%; P < 0.001; NOTION: 44.7% vs. 14.0%, p<0.0001) [72, 78, 79].

Bleeding

TAVR resulted in lower rates of bleeding at 5 years for high and intermediate-risk patients and 2 years for low-risk patients compared to SAVR for all risk levels in 4 studies. For high-risk patients in the PARTNER A RCT or CoreValve U.S. Pivotal High-risk RCT, the 5-year rates of major bleeding were lower with TAVR than SAVR (PARTNER A: 26.6% vs. 34.4%; log-rank p=0.003; CoreValve: 35.9% vs. 43.3%; log-rank p=0.05) [75, 76]. In the PARTNER 2A Trial, intermediate-risk patients with a second-generation device (SAPIEN XT) had significantly lower rates of major bleeding than SAVR patients at 2 years in the overall and transfemoral approach cohorts (TF cohorts (n=1550): 13.6% vs. 44.7%; p<0.001) [39]. In the Evolut Low-risk RCT with the self-expanding valve, the rate of life-threatening or disabling bleeding was lower in the TAVR arm (n=725) than the SAVR arm (n=678) at 2 years (4.5% vs. 9.8%; delta: -5.3; 95% CI: -8.7 – -2.1) [82]. Long-term rates of major bleeding have not been reported from the SURTAVI, PARTNER 3, or NOTION trials.

Vascular complications

TAVR resulted in higher rates of vascular complications than SAVR at 5 years for high and intermediate-risk patients and similar rates at 2 years for low-risk patients. For high-risk patients in the PARTNER A or CoreValve U.S. Pivotal High-risk Trial, vascular complications were more common in the TAVR group than the SAVR group at 5 years (11.9% vs. 4.7%; log-rank p=0.0002; 7.1% vs. 2.0%; long-rank p=0.001) [75, 76]. In the PARTNER 2A Trial of intermediate-risk patients with SAPIEN XT, the rate of major vascular complications was higher in the TAVR cohort than the SAVR cohort at 2 years (TF

cohorts: 9.0% vs. 4.5%; p<0.001) [39]. Long-term rates of vascular complications have not been reported from the PARTNER 2 S3i, SURTAVI, PARTNER 3, or NOTION trials. In the Evolut Low-risk RCT with the self-expanding valve, the rate of major vascular complications was similar in the TAVR and SAVR groups at 5 years (4.1% vs 3.9%; HR: 1.07; 95% CI: 0.65-1.82; p=0.79) [79].

Table 2. TAVR RCT Long-Term Outcomes & Adverse Events

HIGH-RISK						
	PARTNER 1 RCT			**CoreValve High-risk RCT**		
5-yr Outcomes	**TAVR**	**SAVR**	**Relationship**	**TAVR**	**SAVR**	**Relationship**
All-cause mortality	67.8%	62.4%	NS	55.3%	55.4%	NS
Stroke*	15.9%	14.7%	NS	12.3%	13.2%	NS
New permanent pacemaker	9.7%	9.1%	NS	33%	19.8%	TAVR higher
Bleeding	26.6%	34.4%	TAVR lower	35.9%	43.3%	TAVR lower
Vascular	11.9%	4.7%	TAVR higher	7.1%	2.0%	TAVR higher
INTERMEDIATE-RISK						
	PARTNER 2 S3i			**SURTAVI RCT**		
5-yr Outcomes	**TAVR**	**SAVR**	**Relationship**	**TAVR**	**SAVR**	**Relationship**
All-cause mortality	39.2%	41.4%	NS	30.0%	28.7%	NS
Stroke*	5.8%	7.9%	TAVR lower	4.1%	5.8%	NS
New permanent pacemaker	16.2%	11.7%	TAVR higher	39.1%	15.1%	TAVR higher
Bleeding	PARTNER	44.7%	TAVR lower	-	-	-
Vascular	PARTNER	4.5%	TAVR higher	-	-	-
LOW-RISK									
	PARTNER 3 RCT (5-yr Outcomes)			**Evolut Low-risk RCT** (5-yr Outcomes)			**NOTION** (10-yr Outcomes)		
Outcomes	**TAVR**	**SAV**	**Relationship**	**TAVR**	**SAVR**	**Relationship**	**TAVR**	**SAVR**	**Relationship**
All-cause mortality	10.0%	8.2%	NS	13.5%	14.9%	NS	62.7%	64.0%	NS
Stroke*	2.9%	2.7%	NS	3.6%	4.0%	NS	9.7%	16.4%	NS
New permanent pacemaker	13.5%	10.4 %	NS	27.0%	11.3%	TAVR higher	44.7%	14.0%	TAVR higher
Bleeding	10.2%	14.8	TAVR lower	4.5%	9.8%	TAVR lower[†]	-	-	-
Vascular	-	-	-	4.1%	3.9%	NS	-	-	-

*Stroke or TIA for P1, major stroke for CoreValve HR, disabling stroke for both intermediate studies, disabling stroke for P3 and Evolut LR, any stroke for NOTION

[†]Values reflect outcomes at 4 years

TAVR: transcatheter aortic valve replacement; RCT: randomized control trial; Yr: year; Sig: significant; NS: no significant difference (p > 0.05 or 95% confidence intervals overlapping 1.0)

2.2.1.4 "What morbidity and procedure-related factors contribute to TAVR patients' outcomes? Specifically, this must be addressed through a composite metric." (p. 2)

A published composite performance measure incorporating mortality and serious complications is now available, as patients and CMS requested [29]. Reporting on this measure demonstrates that outcomes data used by local hospitals derived from TVT Registry data can be audited or reviewed by appropriate entities to monitor procedural safety and facilitate quality improvement, obviating the need for proxy measurements of quality as a condition of coverage.

Procedure-related factors

A composite measure has been developed using the TVT Registry to help understand the quality of care that TAVR patients receive, in terms of the relationship between short-term procedural outcomes and mortality and health status [29]. The four periprocedural complications included in the composite due to their association with 1-year mortality were stroke (adjusted HR: 2.10; 95% CI: 1.65-2.87; p<0.001), major or life-threatening bleeding (adjusted HR: 1.92; 95% CI: 1.42-2.60; p<0.001), modified Acute Kidney Injury Network stage III acute kidney injury (adjusted HR: 1.81; 95% CI: 1.38-2.37; p<0.001), and moderate or severe perivalvular aortic regurgitation (adjusted HR: 1.50; 95% CI: 1.24-1.81; p<0.001). Of those complications, stroke and moderate or severe perivalvular regurgitation were also independently associated with poorer 1-year patient-reported health status as assessed by the KCCQ-OS score (adjusted effect of any stroke on 1-year KCCQ-OS: –5.8 points; 95% CI: -9.2-2.4; p<0.001; adjusted KCCQ-OS effect of moderate or severe PVR: –2.0 points; 95% CI: –3.8 – -0.30; p=0.021). Periprocedural complications not associated with 1-year mortality included major vascular complications (in the absence of bleeding), mild perivalvular aortic regurgitation, and new permanent pacemaker implantation.

Morbidity factors

According to the 2020 ACC/AHA guidelines for the management of patients with valvular heart disease, treatment decision-making should be individualized based on patient-specific factors that impact longevity or quality of life, such as comorbidities, frailty, and dementia. The consensus document lists advanced age, frailty, smoking or chronic obstructive pulmonary disease, pulmonary hypertension, liver disease, prior stroke, anemia, and other systemic conditions as baseline clinical factors associated with poorer outcomes after TAVR [83].

Disease management quality measures

It is critical to discuss the quality of managing care for the population of patients living with AS, not just procedural outcomes and quality. Lindman et al. conducted the American Heart Association Target: Aortic Stenosis pilot initiative to develop disease management quality metrics to quantify care gaps in patients with AS who were not appropriately diagnosed and referred for treatment. The AHA is expanding this quality initiative to 80 hospitals in the US to improve and formalize a robust quality program for AS management [84]. In addition, performance measures such as time to intervention within 90 days following diagnosis have been published and can be tracked by institutions [85].

2.2.2 The additional key questions from the 2019 NCD regarding important evidence gaps have been answered.

"What are the outcomes (e.g., survival, quality of life, complications, device durability, ancillary needs such as for pacemakers, etc.) for ongoing trials TAVR pivotal studies? What are the long term (5-year) survival and device durability outcomes for each surgical risk group? Are the outcomes of TVT Registry patients similar to those observed in pivotal trials?" (p. 118)

The long-term survival and device durability outcomes for each surgical group are well-evidenced and addressed above in sections 2.2.1.2 and 2.2.1.3. The outcomes of TVT Registry patients are similar to those observed in the PARTNER trials and are detailed in section 2.2.1.1. The 30-day and 1-year outcomes for ongoing TAVR pivotal studies of self-expanding and balloon-expandable THVs are described by outcome, below.

Survival

In 6 trials of TAVR with balloon-expandable or self-expanding valves and including all risk levels, short-term survival was similar or better with TAVR compared to SAVR. In the PARTNER A RCT, 30-day through 5-year survival rates were comparable for high-risk TAVR patients with a first-generation device (n=348) and SAVR patients (n=351) [66, 76, 86]. At 30 days and 1-year after AVR, there was no statistically significant difference in survival rate for TAVR patients versus SAVR

patients (30-day: 96.6% vs. 93.5%, respectively; p=0.07; 1-year: 75.8% vs. 73.2%, respectively; p=0.44) [66]. In the CoreValve High-risk Pivotal Trial, the survival rate at 1 year was higher for patients that underwent TAVR (n=390) than patients that underwent SAVR (n=357) (85.9% vs. 81.1%; p=0.04 for superiority) [87]. In the PARTNER 2 S3i study, survival rates at 30 days and 1 year were higher with the SAPIEN 3 valve (n=1,077) than with SAVR (n=944) in intermediate-risk patients (30-day: 98.9% vs. 96.0%, respectively; 1-year: 92.6% vs. 87.0%, respectively) [67]. In the SURTAVI trial of intermediate-risk patients, survival was similar for TAVR and SAVR patients at 30 days (97.8% vs. 98.3%; 95% Bayesian Credible Interval (BCI): -0.9-1.8) and 1 year (93.3% vs. 93.2%; 95% BCI: -2.7-2.4) [88]. Results from the PARTNER 3 RCT of low-risk patients showed no statistically significant difference in survival rate at 30 days and 1 year with SAPIEN 3 (n=496) compared with SAVR (n=454) (30-day: 99.6% vs. 98.9%; HR: 0.37; 95% CI: 0.07-1.88; 1-year: 99.0% vs. 97.5%; HR: 0.41; 95% CI: 0.14-1.17) [89]. In the Evolut Low-risk trial, there was no statistically significant difference in survival rate for TAVR patients (n=725) compared with SAVR patients (n=678) at 30 days (99.5% vs. 98.7%; 95% BCI: -1.9-0.2) and 1 year (97.6% vs. 97.0%; 95% BCI: -2.6-1.3) [90].

Stroke

Across 6 studies of TAVR and SAVR and all risk levels, TAVR resulted in similar rates of short-term stroke for high- and intermediate-risk patients but significantly lower rates of short-term stroke among low-risk patients. In the PARTNER A trial of high surgical risk patients with AS, rates of major stroke were similar between the SAPIEN and SAVR groups at 30 days (3.8% vs. 2.1%, respectively; p=0.20); at 1 year, there was a trend towards a higher rate with SAPIEN (5.1% vs. 2.4%; p=0.07) [66]. In the CoreValve High-risk RCT, the rates of major stroke at 30 days and 1 year were similar between TAVR and SAVR (30 day: 3.9% vs. 3.1%; p=0.55; 1 year: 5.8% vs. 7.0%; p=0.59) [87]. In the PARTNER 2 S3i study, the rate of major/disabling stroke with SAPIEN 3 was lower than that with SAVR (30-day: 1.0% vs. 4.4%, respectively; 1-year: 2.3% vs. 5.9%, respectively) and was also lower than that observed with SAPIEN XT in the PARTNER 2A trial [67]. In the SURTAVI trial of intermediate-risk patients, the rates of disabling stroke were similar for TAVR and SAVR patients at 30 days (1.2% vs. 2.5%; 95% BCI: -2.6-0.1) and 1 year (2.2% vs. 3.6%; 95% BCI: -3.1-0.4) [88]. In the PARTNER 3 RCT, rates of disabling stroke were lower among patients receiving the SAPIEN 3 valve than those undergoing SAVR at both 30 days (0.0% vs. 0.4%, respectively; Treatment effect: 0.00) and 1 year (0.2% vs. 0.9%; Treatment effect: 0.22; 95% CI: 0.03-2.00) [40]. In the Evolut Low-risk RCT of SEVs (CoreValve, Evolut R, Evolut PRO) versus SAVR, rates of disabling stroke were significantly lower with TAVR than with SAVR at both 30 days (0.5% vs. 1.7%; 95% BCI: -2.4 – -0.2) and 1 year (0.8% vs. 2.4%; 95% BCI: -3.1 – -0.3) [90].

New permanent pacemaker implantation

In 6 pivotal clinical studies, TAVR resulted in similar or higher short-term rates of new permanent pacemaker implantation (PPI) for all risk levels compared to SAVR. In the PARTNER A RCT, rates of new PPI in high surgical risk patients with AS were similar in the SAPIEN and SAVR groups at 30 days and through 5 years of follow-up [66, 76, 86]. At 30 days and 1-year after AVR, the new PPI rate was similar for TAVR and SAVR patients (30-day: 3.8% vs. 3.6%, respectively; p=0.89; 1-year: 6.4% vs. 5.0%, respectively; p=0.44) [66]. In the CoreValve High-risk trial, rates of new PPI were higher for TAVR than SAVR at 30 days (19.8% vs. 7.1%; p<0.001) and 1 year (22.3% vs. 11.3%; p<0.001) [87]. In the PARTNER 2 S3i study, rates of new PPI were comparable between SAPIEN 3 and SAVR in intermediate-risk patients at 30 days and 1-year post AVR (30-day: 10.2% vs. 7.3%, respectively; 1-year: 12.4% vs. 9.4%, respectively) [67]. In the SURTAVI trial, the 30-day rate of new PPI was higher for TAVR patients than SAVR patients (25.9% vs. 6.6%; 95% BCI: 5.9-22.7) [88]. In the PARTNER 3 trial, rates of new PPI were comparable between TAVR and SAVR across all follow-up periods in low-risk patients [40, 81]. At 30 days and 1-year after AVR, the new PPI rate was similar for SAPIEN 3 and SAVR patients (30-day: 6.6% vs. 4.1%, respectively; Treatment effect: 1.65; 95% CI: 0.92-2.95; 1-year: 7.5% vs. 5.5%, respectively; Treatment effect: 1.38; 95% CI: 0.82-2.32) [40]. The Evolut Low-risk trial found that the rate of new PPI was significantly higher with TAVR than SAVR at 30 days (17.4% vs. 6.1%; 95% BCI: 8.0-14.7) and 1 year (19.4% vs. 6.7%; 95% BCI: 9.2-16.2) [90].

Bleeding

TAVR resulted in similar or lower short-term rates of major bleeding compared to SAVR in 6 studies and all risk levels. In the PARTNER A trial, rates of major bleeding events were significantly lower in the SAPIEN group than in the SAVR group at 30 days and through 5 years [66, 76, 86]. At 30 days and 1-year after AVR, the rate of major bleeding was significantly lower among TAVR patients than SAVR patients (30-day: 9.3% vs. 19.5%, respectively; p<0.001; 1-year: 8.6% vs. 16.0%, respectively; p<0.001) [66]. In the CoreValve High-risk trial, rates of major bleeding were lower among TAVR patients than SAVR patients at 30 days (28.1% vs. 34.5%; p=0.05) and 1 year (29.5% vs. 36.7%; p=0.03) [87].

The PARTNER 2 S3i study compared rates of life-threatening or disabling bleeding and showed that the 30-day rate of this outcome was considerably lower with SAPIEN 3 than with SAVR (4.6% vs. 46.7%, respectively) [67]. In the SURTAVI trial, 30-day rates of major bleeding were similar for TAVR and SAVR patients (12.2% vs. 9.3%; 95% BCI: -0.1-5.9) [88]. In the PARTNER 3 trial, rates of major bleeding were significantly lower with SAPIEN 3 than with SAVR at both 30 days (2.6% vs. 13.5%; Treatment effect: 0.18; 95% CI: 0.10-0.33) and 1 year (5.3% vs. 14.2%; Treatment effect: 0.34; 95% CI: 0.22-0.54) [89]. Similarly, the Evolut Low-risk trial showed that rates of life-threatening or disabling bleeding were significantly lower with TAVR than with SAVR at 30 days (2.4% vs. 7.5%; 95% BCI: -7.5 − -2.9) and 1 year (3.2% vs. 8.9%; 95% BCI: -8.4 − -3.1) [90].

Vascular complications

Short-term rates of major vascular complications were higher with TAVR than SAVR in high and intermediate risk patients but similar to SAVR with the introduction of SAPIEN 3 and the expansion of TAVR into low-risk patients. In the PARTNER A trial, patients in the SAPIEN group experienced significantly higher rates of major vascular complications than those in the SAVR group at 30 days and 1 year following AVR (30-day: 11.0% vs. 3.2%, respectively; p < 0.001; 1-year: 11.3% vs. 3.8%, respectively; p=0.0002) [66]. In the CoreValve High-risk trial, rates of major vascular complications were higher in the TAVR group than the SAVR group at 30 days (5.9% vs. 1.7%; p=0.003) and 1 year (6.2% vs. 2.0%; p=0.004) [87]. Further reduction of major vascular complications was observed with the introduction of SAPIEN 3. In the PARTNER 2 S3i study, the 30-day rate of major vascular complications was slightly higher with SAPIEN 3 than with SAVR (6.1% vs. 5.4%, respectively) [67]. In the SURTAVI trial, the 30-day rate of major vascular complications was higher for TAVR than SAVR (6.0% vs. 1.1%; 95% BCI: 3.2-6.7) [88]. In the PARTNER 3 trial, rates of major vascular complications were generally similar with SAPIEN 3 and SAVR at both 30 days (2.2% vs. 1.5%; Treatment effect: 1.44; 95% CI: 0.56-3.73) and 1 year (2.8% vs. 1.5%; Treatment effect: 1.83; 95% CI: 0.74-4.55) [89]. In the Evolut Low-risk trial, the rates of major vascular complication were also similar between TAVR and SAVR at 30 days (3.8% vs. 3.2%; 95% BCI: −1.4-2.5) and 1 year (3.8% vs. 3.5%; 95% BCI: −1.7-2.3) [90].

Acute Kidney Injury (AKI)

Rates of renal failure following TAVR are low across all risk levels and clinical trials for BEVs and SEVs. In the PARTNER A RCT, rates of renal replacement therapy through 1 year were low for high-risk patients in the TAVR and SAVR groups (30-day: 2.9% vs. 3.0%; p=0.95; 1-year: 5.4% vs. 6.5%; p=0.56) [38]. Among intermediate risk patients in the PARTNER 2 S3i, the 30-day rates of stage 3 AKI were numerically lower with TAVR than SAVR (0.5% vs. 3.3%) [67]. In the PARTNER 3 trial, 30-day rates of stage 2 or 3 AKI were lower with SAPIEN 3 than with SAVR (0.4% vs. 1.8%) [40]. Rates of renal failure at 30-days or 1 year were lower for TAVR with SEVs than SAVR for all risk levels in the CoreValve and Evolut trials (CoreValve High-risk trial 1-year: 6.2% vs. 15.1%; p<0.001; SURTAVI 30-day: 1.7% vs. 4.4%; Evolut Low-Risk trial 1-year: 0.9% vs. 2.8%) [88] [90] [90].

Table 3. TAVR RCT Short-Term Outcomes & Adverse Events

HIGH-RISK										
	PARTNER 1 RCT					CoreValve High-risk RCT				
	30-Day		1-Year		Relationship	30-Day		1-Year		Relationship
	TAVR	SAVR	TAVR	SAVR		TAVR	SAVR	TAVR	SAVR	
All-cause mortality	3.4%	6.5%	24.2%	26.8%	NS	3.3%	4.5%	14.2%	19.1%	TAVR lower*
Major stroke	3.8%	2.1%	5.1%	2.4%	NS	3.9%	3.1%	5.8%	7.0%	NS
New permanent pacemaker	3.8%	3.6%	6.4%	5.0%	NS	19.8%	7.1%	22.3%	11.3%	TAVR higher
Bleeding	9.3%	19.5%	8.6%	16.0%	TAVR lower	28.1%	34.5%	29.5%	36.7%	TAVR lower*
Vascular complications	11.0%	3.2%	11.3%	3.8%	TAVR higher	5.9%	1.7%	6.2%	2.0%	TAVR higher
Acute Kidney Injury	2.9%	3.0%	5.4%	6.5%	NS	6.0%	15.1%	6.0%	15.1%	TAVR lower
INTERMEDIATE-RISK										
	PARTNER 2 S3i					SURTAVI RCT				
	30-Day		1-Year		Relationship	30-Day		1-Year		Relationship
	TAVR	SAVR	TAVR	SAVR		TAVR	SAVR	TAVR	SAVR	
All-cause mortality	1.1%	4.0%	7.4%	13.0%	TAVR lower	2.2%	1.7%	6.7%	6.8%	NS
Disabling stroke	1.0%	4.4%	2.3%	5.9%	TAVR lower*	1.2%	2.5%	2.2%	3.6%	NS
New permanent pacemaker	10.2%	7.3%	12.4%	9.4%	NS	25.9%	6.6%	-	-	TAVR higher
Bleeding	4.6%	46.7%	-	-	NR	12.2%	9.3%	-	-	NS
Vascular complications	6.1%	5.4%	-	-	NR	6.0%	1.1%	-	-	TAVR higher
Acute Kidney Injury	0.5%	3.3%	-	-	NR	1.7%	4.4%	-	-	TAVR lower
LOW-RISK										
	PARTNER 3 RCT					Evolut Low-Risk RCT				
	30-Day		1-Year		Relationship	30-Day		1-Year		Relationship
	TAVR	SAVR	TAVR	SAVR		TAVR	SAVR	TAVR	SAVR	
All-cause mortality	0.4%	1.1%	1.0%	2.5%	NS	0.5%	1.3%	2.4%	3.0%	NS
Disabling stroke	0.0%	0.4%	0.2%	0.9%	NS	0.5%	1.7%	0.8%	2.4%	TAVR lower
New permanent pacemaker	6.6%	4.1%	7.5%	5.5%	NS	17.4%	6.1%	19.4%	6.7%	TAVR higher
Bleeding	2.6%	13.5%	5.3%	14.2%	TAVR lower	2.4%	7.5%	3.2%	8.9%	TAVR lower
Vascular complications	2.2%	1.5%	2.8%	1.5%	NS	3.8%	3.2%	3.8%	3.5%	NS
Acute Kidney Injury	0.4%	1.8%	-	-	NR	0.9%	2.8%	0.9%	2.8%	TAVR lower

*Significant difference at 1-year

RCT: randomized control trial; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; TAVR higher/lower: significant; NS: no significant difference ($p > 0.05$ or 95% confidence intervals overlapping 1.0); NR: not reported

Repeat Aortic Valve Procedures

Across clinical trials for TAVR, aortic valve reintervention rates are low, with most reinterventions following TAVR occurring in the first year post-procedure. In the 5 year follow-up from the PARTNER 3 trial, reintervention was not significantly different for TAVR with SAPIEN 3 compared to SAVR (2.6% vs 3.0%; HR=0.86 [0.39–1.92]) [78]. In the 5 year follow up of the PARTNER 2 S3i study, rates of reintervention were not different between TAVR and SAVR (1.3% vs 0.8%, p=0.31) [70]. Data from the PARTNER 1 trial showed that only 0.2% of patients at high or prohibitive surgical risk (N=2,482) required reintervention for SVD (using VARC-2 definitions) at up to 5 years after TAVR with the SAPIEN THV [68]. In a pooled analysis from the CoreValve and Evolut R/PRO randomized trials, the incidence of reintervention through 5 years was low. The

pooled incidence or reintervention was higher with TAVR than SAVR, but when the analysis was limited to more recent generation EVOLUT R/PRO, there was no difference in reintervention through 5 years [91].

Quality of Life

TAVR resulted in improved quality of life for all risk levels in 6 pivotal clinical studies, with short-term gains greater in TAVR patients than SAVR patients. In the TF TAVR subcohort of the PARTNER A RCT, 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. 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 or SAVR at 6 months and 1 year [92]. In the TA subcohort of PARTNER A, patients in the SAPIEN and SAVR groups experienced a significant improvement of KCCQ-OS scores at 30 days, 6 months, and 1 year compared with baseline [93]. Among high-risk patients in the CoreValve High-risk trial, 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). 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. 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) [94]. However, no differences in KCCQ-OS or SF-12 scores were observed between the CoreValve and SAVR groups at 6-month, 1-year, and 5-year follow-up [75].

Patients who received the SAPIEN 3 valve in the PARTNER 2 S3i study experienced a 19.1-point improvement at 1 month and a 23.3-point improvement at 12 months compared with baseline on the KCCQ-OS score (both p<0.001) [95]. At 12 months, this difference corresponded to a large, clinically important improvement (i.e., ≥20-point change) [92]. Significant improvements from baseline were also observed on the SF-36 physical and mental summary scales, with 1-year improvements of 5.1 and 3.9 points, respectively (p<0.001 for both comparisons). TAVR with SAPIEN 3 also resulted in significant improvements in patient QoL than SAVR in the S3i study. At 1 month, patients treated with SAPIEN 3 had a significantly improved mean overall KCCQ score (+15.6 points) compared with those who received SAVR (p<0.001) (Figure 11.19). By 12 months, the improvement with SAPIEN 3 remained statistically significant compared with SAVR (+2.0 points; p=0.04) [95]. The SURTAVI trial evaluated QoL using the KCCQ-OS among intermediate-risk patients after TAVR with CoreValve versus SAVR at 30 days and 2 years [96, 97]. At 1 month, patients who underwent TAVR had a significantly greater improvement in KCCQ-OS score from baseline than those who underwent SAVR (+18.1 points vs. +5.3 points, respectively; p<0.001). However, improvements were similar between both treatment groups at 2 years (+18.4 points vs. +18.2 points, respectively; p=0.873) [97].

The quality of life of low surgical risk patients was evaluated in the PARTNER 3 trial of SAPIEN 3 using the KCCQ score, the SF-36, and the EQ-5D [98]. Relative to baseline, TAVR patients experienced improvements in all QoL measures at 30 days (difference from baseline of 18.5 points on KCCQ-OS scale, 5.0 points on SF-36 physical summary scale, 3.4 points on SF-36 mental summary scale; p<0.001 vs. baseline for all scales). The benefits of TAVR relative to baseline persisted at 6 months and 1 year on all scales. The study showed that at 30 days and 1 year, mean KCCQ-OS scores were significantly better with SAPIEN 3 than with SAVR (TAVR vs. SAVR: 88.9 vs. 72.8 at 30 days, p<0.001; 89.9 vs. 88.1 at 1 year, p=0.03) [98]. At 5 years, the majority (71%) of TAVR patients were alive and well (KCCQ-OS score of ≥ 75), with similar KCCQ-OS scores by AVR type (86.2 vs. 85.9) [78]. The Evolut Low-risk Trial compared the QoL of low surgical risk patients who underwent TAVR with CoreValve, Evolut R, or Evolut PRO or who underwent SAVR. KCCQ-OS scores were found to be higher in the TAVR group than in the SAVR group at 30 days (88.7±14.2 vs. 78.6±18.9, respectively; significance NR); however, scores were similar at both 6 months and 1 year of follow-up [90].

"What is the echocardiographic, CT and/or MR assessment of transcatheter aortic valvular performance, deterioration and durability as compared to surgical AVR?" (p. 118)

When the TAVR NCD was last reconsidered, the stable reduction of mean gradients and increase in effective orifice area (EOA) had been demonstrated in high-risk patients treated with SAPIEN valves through 5 years [68]. Since then, follow-up echocardiography of high, intermediate, and low-risk patients has confirmed the excellent performance and durability of TAVR valves through 5 years, as exhibited by similar or larger decreases in mean gradients and increases in aortic valve areas with TAVR compared to SAVR.

In serial echocardiograms of patients from the CoreValve High-risk RCT, TAVR had significantly larger EOA ($p<0.01$) and smaller mean gradients ($p<0.01$) than SAVR at all time points through 5 years [75].

In the PARTNER 2 S3i study, the improvements in mean aortic valve areas and gradients observed at 30 days after TAVR were maintained at 1 year (valve area, 1.7 cm^2; gradient, 11.4 mmHg) and through 5 years [67, 70]. The 5-year follow-up of SAPIEN 3 in the PARTNER 2 S3i study showed stable echo-assessed gradients and aortic valve area, therefore excellent valve performance. Aortic valve area was modestly greater in the SAPIEN 3 arm than the SAVR arm (1.6 and 1.4 cm^2, respectively; $p<0.0001$) and there was no difference in mean gradients between arms (11.2 and 10.6 mmHg, respectively; NS) through 5 years [80]. This trial further demonstrated the SAPIEN 3 valve durability in terms of the 5-year rates of SVD (0.68 ± 0.18% vs. 0.60 ± 0.17%; p=0.71), SVD-related BVF (0.29 ± 0.12% vs. 0.14 ± 0.08%; p=0.25), and all-cause BVF (0.60 ± 0.15% vs. 0.32 ± 0.11%; p=0.32), none of which were significantly different from SAVR 5-year rates [99]. Among patients from the SURTAVI trial, TAVR demonstrated significantly larger EOAs ($p<0.001$) and lower mean gradients ($p<0.001$) than SAVR at all time points through 5 years [77].

In the 2-year follow-up of the PARTNER 3 Trial with 496 SAPIEN 3 recipients, there were no significant differences in effective orifice areas (1.7 ± 0.37 vs. 1.7 ± 0.42; p=0.34), moderate or severe HVD, and BVF following TAVR, but mean gradients were slightly higher (13.6 ± 5.53 vs. 11.8 ± 4.82; p=0.06) with TAVR compared to SAVR [100]. TAVR and SAVR resulted in similar aortic valve durability at 5 years, including similar mean aortic valve areas (1.9 ± 0.5 cm2 vs. 1.8 ± 0.5 cm^2) and mean aortic valve gradients (12.8 ± 6.5 mm Hg vs. 11.7 ± 5.6 mm Hg) [71]. In the Evolut Low-risk trial, TAVR recipients had consistently significantly larger effective orifice areas (2.2 cm^2 vs. 2.0 cm^2; 95% CI of the difference: 0.2-0.3; $p<0.001$) and lower aortic valve mean gradients (9.1 mm Hg vs. 12.1 mm Hg; 95% CI of the difference: 3.6 to 2.4; $p<0.001$) at 3 years [101]. In the 4-year follow-up of the Evolut Low-risk RCT of self-expanding valve recipients, TAVR had significantly lower aortic valve mean gradients (9.8 ± 5.5 mm Hg [n = 497] vs 12.1 ± 5.4 mm Hg [n = 438]; $P < 0.001$) and greater effective orifice areas (2.1 ± 0.6 cm^2 [n = 438] vs 2.0 ± 0.6 cm^2 [n = 372]; $P < 0.001$) compared to SAVR [82]. See section 2.2.1.2 for additional detail on structural valve deterioration and durability, which are similar or better with TAVR compared to SAVR in recent trials.

"Within patient populations (defined by risk level) for which TAVR has demonstrated a benefit, what are the pre-procedural patient characteristics (including comorbidities), and procedure-related factors, that predict outcomes? Can standardized, patient- and family-friendly, evidence-based risk assessment tools improve patient-physician shared decision making? What subgroups of patients within a given population may benefit substantially more or less from the procedure?" (p. 118)

When considering patient characteristics and procedural factors, an analysis of 161,196 patients treated with TAVR from 2011 to 2018 from the TVT Registry showed that the most important contributors to improved short term outcomes are advances in the technology (e.g., device iteration) and procedural factors (e.g. access site, sheath size, use of anesthesia, contrast volume, and use of embolic protection devices). The improvement in 1-year mortality following TAVR over time was explained mostly by non-cardiovascular patient comorbidities and characteristics (i.e., body surface area, severe lung disease, home oxygen, estimated glomerular filtration rate, dialysis, diabetes) [102]. Among intermediate and high surgical risk TAVR patients from the PARTNER 2 studies (n=3,763), major stroke and stage 3 acute kidney injury were associated

with increased 1-year mortality (HR: 5.4; 95% CI: 3.1-9.5 and HR: 4.9; 95% CI: 2.7-8.8, respectively) and poorer quality of life among survivors (1-year change in KCCQ overall summary score: -15.1; 95% CI: -24.8 – -5.3 and -14.7; 95% CI: -25.6 – -3.8 points, respectively). Moderate or severe PVL, life-threatening bleeding, and major bleeding were associated with a smaller increase in 1-year mortality and decrease in quality of life [103].

Shared decision making and patient-centered outcomes were improved when decision aids for were used by Heart Team clinicians [104]. A multi-center mixed-methods study of patients and caregivers identified 1) trust in the healthcare team, 2) having good information about options, and 3) long-term outlook as the three most important clusters of treatment goals. These results are being incorporated into a shared decision-making tool for AS patients [105]. A recent meta-analysis of four studies regarding AS or coronary artery disease (CAD) patient decision aids found that the use of a decision aid significantly increased patient knowledge compared with "usual care" but did not change the level of uncertainty or discomfort felt by patients when making a healthcare decision (decisional conflict; $p<0.001$) [106]. The Aortic Valve Improved Treatment Approaches (AVITA) online decision aid, which presents options and clarifies patient goals and values to generate a summary for clinician use during an encounter, was reported to help 95.5% of patients choose a treatment and 80.8% of clinicians understand patients' values. Most patients (60%) changed their treatment preference at least once from baseline after their clinical encounter. Initial treatment preferences were associated with low knowledge, high decisional conflict, and poor decision quality, but final preferences after decision aid use by valve clinicians were associated with high knowledge, low conflict, and high quality [107].

The risks and benefits of undergoing a procedure should always be weighed for patient groups; however, all patients with a class I indication for treatment can benefit from aortic valve replacement and TAVR has proved to be safe and effective among patients of all surgical risk levels. The only group for which AVR may not have a benefit per ACC/AHA guidelines is medically futile patients, defined as patients with "1) a life expectancy of <1 year even with a successful procedure or 2) those with a chance of 'survival with benefit' of <25% at 2 years" [83].

"How can complications associated with various TAVR devices and delivery systems, such as paravalvular regurgitation, need for permanent pacemaker implantation, and vascular events, be further reduced in severity and frequency?" (p. 118)

Over the past decade, there have been considerable improvements in TAVR, including advances in procedural technique, device technologies, and patient selection criteria. These improvements have coincided with a 65% reduction in the risk of 30-day complications from 2012 to 2019 for Medicare fee-for-service beneficiaries. The pace of improvement in outcomes with TAVR outpaces that exhibited with SAVR, which had a 9% decrease during the same time period [108]. In addition, research has accumulated to improve the understanding of which pre-procedural and procedural factors are associated with certain complications, which may aid in procedure planning and device selection.

Paravalvular regurgitation

Rates of moderate-to-severe paravalvular regurgitation (PVR, also known as paravalvular leak or PVL) following TAVR are very low with current generation TAVR devices and procedural techniques. In a study of 161,196 TAVR patients from the TVT Registry, moderate or severe PVR decreased from 10.7% in 2011/2012 to 1.9% in 2018 ($p<0.001$) [102]. As demonstrated in TVT Registry data from 2011 to 2017, there was a significant decrease in greater than mild PVR due to design improvements in newer generation devices, such as the SAPIEN 3 skirt and frame modifications for easier positioning [109]. In recent clinical trials with SAPIEN 3, there has been no significant difference in PVR between TAVR and SAVR. In the PARTNER 2 S3i study, there were no significant differences in moderate to severe PVR between TAVR and SAVR at 5 years (0.7% vs. 0.4%; NS) [80]. In the most recent PARTNER 3 Trial of low-risk patients, there was no difference in moderate or greater PVR between TAVR and SAVR patients through 2 years (0.8% vs. 0.0% at 30 days, 0.8% vs. 0.5% at 1 year, 0.5% vs. 0.0% at 2 years, respectively; NS) [100]. Moderate or greater PVR rates were similarly low through 5 years of the PARTNER 3 Trial (0.9% vs 0.0%) and notably, PVR severity at 30 days had no effect on 5-year mortality for TAVR patients (none/trace PVR: 9.1% vs mild PVR: 11.1%; HR: 0.78; 95% CI: 0.42-1.45) [78].

Permanent pacemaker implantation

Rates of new pacemaker in contemporary practice with SAPIEN 3 are low and comparable with surgery [89, 100]. Certain pre-procedural and procedural factors are associated with new pacemaker after TAVR and should be taken into consideration by operators when selecting the right valve for patients. Pre-procedural predictors associated with new onset left bundle branch block (LBBB) with TAVR include female sex, diabetes, prior coronary artery bypass grafting, first degree atrioventricular block (AVB), prolonged QRS duration, aortic annulus calcification, and larger left ventricular end-diastolic volume. Procedural factors associated with need for new pacemaker include use of self-expanding TAVR valve, transapical access, pre-dilation, oversizing, and lower implantation depth [110].

Vascular events

Vascular complications have generally decreased over time with valve technology evolution. In the most recent PARTNER 3 Trial of low-risk patients, major vascular complications were no different between SAPIEN 3 and SAVR (2.2% vs. 1.5% at 30 days and 2.8% vs. 1.5% at 1 year, respectively; NS) [40]. This indicates a meaningful reduction in vascular complications as the SAPIEN valve technology has evolved. The lower delivery profile of the SAPIEN 3 THV has contributed to a reduction in vascular complications [111].

Procedure and non-procedural factors can also be considered when assessing the risk of vascular complications. According to a review from Mach et al., 2021, "Female gender, peripheral vascular disease–especially in patients with a borderline femoral diameter and/or circumferential calcification patterns, a sheath-to-femoral-artery-ratio (SFAR) of less than 1.05 or a sheath diameter that exceeds the minimal femoral diameter, severe iliofemoral tortuosity patterns with an iliofemoral tortuosity score above 21.2, as well as operator experience and planned surgical cut-down are substantiated independent predictors of vascular complications" [112].

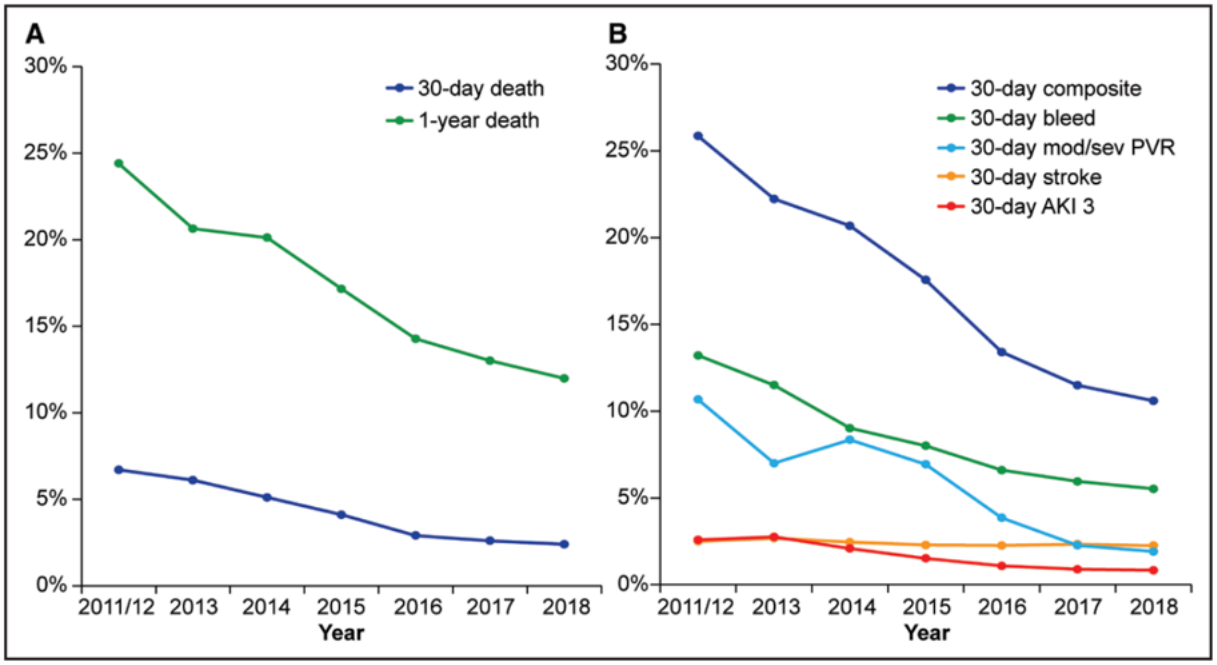
2.3 Updates are needed to remove outdated and burdensome requirements that create barriers to patient care.

2.3.1 TAVR is now a routine AVR treatment option with improved outcomes that are consistently achievable by hospital programs.

Initially approved to treat an inoperable patient population, TAVR has now expanded to treat patients across all surgical risk levels. The proportion of AVRs comprised of TAVRs increased from 12% in 2012 to 72% in 2019 [2]. From 2012 to 2019, the number of TAVR sites increased from 198 to 623 [2, 25]. Following changes to certain criteria in the 2019 NCD update, an additional 95 sites opened, increasing the number of TAVR sites to 718 centers in 2022 and with this patient outcomes continued to improve. The outcomes of patients receiving TAVR are documented within the TVT Registry, and cardiovascular medical societies have played a prominent role to ensure high quality patient outcomes.

Advancements in transcatheter heart valve device technology and procedural techniques drove meaningful improvements in 30-day TAVR outcomes and 1-year mortality in the decade following TAVR approval. According to TVT Registry data of 161,196 TAVR patients from 596 sites from 2012 to 2018, 30-day mortality decreased from 6.7% to 2.4%, 30-day composite adverse events decreased from 25.9% to 10.6%, and 1-year mortality decreased from 24.4% to 12.0% (**Figure 1**) [102].

Figure 1. Outcomes After Transcatheter Aortic Valve Replacement Over Time*



*A: 30-day and 1-year mortality; B: 30-day composite adverse events and major complications
AKI: acute kidney injury; PVR: paravalvular regurgitation

Improvements in length of stay, cost, and early discharge rates are likely attributable to improvement in procedural characteristics [113]. The rate of readmissions post-TAVR have also decreased over time, with significant decreases in 30-, 90-, and 180-day rehospitalizations between 2012 and 2017 [114].

Consistent with the outcomes achieved by experienced TAVR centers, excellent TAVR outcomes were also achieved in new centers opened after the 2019 NCD, as shown by similar unadjusted 30-day rates of the composite endpoint of mortality, complications, or reintervention between new and existing centers (18.8% and 17.07%, respectively; p=0.07) [115]. In addition, flexibilities to the NCD permitted during the public health emergency (PHE) demonstrated program and provider ability to make appropriate care decisions to maintain excellent care in contemporary practice while balancing patient access needs and challenges to care practices. No significant difference in all-cause mortality, stroke, valve-related complications, quality of life, or readmissions has been observed between pre- and post-PHE registry data for TAVR [44].

Based on improved outcomes and modern treatment practices, valve disease guidelines have evolved since the NCD policy was reconsidered in 2019. American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines for the treatment of valvular heart disease were published in 2020 recommending transfemoral (TF) TAVR in preference to SAVR for symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to TF-TAVR. For patients 65 to 80 years of age, either SAVR or TF-TAVR is recommended for symptomatic patients with severe AS who have no anatomic contraindication to TF-TAVR, after shared decision-making about potential valve durability [116].

2.3.2 Patients experience significant and costly delays in care for TAVR procedures.

AS is vastly undertreated; less than half of indicated patients ever receive an aortic valve replacement (AVR) [5, 7]. Yet among those who receive treatment, TAVR patients have a 59 day longer median time from AS diagnosis to treatment

than SAVR patients (157 days and 98 days, respectively) [33]. Approximately 25% of patients with severe symptomatic AS waited more than 10 weeks for TAVR after referral. The consequences of this delay are high, with a 3.8% mortality rate at 1 month and 10.4% mortality rate at 3 months on the TAVR waiting list [117]. The healthcare costs of this delay are also high; in a recent analysis, a one-year wait for TAVR was associated with $10,080 in excess total costs of care, emphasizing the need for timely intervention [118]. In the year prior to TAVR, hospitalization rates are significantly higher than post-procedure, suggesting that earlier diagnosis and treatment are essential to improving the care of AS patients [119]. Earlier intervention in AS disease progression could reduce cardiac decompensation that necessitates urgent/emergent AVR in severe AS patients as well. Urgent/emergent AVR is associated with worse outcomes, increased resource utilization, and increased strain on the healthcare system [120].

Capacity constraints on hospitals, and structural heart programs in particular, are evident by the large (53%) increase in procedure volume accompanied by a small (-1%) decrease in the number of programs from 2016 to 2023 [121]. Burdensome pre-procedural, peri-procedural and infrastructure requirements exclusive to TAVR procedures have contributed to delays in care that impact patient outcomes. Future TAVR procedure growth due to increased patient demand and widespread AS undertreatment, growing demand for structural heart procedures overall, and provider shortages contribute to program and provider inability to provide timely treatment. Worse still, an assessment of the U.S. surgical workforce anticipated up to 50% increased clinical workload for cardiothoracic surgeons remaining in the profession by 2030 [34].

2.3.3 Access barriers to TAVR are well-documented.

TAVR patients must navigate complicated diagnostic and referral pathways before receiving the procedure, which contributes to access barriers that disproportionately impact marginalized groups [122]. Between 2012 and 2018, the majority of new TAVR centers were established in hospitals with fewer dual eligible patients, higher median income, and lower distressed communities index scores [123]. This led to an inequitable dispersion of TAVR in areas with more socioeconomically disadvantaged patients and contributed to disparities in access. [124, 125] Although rural counties have the highest proportion of Americans aged 65+ years, treatment disparities exist between rural and urban regions of the US. More than 70% of TAVRs are performed at urban sites, suggesting that rural residents may have limited access to postprocedural care at the implanting TAVR center [124, 126]. To understand if these disparities in access persisted for healthcare services in general or increasingly for TAVR, findings from a study comparing access to TAVR, SAVR, CABG, and laparoscopic colectomy across 18 states in the US found that even when TAVR was available locally, residents from disadvantaged areas were less likely to undergo the procedure; this difference did not exist for CABG. A potential contributor to this could be the larger volume of hospitals performing CABG, where no NCD requirements limit access [127].

2.3.4 Restricting TAVR centers can cause unintended geographic disparities in access.

Hospital and operator volume criteria can be a barrier for hospitals in under-resourced areas to initiate or maintain TAVR programs. Implemented with the intent to protect patient outcomes, these policies can lead to inequitable dispersion of TAVR in areas with more socioeconomically disadvantaged patients. In a recent study by Nelson, et al., there was a larger proportion of lower-volume sites located rurally, located in the South, and treating Black and Hispanic patients, highlighting the importance of these sites in treating patients who historically have lower rates of TAVR [126, 128-130]. Applying a volume threshold that moved care to the nearest higher-volume site did not improve their predicted 30-day outcomes but increased driving time by up to 88 minutes for rural patients. For elderly patients residing in rural areas, travel distances exceeding 10 miles are associated with reduced healthcare utilization [131]. Geographic barriers to health care access are particularly relevant for low-income patients who are less able to travel for care than the general population [132]. Among Medicare beneficiaries, TAVR rates are lower in socioeconomically disadvantaged zip codes within metropolitan areas offering TAVR, even after adjusting for age and comorbidities. Treatment disparities also exist between rural and urban regions of the US, with more than 70% of transfemoral TAVRs performed at urban sites, suggesting that rural residents may have limited access to postprocedural care at the implanting TAVR center [126].

Restricting TAVR centers based on volume can create longer travel distances and wait times for TAVR, as well as lower utilization rates [133].

Access to TAVR becomes more equitable as the number of hospitals offering TAVR increases, as demonstrated by a 30% increase in TAVR hospitals from 2016 to 2019 and a simultaneous 31% decrease in procedure access inequality [127]. Notably, greater uptake of less-invasive TAVR has narrowed treatment gaps among Black patients with AS suggesting this technology can be leveraged to mitigate disparities in underrepresented groups rather than exacerbate them [7]. Reducing disparities in the treatment of AS requires a multi-faceted approach. Proposed strategies include shared-decision making between providers and patients, increasing enrollment of underrepresented populations in clinical trials, enhancing physician awareness of disparities in AS, team-based healthcare, and improving patient education and access [134-137].

2.3.5 TAVR quality can be measured directly to enable patient access.

Standards for physician, care team, and facility requirements adequately exist in society guidelines and continue to evolve. In addition, outcomes data housed at local facilities can be audited or reviewed by appropriate entities to monitor procedural safety and facilitate quality improvement. Importantly, a TAVR 30-day composite quality measure is now available [29]. The quality measure was rigorously tested and designed to ensure that it could appropriately identify deficiencies in TAVR outcomes at the site level. It is also publicly reported and mirrors the existing quality indicator in place for SAVR procedures. STS online public reporting enables participants to voluntarily report and inform the public of their hospitals or program's heart surgery scores and star ratings.

According to the National Quality Forum, which was the CMS-contracted "consensus-based entity" at the time of its publication,

> The TAVR 30-day morbidity/mortality composite is a hierarchical, multiple outcome risk model that estimates risk standardized results (reported as a "site difference") for the purpose of benchmarking site performance. This measure estimates hospital risk standardized site difference for 5 endpoints (death from all causes, stroke, major or life-threatening bleeding, acute kidney injury, moderate or severe paravalvular aortic regurgitation) within 30 days following transcatheter aortic valve replacement. The measure uses clinical data available in the STS/ACC TVT Registry for risk adjustment for the purposes of benchmarking site to site performance on a rolling 3-year timeframe (Measure Type: Composite; Level of Analysis: Facility; Setting of Care: Inpatient/Hospital; Data Source: Registry Data)
>
> This new composite measure estimates the hospital risk-standardized site difference for five endpoints (death from all causes, stroke, major or life-threatening bleeding, acute kidney injury, and moderate or severe paravalvular aortic regurgitation) within 30 days following TAVR. The developer provided a general overview and description of the measure. The developer indicated a goal during development: respond to the Centers for Medicare & Medicaid Services' (CMS) interest regarding a 2019 coverage decision in which CMS was interested in a periprocedural composite metric that incorporated relevant patient health outcomes to satisfy Coverage with Evidence Development (CED) for TAVR reimbursement [138].

3. Summary of Request to Reconsider TAVR NCD 20.32

Based on the above, we formally request that CMS reconsider the Transcatheter Aortic Valve Replacement (TAVR) NCD 20.32. Since the TAVR NCD was last reopened in 2019, new guidelines for the treatment of valvular heart disease, practice patterns, patient selection criteria, indications, and technological innovation have evolved. A robust body of available evidence, including the EARLY TAVR randomized trial, in tandem with other randomized trials, observational studies, and meta-analyses, uniformly highlight the benefit of timely intervention in asymptomatic AS patients not covered under current NCD criteria. Further, the totality of published evidence demonstrating excellent TAVR outcomes

has answered CED questions and solidified TAVR as the standard of care for AS treatment. In addition, a direct measure of procedural quality is now available. Now outdated and burdensome pre-procedural, peri-procedural and infrastructure requirements exclusive to TAVR procedures contribute barriers to patient access that delay care and impact patient outcomes.

As evidence evolves and technology matures, it is necessary to update coverage policy to preserve quality, maintain patient access, and ensure timely TAVR treatment**. Substantive changes to TAVR coverage policy are required. Specifically:**

a) **Expanding Indications:** Updates to the TAVR NCD are needed to include asymptomatic patients not covered under the current policy.

b) **Sunset CED:** Cumulative evidence demonstrates that TAVR no longer requires CED and is reasonable and necessary for the benefit category of inpatient hospital services and physician services in the treatment of AS.

c) **Remove Barriers to Access:** Updates to the TAVR NCD are needed to streamline and remove outdated and burdensome requirements that create barriers to patient care.

Edwards requests CMS update the TAVR NCD to address new evidence and FDA approval for indications not currently covered, as well as the totality of evidence supporting the use of TAVR as reasonable and necessary for Medicare beneficiaries.

Appendix A: Systematic Literature Review of AVR in patients with Asymptomatic Severe Aortic Stenosis

AS is one of the most common valvular heart conditions in Western countries [139]. Over the last 20 years, population ageing has resulted in a dramatic increase in the prevalence of calcific aortic valve disease globally [140]. Fifty years ago, Braunwald published his landmark article based on observational evidence that still influences practice today, demonstrating the association between hallmark symptoms—chest pain, dyspnea with heart failure, and exertional syncope—and poor outcomes [141]. Current ACC/AHA guidelines recommend AVR after the development of symptoms or a reduction in ejection fraction in the absence of symptoms but rely largely on non-randomized data and expert opinion [83]. However, in modern clinical practice the assessment of symptoms is challenging, particularly in elderly patients who may be frail, less mobile, or have multiple comorbidities.

Access to timely AVR in asymptomatic patients with severe AS is gaining increased attention as evidence suggests that LV remodeling and diastolic dysfunction begin long before patients present symptoms, with the onset of symptoms being a clear indicator of poor prognosis [48, 84]. As many as 50% of patients with asymptomatic severe AS progress to symptomatic status and require treatment within the first 2 years of follow-up [142].

TAVR is a less invasive alternative to SAVR and has now been established as the standard of care for patients with severe AS across the spectrum of surgical risk [37-40, 87, 88, 90]. Over the last decade, evidence for timely AVR intervention has primarily focused on SAVR, with several observational studies and randomized trials providing strong signals favoring SAVR over CS [8-13, 20, 21, 143]. Emerging trial data comparing TAVR and CS has further strengthened the body of evidence, demonstrating favorable outcomes for patients with asymptomatic severe AS [22, 23].

Relevant literature to support in asymptomatic patients with severe AS

A systematic review of randomized and observational studies was conducted to characterize the totality of the evidence evaluating timely AVR (SAVR or TAVR) versus routine CS in patients with asymptomatic severe AS.

The review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [144, 145].

The Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework was utilized as an eligibility criterion to search, select, and review relevant studies (**Appendix Table A1**)**.**

Appendix Table A1. PICOS framework

	Inclusion Criteria
Population	Patients with asymptomatic severe or very severe aortic stenosis
Intervention	Aortic valve replacement: either surgical AVR or transcatheter AVR
Comparator	Clinical surveillance
Outcomes	Clinical outcomes: all-cause mortality, cardiovascular mortality, heart failure hospitalization, unplanned cardiovascular or HF hospitalization, and stroke; QoL outcomes: Kansas City Cardiomyopathy questionnaire (KCCQ)
Study Design	• Randomized controlled trials • Observational studies (prospective and retrospective) • Post-hoc analyses

PubMed, EMBASE, and clinicialtrials.gov were systematically searched using pre-specified criteria from their inception to April 15, 2024.

Studies were excluded based on no clinical outcome data reported in addition to abstracts, case reports, review articles, editorials, letters, and non-journal literature. To increase the sensitivity of the search, variants of the words “asymptomatic aortic stenosis,” “severe aortic stenosis,” “aortic valve replacement,” “surgical aortic valve replacement,” “intervention,” “conservative treatment,” and “conservative management” were developed as either Medical Subject Heading (MeSH) terms in PubMed, Emtree terms in EMBASE, and text words related to AVR in asymptomatic severe AS. The search strategy did not have any restrictions on language, publication date, age, living setting, gender, race, ethnicity, or geographical region of the patient population. To ensure all relevant studies were captured, grey literature searches were conducted in ClinicalTrials.gov using the same search strategy to identify unpublished trial records. References of excluded reviews were manually reviewed for eligibility. Details of the search strategy are presented in **Appendix Table A2** below.

Appendix Table A2. Search Strategy

Database	Time Period	Raw text string	MeSH terms
PubMed	Inception to April 15, 2024	asymptomatic AND severe AND "aortic stenosis" AND ("aortic valve replacement" OR SAVR OR TAVR OR TAVI OR "transcatheter aortic valve" OR "conservative management" OR "watchful waiting")	("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND "aortic stenosis"[All Fields] AND ("aortic valve replacement"[All Fields] OR "SAVR"[All Fields] OR "TAVR"[All Fields] OR "TAVI"[All Fields] OR "transcatheter aortic valve"[All Fields] OR "conservative management"[All Fields] OR "watchful waiting"[All Fields]) NOT (casereports[Filter] OR editorial[Filter] OR letter[Filter]
EMBASE			asymptomatic AND severe AND ('aortic stenosis'/exp OR 'aortic stenosis') AND ('aortic valve replacement'/exp OR 'aortic valve replacement' OR savr OR tavr OR 'tavi'/exp OR tavi OR 'transcatheter aortic valve'/exp OR 'transcatheter aortic valve' OR 'conservative management'/exp OR 'conservative management' OR 'watchful waiting'/exp OR 'watchful waiting’) NOT ('editorial'/it OR 'letter'/it OR 'animal model'/de OR 'conference abstract'/it)
Clinicaltrials.gov			“asymptomatic severe aortic stenosis” in Condition/disease keyword AND “aortic valve replacement” OR “SAVR” OR “TAVR” OR “TAVI” OR “transcatheter aortic valve” OR “conservative management” OR “watchful waiting” in Other terms keyword (Word variations were searched)

Two researchers independently screened against predefined eligibility criteria in two phases, title/abstract screening (Phase 1) and full-text screening (Phase 2) via DistillerSR, a literature review and reference management platform.

Subsequently, data were extracted from eligible articles that passed Phase 2 screening utilizing the Nested Knowledge platform for data aggregation and analysis. The two independent abstractors resolved any disagreement between them by consulting a third reviewer. Data was abstracted on the study population, baseline demographics, interventions, and outcomes of interest. Study quality was assessed using the Cochrane Risk of Bias 2 (RoB2) tool and the Newcastle-Ottawa Scale (NOS) for randomized and non-randomized (observational) studies, respectively [146, 147].

The search identified a total of 898 records from PubMed and Embase; 7 additional records from Clinicaltrials.gov, as well as 3 identified from supplemental manual searches after the initial April 15, 2024 search date.

Thereafter, 320 duplicates and 321 additional irrelevant titles and abstracts were excluded. The remaining 257 records were subject to full-text screening. Sixteen publications were included in the analysis of clinical outcomes following full-text review (12 observational studies and 4 RCTs; **Appendix Figure A1**) [8-23].

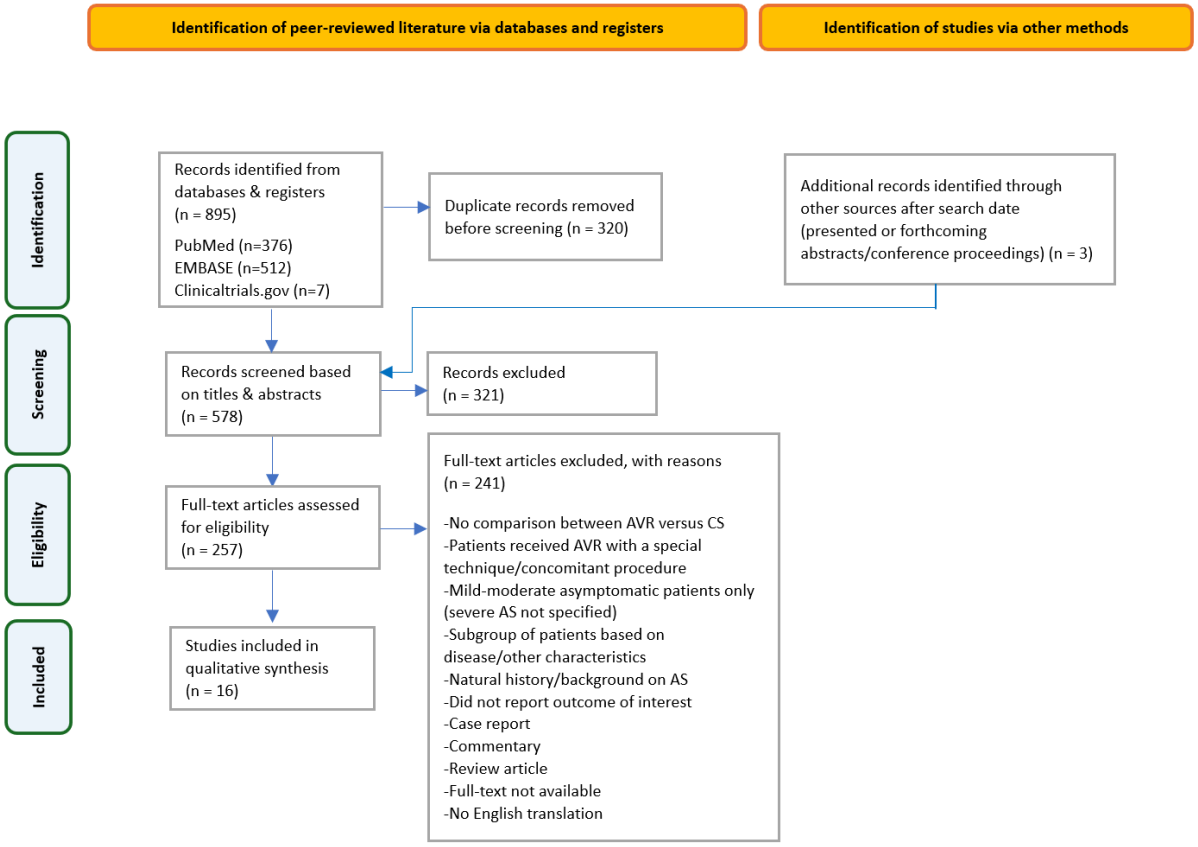
In addition to the 16 studies comparing AVR to CS noted above, two studies that did not meet full criteria for inclusion in the review were evaluated separately for the purpose of summarizing QoL data (in addition to EARLY TAVR): 1) Huded (2023) compared TAVR in minimally symptomatic versus moderate/severe symptomatic patients with severe AS; 2) Merhi (2022) compared timely SAVR versus TAVR in low-risk asymptomatic patients with severe AS [22, 148, 149] .

Nine studies reported outcomes with the modality of AVR being SAVR, 5 studies did not specify AVR type, 1 study reported outcomes with TAVR only, and 1 study included both TAVR and SAVR as interventions but did not report outcomes by modality. Asymptomatic status was confirmed via exercise stress testing for the majority of patients (≥ 50%) in 6 studies.

The final qualitative analysis included a total of 5,346 patients; 2,406 patients were treated with AVR, and 2,940 patients were managed with CS. Five studies reported on patients treated in the US, 3 were multinational, 3 were conducted in Korea, 2 in the Netherlands, and 1 each in Japan, Norway, and the UK, providing robust geographic generalizability.

Mean follow-up across all studies was 4.6 years overall (range: 1.5-8.8 years; 4.2 years in RCTs and 4.8 years in observational studies). The mean age of patients reported at the time of enrollment across all 16 studies was 70.6 years (range 63-79 years). The mean age of patients weighted across the 4 RCTs was 73.3 years (range 64.5-75.8 years). The mean age of patients weighted across the 12 observational studies was 69.5 years (range 63-79 years) [8-23].

Appendix Figure A1. PRISMA flow diagram of the identification, eligibility assessment, and inclusion of articles



Assessment of Study Quality/Risk of Bias

***Randomized Controlled Trials*:** The quality assessment for the 4 RCTs (Genereux (2024), Loganath (2024), Banovic (2024), Kang (2020)) and post-hoc analysis (Merhi (2022)) utilized the RoB 2 Tool from the Cochrane Handbook for RCTs [144, 146]. The overall RoB was assessed as 'low' for the majority of studies. Risk of bias was rated as 'unclear/some concerns' for Merhi (2022) and Banovic (2024). The observed factors which had the greatest impact on these assessments include:

- Post-randomization cross-over (addressed by intention-to-treat)
- Post-hoc analysis of asymptomatic subgroup not pre-specified (Merhi (2022))
- Protocol amendment modifying inclusion criteria (Merhi (2022))
- Imbalanced enrollment by sites (Banovic (2024)), with 75% of patients enrolled at one site

It should be noted that patients randomized to AVR who experienced a delay in intervention due to the COVID-19 public health emergency were documented across all studies. Overall ratings of RoB for clinical trials are summarized in **Appendix Table A3.**

Appendix Table A3. Risk of Bias Assessment, Cochrane Risk-of-Bias Tool for RCTs V.2

First Author (Year) Trial	Random sequence generation	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Bias
Genereux (2024) EARLY TAVR	+	+	+	+	+	+
Loganath (2024) EVoLVeD	+	+	+	+	+	+
Banovic (2024) AVATAR	+	!	+	+	+	!
Kang (2020) RECOVERY	+	+	+	+	+	+
Merhi (2022) Evolut Low risk*	+	+	+	+	!	!

*Study is only included in QoL evaluation
Note: Judgements of risk for each domain include "low risk of bias (+)," some concerns (!), or high risk of bias (-)."

EARLY TAVR: Evaluation of TAVR compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis
EVoLVeD: Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS
AVATAR: Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis
Evolut LR: Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients
RECOVERY: The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis

Observational Studies: Similarly, RoB was assessed for the 12 observational studies (as well as Huded (2023)) using the NOS for observational studies [147]. The total rating has a maximum of 9 points (indicating the lowest RoB). The overall ratings across studies ranged between 5-8 points, with 9 studies rated at 8 points, 3 studies received an overall rating of 7 points, and 1 study rated at 6 points (Bohbot (2018)). Bohbot (2018) had a low rating for comparability because very little detail was provided for the baseline characteristics of the AVR and CS groups. Overall ratings for RoB of observational studies are summarized in **Appendix Table A4.**

Appendix Table A4: Risk of Bias Assessment, Newcastle-Ottawa Scale for Observational Studies

First Author (Year)	Selection	Comparability	Outcome	TOTAL (max 9)
Huded (2023)†	***	**	***	8
Çelik (2021)	***	**	***	8
Campo (2019)	***	**	***	8
Kim (2019)	***	**	***	8
Bohbot (2018)	***	-	***	6
Oterhals (2017)	***	**	**	7

First Author (Year)	Selection	Comparability	Outcome	TOTAL (max 9)
Masri (2016)	***	**	**	7
Taniguchi (2015)	***	**	***	8
Heuvelman (2012)	***	**	***	8
Le Tourneau (2010)	***	**	***	8
Kang (2010)	***	**	***	8
Pai (2006)	***	**	**	7
Pellikka (2005)	***	**	***	8

*Each asterisk represents one point in each category on the Newcastle-Ottawa Scale; total scores range from 0 to 9 stars, with scores of 7 or more considered high quality and scores less than 7 considered low quality
†Study is only included in QoL evaluation

Overview of Studies

Randomized Controlled Trials (4 studies): Four published RCTs, summarized in **Appendix Table A5**, provide the strongest evidence to date supporting timely AVR in the management of asymptomatic patients with severe AS.

The RECOVERY trial enrolled younger patients with predominantly bicuspid (61%) valve disease. The AVATAR trial also enrolled younger patients with very severe aortic stenosis, and a negative exercise test was mandatory for inclusion in the trial. The extended AVATAR trial follow-up (5 years) further strengthens the evidence base in support of timely AVR in asymptomatic patients with severe AS and normal LV systolic function.

EARLY TAVR is a large, prospective trial to evaluate whether timely intervention with exclusively TAVR is superior to the guideline-recommended strategy of CS among asymptomatic patients with severe AS. The EVoLVeD trial evaluates AVR (either TAVR or SAVR) against CS in patients with asymptomatic severe AS and myocardial fibrosis. Both EARLY TAVR and EVoLVeD enrolled older patients with multiple comorbid conditions.

Appendix Table A5: Summary of Randomized Controlled Trials [20-23]

First Author (Year), Study, NCT#	Country; Study Period	Number of Patients			Mean Age	Median (IQR) Follow-up		Median Time to AVR	Inclusion Criteria
		Total	AVR	CS		AVR	CS		
Genereux (2024) EARLY TAVR, NCT03042104	US & CAN (MC); 2017-2021	901	TAVR: 455	446	75.8	3.7 (3.0, 5.1) years	3.8 (2.8, 4.8) years	14.0 (9.0, 24.0) days	· Age ≥65 years; LVEF ≥50%; AVA ≤1 cm^2 or iAVA ≤0.6 cm^2/m^2 and (V_{max} ≥4.0 m/s or MG ≥40 mmHg); Asymptomatic (confirmed exercise testing); STS score ≤10 · LVEF≥50% · Low level stress test in 90.6%
Loganath (2024) EVoLVeD, NCT03094143	UK & AUS (MC); 2017-2022	224	SAVR/ TAVR: 113	111	73.4	4.0 (1.0, 4.3) years	3.0 (1.1, 4.1) years	152.1 (103.4, 243.3) days	· Age ≥18 years; V_{max} ≥4.0 m/s or (iAVA <0.6 cm^2/m^2 and V_{max} ≥3.5 m/s); Midwall LGE on CMR; No symptoms attributable to AS that require AVR · LVEF≥50% · No stress test reported

First Author (Year), Study, NCT#	Country; Study Period	Number of Patients			Mean Age	Median (IQR) Follow-up		Median Time to AVR	Inclusion Criteria
		Total	AVR	CS		AVR	CS		
Banovic (2024) AVATAR, NCT02436655	Europe (MC); 2015-2023	157	SAVR: 78	79	67.0	63 (48, 75) months	63 (48, 75) months	55 (36,79) days	· Age ≥18 years; (AVA ≤1 cm^2 or iAVA ≤0.6 cm^2/m^2 at rest) and (V_{max} >4.0 m/s or MAG ≥40 mmHg); Without reported symptoms; STS score <8% · LVEF ≥50% · Low level stress test in 100%
Kang (2020) RECOVERY, NCT01161732	KOR (MC); 2010-2015	145	SAVR: 73	72	64.5	6.2 (5.0, 7.4) years	6.1 (4.5, 7.3) years	23 (10, 36) days	· Age 20-80 years; AVA ≤0.75 cm^2 and (V_{max} ≥4.5 m/s or MAG ≥50 mmHg); Asymptomatic; Candidate for early surgery · LVEF ≥50% · Low level stress test in 17%

AS = aortic stenosis; AUS = Australia; (i)AVA = (indexed) aortic valve area; AVR = aortic valve replacement; CI = confidence interval; CMR = cardiac magnetic resonance; CS = clinical surveillance; HF = heart failure; HR = hazard ratio; indic. = indication; IQR = interquartile range; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MG = mean gradient; MC = multicenter; Med. = median; NCT = national clinical trial; NR = not reported; Pmean = mean transaortic valvular gradient; p = p-value; RCT(s) = randomized controlled trial(s); SAVR = surgical aortic valve replacement; SD = standard deviation; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; US = United States; Vmax = maximal systolic aortic flow velocity; vs = versus; yrs = years.

Observational Studies (12 studies): Key study characteristics of the 12 observational studies included in the review are summarized in **Appendix Table A6** below.

Appendix Table A6: Summary of Observational Studies [8-19]

First Author (Year)	Country	Study Period	Number of Patients			Mean Age	Follow up (mo)	Time to AVR	LVEF Criteria	ST (% pts)	AS Severity
			Total	AVR	CS						
Çelik (2021)	NLD	2006-2009	**8**	3	5	68.8	Mean 106.8	NA	Yes (≥50%)	Yes (79.7%)	AVA ≤1 cm^2 or Vmax ≥4.0 m/s
Campo (2019)	US	2005-2013	**265**	104	161	70.6	Study Length 60.0	AVR within 60 days	None	Yes (30%)	AVA ≤1 cm^2 or Vmax ≥4.0 m/s or MAG ≥40 mmHg
Kim (2019)	KOR	2000-2015	**468**	SAVR: 221	247	64.2	Median 60.9; PYs 2755	Median time to SAVR: 49 days	Yes (≥50%)	No	AVA ≤1 cm^2 or iAVA ≤0.6 cm^2/m^2 or Vmax ≥4.0 m/s or MAG ≥40 mmHg
Bohbot (2018)	BEL & FRA	2000-2015	**439**	SAVR: 192	247	73.0	Median 42.0	Mean time to SAVR: 51 days	Yes (≥50%)	Yes (64%)	MAG ≥40 mmHg
Oterhals (2017)	NOR	2013	**31**	AVR: 5 TAVR: 2	24*	79.0	Study Length 18.0	NA	Yes (≥50%)	Yes (15%)	AVA <1 cm^2 or Vmax >4.0 m/s or MAG >40 mmHg
Masri (2016)	US	2001-2012	**533**	SAVR: 341	192	66.0	Mean 82.8	NA	Yes (≥50%)	Yes (100%)	iAVA ≤0.6 cm^2/m^2
Taniguchi (2015)	JPN	2003-2011	**582**	291	291	72.4	Median 44.7	Median time to AVR: 44 days	None	No	AVA <1 cm^2 or Vmax >4.0 m/s or MAG >40 mmHg
Heuvelman (2012)	NLD	2006-2009	**59**	22	37	69.9	Study Length 24.0	NA	None	Yes (79.6%)	AVA ≤1 cm^2 or Vmax ≥4.0 m/s
Le Tourneau (2010)	US	1984-1995	**674**	SAVR: 160	514	71.0	Avg >60; PYs 3817	NA	None	No	Vmax ≥4.0 m/s
Kang (2010)	KOR	1996-2006	**197**	SAVR: 102	95	63.0	Median 50.0	SAVR within 90 days echo	Yes (≥50%)	No	AVA ≤0.75 cm^2 and Vmax ≥4.5 m/s or MAG ≥50 mmHg
Pai (2006)	US	1993-2003	**338**	SAVR: 99	239	70.0	Mean 42.0	NA	None	No	AVA ≤0.8 cm^2

First Author (Year)	Country	Study Period	Number of Patients			Mean Age	Follow up (mo)	Time to AVR	LVEF Criteria	ST (% pts)	AS Severity
			Total	AVR	CS						
Pellikka (2005)	US	1984-1995	**325**	SAVR: 145	180	72.0	Mean 64.8	SAVR within 90 days of dx	None	No	Vmax ≥4.0 m/s

*13/24 patients in the CS group had severe AS and 11 had moderate AS

(i)AVA: (indexed) aortic valve area; AVR: aortic valve replacement; BEL: Belgium; CS: clinical surveillance; dx: diagnosis; FRA: France; JPN: Japan; KOR: Korea; LVEF: left ventricular ejection fraction; MAG: mean aortic valve gradient; mo.: month; NA: not available; NLD: Netherlands; NOR: Norway; pts: patients; PYs: patient-years; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; US: United States; Vmax: maximal systolic aortic flow velocity

Clinical Outcomes Evaluated

All 16 studies assessed all-cause mortality, 7 studies assessed cardiovascular mortality, 5 studies assessed HF hospitalization, 6 studies assessed unplanned cardiovascular or HF hospitalization, 6 studies assessed stroke, and 3 studies assessed patient reported QoL. Primary endpoints for the 4 RCTs are also summarized below.

All-Cause Mortality: AVR was associated with a lower rate of all-cause mortality when compared to CS across the majority of studies (14 out of 16). Results are summarized by study in **Appendix Table A7** below.

Two out of 4 RCTs reported lower rates of all-cause mortality with SAVR and the remaining 2 RCTs reported no difference in mortality. Genereux et al. note that the most likely explanation for the differences in mortality benefit between the various studies relates more to outcomes in the clinical surveillance groups and the short time interval between symptom onset and conversion to AVR. That is, the lower threshold to convert to TAVR due to the less invasive nature of the procedure (in EARLY TAVR), and the promptness to offer treatment attenuated the mortality benefits of timely AVR compared to clinical surveillance in both the trial and the analysis. In particular, the study noted that the time from onset of AS symptoms to AVR differed substantially between the trials which included SAVR as the modality of AVR versus TAVR [24].

Eleven observational studies comparing AVR to CS reported reductions in all-cause mortality associated with AVR, with 6 reporting a significant reduction, 1 not significant, and 3 reporting mortality reductions for which statistical comparisons were not reported. One additional study reported a numerical increase in all-cause mortality in patients treated with AVR compared to CS for which a statistical comparison was not reported.

Appendix Table A7: All-Cause Mortality Event Counts

	First Author (Year)	All-Cause Mortality Events (AVR vs CS)
RCT	Genereux (2024)	38/455 vs 41/446
	Loganath (2024)	16/113 vs 14/111
	Banovic (2024)	11/78 vs 27/79*
	Kang (2020)	5/73 vs 15/72*
Observational	Kim (2019)	37/221 vs 109/247*
	Bohbot (2018)	21/192 vs 91/247*
	Taniguchi (2015)	40/291 vs 69/291*
	Kang (2010)	3/102 vs 28/95*
	Pellikka (2005)	41/145 vs 103/180
	Celik (2021)	1/3 vs 4/5
	Campo (2019)	9/104 vs 34/161
	Oterhals (2017)	1/7 vs 4/24
	Masri (2016)	44/341 vs 60/192*

	First Author (Year)	All-Cause Mortality Events (AVR vs CS)
	Heuvelman (2012)	3/22 vs 2/37
	Le Tourneau (2010)†	31/160 vs 181/514
	Pai (2006)	9/99 vs 129/239*

AVR: aortic valve replacement; CS: clinical surveillance; ; *p<0.05

***Primary Endpoints*:** Three of out 4 RCTs achieved their primary endpoints (**Appendix Table A8**).

Appendix Table A8: Primary Endpoint Event Counts by Study

First Author (Year)	Primary Endpoint	Events (AVR vs CS)	Key Findings
Genereux (2024)	All-cause death, all stroke, and unplanned cardiovascular hospitalization when all patients have reached 2-year follow-up	122/455 vs 202/446	**· Met primary endpoint (superiority)†** · Significantly lower incidence of the composite endpoint in early TAVR arm compared with CS arm (26.8% vs 45.3%; HR: 0.50; 95% CI: 0.40-0.63; p<0.0001)
Loganath (2024)	Composite of all-cause mortality or unplanned aortic stenosis-related hospitalization from randomization through study completion (mean follow-up expected to be an average of 2.75 years)	20/113 vs 25/111	**· Did not meet primary endpoint** · Significantly lower incidence of AS-related hospitalizations in AVR arm compared with CS arm (6.2% vs 17.1%; HR: 0.37; 95% CI: 0.16-0.88; p=0.024)
Banovic (2024)	All-cause mortality or major adverse cardiovascular events (MACEs) composed of acute myocardial infarction, stroke, and unplanned HF hospitalization needing intravenous treatment within 5-year follow-up	18/78 vs 37/79	**· Met primary endpoint (superiority)** · Significantly lower incidence of the composite endpoint in SAVR compared with CS arm (23.1% vs 46.8%; HR: 0.42; 95% CI: 0.24-0.73; p=0.002)
Kang (2020)	Operative mortality (during or within 30 days of surgery) or cardiac mortality during entire follow-up (a minimum of 4 years)	5/73 vs 15/72	**· Met primary endpoint (superiority)** · Significantly lower incidence of the composite endpoint in SAVR compared with CS arm (1% vs 15%; HR: 0.09; 95% CI: 0.01-0.67; p=0.003)

AVR: aortic valve replacement; CS: clinical surveillance

Cardiovascular Mortality: AVR was associated with a lower rate of cardiovascular mortality when compared to CS across the majority of studies (6 out of 7). Results are summarized by study in **Appendix Table A9** below.

Appendix Table A9: Cardiovascular Mortality Event Counts by Study

	First Author (Year)	Cardiovascular Mortality Events (AVR vs CS)
RCT	Genereux (2024)	18/455 vs 23/446
	Loganath (2024)	10/113 vs 8/111
	Banovic (2024)	8/78 vs 17/79
	Kang (2020)	1/73 vs 11/72
Obs.	Kim (2019)	26/221 vs 74/247*
	Taniguchi (2015)	25/291 vs 46/291*
	Kang (2010)	0/102 vs 18/95*

*p< 0.05 AVR: aortic valve replacement; CS: clinical surveillance; Obs: observational

HF hospitalization: : AVR was associated with a significantly lower rate of HF hospitalization events when compared to CS across the majority of studies (3 out of 5). Results are summarized by study in **Appendix Table A10** below.

Appendix Table A10: HF Hospitalization Event Counts by Study

	First Author (Year)	HF Hospitalization Events (AVR vs CS)
RCTs	Genereux (2024)	15/455 vs 44/446*
	Banovic (2024)	3/78 vs 13/79*
	Kang (2020)	0/73 vs 8/72
Obs.	Kim (2019)	2/221 vs 3/247
	Taniguchi (2015)	10/291 vs 50/291*

*p< 0.05 AVR: aortic valve replacement; CS: clinical surveillance; Obs: observational

Unplanned cardiovascular or HF hospitalization: AVR was associated with a significantly lower rate of unplanned CV or HF hospitalization events when compared to CS across the majority of studies (4 out of 6). Results are summarized by study in **Appendix Table A11**.

- Unplanned cardiovascular hospitalization in EARLY TAVR was defined as admission through emergency department or same day admission from a clinic for congestive heart failure or AS-related causes, as well as other cardiovascular causes like arrhythmia/conduction system disturbance, bleeding, coronary artery disease, stroke/transient ischemic attack, thromboembolic event, and any aortic valve intervention within 6 months of randomization in the CS arm, including conversion to AVR, and any aortic valve reintervention within 6 months of the procedure in the TAVR arm.

- Unplanned AS hospitalization in EVoLVeD was defined as any unplanned admission before or after aortic valve replacement with syncope, heart failure, chest pain, ventricular arrythmia or second- or third-degree heart block, attributed to aortic valve disease.

Appendix Table A11: Unplanned cardiovascular or HF hospitalization Event Counts by Study

	First Author (Year)	Unplanned CV or HF hospitalization Events (AVR vs CS)
RCT	Genereux (2024)	95/455 vs 186/446*
	Loganath (2024)	7/113 vs 19/111*
	Banovic (2024)	3/78 vs 13/79*
	Kang (2020)	0/73 vs 8/72
Obs.	Kim (2019)	2/221 vs 3/247
	Taniguchi (2015)	10/291 vs 50/291*

*p< 0.05 AVR: aortic valve replacement; CS: clinical surveillance; Obs: observational

Stroke: AVR was associated with a lower rate of stroke events when compared to CS across 3 out of 6 studies, with 2 studies showing no difference. Results are summarized by study in **Appendix Table A12**.

Appendix Table A12: Stroke Event Counts by Study

	First Author (Year)	Stroke Events (AVR vs CS)
RCT	Genereux (2024)	19/455 vs 30/446
	Loganath (2024)	8/113 vs 14/111
	Banovic (2024)	4/78 vs 4/79
	Kang (2020)	1/73 vs 3/72

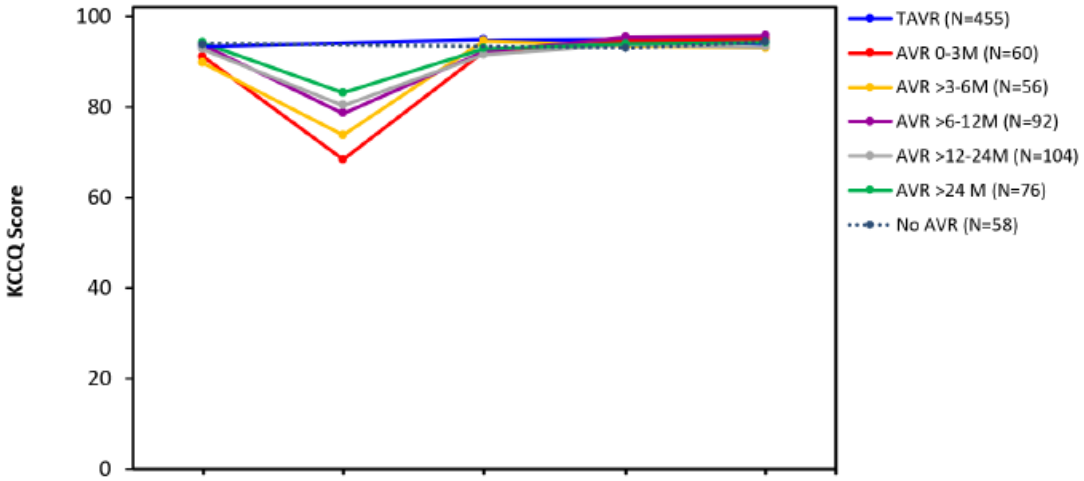
	First Author (Year)	Stroke Events (AVR vs CS)
Obs.	Kim (2019)	4/221 vs 2/247
	Taniguchi (2015)	23/291 vs 18/291

AVR: aortic valve replacement; CS: clinical surveillance; Obs: observational

QoL: AVR is associated with significant improvements in patient-reported QoL following intervention (both TAVR and SAVR), with more rapid improvement observed in TAVR patients across 3 studies.

Results from the EARLY TAVR trial demonstrated that symptom onset was associated with a clinically meaningful and rapid decline in QoL for patients. Within the first 6 months, approximately ~25% of patients assigned to CS received AVR, with more than one third of these patients assigned to CS presented with advanced signs and symptoms of aortic-valve disease. Patients receiving CS had a decline in QoL (KCCQ) before conversion to AVR, with KCCQ improvement occurring within 30 days following TAVR. After 2 years, more than 70% of patients assigned to CS received AVR. CS was associated with worsening left ventricular and left atrial function, highlighting the unpredictable nature of AS progression and cardiac damage in asymptomatic patients (**Appendix Figure A2**). [22]

Appendix Figure A2: KCCQ Scores by Treatment and Timing of Intervention



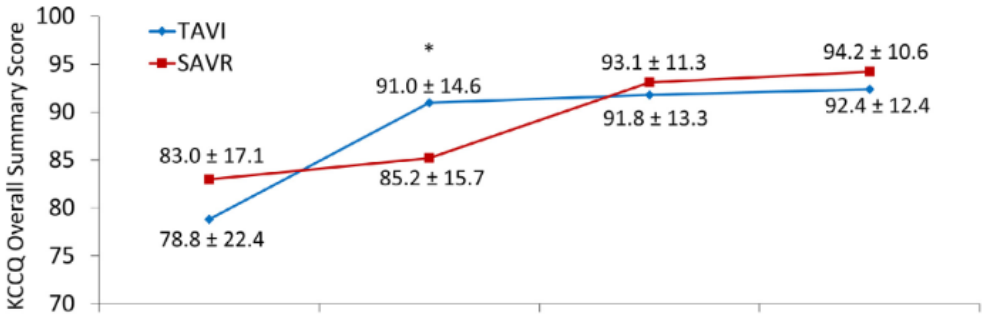
No. of Pts:					
TAVR	441	-	437	422	395
AVR 0-3M	60	56	58	54	50
AVR >3-6M	56	54	55	52	46
AVR >6-12M	91	89	90	85	79
AVR >12-24M	102	94	95	88	71
AVR >24M	76	74	73	55	29
No AVR	55	-	-	46	36

AVR denotes aortic valve intervention, KCCQ Kansas City Cardiomyopathy Questionnaire, TAVR transcatheter aortic valve replacement.
The mean change in KCCQ score for patients who converted to AVR was 14.8, with larger changes among patients who converted within the first 6 months.
*Post-screening visits in the TAVR arm reflect time from index procedure. For CS patients who converted to AVR, pre-procedure visits occurred within 30 days prior to the AVR procedure, and subsequent visits reflect time from AVR procedure. Post-screening visits reflect time from randomization in the group of CS patients who did not convert to AVR. The no AVR group did not have a pre-procedure or 30-day post-procedure visit.

Two additional studies, 1 RCT (Merhi (2022)) and 1 observational study (Huded (2023)), evaluated changes in patient-reported QoL following AVR therapy as measured by the KCCQ Overall Summary Score. Merhi (2022) reported a significant difference in change from baseline at 30 days following surgery between patients treated with TAVR compared to SAVR,

with TAVR patients reporting a significantly greater improvement from baseline at 30 days (**Appendix Figure A3**). These differences between treatments were not sustained at the 6- and 12-month assessments following surgery, suggesting that intervention with both TAVR and SAVR improves patients' long-term QoL, but that the recovery following TAVR is much more rapid, likely due to the much less invasive approach compared to SAVR [149].

Appendix Figure A3: Summary of QoL change from baseline to 12 months between patients receiving timely TAVR/TAVI vs SAVR



Change from baseline			
TAVI (76)	12.1 ± 23.6 (76)	13.1 ± 18.3 (73)	15.5 ± 19.7 (65)
SAVR (61)	2.2 ± 20.3 (59)	7.9 ± 17.0 (56)	10.6 ± 18.9 (52)
P value	P=0.01	P=0.10	P=0.18

*Significant difference in change from baseline between TAVI and SAVR asymptomatic patients
KCCQ overall summary score for asymptomatic patients. Mean KCCQ overall summary score for TAVI (blue lines) asymptomatic patients and SAVR (red lines) asymptomatic patients. p value comparison was performed with TAVI versus SAVR asymptomatic patients using a paired t test.[Error! Bookmark not defined.]

Huded (2023) evaluated the outcomes of patients with minimally symptomatic severe AS treated with TAVR in the TVT registry. Minimally symptomatic status was defined as a baseline KCCQ overall summary score (KCCQ-OS) ≥75. Clinical and health status outcomes of TAVR in patients with sAS and normal LVEF were compared between minimally symptomatic patients and those with moderate or severe symptoms. Among 231,285 patients who underwent TAVR between 2015 and 2021, 46,323 (20.0%) were minimally symptomatic before TAVR. Mean KCCQ-OS increased by 2.7 points (95% CI: 2.6-2.9 points) at 30 days and 3.8 points (95% CI: 3.6-4.0 points) at 1 year in minimally symptomatic patients compared with increases of 32.2 points (95% CI: 32.0-32.3 points) at 30 days and 34.9 points (95% CI: 34.7-35.0 points) at 1 year in more symptomatic patients. Minimally symptomatic patients had higher odds of being alive and well at 1 year (OR: 1.19 [95% CI: 1.16-1.23]) [148].

Mortality While Waiting for AVR in Asymptomatic Severe AS: 13 studies reviewed that suggest delays in access to timely AVR adversely impacts survival

Determining the optimal timing of AVR in patients with asymptomatic severe AS depends on a variety of factors, including the severity of the AS, balancing the surgical risks and benefits including safety, efficacy and long-term results of the procedure being recommended. Assessing the risks of early intervention while the patient is asymptomatic remains a complex clinical challenge faced by both clinicians and patients seeking to gain long-term benefits, including reduced mortality risk while minimizing procedure-related complications. Access to timely intervention in asymptomatic patients with severe AS is gaining increased attention as evidence suggests that LV remodeling and diastolic dysfunction begin long before patients present symptoms, with the onset of symptoms being a clear indicator of poor prognosis. In this review, we also sought to highlight available data documenting the impact of delay in planned or scheduled AVR on mortality. In studies that specifically reported mortality associated with delays in access to timely AVR, the mean proportion of patients who died while waiting for AVR was 6.7% (range: 0 - 28.1%)[14, 16-18, 47, 149-156].

Key Conclusions & Recommendations

This report provides a comprehensive assessment of literature evaluating the clinical benefits associated with timely AVR compared to CS in the management of asymptomatic severe AS. The evidence is based on clinical and QoL data from 4 RCTs and 12 observational studies, including 5,346 asymptomatic severe AS patients (LVEF ≥50%), 2,406 patients who underwent AVR and 2,940 patients who were managed with conservative CS, from a diverse geographic and representative age population of asymptomatic severe AS patients. All 16 studies were rated as having a low RoB using standardized assessment methods. The key takeaways based on this substantial evidence base suggest that a strategy of timely AVR is associated with improved outcomes for asymptomatic severe AS patients, including:

- Reductions in the rates of **all-cause mortality** in 14 of the 16 studies reporting all-cause mortality;
- Significant reductions of the **primary composite endpoint** in 3 of the 4 studies evaluating composite endpoints;
- Reductions in **cardiovascular mortality** in 6 of the 7 studies reporting cardiovascular mortality;
- Significant reductions in the rates of **HF hospitalizations** in 3 of the 5 studies reporting this endpoint;
- Significant reductions in the rates of **unplanned CV or HF hospitalizations** in 4 of the 6 studies reporting this endpoint;
- Reductions in the rates of **stroke** events in 3 of the 6 studies reporting this endpoint;
- Significant improvements in **patient-reported QoL** in 3 of the 3 studies reporting this endpoint, and a **more rapid improvement observed with TAVR** in 2 of the 3 studies.

The most likely explanation for the differences in mortality benefit between the various studies relates more to outcomes in the CS groups and the short time interval between symptom onset and conversion to AVR. That is, the lower threshold to convert to TAVR due to the less invasive nature of the procedure (in EARLY TAVR), and the promptness to offer treatment attenuated the mortality benefits of timely AVR compared to CS in both the trial and the analysis. In particular, the study noted that the time from onset of AS symptoms to AVR differed substantially between the trials that included SAVR as the modality of AVR versus TAVR.

Considered together, the results of the observational studies of AVR summarized above provide strong support for the favorable outcomes also observed in RCTs such as EARLY TAVR. These studies also highlight the evolution of best practices over time as patient outcomes have continued to improve since the introduction of TAVR. The increasing body of evidence that suggests waiting for symptoms to occur or LV function to decline may endanger patients in ways not previously appreciated, particularly in patients who do not undergo routine follow-up. The recent emergence of additional trial data presented above demonstrates positive clinical and QoL outcomes associated with TAVR while reducing surgical morbidity associated with SAVR in asymptomatic severe AS patients and necessitates the reevaluation of the long-held treatment paradigm of a strategy of CS for these patients.

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